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PPAR-α AS A THERAPEUTIC TARGET OF PSYCHIATRIC DISEASES

BIO/14-Pharmacology

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Abstract

Currently available psychopharmacological therapies have limited efficacies; consequently, developing novel pharmacological targets beyond the existing ones for treating mood disorders has become increasingly critical. Increasing preclinical evidences that peroxisome proliferator-activated receptor alpha PPAR-α agonists can impact mood regulation have opened a new line of research in psychopharmacological discovery. However, the effects of clofibrate; a fibric acid derivative acting as a synthetic PPAR-α agonist; on psychiatric behavior are poorly understood. The present thesis was designed to evaluate the prospective anxiolytic and antipsychotic effect of the synthetic PPAR-α agonist clofibrate in pharmacological animal models of anxiety and schizophrenia in Sprague-Dawley rats.

Open field test, social interaction test, and elevated plus maze test were used to evaluate anxiety-like behaviors after clofibrate treatments. Anxiogenic effects were produced upon injecting clofibrate (25 mg/kg) acutely, by increasing the number of entries and time spent in the corners of the open field test, and decreasing the duration of time spent in social interaction in the social interaction test. These effects were normalized in the open field test after giving clofibrate once daily for 3 consecutive days only, and reversed into anxiolytic effects upon chronic treatment. In contrast, no significant effects were detected in the elevated plus maze test by acute clofibrate treatment.

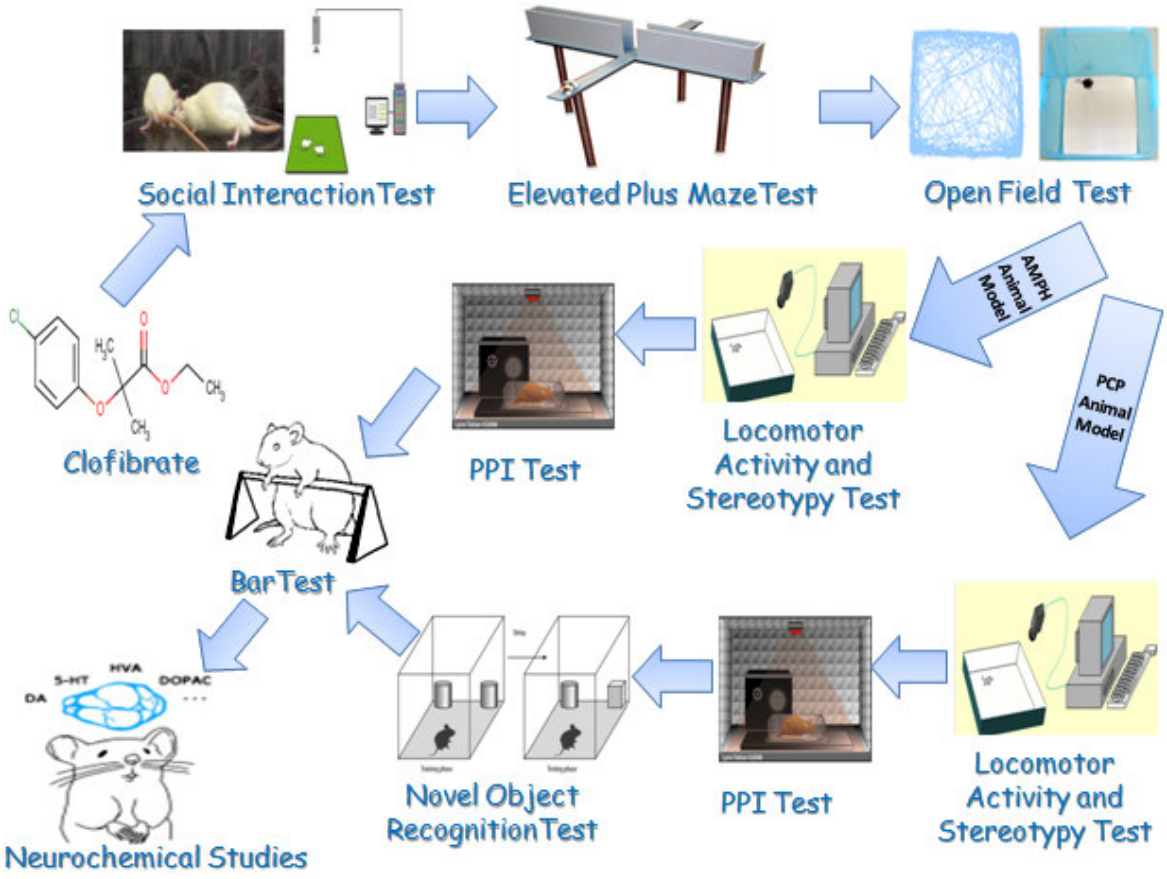
Moreover, it has been showed that an acute administration of the non-competitive N-methyl-D-aspartate receptor antagonist phencyclidine (PCP 5 mg/kg intraperitoneally), or amphetamine (Amph 3 mg/kg intraperitoneally), was able to induce positive-like symptoms of schizophrenia such as hyperactivity, stereotypies and impaired sensorimotor gating in the prepulse inhibition (PPI) test of the acoustic startle reflex. Using these glutamatergic and dopaminergic models, we found that an acute injection of clofibrate, at dose that by itself does not affect spontaneous locomotor activity (25 mg/kg), was unable to revert hyperlocomotion,

stereotypies and impaired PPI induced by the acute injections of phencyclidine or amphetamine. However, when we used the sub-chronic treatment of PCP (5 mg/kg i.p. twice day for 7 consecutive days) that induced cognitive deficits in the novel object recognition (NOR) test, acute clofibrate (25 mg/kg i.p.) that by itself does not affect recognition memory in NOR paradigm, was able to significantly attenuate the cognitive deficits. In preclinical research, catalepsy is an animal behavior widely used to evaluate the antipsychotic-induced extrapyramidal symptoms in humans. Compared to haloperidol, clofibrate did not induce catalepsy in the bar test at any dose tested (100, 250 and 500 mg/kg i.p.).

Finally, the activity of clofibrate (25 mg/kg) was also obtained by determining the levels of dopamine, serotonin and and their metabolites in the prefrontal cortex, nucleas accumbens, striatum, amygdala, hippocampus and hypothalamus of rats, following the acute and chronic administration regimes. No significant alteration in the selected neurotransmitters and their metabolites was revealed in any brain site upon acute administration of clofibrate (25 mg/kg). In contrast, the chronic administration of clofibrate at the same dose showed some significant alterations in the selected neurotransmitters and their metabolites, manifested as a reduction the levels of dopamine and its metabolites; DOPAC and HVA, in the amygdala, the levels of DOPAC and HVA in the prefrontal cortex, and the level of the serotonin metabolite 5-HIAA in both the hippocampus.

Taken together, these results suggest that despite the anxiogenic profile produced by acute clofibrate treatment, the synthetic PPAR-α agonist, on specific animal models of anxiety, only 3 repeated administrations were sufficient for normalizing it, a phenomenon observed classically after much longer period of time in other anxiolytics, and then reverted into an anxiolytic profile upon chronic clofibrate treatment, meanwhile just a single dose of it was able to revert the cognitive deficits induced by phencyclidine in animal model of schizophrenia. These data unravel a previously unknown role of clofibrate; the clinically used hypolidimic agent, in behavior and cognitive regulation and may suggest a new strategy for treating mood disorders, without having undesirable central nervous system side effects.

Keywords: Clofibrate, Peroxisome proliferator-activated receptor-*α*, anxiety, schizophrenia, cognitive, dopamine, serotonin.



Graphic Abstract

Astratto

Le terapie psicofarmacologiche attualmente disponibili hanno un'efficacia limitata; di conseguenza, lo sviluppo di nuovi bersagli farmacologici al di là di quelli esistenti per il trattamento dei disturbi dell'umore è diventato sempre più critico. La crescente evidenza preclinica che gli agonisti PPAR-α attivato possono influenzare la regolazione dell'umore ha aperto una nuova linea di ricerca nella scoperta psicofarmacologica. Tuttavia, gli effetti del clofibrato; un derivato dell'acido fibrico che agisce come agonista sintetico di PPAR-α; sul comportamento psichiatrico sono poco compresi. La presente tesi è stata concepita per valutare il potenziale effetto ansiolitico e antipsicotico del clofibrato, agonista sintetico di PPAR-α, nei modelli farmacologici animali di ansia e schizofrenia nei ratti Sprague-Dawley.

“Open field test”, “social interaction test”, e “elevated plus maze test” sono stati utilizzati per valutare i comportamenti ansiolitici dopo i trattamenti con il clofibrato. Effetti di ansia sono stati prodotti iniettando acutamente clofibrato (25 mg/kg), aumentando il numero di ingressi e il tempo trascorso negli angoli della “open field test”, e diminuendo la durata del tempo trascorso nell'interazione sociale nel test di “social interaction”. Questi effetti sono stati normalizzati nel “open field test” dopo aver somministrato clofibrato una volta al giorno solo per 3 giorni consecutivi, e sono stati invertiti in effetti ansiolitici nel trattamento cronico. Al contrario, non sono stati rilevati effetti significativi nel “elevated plus maze test” mediante trattamento acuto con clofibrato.

È stato inoltre dimostrato che una somministrazione acuta di fenciclidina (PCP 5 mg/kg per via intraperitoneale) o di anfetamina (Amph 3 mg/kg via intraperitoneale) è stato in grado di indurre sintomi simili alla schizofrenia come l'iperattività, stereotipi e disturbi sensorimotori nel “prepulse inhibtion test” (PPI) del riflesso di startle acustico. Utilizzando questi modelli glutamatergici e dopaminergici, abbiamo scoperto che un'iniezione acuta di clofibrato, alla dose che di per sé non influisce sull'attività locomotoria spontanea (25 mg/kg), non è riuscita a ripristinare l'iperlocomozione, gli stereotipi e la ridotta PPI indotti dalle iniezioni

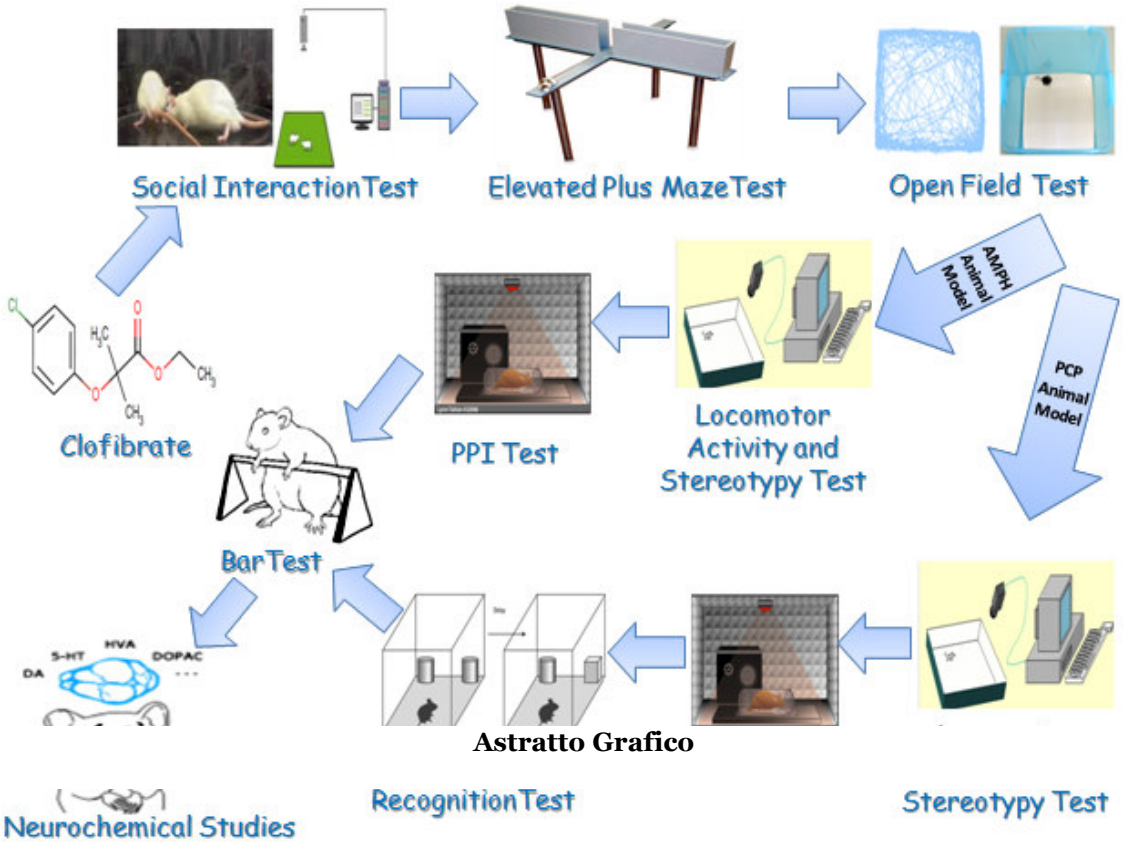
acute di fenciclidina o anfetamina. Tuttavia, quando abbiamo usato il trattamento sub-cronico di PCP (5 mg/kg i.p. due volte al giorno per 7 giorni consecutivi) che ha indotto deficit cognitivi nel “novel object recognition test” (NOR) test, clofibrato acuto (25 mg/kg i.p.) che di per sé non influisce sulla memoria di riconoscimento nel NOR paradigma, è stato in grado di attenuare significativamente i deficit cognitivi. Nella ricerca preclinica, la catalessi è un comportamento animale ampiamente utilizzato per valutare i sintomi extrapiramidali antipsicotici indotti negli esseri umani. Rispetto all'aloperidolo, il clofibrato non ha indotto la catalessi nel “bar test” ad alcuna dose testata (100, 250 e 500 mg/kg i.p.).

Infine, l'attività del clofibrato (25 mg/kg) è stata ottenuta anche determinando i livelli di dopamina, serotonina e dei loro metaboliti nella corteccia prefrontale, nuclei accumbens, striato, amigdala, ippocampo e ipotalamo dei ratti, seguendo i regimi di somministrazione acuta e cronica. Non sono state rilevate alterazioni significative nei neurotrasmettitori selezionati e nei loro metaboliti in nessun cervello in seguito alla somministrazione acuta di clofibrato (25 mg/kg). Al contrario, la somministrazione cronica di clofibrato alla stessa dose ha mostrato alcune alterazioni significative nei neurotrasmettitori selezionati e nei loro metaboliti, che si sono manifestate come riduzione dei livelli di dopamina e dei suoi metaboliti; DOPAC e HVA, nell'amigdala, i livelli di DOPAC e HVA nella corteccia prefrontale, e il livello del metabolita serotonina 5-HIAA sia nella ippocampo.

Questi risultati suggeriscono che, nonostante il profilo ansiogeno prodotto dal trattamento con clofibrato acuto, l'agonista sintetico di PPAR-α, su specifici modelli animali di ansia, solo 3 somministrazioni ripetute sono state sufficienti per normalizzarlo, un fenomeno osservato classicamente dopo un periodo di tempo molto più lungo in altri ansiolitici, per poi tornare ad un profilo ansiolitico dopo il trattamento cronico con clofibrato, nel frattempo solo una singola dose di esso è stato in grado di ripristinare i deficit cognitivi indotti da fenciclidina nel modello animale di schizofrenia. Questi dati svelano un ruolo precedentemente sconosciuto di clofibrato; l'agente ipolidimico clinicamente utilizzato, nella regolazione

comportamento e cognitiva e può suggerire una nuova strategia per il trattamento dei disturbi dell'umore, senza effetti indesiderati sul sistema nervoso centrale.

Parole chiave: clofibrato, peroxisome proliferator-activated receptor-α, ansia, schizofrenia, cognitivo, dopamina, serotonina.



Astratto Grafico

1. Chapter I: Introduction

1.1 PPARs: From Orphan Receptors to Research Advances

1.1.1 Orphan nuclear receptors

Orphan nuclear receptors were discovered in the early 1990s. They function as ligand-activated transcription factors that regulate the expression of a large number of genes that are involved in development, homeostasis and energy metabolism, by binding directly to the DNA of their target genes. Each receptor recognizes a specific DNA sequence, which is usually located in the promoter region of the target gene.

Under the name of the nuclear receptor superfamily, we have the "classic" nuclear steroid receptors which include the receptors for the hormones estrogen, progesterone, androgens, and the corticoid hormones. In addition to these well-known nuclear receptors, and based on the discovery of a great number of receptor-related molecules in a wide range of species, Evans hypothesized that more hormonal systems could be involved in complicated processes like homeostasis and development. After the finding that the classic nuclear receptors share extensive homology at the DNA sequence level, well-conserved receptor fragments were used as probes to screen cDNA libraries to identify new receptors. Subsequently, more receptors were isolated (Raalte et al., 2004). And since their ligands and functions were unknown, they were initially called "Orphan Nuclear Receptors". And now, they form the second part of the nuclear receptor superfamily (Raalte et al., 2004). Currently, a total of 48 members of this superfamily have been identified in the human genome (Raalte et al., 2004). In this thesis, we will focus on the peroxisome proliferator activated receptor PPARα, an orphan nuclear receptor involved in several physiological and behavioral functions.

1.1.2 Discovery of Peroxisome Proliferator-Activated Receptors

Existence of a specific mediator for the effects of chemicals which are known to cause peroxisome proliferation (peroxisome proliferators) was suggested by the tissue and cell specificity of the pleiotropic effects of these chemicals. In attempting to identify such a molecular target, a cytosolic protein was detected in rat liver and a receptor-mediated mechanism for peroxisome proliferation was consequently postulated (Lalwani et al., 1983a). A peroxisome proliferator-binding protein was later purified from rat liver cytosol and was identified as a dimer protein with a molecular weight of 140,000 – 160,000 KDa. This protein was capable of binding to peroxisome proliferators structurally related to clofibrate (Lalwani et al., 1987). Further analysis of the isolated protein revealed that it is homologous with the heat shock protein HSP70 but its role in the process of peroxisome proliferation remained unclear at that time(Alvares et al., 1990). Thus, efforts continued in order to identify the putative mediator of these observed prominent effects.

The ability of peroxisome proliferators to modulate specific gene transcription suggested that they could act via a mechanism similar to that of steroid hormones. This assumption paved the way to a significant discovery when Issemann et al. (Issemann and Green, 1990) discovered in 1990 that peroxisome proliferators, activated one of the orphan nuclear receptors that is structurally related to steroid hormone receptors and was activated by a wide range of molecules including fatty acids and fibrates. And since the pattern of expression of the receptor mRNA mirrored the tissue-specific effects of peroxisome proliferators (Lalwani et al., 1983b), the orphan nuclear receptor was named “Peroxisome Proliferator Activated Receptor”.

Following the initial discovery of mouse PPAR, the receptor was identified in other species including rat (Göttlicher et al., 1992) and human (Schmidt et al., 1992). In addition, three related *xenopus* receptors belonging to nuclear hormone receptor superfamily were cloned and named PPAR-α, PPAR-β, and PPAR-ɣ proving the existence of more than one form of PPAR in a given species (Dreyer et al., 1992). PPAR-δ was initially identified in human as an additional form of PPAR (Schmidt et

al., 1992) but was found later to be closely related to PPAR-β described in *xenopus* . And although none of the members of the PPAR family actually induce peroxisome proliferation in humans, the name has not been changed (Raalte et al., 2004).

1.1.3 Molecular Aspects of Peroxisome Proliferator-Activated Receptors

Subsequent studies indicated that the three PPAR subtypes, PPAR-α, PPAR-β /-δ, and PPAR-ɣ, share a high degree of homology but differ in tissue distribution and ligand specificity, and each subtype is encoded by a different gene (Berger and Moller, 2002). Human PPAR-α gene is located on chromosome 22 slightly telomeric to a linkage group of six genes and genetic markers existing in the general region 22q12– q13.1(Sher et al., 1993), while PPAR-β/-δ gene is located on chromosome 6 at position 6p21.1–p21.2 (Yoshikawa et al., 1996) and PPAR-δ gene is mapped to chromosome 3 at position 3p25(Greene et al., 1995).

PPARs share a common structure with four functional domains identified as A/B, C, D and E/F. Figure 1 shows a schematic representation of the functional domains of PPARs. Briefly, the schematic shows that the A/B domain contains a ligand-independent activation function 1 (AF-1) (Werman et al., 1997), which, when phosphorylated, aids the regulation of PPARα and PPARɣ activation (Shalev et al., 1996), (Juge-Aubry et al., 1997), (Zhang et al., 1996). The C domain or DNA-binding domain (DBD) is highly conserved between the three PPAR isotypes and composed of two zinc fingers and binds to the PPRE. The structure of the docking domain is very flexible and may be crucial for efficient binding of the DBD domain to the promoter region of the target gene(Kliewer et al., 1992). The D domain is a docking site for co-factors. The E/F domain or the ligand binding domain (LBD) has ligand specificity which when bound activates PPAR binding to the PPRE. This domain depends on the ligand-dependent transactivation function 2 (AF-2) positioned at the carboxy terminus of PPAR LBD, and which recruits PPAR co-factors (Berger and Moller, 2002).

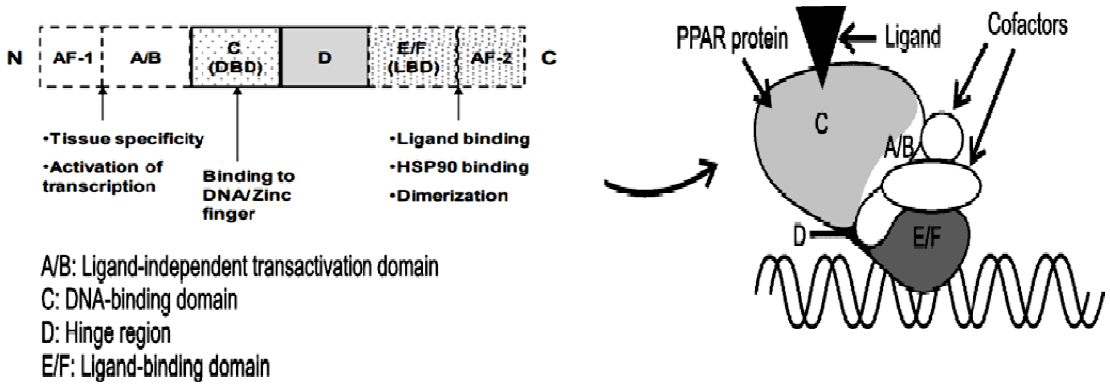


Figure 1: Schematic representation of primary and tertiary structure of PPARs (reproduced and combined from different figures from internet).

When a ligand binds, PPARs are translocated to the nucleus and form heterodimers with the retinoic acid receptor (RXR), which also belongs to the nuclear hormones family of receptors (Kliewer et al., 1992),(Gearing et al., 1993). The RXR forms a heterodimer with a number of other receptors (e.g., vitamin D or thyroid hormones) (Grygiel-Górniak, 2014). PPAR/RXR heterodimers recognize and bind to a specific DNA sequence of target genes known as PPAR response element (PPRE). The PPREs are found in the promoters of PPAR responsive genes (Berger and Moller, 2002), and have an exclusive directly repeating sequence (DR-1) of two hexanucleotides, 5' AGGTCA 3' separated by a single spacer nucleotide (Lemberger et al., 1996a). The 5' flanking nucleotides of the core PPRE may play an important role in PPAR subtype specificity (Nielsen et al., 2006). This process activates transcription of various genes involved in diverse physiological and pathophysiological processes related to neuroprotective effects, fatty acid and glucose metabolism, inflammation, differentiation and proliferation (Kersten et al., 2000), (Pyper et al., 2010), (Laudet and Gronemeyer, 2002), and the three PPARs activate both overlapping and distinct sets of target genes.Figure 2 shows a schematic diagram of the gene transcription mechanism of PPARs.

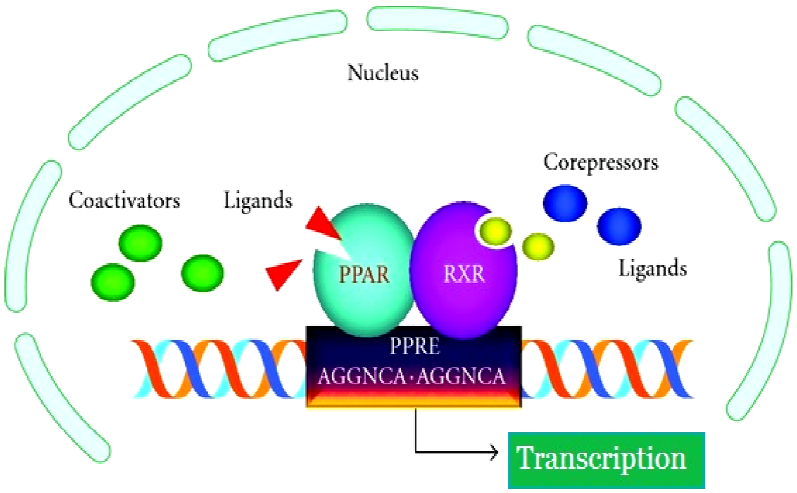


Figure 2: The gene transcription mechanism of PPARs. (Internet)

Intrinsic properties of each PPAR subtype, including post-translational modifications, are modified by a number of co-activators and co-repressors, the presence of which can either stimulate or inhibit transcription, respectively (Lemberger et al., 1996a). When unliganded, the PPAR/RXR dimer associates with a co-repressor with histone deacetylase activity, for example, nuclear receptor co-repressor (NCoR) or silencing mediator for retinoid and thyroid hormone receptor (SMRT). This inhibits transcription. Oppositely, PPAR subtype specificity may also be partly imposed by differential affinity of the receptors towards co-activators; such as steroid receptor co-activator (SRC)-1 or PPAR binding protein (PBP) which has histone acetylase activity(Ricote and Glass, 2007),(Pascual and Glass, 2006). Each PPAR ligand induces a specific change in receptor conformation, resulting in the differential recruitment of cofactors and gene-specific transcriptional activity or specificity (Oberkofler et al., 2002). Thus, in addition to a panel of common genes regulated in a similar manner by all PPAR agonists, each agonist regulates its unique profile of genes, resulting in specific biological effects. This concept inspired the creation of new compounds with differential gene regulating properties as novel therapeutic agents without significant adverse effects. Table 1 summarizes transcriptional co-factors, mechanism of action and their effects in PPARs. However, human cells are characterized by a different availability of cofactors that depends on the type of cell and the association of specific cofactors to other genes.

Heterodimerized nuclear receptor	*Cofactors*	*Mechanism of action*	*Effect*
No ligand	**Co-repressors:** Nuclear receptor co-repressor (NCor) & Silencing mediator for retinoid and thyroid hormone receptor (SMRT)	Histone deacetylase activity	Inhibition of transcription
+ Ligand	**Co-activators:** Steroid receptor co-activator (SRC)-1 & PPAR binding protein (PBP)	Histone acetylase activity	Initiation of transcription

Table 1: Transcriptional co-factors of PPARs (reproduced from the work of: Ricote and Glass, 2007 and Pascual and Glass, 2006.

1.1.4 Peroxisome Proliferator-Activated Receptors ligands

The discovery and designation of PPARs was made possible by experimental works on peroxisomes and peroxisome proliferators (Issemann and Green, 1990). Peroxisome proliferators are a group of non-genotoxic, structurally diverse chemicals, that lower serum lipids, and induce massive proliferation of peroxisomes in liver cells (Reddy, 2004). Peroxisome proliferators comprise drugs used for therapeutic treatment (e.g. fibrates and non-steroidal anti-inflammatary drugs) and NSAIDS (Fidaleo, 2009), (Fidaleo et al., 2008).

Even though extensive work has been done using xenobiotics as PPAR ligands, studies focusing on PPAR activation in physiological and pathological conditions have demonstrated natural fatty acids and their metabolites as endogeneous receptors, leading to the concept that PPARs function as lipid sensors to regulate energy metabolism (Keller et al., 1993). But what characterizes the PPAR ligand binding cavity is its size, which is 3–4 times larger than that of other nuclear receptors (Grygiel-Górniak, 2014). Thus, PPARs have the capability to accommodate and bind a variety of natural and synthetic lipophilic acids, such as essential fatty acids like docosahexaenoic acid and eicosapentaenoic acid (Krey et al., 1997), (Plutzky, 2000), (Neschen et al., 2007). Not only fatty acids, but also eicosanoids are natural ligands of PPARs, including leukotriene and prostaglandins (Krey et al., 1997). However, both fatty acids and eicosanoids are required in

relatively high concentrations (approximately 100 μM) for PPAR activation (Plutzky, 2000). Moreover, a number of cannabinoid CB1/CB2 agonists have been reported to be PPAR agonists. These include the archetypal endocannabinoids anandamide (AEA) and 2-arachidonoylglycerol, as well as other natural and synthetic cannabinoids (Pertwee et al., 2010).

It is worthy to note that these ligands have different properties and specificities for individual PPAR receptors, different absorption/distribution profiles, and distinctive gene expression profiles, which ultimately lead to different clinical outcomes (Berger and Moller, 2002), (Lehrke and Lazar, 2005), (Krey et al., 1997), (Margeli et al., 2003).

1.1.5 Recent Advances in PPAR Research

PPARs have been implicated in several important diseases and pathological conditions. The loss of and/or abnormal PPAR function has been seen in various diseases, including cancer, obesity and type II diabetes. Interestingly, recent discoveries suggest that PPAR subtypes and ligands present a valuable target for the treatment of several significant diseases and pathological conditions in various organs (Rangwala and Lazar, 2004). Briefly, these ligand-activated transcription factors have been recognized to regulate genes that control the number of peroxisomes and mitochondria in cells, modulate glucose and fatty acid metabolism, and regulate energy homeostasis and nutritional status. Most of PPARs reside in the nucleus in the repressed state, but a fraction of repressed PPARs are found in the cytoplasm and mitochondria, proposing the involvement of multiple pathways to regulate the transcriptional function of PPARs in response to external signals (Umemoto and Fujiki, 2012), (Miglio et al., 2009), (Minnich et al., 2001).

These receptors are expressed also in the heart, and PPAR agonists have shown promising effects in preventing progression of atherosclerosis in experimental models as well as in clinical trials(Calkin and Thomas, 2008),(Duval et al., 2002).

In addition, the discovery of anti-inflammatory and immunomodulatory roles of PPARs has prompted the investigation of these receptors as potential targets

for treatment of asthma and other inflammatory lung diseases(Standiford and Roman, 2007), as well as for several gastrointestinal diseases(Matthiessen et al., 2005),(Pathak et al., 2007),(Peters et al., 2008).

In the musculoskeletal system, PPARs are reported to play an interesting role. It appears that PPAR-α and PPAR-ɣ activations have opposite regulatory effects in bone formation(Syversen et al., 2009). The role of PPAR-β /-δ, however, is not yet defined although studies suggest that it may contribute to bone anabolism(Still et al., 2008). In the skeletal muscle, PPAR-β/-δ is the most abundant PPAR isotype with a higher expression level in oxidative type I muscle fibers compared to glycolytic type II muscle fibers (Braissant et al., 1996),(Wang et al., 2004). Evidence suggests that PPAR-β/-δ plays an important role in regulation of skeletal muscle metabolism particularly lipid oxidation by acting as an activator of fat burning with subsequent beneficial effects in metabolic disease(de Lange et al., 2008). Activation of PPAR-ɣ has been shown to increase physical performance and improve endurance performance(Narkar et al., 2008). PPAR-ɣ agonists are, therefore, characterized as *exercise mimetics*(Narkar et al., 2008), and are claimed to be, therefore, abused by athletes(Thevis et al., 2010).

The thiazolidinedione (TZD) drug group was developed to improve diabetic conditions through the direct regulation of PPARɣ activation. For example pioglitazone (Actos®) are potent PPARɣ agonist used in management of diabetes. Rosiglitazone (Avandia®) is another example of a TZD drug. It directly binds to PPARɣ's LBD to induce insulin sensitivity, adipocyte differentiation, lower hyperglycemia, and growth inhibitory effects on several carcinoma cell lines (Chandra et al., 2008), (Valentiner et al., 2005).

While in the central nervous system, PPARs mediate important neuroprotective effects. PPAR agonists have been proven useful in animal models of several CNS diseases, including Alzheimer's disease (Landreth and Heneka, 2001), multiple sclerosis (Feinstein et al., 2002), Parkinson's disease (Randy and Guoying, 2007), excitatory damages that occur in stroke (Uryu et al., 2002), brain tumors including glioma and neuroblastoma (pubmeddev and al, n.d.), and regulation of

cerebral blood flow and metabolism (De Silva et al., 2014). The molecular mechanisms by which PPARs activation can exert neuroprotective effects are still to be examined, but the fact that inflammatory gene activation contributes to neurological damage, and that PPARs increase the expression of inflammation inhibitor proteins could account for some of its effects(Feinstein et al., 2002). In addition, PPAR activation has also been shown to induce a heat shock response, a basic cell and tissue mechanism that has been shown to provide neuroprotection in stroke and models of neuro-inflammatory diseases (Colville-Nash et al., 1998). Also since that PPAR agonists increase glucose uptake in certain cell types, there is a possibility that these drugs could influence glial or neuronal energy metabolism in a similar manner, thus providing needed energy supplies under conditions (such as may occur in stroke, Alzheimer's disease, or multiple sclerosis) where blood flow or glucose supplies are limited (Feinstein, 2003).

Moreover, since PPARs exert significant therapeutic action in inflammation processes, which in turn could contribute at different degrees to the occurrence or the maintenance of neurodegenerative mechanisms in certain psychiatric disorders, such as schizophrenia and mood disorders (Bordet et al., 2006), PPARs could have a significant influence on both the propagation and the cessation of such disease-modifying strategies in several psychiatric disorders. Besides, increasing evidences revealed the implication of PPARs in the direct regulation action on many neuronal proteins that are involved in the synaptic transmission and the propagation of the nerve signal (Melis et al., 2010), (Ni et al., 2018), (Roy et al., 2013). Thus, modulating PPARs via their different agonists could mean modulating some of the different neurotransmission systems in the brain, which could deeply influence the clinical expression of different psychiatric disorders (De Felice et al., 2018), (Sun et al., 2008), (Salehi-Sadaghiani et al., 2012), (Kemp et al., 2014).

From this standpoint, we will focus on PPAR-α which has been suggested by different researchers as a promising target that is useful as a novel approach to treat diverse psychiatric disorders.

1.2 Peroxisome proliferator activated receptor-α

1.2.1 Background

Among the PPAR subfamily, which also comprises β/δ and ɣ isoforms, PPAR-α is the predominant PPAR subtype. PPAR-α was first isolated from mouse liver (Issemann and Green, 1990) and subsequently cloned from *Xenopus* (Dreyer et al., 1992),(Krey et al., 1993), rat (Göttlicher et al., 1992), guinea-pig (Tugwood et al., 1998), human (Reddy and Hashimoto, 2001), koala (Ngo et al., 2007), chicken(Diot and Douaire, 1999), and some marine species (Batista-Pinto et al., 2005),(Tsai et al., 2008),(Raingeard et al., 2006),(Raingeard et al., 2009). The human PPARα gene spans ~93.2 kb on chromosome 22 and gives rise to a 9.9 kb transcript in humans (8.5 kb in mouse). This transcript encodes a 468 amino acid and 52 kDa protein (Sher et al., 1993). In species studied thus far, PPAR-α can be activated by a class of structurally diverse compounds collectively classified as peroxisome proliferators. Fatty acids, fatty acid derivatives, and non-metabolizable fatty acids have also been identified as potent activators of PPAR-α (Issemann and Green, 1990),(Göttlicher et al., 1992).

1.2.2 PPAR-α Localization

Analysis of PPAR-α tissue distribution in rodents and humans revealed that is highly expressed in the central nervous system; specifically in the prefrontal cortex, basal ganglia, amygdala, hippocampus, reticular formation, the large motoneurons of the spinal cord, and astrocytes (Warden et al., 2016), (Moreno et al., 2004). Interestingly, expression of PPAR-α and of its heterodimeric partner RXR-α was found to increase in differentiating astrocytes (Fidaleo et al., 2014). PPAR-α is also highly expressed in other body organs that have high rates of mitochondrial fatty acid oxidation, such as liver, heart, proximal tubules of the kidney cortex, skeletal muscle, intestinal mucosa, and brown adipose tissues (Beck et al., 1992). PPAR-α as well is present in cells of the arterial wall, in monocytes/macrophages, smooth muscle cells, and endothelial cells (Chinetti et al., 1998), (Staels et al., 1998b), (Inoue et al., 1998). Its expression is relatively species-specific. For

example, in rat and mouse livers, PPAR-α mRNA is highly expressed, while in guinea-pig livers, PPAR-α mRNA is much less abundant (Tugwood et al., 1998),(Reddy and Hashimoto, 2001).

1.2.3 The functional role of PPAR-α

PPAR-α regulates the effects of peroxisome proliferators via transcriptional activation of PPAR-α target genes. PPAR-α proteins from different species have been found to have similar function when studied in vitro (Tugwood et al., 1998) . As mentioned before and briefly, upon activation by natural or synthetic ligands, PPAR-α binds as a heterodimer with the retinoid X receptor (RXR-α) and undergoes conformational changes, which enables binding of the PPARα-RXRα vehicle to the peroxisome proliferator responsive element (PPRE) located in the promotor region of PPAR-α target genes (Krey et al., 1993),(Hsu et al., 1995). We should note that the ligands of each of PPAR-α and RXR-α alone can induce transcription, however, when both receptors are activated by their ligands at the same time, they synergistically enhance the transcription of genes (Kliewer et al., 1992),(Mangelsdorf and Evans, 1995). In addition to ligand-dependent activation, PPAR-α can also be regulated by phosphorylation of two mitogen-activated protein (MAP) kinase sites located in the modulator region of the receptor (Juge-Aubry et al., 1999). Also, a number of hormones, for instance insulin, can modulate PPAR-α activity through this pathway (Shalev et al., 1996). PPAR-α functions are investigated, in physiological and pathological conditions, to clarify its mechanism of action and therapeutic potential.

a. Role in lipid metabolism: PPAR-α functions in fatty acid catabolism. It is important in regulation of genes involved in the stimulation of mitochondria- and peroxisome-driven β-oxidation of fatty acids. Key genes upregulated by activation of PPARα include Carnitine palmitoyl transferase (CPT-1α) in mitochondria and acylCoA oxidase (ACO), a rate-limiting enzyme involved in oxidation in peroxisomes (Meyer et al., 2002). Hence, defects in PPARα are highly associated with metabolic diseases. PPAR-α is also an important regulator of genes essential in

ketogenesis, adipocyte differentiation, cholesterol metabolism, gluconeogenesis, lipid transport, and anabolic effects on muscle and bones (Lefebvre et al., 2006). Thus, drugs with potent activity on human PPAR-α are considered as useful adjuncts to current therapies for treatment of dyslipidemias and diabetes (Willson et al., 2000). PPARα-dependent dysmetabolism of these fattyacids may result in neurodegeneration, possibly oxidative stress (Baarine et al., 2012).

b. Role in Oxidative Stress: Co-lacolization of PPAR-α with catalase CAT (major peroxisomal H_2O_2 scavenging enzyme) and SOD1 (cytosolic superoxide anion detoxifier) in the central nervous system (Moreno et al., 2004), (Moreno et al., 1995), (Moreno et al., 1995), strongly supports a role of the receptor in the protection against oxidative damage, which in turn crucially contributes to normal brain aging and to the onset and progression of neurodegenerative diseases (Sayre et al., 2008), (Dröge and Schipper, 2007). Previous reports suggested the role of PPARα in modulating the oxidative stress in injured rat brains. PPAR-α agonist enhances the expression of antioxidant enzymes i.e. Cu/Zn2 + superoxide dismutase, catalase and glutathione peroxidase (Bordet et al., 2006). Wang et al. demonstrated that chronic treatment with fenofibrate or gemfibrozil was also shown to protect brain against ischemia through an increase of mRNAs and activities of SODs levels in brain microvessels (Wang et al., 2010). Importantly, PPAR-α expression is itself induced by oxidative stress associated with neurodegenerative conditions (Clark and Simon, 2009).

In physiological conditions, PPAR-α seems to play a role in the control of redox status, since it doesn't only upregulate ROS scavengers, but also induces ROS-generating enzymes (Farioli-Vecchioli et al., 2001).

c. Role in Cardiovascular Diseases: Studies have linked impaired PPAR-α to heart hypertrophy due to irregular myocardial fatty acid transport and β-oxidation enzymes (Smeets et al., 2008). Moreover, atherosclerotic lesion formation requires recruitment of monocytes into the arterial wall through expression of adhesion molecules by activated endothelial cells(Libby Peter et al., 2002). Expression of the adhesion molecule VCAM-1 was down-regulated by PPAR-α agonists in human

vascular endothelial cells (Marx Nikolaus et al., 1999). This process was mediated in part by inhibition of NF-κB, IL-6 and inflammatory prostaglandins in vascular smooth muscle cells (Spencer et al., 1997), (Staels et al., 1998b), since inflammatory processes have been implicated in disruption of the atherosclerotic plaque that leads to thrombolytic events (Kinlay et al., 1998). Patients with coronary artery disease also responded favorably to fenofibrate treatment, showing reduced plasma levels of IL-6, fibrinogen, and C-reactive protein (Staels et al., 1998b), possibly through negative regulation of NF-κB and AP-1 by PPAR-α (Delerive et al., 2000).

d. Role in Feeding and Fasting Responses: PPAR-α appears to be involved in modulating the neurobiological mechanisms of feeding and fastng responses. The satiety response seems to depend on PPAR-α activation, through the PPAR- α natural agonist oleoylethanolamide "OEA", peripherally produced by the small intestine after feeding. In fact, PPAR-α has been recognized as an important factor in OEA-mediated stimulation of vagal innervation and induction of oxytocin neurosecretion by hypothalamic neurons (Schwartz et al., 2008), (Sarro-Ramírez et al., 2013), (Romano et al., 2013).

On the other hand, fasting activates PPAR-α, possibly by free fatty acids released from adipose tissue, upregulating its target genes in specific brain regions, including hypophysis, frontal cortex and diencephalon (König et al., 2009). PPAR-α is involved in mobilizing peripheral glucose as a fasting response also (Knauf et al., 2006a).

e. Role in Cell Proliferation, Death, and Proliferation: Since some PPAR-α target genes control ell cycle, the receptor appears o be involved in modulating cell proliferation and apoptosis (Roberts et al., 2002), (Mandard et al., 2004). PPAR-α expression is associated also in the nervous system in proliferating cells, where it was demonstrated the presence of the receptor in neural stem cells and prognosis (Cimini et al., 2007), (Cimini and Cerù, 2008). In rodent spinal cord, PPAR-α was found in ependymal cells, which have the potential to proliferate and differentiate into several neural types (Moreno et al., 2004), (Fandel et al., 2013). Spinal cord

injury induces proliferation of these stem cells and migration towards the site of damage, while enhacing their PPAR-α expression (Fandel et al., 2013).

Regarding the regulation of cell death in the brain, as well as in the liver, the role of PPAR-α is anti-apoptotic, markedly in pathological conditions. In challenging situations, PPAR-α agonists exert a pro-survival action towards neuronal cells, lowering the levels of activated apoptosis inducing factors (Kreisler et al., 2007), (Khalaj et al., 2013).

A growing body of evidences also demonstrated a role of PPAR-α in differentiation of several neural cell types. Astroglial differentiation was linked to increased PPAR-α expression (Cristiano et al., 2005). Concerning oligodendroglia, PPAR-α induces enzymes responsible for myelin synthesis (Leisewitz et al., 2008). Also, both microglial and astroglial activations are modulated by PPAR-α (Xu et al., 2006), (Crisafulli and Cuzzocrea, 2009). Interestingly, PPAR-α was recognized to preserve hippocampal neurogenesis, highliting the pleiotropic action of this receptor (Ramanan et al., 2009).

Taken together, these finding may suggest PPAR-α as a potential therapeutic target for central nervous system diseases including neuroinflammation.

f. Role in Neuro-inflammation: The anti-inflammatory effects of PPAR-α have been extensively studied. The expression and activation of PPARα in T lymphocytes also decreases IL-2 production and proliferation. PPAR-α agonists, gemfibrozil and ciprofibrate, reduced lymphocyte and macrophage infiltration into the central nervous system of mice (Dasgupta et al., 2007), (Bright et al., 2008), and decreased IFNγ production (Bright et al., 2008). WY14,643, a synthetic PPARα agonist, impaired generation of IFNγ, TNF-α, and IL-6 in response to inflammatory-induced peptides (Bright et al., 2008). PPAR-α has also been shown to inhibit the actions of NF-κB (Okamoto et al., 2005), a ubiquitous transcription factor that transduces the effects of many inflammatory stimuli, suggesting the use of PPAR-α agonists in the treatment of inflammatory diseases.

PPAR-α ligands have been proven effective in the treatment of neuroinflammatory diseases also. In Alzeheimer's disease, the neuroinflammatory components include microglia, astrocyte, the complement system, cytokines, and chemokines. Microglia and astrocytes, where PPAR-α is expressed highly (Drew et al., 2006), (Xu et al., 2005), generate beta-amyloid (Aβ) proteins that stimulate proinflammatory cytokines in Alzeheimer's disease brain. PPAR-α agonists inhibit Aβ-stimulated expression of TNFα and IL-6 in a dose dependent manner (Hirohata et al., 2005), (Combs et al., 2001). Concernin trauma and brain injury-induced edema, and as we mentioned previously, a study demonstrated that fenofibrate, a PPAR-α agonist, exerts neuroprotective effects in traumatic brain injury. It decreased the neurological deficit induced by traumatic brain injury, and reduced brain edema and ICAM-1 expression (Besson et al., 2005). PPAR-α could be a therapeutic target for Parkinson's disease also. Uppalapati et al. showed that fenofibric acid, the active metabolite of fenofibrate, was present in the brain of animals treated with fenofibrate, suggesting that this compound was metabolized and that crossed the blood-brain barrier in vivo, inducing a neuroprotective effect by decreasing inflammation (Uppalapati et al., 2014). Another study reported that fenofibrate prevent the dopaminergic neurons loss in the substantia nigra in Parkinson's disease animal model, and it attenuates the loss of tyrosine hydroxylase immune reactivity in the striatum (Kreisler et al., 2007). In a word, the potential use of PPAR-α agonists as neuroprotective agents against neurodegenerative disorders is an important start point to find new drugs that could cure definitively these pathologies.

g. Role in Cognitive Functions: Imperative effects are exerted by PPAR-α agonists in enhancing memory and considilation, and improving spatial learning. This role is supported by studies on a PPAR-α activator, dehydroepiandrosterone sulphate, and which demonstrated its effect on ameliorating cognitive and memory decline associated with its decrease in ageing (Dong and Zheng, 2012), (Zhou and Waxman, 1998). Also, investigations employing PPAR-α null mice demonstrated its involvement in spatial learning and memory, through regulation of cyclic AMP response element binding (CREB) and hippocampal plasticity-related genes (Roy et

al., 2013). Interestengly aslo, ω-3 polyunsaturated fatty acid, which increases hippocampal PPAR-α gene expression, improves memory function in spatial learning (Hajjar et al., 2012). Similar effects are induced by a PPAR-α agonist Oleoylethanolamide, OEA, which facilitates memory considialtion through noradrenergic activation of the basolateral complex of the amygdala, a mechanism that is also critically involved in memory enhancement induced by emotional arousal (Campolongo et al., 2009), and reverse the cognitive deficits induced by the amphetamine derivative 3,4-Methylenedioxymethamphetamine; MDMA, by protecting against the MDMA-induced oxidative damage (Plaza-Zabala et al., 2010). In line with these findings, increased levels of endogeneously produced OEA, due to inhibition to its main catabolic enzyme FAAH, enhance memory acquisition (Mazzola et al., 2009).

h. Role in Neurotransmission: In fact, PPAR-α role in regulating H_2O_2 concentration may also be relevant to neurotransmission, as this molecule acts as a physiological modulator of glutamate and dopamine release (Chen et al., 2003), (Avshalumov and Rice, 2002). Gonzalez-aparicio et al. suggested that PPAR-α seems to be necessary for a normal number of dopamine neurons in the substantia nigra, as well as normal levels of antioxidant molecules (Gonzalez-Aparicio et al., 2011). Notably, dopaminergic neurons are subject to firing activity modulation by PPAR-α, through a mechanism involving α7 nicotinic acetylcholine receptors (Melis et al., 2013a), (Melis et al., 2010). Besides, PPAR-α agonist administration decreased nicotine seeking behavior and nicotine self-administration (Mascia et al., 2011). In rats given PPAR-α agonists, nicotine-induced firing of ventral tegmental area neurons and nicotine-induced dopamine release in the nucleus accumbens were decreased (Panlilio et al., 2012). Therefore, PPAR-α agonists may interfere with the rewarding effects of nicotine. PPAR-α may also directly enhances the cholinergic system, by controlling the peroxisomal β-oxidation pathway, which produces acetyl-coA units, necessary for acetylcholine biosynthesis (Farioli-Vecchioli et al., 2001). Other studies suggested that PPAR-α could modulate serotonin level (Fakhraei et al., 2017). Therefore, increasing attention has been dedicated to PPAR-α within the psychiatric field. Several studies have reported an

association between PPAR-α and some psychiatric disorders such as depression (Jiang et al., 2015), (Yu et al., 2011),(Ghazizadeh-Hashemi et al., 2018), anxiety (D'Agostino et al., 2012),(Crupi et al., 2013), and schizophrenia (Rolland et al., 2012), (Costa et al., 2013), (Melis et al., 2010). Our laboratory's previous examinations have revealed the antidepressant effects of the PPAR-α ligand, clofibrate, in acute and chronic animal models of deression. In our thesis, we will investigate the potential action of PPAR-α ligand, clofibrate, in anxiety and schizophrenia.

1.2.4 PPAR-α natural and synthetic ligands

PPAR-α is a receptor for a structurally diverse group of compounds, including natural and synthetic ligands. The molecule ligand is bound into the large pocket within the PPAR-α ligand binding domain, which is about 1400 mm^3. The ligand adopts a conformation within the receptor that allows formation of hydrogen bond interactions; these interactions stabilize the receptor in a configuration that leads to the transcriptional activation of PPARα via recruitment of coactivator proteins (Xu et al., 2001). Initially, PPAR-α was identified as the receptor for "clofibrate". Then, numerous groups searched for alternative ligands.

a. Natural Ligands: Researchers discovered that a range of saturated and unsaturated fatty acids could activate PPAR-α (Göttlicher et al., 1992). Some cells are able to generate endogenous PPAR-α ligands, such as the phospholipid 1-palmitoyl-2-oleoyl-sn-glycerol-3-phosphocholine (16:0/18:1-GPC), which is synthesized by the enzyme fatty acid synthase (Chakravarthy et al., 2009). In addition, other natural ligands such as poly-unsaturated fatty acids (PUFAs) are provided by the diet (linoleic acid, α-linolenic acid, γ-linolenic acid, and arachidonic acids), which bind to PPARα at physiological concentrations (Göttlicher et al., 1992), (Forman et al., 1997). Moreover, it has been demonstrated that phytanic acid, a branched-chain fatty acid generated from phytol present in dairy products, is also a natural ligand of PPAR-α (Goto et al., 2005).

Eicosanoids and leukotriene β_4 were shown to induce PPAR-α activity also (Yu et al., 1995), (Devchand et al., 1996). Furthermore, other natural compounds such as polyphenols have been described as ligands of PPAR-α (Radler et al., 2011). Resveratrol, a natural polyphenol found in grapes, peanuts, and berries, activate PPAR-α also, resulting in brain protection against stroke (Tsukamoto et al., 2010),(Inoue et al., 2003), (Mizuno et al., 2008); for instance, the derivate compound phosphate 15 has a potency higher than that of the drug ciprofibrate (Mizuno et al., 2008). Additional PPAR-α ligands from diet with hypolipidemic activity have been reported, such as the natural carotenoid abundant in seafood, astaxanthin, and the active compound extracted from the tomato, 9-oxo-10(E),12(E)-octadecadienoic acid (Jia et al., 2012),(Kim et al., 2011). PPAR-α is induced also by glucocorticoids in response to stress and follows a diurnal rhythm (Lemberger et al., 1996b).

Among these natural ligands, the neuroscience research has focused on identifying the psychiatric relationship between PPAR-α and its two endocannabinoid-like ligands *N*-oleoylethanolamide (OEA) and *N*-palmitoylethanolamide (PEA) (Locci and Pinna, 2019), (Fu et al., 2003). These naturally occurring products of ethanolamide and oleic/palmitic acids are representatives of a number of acylethanolamides which have negligible effect for cannabinoid receptors (O'Sullivan and Kendall, 2010), (Fu et al., 2003), (Lo Verme et al., 2005). Interestingly, several reports have descrived neuroprotective ans behavioral effects of OEA and PEA; including depression, anxiety, pain perception, convulsions, neurotoxicity, and neuroinflammation (Yu et al., 2011), (D'Agostino et al., 2012), (Lombardi et al., 2007), (Sun et al., 2007), (Bisogno and Di Marzo, 2010).

b.Synthetic Ligands: In addition to the natural ligands, other synthetic compounds can also activate PPAR-α, such as hypolipidemic drugs that include *clofibrate*, fenofibrate, bezafibrate, and Wy14643 that induce up- and down-regulation of expression of several PPAR-α target genes (Issemann and Green, 1990), (Yamazaki et al., 2002). Table 2 shows the potencies of several fibrate drugs on the human and murine PPAR-α. PPAR-α exhibits about the same affinity for bezafibrate and their CoA thioesters (bezafibroyl-CoA) as for unsaturated long chain

fatty acids (Hostetler et al., 2005), while a lower affinity for fenofibrate (Reifel-Miller et al., 2005),(Velkov et al., 2010). Wy14643 is a potent ligand that has a binding affinity to PPAR-α higher than that for the endogenous ligand 16:0/18:1-GPC, which in turn results in competition and a rapid displacement of the natural by the synthetic ligand (Chakravarthy et al., 2009). The piperidine synthetic agonists bind also to PPAR-α very strongly. These compounds have been very useful in acute preclinical models for treating dyslipidemia (Kane et al., 2009).

Besides, synthetic compounds include also carbaprostacyclin, nonsteroidal anti-inflammatory drugs, and phthalate ester plasticizers(Hertz et al., 1996),(Lehmann et al., 1997),(Gonzalez et al., 1998). Many groups have synthesized synthetic ligands to restore PPAR-α functionalities, but no synthetic drugs have been identified that do not have side effects yet (Tan et al., 2005).

Compound	Murine PPARα receptor EC_{50} (μM)	Human PPARα receptor EC_{50} (μM)
Clofibrate	50	55
Fenofibrate	18	30
Bezafibrate	90	50
Wy-14643	0.63	5.0
GW 9578	0.005	0.05
KRP-297	10	0.85
JTT-501	4.3	1.9
SB 213068	0.93	0.74
L-796449	7.6	0.0041
GW 2433	0.27	2.5

Table 2: The potencies of several PPAR-α agonists in humans and mice (Willson et al., 2000)

1.3 Fibrates

Fibrates are a group of hypolipidemic agents which have been in clinical use for several decades in humans (Staels et al., 1998a),(Zambon et al., 2006). These drugs are currently used in pharmaceutical approaches to regulate free fatty acids, triacylglyceride homeostasis and lipoprotein levels, providing a beneficial response for patients suffering from hypertriglyceridemia (Li and Glass, 2004). Fibrates are also recognized to protect against atherosclerosis by inducing high-density

lipoproteins (HDL) and regulating lipid homeostasis (Desvergne and Wahli, 1999). Hence, by targeting these genes and increasing its transcription, fibrates result in elevated HDL levels, benefiting patients suffering from atherosclerosis and coronary heart disease (Ogata et al., 2009). Fibrates including clofibrate, bezafibrate, and fenofibrate act as synthetic agonists of PPAR-α (Beck et al., 1992), and they have been implemented in multiple studies to further characterize the role of PPAR-α (Ferré, 2004).

In neuroinflammation-related disorders, studies revealed that treatment with fibrates may decrease neurological deficits. Chronic treatment with fenofibrate or gemfibrozil was shown to protect brain against ischemia through an increase of mRNAs and activities of SODs levels in brain micovessels (Wang et al., 2010). Another study reported that fenofibrate attenuates NO-mediated neuronal and axonal damage and increases PPAR-α protein levels and catalase activity (Gray et al., 2011). In an in vivo model of neuroinflammation induced by LPS injection into the mouse sematosensory cortex, chronic systemic treatment with fenofibrate profoundly attenuated microglia/macrophage activation, neutrophil recruitment, and neuronal injury. It inhibited TNF-α, IL-1β, IL-6, COX-2, intercellular adhesion molecule 1 (ICAM-1) elevations and increased PPAR-α mRNA and protein in the brain (Wang and Namura, 2011). Moreover, fenofibrate inhibited microglial activation and preserved hippocampal neurogenesis after whole-brain irradiation, via decreasing the NF-κBp65 nuclear translocation and the phosphorylation of activator protein-1 (AP-1) c-jun subunit (Ramanan et al., 2009). It has also been shown that pretreatment with fenofibrate markedly reduced the mortality in a murine model of encephalitis viral infection, by repressing NF-κB and inhancing transcription of antioxidant and anti-inflammatory genes (Sehgal et al., 2012).

Concerning the neurodegenerative disorders, fenofibrate has a neuroprotective effect towards dopaminergic cells in the substantia nigra pars compacta in the MPTP mouse model of Parkinson's disease, and attenuates the loss of tyrosine hydroxylase in the striatum (Kreisler et al., 2007). Consistently, other studies stated that it protects against hypolocomotion, depressive-like behavior,

impairment of learning and memory, and dopaminergic neurodegeneration in MPTP-rat models of Parkinson's disease (Barbiero et al., 2014), by protecting against oxisative stress and neuro-inflammation (Uppalapati et al., 2014) . Besides, it reduces β-amyloid production in an Alzheimer's disease transgenic mouse model (Zhang et al., 2014). Fenofibrate prevented also the short-term motor and cognitive post-stroke consequences in mice (Baarine et al., 2012).

The therapeutic prospects of fibrates have also been investigated in certain neuropsychiatric disorders; including schizophrenia and epilepsy. Indeed, one study demonstrated that after a neonatal lesion, inducing delayed prepulse inhibition (PPI) anomalies in rats, the post-weaning administration of PPAR-α agonist fenofibrate allows to partially reverse the PPI disruption (Rolland et al., 2012). Grover et al. demonstrated that fenofibrate decreased the elevated levels of lipid peroxidation products, lactate dehydrogenase activity, elevated the levels of reduced glutathione and catalase activity, and prevented the symptoms of oral dyskinesia by attenuating oxidative stress and neuroinflammation. Another study on epileptic seizures showed that nicotine-induced behavioral and electrophysiological effects were reduced by fenofibrate (Puligheddu et al., 2013). Other studies showed that fenofibrate induces antidepressant and anxiolytic-like effects via the PPAR-α-mediated promotion of the hippocampal BDNF signaling pathway (Jiang et al., 2017)·(Locci and Pinna, 2019).

A role of fibrates related to tumors of the nervous sytem also emerged. Bezafibrate and grmfibrozil inhibited viability of glioblastoma cell lines, by modulating cell cycles and apoptosis-related molecules (Strakova et al., 2005). When glioblastoma cells were treated with clofibrate, a strong down-regulation of the expression of semaphorin B6 was detected, suggesting its suppression of glioma invasiveness (Collet et al., 2004), whereby Drukala et al. correlated ROS accumulation, coequent to fenofibrate-induced metabolic switch, with inhibition of glioma invasiveness (Drukala et al., 2010).

1.4 Clofibrate

1.4.1 Background

Researchers in France observed in 1953 that structures derived from dehydrocholic acid, phenylethyl acetic acid, and certain other disubstituted acetic acids exhibited hypocholesterolemic properties in rats and humans (Lalloyer and Staels, 2010). Several years later, Thorp and Waring discovered clofibrate as an effective compound for lowering lipids in animal models, with minimal toxicity. Its mode of action was not known but, initially, its hypolipidemic effect was attributed to seasonal variations in adrenal and thyroid function, and the administration of androsterone in rats and monkeys potentiated the hypocholesterolemic effect of this compound (Lalloyer and Staels, 2010). Subsequently, several clinical trials were performed which showed that clofibrate decreases lipid levels in hypercholesterolemic patients, mainly as the result of a reduction in the very-low-density lipoprotein (VLDL), and less in the low-density lipoprotein (LDL) fraction, and that the coadministration of androsterone was not necessary for its hypolipidemic effect (Lalloyer and Staels, 2010).

Clofibrate can be chemically synthesized by the condensation of phenol with ethyl 2-chloro-2-methylpropionate in the presence of a dehydrochlorinating agent, followed by chlorination and purification. It can also be synthesized by the condensation of p-chlorophenol with acetone and chloroform followed by esterifying the resultant acid to give clofibrate (Pubchem, n.d.). Table 3 presents the basic chemistry of clofibrate.

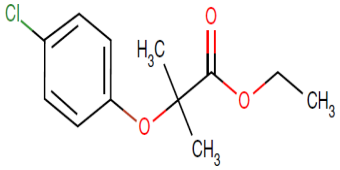
Name	Chemical Formula	Molecular weight	Physical Properties	Solubility	Structure
Clofibrate	$C_{12}H_{15}O_3Cl$	242.701 g/mol	Clofibrate is a stable, colorless to pale-yellow liquid with faint characteristic odor and taste	Clofibrate is soluble in organic solvents, but not in water	

Table 3: The basic chemistry of clofibrate (Pubchem, n.d.)

1.4.2 Uses

Like other fibrates, most of research studies focused mainly on the effects of clofibrate on lipid and carbohydates metabolism, and cardiovascular diseases.

a. **Lipid metabolism:** Clofibrate is a lipid-lowering agent (antilipidemic) used for controlling high cholesterol (anticholesteremic) and triacylglyceride levels in the blood (Anderson et al., 2005). It promotes the conversion of VLDL to LDL by increasing the lipoprotein lipase activity, and thus, reducing the VLDL and LDL levels (Kesäniemi and Grundy, 1984). Clofibrate is indicated only in subjects with increased concentrations of VLDL and LDL (such as patients with familial type-III hyperlipoproteinemia) who have failed to respond adequately to gemfibrozil or nicotinic acid (Pubchem, n.d.). Clofibrate has no effect on hyperchylomicronemia, nor does it affect concentrations of HDL. Thus, clofibrate appears to have specific efficacy only in patients with familial type-III hyperlipoproteinemia (Pubchem, n.d.).Because more effective agents are available for lowering the concentration of LDL, the drug is of limited utility for patients with either familial hypercholesterolemia or polygenic hypercholesterolemia (Pubchem, n.d.).

   The drug has several proposed antilipidemic actions, including increased triglyceride and VLDL clearance, potentiating the action of lipoprotein lipase, mobilization of cholesterol from tissues, increased fecal excretion of neutral sterols, decreased hepatic lipoprotein synthesis and/or secretion, decreased free fatty acid release, and decreased triglyceride synthesis (Pubchem, n.d.),(Theobald, 2017). The precise mechanism of action of clofibrate is not completely defined, but it is stated that its effects are mediated by PPAR-α (Theobald, 2017).

   b. Atherosclerosis: The early clinical trials of clofibrate demonstrated that this drug had a protective effect against the development of new myocardial infarction and sudden death(Krasno and Kidera, 1972), (J. B. Arthur et al., 1971). Other studies revealed that clofibrate causes a a reduction in the incidence and

severity of the arteriosclerosis, and that this effect may be mediated by the ability of clofibrate to change corticosterone levels in the circulation (Wexler and Greenberg, 1978a), (Wexler and Greenberg, 1978b). A direct action of clofibrate on arterial wall glycosaminoglycans and proteins has been reported (Bihari-Varga et al., 1973), as has a direct action on blood coagulation (Cotton, 1972). The proposed effects on clotting mechanisms may reduce thromboembolic complications of atherosclerosis.

c. Diabetes: Certain data indicate that clofibrate also affects carbohydrate metabolism, since an improved glucose tolerance has been observed both in hyperlipemic patients after chronic treatment (Berkowitz, 1971),(Eaton and Nye, 1973), and in normal subjects after short-term administration of the drug (Eaton and Schade, 1974). This effect has been demonstrated by increasing the insulin sensitivity (Ferrari et al., 1977).

There are only few clinical studies that examined the potential effect of clofibrate on neuropsychiatric animal models. Our team had conducted previously a series of behavioral experiments which revealed that clofibrate produced antidepressant effects in a set of animal experimental models. Fakhraei et al. (Fakhraei et al., 2017) reported also that clofibrate may have antidepressant-like effects, however, literature haven't recorded any previous report studying the potential effects of clofibrate on anxiety or schizophrenia.

1.5 Mental Disorders

The number of people suffering from mental illness in the 21st century is increasing. One in four people in the world will be affected by mental illness or behavioral disorder at some point in their lives. Approximately 450 million people worldwide currently suffer from such conditions, which account for 12.3% of the global burden of disease ("WHO | Mental disorders affect one in four people," n.d.), ("WHO | The world health report 2001 - Mental Health," n.d.). It is estimated that this percentage will reach 15% by 2020 (Reynolds, 2003). The outcomes of mental disorders are not only devastating for patients, but also for their relatives and surroundings. And since in the area of mental disorders the development of new drugs is very limited (Craven, 2011), besides the increasing number of affected people, there is a growing demand for developing new treatments.

Among the various aspects of mental illnesses and behavioral disorders, anxiety and schizophrenia remain two of the most common psychiatric disorders. Each of these disorders will be further described in the following sections, identifying their features and discussing the therapeutic potentials of PPAR-α in these two disorders.

1.5.1 Anxiety

1.5.1.1 Background

Anxiety disorder including its different subtypes afflicts approximately 20% of the world's population (Munir and Takov, 2019), and contributes to the etiology of major depression, substance abuse, and schizophrenia (Buckley et al., 2009), (Koob, 2009), (Ressler and Mayberg, 2007). It is among the most persistent mental health disorder, with spontaneous remission occurring in ≤23% (Wittchen et al., 2000), (Bittner et al., 2004). It can significantly impair several areas of cognitive development, meaning that they can also be a risk marker for disease burden (Beesdo et al., 2010), (Castaneda et al., 2008), (Eysenck et al., 2007).

The diagnostic criteria for anxiety disorders are similar across the two most common classification systems: the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM5) (Association, 2013) and the International Classification of Diseases, Tenth Edition (ICD10) (*World Health Organization, 2010. International Statistical Classification of Diseases and Related Health Problems.*, n.d.). They outlined the criteria for several distinct subtypes of anxiety disorders, which are generally conceptualized as exaggerated chronic fear states that persist in the absence of a direct threat. Although fear and anxiety are normal emotional responses to danger, threat, or an aversive situation, this adaptive fear response must subside when the aversion diminishes. This differs from the pathological anxiety disorders in which the emotional responses are chronically dysfunctional (Rosen and Schulkin, 1998). Anxiety has been described as a sense of uncontrollability, during which the individual is predominantly focused on future threats, danger or upcoming potentially negative events (Barlow, 2000). During an anxious episode the sufferer often has difficulty in the identification of the cause of the uneasy tension or the nature of the anticipated threat, and his automatic physiological response increases in arousal. The physiological arousal is experienced as symptoms associated with the fight-flight response, or anxiety (Sundaralingam, 2006).

This definition implies that anxiety is a subjective experience, involving more than just physical stressors. Commonly, it is evaluated clinically in humans by verbal reports. However, anxiety symptoms include also nonverbal changes in behavior such as heart palpitations, dry mouth, nausea, gastrointestinal discomfort, difficulty breathing, hyperventilation, numbness, dizziness, muscle tension, and trembling (Sundaralingam, 2006),(Wiedemann, 2015). As showm in Table 4, anxiety is divided into a range of different symptoms, covering generalized anxiety disorder, panic disorder, post-traumatic stress disorder, phobias, and obsessive compulsive disorder (OCD) (American Psychiatric Association, 2013). While distinct, anxiety disorders are highly co-morbid with each other and with other serious mental disorders, such as depression (Goldstein-Piekarski et al., 2016) and schizophrenia (Braga et al., 2013). This is in part due to the fact that symptoms often overlap (Goldstein-

Piekarski et al., 2016), (Cryan and Holmes, 2005), in addition to sharing common pharmacotherapeutic interventions(Goldstein-Piekarski et al., 2016),(Vaswani et al., 2003).

Disorder	*Symptoms*	*12-month Prevalence (%)*
Generalized Anxiety Disorder	Excessive and long-lasting worry, Difficult to control, Restlessness, Irritability, Difficulty concentrating, Muscle tension, Sleep disturbance	0.4% - 3.6%
Panic Disorder	Recurrent unexpected abrupt surge of intense fear, Palpitations, Sweating, Trembling, Shortness of breath, Chest pain, Nausea and dizziness, Fear of dying or losing control	2%-3%
Post-traumatic Stress Disorder	Recurrent episodes of fear following a traumatic event, often triggered by reminders of event, autonomic arousal	0.5%-1%
Social Anxiety Disorder (Social Phobia)	Marked fear and autonomic arousal in social situations, Avoidance, Long-lasting	0.5%-2.0%
Specific Phobia	Marked fear and autonomic arousal in specific situations, Avoidance, Long-lasting	2%-6%
Obsessive-Compulsive Disorder	Presence of obsessions, compulsions, or both	1.1%-1.8%

Table 4: Summary of anxiety disorders and their prevalence (American Psychiatric Association, 2013)

1.5.1.2 Prevalence

According to the World Mental Health Survey, approximately one in four individuals is likely to have, or have previously had, an anxiety disorder (KESSLER et al., 2007). The global 12-month prevalence for anxiety disorders has been estimated to be ~14% (Baxter et al., 2013). Country-specific 12-month prevalence rates vary, ranging from 2.4% in Italy to 29.8% in Mexico (Baxter et al., 2013), and more than half of patients with an anxiety disorder have multiple anxiety disorders (Kessler et al., 2005).

Most anxiety disorders start early in life, and the 12-month prevalence in childhood and adolescence is similar to that in adults (Beesdo et al., 2009). Phobias and separation anxiety have a particularly early onset, with the highest incidence risk between 6 and 17 years of age (Kessler et al., 2005). Nonetheless, anxiety can emerge in adulthood and late in life in some anxiety disorders, such as generalized anxiety disorder (Kessler et al., 2010), (Zhang et al., 2015).

Vulnerability and risk factors for anxiety disorders include female sex and a family history of anxiety or depressive disorders. For example, female sex almost doubles the risk for anxiety disorders (American Psychiatric Association, 2013); sex differences are relatively small during childhood but develop throughout adolescence (McLean et al., 2011). In addition, having parents with anxiety and depression amplifies this risk, also revealing that parental depression is an independent risk factor for child anxiety (Lieb et al., 2002), and that the familial risk for anxiety disorders partially reflects a heritable component (Shimada-Sugimoto et al., 2015). Moreover, adverse childhood experiences, such as physical and sexual abuse (Sareen et al., 2013),(Afifi et al., 2012), parental separation (Otowa et al., 2014) and emotional maltreatment (Taillieu et al., 2016) are associated with anxiety didorders, especially post-traumatic stresss disorder PTSD.

1.5.1.3 Neuroanatomical background of anxiety

Several anatomical structures are implicated in generating the state of anxiety, including the endocrine systems. Some studies suggest that alterations of the hypothalamic-pituitary-adrenal axis (HPA) have been widely reported in psychiatric disorders, including anxiety disorders (MacKenzie et al., 2007),(Faravelli et al., 2012),(Abelson et al., 2007),(Condren et al., 2002),(Erhardt et al., 2006). Furthermore, scientists have recognized several areas in the central nervous system (CNS) that are involved in anxiety, such as the prefrontal cortex (PFC), amygdala, and hipoccampal formation.

The **prefrontal cortex PFC** is a region of interest in anxiety disorders. It is one of the cortical regions that is profusely and reciprocally connected with sub-cortical and other cortical structures, notably the thalamus, the basal ganglia, the hypothalamus, the amygdala, the hippocampus, and cortices of association of the temporal and parietal lobes (Fuster, 2009). Many studies have shown that altered activation in different regions of the PFC, especially the medial prefrontal cortex, is involved in a variety of anxiety disorders (Blanco et al., 2009), (Canteras et al., 2010), (Etkin, 2010), (Shin and Liberzon, 2010).

The **amygdala** is located in the cortico-temporal area of the brain, ventromedial to the striatum, and anterior to the ventral hippocampus. It is part of the limbic system structure, which is intensively studied for its critical functions in fear and anxiety. It is responsible for the expression of fear and aggression as well as species-specific defensive behavior, and it plays a role in the formation and retrieval of emotional and fear-related memories (Martin et al., 2009). The amygdala consists of multiple subdivisions, of which the basolateral amygdala (BLA) and central amygdala (CeA) are particularly important in anxiety processing (LeDoux, 2007) . The BLA receives sensory information from the prefrontal cortex (PFC), thalamus, and cortical association areas, process this information, and sends it to the central amygdala (CeA), whose efferents have several targets, for example, the parabrachial nucleus producing an increase in respiratory rate, the lateral nucleus of the hypothalamus activating the sympathetic system, the locus coeruleus resulting in an

increase in noradrenaline release with its sequelae of increased blood pressure and heart rate and behavioral fear responses, and the nucleus paraventricularis of the hypothalamus causing an increase in corticosteroids via release of neuropeptides like CRF (Davis et al., 2003), (Babaev et al., 2018).

The **hippocampus** is another limbic system structure; it has tonic inhibitory control over the hypothalamic stress-response system and plays a role in negative feedback for the hypothalamic-pituitary-adrenal (HPA) axis. Hippocampal volume and neurogenesis in this structure have been implicated in stress sensitivity and resiliency in relationship to mood and anxiety disorders (Martin et al., 2009). Besides, another study revealed that the pharmacological stimulation of different neurotransmitter systems in the hippocampus produced robust anxiolytic effects in a variety of animal models of anxiety (Engin and Treit, 2007).

Also, several other CNS structur play an important role in the expression of anxiety, such as the nucleus accumbens, hypothalamus, a number of brain stem nuclei, thalamic nuclei, insular cortex, and periaqueductal gray (Shin and Liberzon, 2010). And since all these brain regions demonstrate a complex interconnectivity with other parts of the brain and the neuroendocrine system, we cannot fix our attention on just one region to develop a solution for anxiety disorders. It is crucial to have extensive researches for the identification of neurotransmitter systems and their respective synaptic receptors utilized by potential anxiolytic compounds.

1.5.1.4 Anxiety neurotransmitter system

The neuroanatomical circuits associated with anxiety are modulated by a variety of chemical neurotransmitter systems. These include serotonin (5-hydroxy-tryptamine, 5-HT), dopamine (DA), norepinephrine (NE), glutamate (GLU), and gamma-aminobutyric acid (GABA). These neurochemical systems are important for adaptive functions in preparing the organism for responding to the stressor by the modulation of various survival mechanisms. When dysfunction occurs, these biological responses to threat or stress may become maladaptive if they are chronically or inappropriately activated.

a. Serotonin: Serotonin (5HT) is synthesized from the dietary essential amino acid tryptophan, with tryptophan hydroxylase being the rate limiting enzyme. Following its release, it is actively removed from the synaptic cleft by serotonin transporters back into the neuron. The degradation product of serotonin is 5-hydroxyindolacetic acid (5-HIAA) (Ruddick et al., 2006).The main receptors and their subtypes, e.g., 5-HTI (5-HT1A, 5-HT1B, 5-HTID, 5-HTIE and 5-HT1F), 5-HT2 (5-HT2A, 5-HT2B and 5-HT2C), 5-HT3, 5-HT4, 5-HT5 (5-HT5A, 5-HT5B), 5-HT6 and 5-HT7 have been identified (Pithadia and Jain, 2009). Serotonin coordinates many functions including: appetite, sleep, neuroendocrine regulation (such as prolactin release) and impulse control. This diversity of effects may be explained by the extensive distribution of serotonergic neuron projections and multiple receptors (Frazer and Hensler, 1999).

Serotonergic neurons arise from the median and dorsal raphe nuclei in the brainstem and project throughout the forebrain (figure 3). This pathway plays an important role in the regulation of responsiveness of cortical neurons involved in mood. Projections from the raphe nuclei project to brain regions such as the prefrontal cortex and forebrain.

Exposure to various stressors results in increased 5-HT metabolism in the medial pre-frontal cortex (mPFC), amygdala, lateral hypothalamus and nucleus accumbens in rat brains (Inoue et al., 1994)

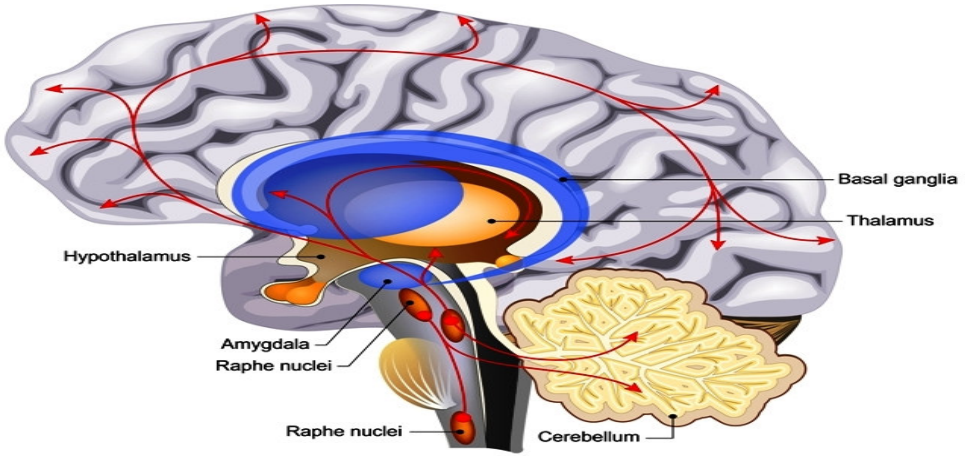


Figure 3: Schematic representation of the human central serotenergic systems (internet).

b.Dopamine: Dopamine is synthesised from the dietary essential amino acid tyrosine. Tyrosine hydroxylase converts tyrosine to L-Dopa, which in turn is converted to dopamine by dopa decarboxylase. Dopamine can then be further metabolised to noradrenaline in noradrenergic neurons. However, it is commonly catabolised into homovanillic acid (HVA) by pathways involving either monoamine oxidase (MAO) or catechol-O-methyltransferase (COMT). Like serotonin, dopamine is actively transported back into the neuron by specific transporters following release into the synaptic cleft (Ayano, 2016). Dopamine acts upon five different receptors (D1–D5), which are clustered into two families. The D1-like (D1 andD5) family are excitatory receptors, and the D2-like family (D2, D3 and D4) are inhibitory receptors (Ayano, 2016). It influences variety of functions, including locomotor activity, cognition, emotion, food intake, endocrie regulation, cardiovascular function, renal function, gastrointestinal function, reward, learning, memory, pain, and fear (Zarrindast and Khakpai, 2015).

Ascending dopaminergic projections originate in the ventral tegmental area (VTA) and the substantia nigra (SN). There are four main dopaminergic pathways in the human brain: nigro-striatal, meso-limbic, meso-cortical and tuberoinfundibular pathways, each of which mediates different functions (figure 4). The nigro-striatal pathway projects from the substantia nigra to the striatum and is involved in motor control. The tuberoinfundibular pathway, originating in the hypothalamus and projecting to the pituitary gland, is inhibitory to prolactin release by the pituitary (Ayano, 2016). Dopaminergic neurons in the mesocortical pathway project from the VTA of the midbrain to the prefrontal cortex, whereas the mesolimbic pathway extends from the VTA to areas of the limbic system. The limbic system includes the nucleus accumbens, amygdala and hippocampus and is associated with reward and pleasure as well as motivational valence for aversive behaviors (Arias-Carrión et al., 2010). Some studies have indicated that the mesolimbic and mesocortical dopaminergic system are involved in mediating stress, fear, anxiety, motivated behaviors, and various types of reward and cognitive processes (Zarrindast and Khakpai, 2015). Stress activates the mesolimbic dopamine system (Nasehi et al., 2010), (Trainor, 2011), and causes an increase in dopamine level in the synaptic cleft,

e.g. through inhibition of dopamine reuptake, which may induce anxiety-like behavioral effects (Nasehi et al., 2010), (Duterte-Boucher et al., 1990), (Simon et al., 1993).

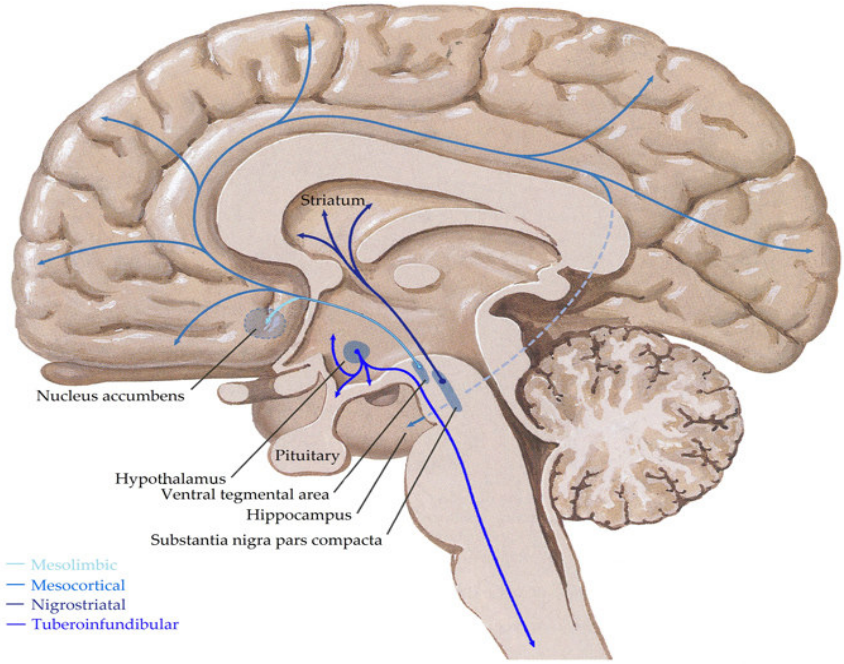


Figure 4: Schematic representation of the human central dopaminergic systems (Scarr, Gibbons, Neo, Udawela, & Dean, 2013)

c.Noradrenaline: The catecholamine noradrenaline is produced from hydroxylation of dopamine by dopamine β-hydroxylase. Although it can then be converted to adrenaline (epinephrine) by phenylethanolamine N-methyltransferase, the major catecholamine transmitter in the brain is noradrenaline. After its release, noradrenaline is actively transported back into neurons via specific transporters. In neurons, it is catabolised by monoamine oxidase (MAO) to form 3-methoxy-4-hydroxyphenylglycol (MHPG). Noradrenaline can also be catabolised in the glial cell by catechol-O-methyltransferase (COMT) to form normetanephrine (Alousi and Weiner, 1966). There are two main types of adrenoreceptors: α and β receptors. The α comes as subtypes, e.g., a1 or a2, each of which have further subtypes. α2 is the most implicated in anxiety disorders. This receptor is both pre-synaptic and postsynaptic. The pre-synaptic α2 receptors act as autoreceptors (Hein et al., 1999), inhibiting further noradrenaline release. They are also present pre-synaptically on serotonergic (Trendelenburg et al., 1994b) and dopaminergic (Trendelenburg et al., 1994a) neurons where they act as inhibitory heteroreceptors. Peripheral β receptors

are well known to mediate the peripheral autonomic effects of anxiety (such as increased heart rate, tremor and sweatiness) (McCorry, 2007).

Most noradrenergic neurons arise in the locus coeruleus in the brainstem and project extensively to the cerebral cortex and cerebellum, and are important for maintaining responsiveness to unexpected stressors. Projections from the locus coeruleus that extend to the limbic system regulate anxiety (Cheeta et al., 2001),(Weiss et al., 1994).

d. Glutamate: Glutamate is the most abundant neurotransmitter in the brain and it is thought to mediate effects upon memory, learning, performance and anxiety (Choi, 1992). Aside from being an important neurotransmitter, glutamate also functions as a putative gliotransmitter and an important neuronal metabolite involved in protein synthesis and energy production, as well as its vital role in excitatory neurotransmission. This direct regulatory effect on metabolism distinguishes it from 'classical' neurotransmitters such as dopamine and serotonin. There are eight metabotropic receptors which can be classified into three groups; group 1 (mGlu1 and mGlu5), group 2 (mGlu2 and mGlu3), and group 3 receptors (mGlu4, mGlu6, mGlu7, mGlu8) (Niswender and Conn, 2010).Whereby the ionotropic receptors consist of N-methyl-D-aspartate (NMDA), a-amino3-hydroxy-5-methylisoxazole-4-propionate (AMPA) and kainite receptors. NMDA receptors comprise two NR1 subunits and two or three NR2 subunits. There are eight different NR1 and four different NR2 subtypes available, thus allowing for significant heterogeneity between different NMDA receptors (Li et al., 2007). AMPA and kainite receptors are frequently co-localized with NMDA receptors and are synergistic to NMDA mediated transmission (Sundström et al., 1998),(Sheets, 2017).

Pre-clinical evidences have shown anxiolytic effects of blocking NMDA glutamatergic receptors. MK 801 (a non-competitive NMDA antagonist) and AP-7 (competitive NMDA antagonist) both decrease anxiety behaviours in rats(Plaznik et al., 1994).

e.GABA: GABA is the major inhibitory neurotransmitter in the CNS and is found in nearly every region of the brain. Released at an estimated 20–50% of central synapses, GABAergic neurotransmission plays a crucial role in controlling the excitability of neuronal activity in the brain (Sieghart, 1995). GABA receptor function can be altered by exposure to stress, and activation of this pathway leads to decreased anxiety.

GABA is synthesized from glutamate by L-glutamic acid decarboxylase, after which GABA is stored in synaptic vesicles. Neuronal activation results in the release of GABA into the synaptic cleft, activating clusters of post-synaptic receptors, resulting in rapid inhibitory 'phasic' neurotransmission. Released GABA can also 'spillover' into the extra-synaptic space, activating a range of extra-synaptic receptors found both pre- and post-synaptically on adjacent neurons so providing a 'tonic' inhibition that controls background levels of neuronal excitation (Farrant and Nusser, 2005). Uptake transporters located on presynaptic neurons and supporting glial cells terminate GABAergic neurotransmission by removing GABA from the synapse and extra-cellular space (Nutt, 2006). Three main types of GABA have been identified; $GABA_A$, $GABA_B$, and $GABA_C$. The $GABA_A$ receptor is the most prominent type of GAB_A receptor in the brain. It plays a key role in regulating the excitatory tone of many other types of neurons including dopaminergic, cholinergic and serotonergic (Fritschy et al., 1992),(Gao et al., 1995). Abnormalities of $GABA_A$ receptor expression and function have been the focus of intense research in anxiety as the majority of anxiolytics target this receptor complex (Liberzon et al., 2003).

Taken together, these neural networks provide a various mechanisms by which a stressor can influence behavior and mood.

1.5.1.5 Treatment of Anxiety

Current treatments range from cognitive-behavioral psychotherapy to pharmacotherapy (Bandelow et al., 2017). The goal of the cognitive treatment is to help the patients with managing the negative thoughts and behavioral patterns, which is often the disablitating factors in anxiety disorders. Typically, treatment with pharmacotherapy act by inhibiting neuronal activity in brain structures that mediate fear expression and the behavioral sensitization and facilitation of endogenous mechanisms necessary for the modulation of the neural transmission of information about aversive stimuli and responses to such stimuli, including drugs that influence serotonergic, adrenergic, glutamatergic, various neuropeptide and endocannabinoid systems (Griebel and Holmes, 2013), (Murrough et al., 2015).

More specifically, antidepressants are considered the first-line pharmacological treatment for most anxiety disorders. The most widely used antidepressants for treating anxiety disorder are selective serotonin reuptake inhibitors SSRIs (fluoxetine, citalopram, sertraline, paroxetine, fluvoxamine), and serotonin-norepinephrine reuptake inhibitors SNRIs (reboxetine, venlafaxine) (Farach et al., 2012). Unfortunately, besides having a delay of weeks or months for achieving their anxiolytic effect, many patients do not respond well to SSRIs and SNRIs, and some suffer from various side effects, including an exacerbation of anxiety during the initial phase of treatment(Bandelow et al., 2017). Other antidepressants, such as tricyclic antidepressants TCAs (desipramine, clomipramine, imipramine) and monoamine oxidase inhibitors MAOIs (moclobemide, phenelzine), have been widely used in the past for the treatment of anxiety disorders, but their adverse effects have made them much less popular recently ("Kaplan & Sadock's Comprehensive Textbook of Psychiatry," n.d.). Benzodiazepines (diazepam, alprazolam, clonazepam), which are known to act through the GABAergic system, are efficacious for the treatment of anxiety disorders, and most expert guidelines recommend their use as second-line or third-line agents (Katzman et al., 2014), (Baldwin et al., 2014). They were initially considered first-line treatments for anxiety because of their tolerability and equal efficacy to tricyclic antidepressants (TCAs),

but became second-line options when it became clear that SSRIs were both more tolerable and efficacious (Farach et al., 2012). Anti-epileptic drugs that modulate γ-aminobutyric acid (GABA) signaling such as gabapentin and pregabalin, are sometimes used as alternatives to benzodiazepines (Bandelow et al., 2017). Furthermore, atypical antipsychotics (such as risperidone or quetiapine) might also be useful for the treatment of anxiety disorders, particularly as an adjunct to SSRIs or SNRIs. However, treatment with atypical antipsychotics is associated with risk of weight gain and metabolic syndrome; these risks should limit their use to patients with treatment-refractory anxiety (Kreys and Phan, 2015). Other pharmacological tools to treat anxiety disorders include 5-HT1A receptor agonists (buspirone, gepirone, ipsapirone, tandospirone) which enhances GABA receptor activity also, neuroleptics/major tranquilizers, adrenergic-blocking drugs (propranolol, atenolol, pindolol), lithium, barbiturates, anticonvulsants (carbamazepine, sodium valproate, gabapentin, pregabalin, lamotrigine, tiagabine, topiramate, vigabatrin) and novel anxiolytics (mirtazapine and hydroxyzine) (Bandelow et al., 2017).

Given the negative influence of exacerbated anxiety on long-term patient function and quality of life, combined with the fact that one-third of patients do not respond to treatment (Bystritsky, 2006), the lack of effective treatment is clearly a key clinical need. Generally, literature has reported no consistent substantial improvement concerning the exaggerated anxious behavioral response with the current first-line pharmacotherapies, except at best only some marginal improvements (Marcinkiewcz et al., 2016), which provides further evidence for the urgent need for faster acting and more effective anxiolytics.

1.5.1.6 PPAR- α and Anxiety

Researchers found that PPAR-α ligands have predictably and successfully stabilized emotions in preclinical models. In particular, palmitoylethanolamide (PEA); an endogenous fatty acid amide acting as a PPAR-α agonist, normalized the anxiety behavior (D'Agostino et al., 2012),(Crupi et al., 2013), induced a dose-dependent anti-depressant effect (Yu et al., 2011),(Ghazizadeh-Hashemi et al., 2018),

and reduced aggressive behavior that was blocked by pre-treatment with antagonists (Locci et al., 2017). It's suggested that PPAR-α agonists might have therapeutic efficacy in treatment of mood disorders through targeting the PPAR-α pathway in the hippocampus (Li et al., 2019), regulation of dopamine, and possibly serotonin, neuron activities via nicotinic acetylcholine receptors (Melis et al., 2013b), or by stimulating the synthesis of allopregnanolone (Allo); a positive allosteric modulator of GABA action at $GABA_A$ receptors (Sasso et al., 2010),(Raso et al., 2011), which in turn induces anxiolytic and antidepressant effects (Pinna et al., 2000). Moreover, another study reported that PAE and oleoylethanolamide (OEA) levels, another endogenous PPARα agonist, are detectable in the brain at physiologically relevant concentrations, and their levels reduce upon exposure to stressful stimuli (Hill et al., 2009).This effect of OEA seems to be related to the regulation of BDNF in the hippocampus and cortex (Jin et al., 2015) and to increased levels of serotonin and norepinephrine in brain homogenates (Yu et al., 2015). Those evidences may present PPAR-α as a good candidate for neuroprotection in anxiety.

1.5.2 Schizophrenia

1.5.2.1 Background

Schizophrenia is a complex, chronic, neuropsychiatric disorder that not only causes a high burden of disease, but also challenges our understanding of how the mind and brain work. It affects approximately 21 million people worldwide; an estimation that is set to continue to rise with population aging and growth (Charlson et al., 2018). Apart from the high financial perspectives, it is a major burden for the patients and families also (Ganguly et al., 2010), (von Kardorff et al., 2016), (Chong et al., 2016). Despite intensive and ongoing research, there is no known cure for the disorder and outcomes from best-practice treatment are often suboptimal. Using of the antipsychotic drugs, the most common treatment, is frequently accompanied by debilitating side effects and low compliance. Hence, alternative and more efficient treatments treatment options are required to improve the treatment and quality of life for individuals suffering from this disease.

Schizophrenia was first described as dementia praecox by Emil Kraepelin in 1887 , but was renamed as schizophrenia by Eugen Bleuler (Jablensky, 2010). Schizophrenia comes from the Greek words skhizein (*σχίζειν* - "to split") and phren (φρήν - "mind"), describing the detachment from reality caused by positive symptoms rather than a 'split mind' which would be clinically characterised as multiple personality disorder. The diagnosis is based on a constellation of clinical symptoms and not on a common pathomechanism. The diagnostic systems DSM-V (Diagnostic and Statistical Manual of Mental Disorders, American Psychiatric Association, (American Psychiatric Association, 2013)), provides a set of symptoms and demand that a certain number of this pool must to be present over a given period of time for a diagnosis to be made (Table 5). The symptoms of this psychotic disease psychotic disorder are classified into two main clusters; positive and negative symptoms (American Psychiatric Association, 2013). Cognitive deficits, whilst not part of the diagnostic criteria of schizophrenia, have been shown to be a key component in the disorder as described below.

DSM-V
Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated). **At least one of these should include 1–3.** **1. Delusions** **2. Hallucinations** **3. Disorganized Speech** **4. Grossly disorganized or catatonic behavior** **5. Negative symptoms (i.e. diminished emotional expression or avolition)**

Table 5: Diagnostic Criteria for Schizophrenia According to DSM-V (American Psychiatric Association, 2013

Positive symptoms are normally not experienced by healthy people, defined as an excess or distortion of normal functions, and include delusions (fixed beliefs persisting despite being in conflict with reality or rational arguments and the content can include persecutory, referential, somatic, religious or grandiose themes), hallucinations which may occur in any sensory modalities (most commonly auditory such as hearing voices), and disorganized speech and behavior (incoherence or difficulty ordering words/sentences, often resulting in the use of unnecessary or meaningless words; often called "word salad"). In contrast, negative symptoms of schizophrenia are features which are present in healthy subjects but absent or reduced in patients. They are defined as restrictions in the range and intensity of normal behaviors, including diminished emotional expression and reaction, diminished participation in interpersonal relationships, diminished production of speech, and apathy, with loss of energy, drive, and interests (American Psychiatric Association, 2013),(Ross et al., 2006).

Since dementia praecox was first described in 1887, cognitive dysfunction has been identified as a core schizophrenia symptom group, although they are not currently part of the diagnostic criteria for schizophrenia. The cognitive deficits in schizophrenia have been studied intensively over the last 2 decades as they have been shown to be also positively correlated with symptom severity and negatively with age-of-onset and response to pharmacological treatment (Niemi et al., 2003), (Green, 2006). Actually, schizophrenia is characterized by disabilities in various cognitive domains, with estimates of 90% of patients having deficits in at least one

cognitive domain and 75% in at least two (Green, 2007). An initiative named MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) was sponsored by the National Institute of Mental Health with the goal to formulate standards in clinical research on cognition in schizophrenia to unitize clinical studies (Marder and Fenton, 2004), (Nuechterlein et al., 2004). The project identified seven cognitive domains affected in patients with schizophrenia: working memory, attention/vigilance, verbal learning and memory, visual learning and memory, speed of processing, reasoning and problem solving, and social cognition (Nuechterlein et al., 2004), (Nuechterlein et al., 2008).

Some theories postulate that deficits in fundamental cognitive processes, such as attention and memory deficits, may be recognized as a core feature of schizophrenia, rather than simply a symptom of schizophrenia (N. C. Andreasen, 1997), (Nancy C. Andreasen, 1997), (Andreasen et al., 1996). A theory that is supported by various studies, demonstrating the presence of cognitive deficits before the onset of psychosis, often already during childhood (Woodberry et al., 2008), the same intensity of impairments between never-medicated and chronic patients (Barnett et al., 2010), (Carbon and Correll, 2014) and relatively stable intensity of cognitive impairment across different schizophrenia states, like psychosis or remission (Albus et al., 2002), (Barder et al., 2013).

Cognitive deficits contribute substantially to the functional impairments associated with schizophrenia, and schizophrenics suffering from stronger cognitive deficits are predicted to have worse overall prognosis (Bowie and Harvey, 2006), (Green, 2006). Hence, targeting cognitive deficits for therapeutic interventions would ameliorate the overall functional performance (Green, 2006),(Green, 2007). However, antipsychotics can have deteriorating effects on cognition (Moritz et al., 2013).

1.5.2.2 Prevalence

Based upon data from the Global Burden of Disease Project (GBD, 2016), prevalent cases of schizophrenia rose from 13.1 million in 1990 to 20.9 million cases in 2016. An estimated 70.8% (or 14.8 million) of these cases occurred in the 25–54 years age group, and diagnoses before 20 years are considered as early onset schizophrenia (Charlson et al., 2018). Rarely, cases are diagnosed before the onset of puberty, called childhood schizophrenia. In comparison to those with a later age of onset of schizophrenia, individuals with both early forms manifest worse premorbid function, more severe negative and disorganization symptoms, greater cognitive deficits, and inferior overall prognosis (Tandon et al., 2009).

Historically, it has been reported that men are more likely to develop schizophrenia than women. However, new and more standardized data reported approximately equal prevalence rates for men and women (Charlson et al., 2018), (Goldner et al., 2002).

1.5.2.3 Onset and course

Schizophrenia is characterized by a sequential trajectory that starts with a *premorbid phase* with subtle and nonspecific cognitive, motor and/or social dysfunction. Those individuals, who are going to develop schizophrenia, exhibit a range of developmental behavioral, emotional and cognitive problems, accompanied by impairments in academic and social function. These abnormalities may include delays in motor development, attention dysfunction, deficits in receptive language, poor academic achievement, social isolation, and emotional detachment (Schenkel and Silverstein, 2004).

The period of time preceding the first onset of psychosis has been described as the *prodromal phase* and is characterized by subthreshold psychotic symptoms, as well as a constellation of other clinical signs including cognitive decline in processing speed, working memory, verbal episodic memory, executive functioning, general intelligence domains, and other mood symptoms like anxiety, depression,

irritability and anger, social withdrawal (Eastvold et al., 2007), (Cornblatt et al., 2007), (Larson et al., 2010). The prodromal phase may last from months to years, with a mean of ~5 years (Häfner and an der Heiden, 1999), (Klosterkötter et al., 2008). There has been significant attempt in trying to prevent the evolution of prodromal subpsychotic symptoms into the overt psychosis of schizophrenia via a range of psychopharmacological and psychological approaches among those meeting criteria for "ultra-high risk" of developing schizophrenia (Mokhtari and Rajarethinam, 2013).

The prodromal phase ends with reaching the psychotic threshold, called *psychotic phase*, based on the severity of symptoms and presence of frank psychotic symptoms , consistent with criteria in the DSM-V (American Psychiatric Association, 2013), which itemizes hallucinations, delusions, disorganized speech or behavior, and negative symptoms. After the onset of psychosis, Kraepelin and others observed that the longer that psychotic symptoms went untreated, the greater the functional disabilities and symptom severity. This duration of untreated psychosis is positively linked with symptom severity, cognitive dysfunction and poor response to antipsychotics (Marshall et al., 2005), (Perkins et al., 2005).

After first psychotic break, the course of schizophrenia is characterized by exacerbations and remissions (Andreasen et al., 2005). Following the initial years of vulnerability to further exacerbations, a plateau is usually reached, characterized by either *remission or chronicity*. The illness stabilizes and there is generally no further illness-driven deterioration in functioning and increase in residual symptoms (Thara, 2004).

1.5.2.4 Neuropathology in Schizophrenia

Most psychiatrists now believe that schizophrenia is associated with global brain atrophy and ventricular enlargement (Fusar-Poli et al., 2013),(Johnstone et al., 1976), reduction of cerebral (cortical and hippocampal) volume (Harvey et al., 1993), grey matter volume including the frontal and medial temporal lobe, thalamus, and amygdala regions (Matheson et al., 2014), as well as reduced brain lateralization,

reflected in a defect in brain hemisphere (Ribolsi et al., 2009). Besides, the amount of amyloid plaques and neurofibrillary tangles was noticeably higher in schizophrenia as compared to controls (Radewicz et al., 2000). These abnormalities have been correlated with positive, negative, and cognitive symptoms of schizophrenia. The left temporal abnormality has been shown to be strongly correlated with severity of positive symptoms (Ribolsi et al., 2009), whereas negative and cognitive symptoms have been shown to be associated with prefrontal lobe dysfunction (Capleton, 1996),(General et al., 1999).

1.5.2.5 Neuroanatomical background of schizophrenia

The anatomy of schizophrenia involves multiple brain regions. Postmortem studies on the **prefrontal cortex** of schizophrenic patients revealed altered dopamine signaling, as well as deficits in the GABAergic system, especially in parvalbumin positive interneurons. Impaired cognitive functions and negative symptoms are related with deficits in the prefrontal cortex of schizophrenic patients (Capleton, 1996),(Lewis et al., 2012),(Winterer and Weinberger, 2004).

The **hippocampus** is widely investigated in schizophrenic patients, and mainly linked to the cognitive deficits observed in those patients (Heckers and Konradi, 2015). Early speculations about changes in the hippocampal formation among those patients were based on anatomy. Hippocampal size is reduced bilaterally in schizophrenia, with volumetric reductions (~5%) found more often for the hippocampus than for any other brain region (Bogerts, 1997), (Heckers and Konradi, 2002), besides to smaller neuron size (Benes, 2010). Moreover, other studies revealed its altered expression of proteins involved in dopaminergic, gltamatergic, and GABAergic signaling, as well as variable synaptic structures and functions (Knable et al., 2004), (Torrey et al., 2005). Hippocampal hyperactivity is proposed to be an important feature of schizophrenia, and which is associated with the graveness of positive symptoms (Heckers et al., 1998), (Malaspina et al., 1999), whereas reduced hippocampal activations were observed during memory-related tasks (Heckers et al., 1998), (McCarley et al., 1993), (Weiss et al., 2003).

Not only the hippocampus, but also the volume of **amygdala** in the high-risk subjects is significantly smaller than in controls (Lawrie et al., 2003), (Makowski et al., 2017). And despite the role of amygdala in abnormal emotional responses such as anxiety and deficits in social interaction that are exhibited by schizophrenic patients also, and the correlation between premorbid anxiety and onset of psychosis (Owens et al., 2005), the role of the amygdala in schizophrenia has been little studied. An early study suggested that the amygdala plays a role in positive symptoms (before that term was in use) (Stevens, 1973), but few data from clinical settings have been collected to support this view. In fact, Berretta et al. revealed that a disruption of GABAergic transmission within the amygdala may play a significant role in the induction of hippocampal abnormalities, by decreasing the density of parvalbumin interneurons and the expression of glutamate decarboxylase in the hippocampus (Berretta et al., 2001), (Berretta et al., 2004).

Evidences demonstrated a dopamine hyperfunction in the **striatum** of patients with schizophrenia also, manifested as both an increase in striatal dopamine and an increase in striatal dopamine receptors. Besides to the fact that the striatum and its cortical connections are critical for complex cognition, some studies suggest the involvement of the striatum in cognitive symptoms of schizophrenia, and related it mainly to the striatal D2 overexpression (Simpson et al., 2010) .

1.5.2.6 Schizophrenia Neurotransmitter System

Most research efforts have focused on alterations in dopamine, serotonin, glutamate, and γaminobutyric acid (GABA) systems, and their link to the pathophysiology and symptoms of schizophrenia.

a.Dopamine: The “dopamine hypothesis” of schizophrenia arose from studies done in 1963 by Arvid Carlsson and Margit Lindqvist on chlorpromazine and haloperidol, who found that these drugs increase the concentration of dopamine metabolites in mouse brain, without altering the dopamine concentration, leading to their proposal that blockade of dopamine neurotransmission relieves psychotic symptoms (Carlsson and Lindqvist, 1963). This was the basis for the formulation of the

"original dopamine hypothesis" that excessive dopamine transmission represents a core feature of schizophrenia (van Rossum, 1966). Administration of high doses of amphetamine can produce in normal individuals an acute psychosis that is indistinguishable from the paranoid subtype of schizophrenia and that is rapidly ameliorated by antipsychotic treatment (Angrist et al., 1974); given that amphetamine is a powerful releaser of catecholamines in brain, this clinical observation lent further support to the dopamine hypothesis, which soon became the most popular theory for the integration of diverse biological and clinical findings in schizophrenia research (Meltzer and Stahl, 1976).

As we stated before, there are four main dopaminergic pathways in the human brain: nigro-striatal, meso-limbic, meso-cortical and tuberoinfundibular pathways. Dysfunction of the nigro-striatal pathway, either through pharmacological intervention (eg: typical antipsychotic administration) or pathological loss of dopaminergic neurons (as observed in Parkinson's disease), causes movement disorders (dyskinesias). The positive and negative symptoms of schizophrenia are thought to be caused by dysfunction of the meso-cortical and meso-limbic pathways. Reduced dopaminergic activity in the prefrontal cortex gives rise to cognitive deficits, reduced motivation and other negative symptoms, whereas hyperactivity of the dopaminergic system in the meso-limbic circuitry mediates the positive symptoms (Laruelle et al., 2003). Dopaminergic release at the median eminence of the tuberoinfundibular pathway regulates the secretion of prolactin. If dopaminergic activity is blocked, for example by antipsychotics, this leads to increased blood prolactin levels and subsequent reduced estrogen levels, which can give rise to abnormal lactation and menstrual or sexual dysfunction (Meltzer and Stahl, 1976).

The "version II" hypothesis postulated that positive symptoms of schizophrenia result from the increased subcortical release of dopamine, which augments D_2 receptor activation (Shen et al., 2012), and are thought to be due to a disturbed cortical pathway through the nucleus accumbens (O'Donnell and Grace, 1998). Genes downstream of D2 receptors have also been linked to cognitive ability, including COMT and AKT phosphorylation signalling, indicating that dopamine

dysfunction remains an integral part of schizophrenia symptomatology (Arguello and Gogos, 2008), (Yavich et al., 2007). The negative symptoms and cognitive deficits result from reduced D_1 receptor activation (Shen et al., 2012) in the prefrontal cortex and decreased activity of the nucleus caudatus (O'Donnell and Grace, 1998). Alterations in D_3 receptors might also be involved in the negative symptoms of schizophrenia (Simpson et al., 2014). This hypothesis has been supported by PET-studies (positron emission tomography) showing differences in dopamine contents in several brain sites such as the hippocampus, cingulated cortex, and prefrontal cortex between schizophrenia patients and neuropsychiatric healthy control subjects. In particular, increased striatal dopaminergic transmission (Breier et al., 1997), (Abi-Dargham et al., 1998), and elevated dopamine synthesis capacity (Howes et al., 2007) have been revealed in schizophrenic patients. Reduced dopaminergic transmission in the prefrontal cortex, particularly via the D1 receptor subtype has been linked with impairments in working memory, a core feature of schizophrenia, and has been shown in the brains of patients with schizophrenia (Goldman-Rakic et al., 2004). The dopamine system in the hippocampus is overactive in schizophrenia patients (Grace, 2012), and the exacerbation of psychosis which is correlated with hyperactivity in the limbic hippocampus (Malaspina et al., 1999), (Medoff et al., 2001), (Molina et al., 2003), is also correlated with an increase in amphetamine-induced dopamine release in schizophrenia (Laruelle et al., 1999). Lodge et al. demonstrated a direct link between hippocampal dysfunction and the hyper-sensitivity of the dopamine system that is believed to underlie the psychosis in schizophrenia patients (Lodge and Grace, 2007). This excessive activity and sensitivity are attained through various mechanisms; including increased dopamine release, decreased dopamine reuptake, increased receptor density and availability.

The "final common pathway hypothesis" has emerged, expanding on the idea proposed by Davis and colleagues (Davis et al., 1991) that region-specific dopaminergic dysfunction gave rise to schizophrenia symptomatology. It has been suggested that presynaptic striatal hyperdopaminergia is the point of convergence for multiple neurotransmitter dysfunctions, including glutamate and GABA, which in turn gives rise to psychosis (Howes and Kapur, 2009). Antipsychotic blockade of

presynaptic D2 autoreceptors may result in a compensatory increase in dopamine synthesis, worsening the underlying hyperdopaminergia, which would explain why patients show increased dopamine synthesis following chronic antipsychotic medication regimes (McGowan et al., 2004). Howes and Kapur (Howes and Kapur, 2009) created a novel distinction with this hypothesis, compared to the previous hypotheses; that the dopaminergic dysfunctions mentioned may give rise to "psychosis", but not necessarily schizophrenia as a whole. The cognitive deficits and negative symptoms are suggested to be partially independent from psychosis and are likely to involve other neurotransmitter systems; a hypothesis strongly supported by clinical observations showing that dopaminergic drugs that show efficacy in treating psychosis, such as current anti-psychotics, show no significant effect in treating the cognitive and social deficits observed in schizophrenia (Naber and Lambert, 2009).

Howes and Kapur (Howes and Kapur, 2014) have then suggested that there are two populations of patients with schizophrenia: 'hyperdopaminergic' patients who show elevated dopamine levels and who respond well to dopamine-depleting pharmacological therapies, and 'normodopaminergic' patients who show unvaried dopamine levels and who do not respond to antipsychotic medication, despite high levels of dopamine receptor blockade (Yoshimura et al., 2003), (Demjaha et al., 2012)(Yoshimura et al. 2003, Reviewed in Demjaha et al. 2012). These suggest that dopamine dysregulation, eventhough is afrequentobserved phenotype in schizophrenia, may not be the only final common pathway for all patients in the pathogenesis of schizophrenia, and particularly psychosis.

b.Serotonin: Although the serotonin hypothesis of schizophrenia is one of the oldest neurochemical hypotheses on the pathogenesis of this disease, it is still highly topical. The first step in the direction of the idea that the serotonin system may contribute to schizophrenia was probably made by the German psychiatrist Kurt Beringer in 1923 (Halberstadt and Geyer, 2013). He was the first to propose the use of the hallucinogen mescaline as an experimental model of psychosis, despite the fact that he had no knowledge of serotonin receptors or the principles of neurotransmission. Subsequently, they have come to understand that mescaline is a

selective serotonin-2A (5-HT 2A) receptor agonist that played an important role in the development of schizophrenia (Halberstadt and Geyer, 2013).

One of the strongest arguments for the involvement of 5-HT in schizophrenia was the discovery of atypical antipsychotics such as clozapine, risperidone, and olanzapine, which act in part by blocking 5-HT_{2A} receptors with some selectivity over the dopamine D_2 receptor (Meltzer et al., 1989), (Meltzer, 1991), (Meltzer, 1999), (Seeman, 2002). Besides, animal studies have indicated that selective 5-HT_{2A} antagonists have antipsychotic-like effects (Varty et al., 1999), (Geyer et al., 2001). Serotonin may be acting by itself or in connection with dopamine to produce symptoms of schizophrenia (Harrison, 1999).

c. Noradrenaline: Also, noradrenalin, has been implicated in the pathogenesis of schizophrenia (Friedman et al., 1999), (Yamamoto and Hornykiewicz, 2004).Increased noradrenaline levels has been found in cerebrospinal fluid , autopsy brain and plasma in psychosis (Goekoop et al., 2012). The evidence of norepinephrine dysfunction occurring concomitantly with dopamine dysfunction in schizophrenia, highlight the multiplicity of neurotransmitter abnormalities involved in the pathophysiology of schizophrenia, especially in the manifestation of cognitive impairments associated with these disease (Friedman et al., 1999).

d.Glutamate: The progressive loss of brain tissue in schizophrenia may represent an ongoing pathophysiological process, which could be an important target for therapeutic intervention. One of the possible mechanisms that may be involved is dysfunction of the glutamatergic system, which might affect synaptic plasticity and cortical microcircuitry, in particular (N-methyl-D-aspartate) NMDA-receptor signaling (Harrison and Weinberger, 2005). Depending on the severity and duration of the NMDA-receptor hypofunction state, postsynaptic neurons can develop morphological changes and may cause chronic psychosis and structural brain changes (Olney et al., 1999), (Kondziella et al., 2007), (Stone et al., 2007).

Recent research has concentrated on the ‘glutamate hypothesis’, as an explanation for the cause of negative and cognitive symptoms, as these are poorly

treated by dopaminergic antipsychotics (Stahl, 2007a), (Stahl, 2007b). The basis of the glutamate hypothesis; which states that many of the symptoms in schizophrenia are caused by hypofunction of glutamate signalling at NMDA receptors, arose from the observations that schizophrenia patients showed reduced levels of CSF glutamate (Kim et al., 1980) and that administration of phencyclidine PCP, an NMDA receptor antagonist, gave rise to schizophrenia-like symptoms in humans (Luby et al., 1959).

NMDA receptor antagonist phencyclidine (PCP) has been used to model symptoms of psychosis in humans (Abi-Saab et al., 1998), (Marcotte et al., 2001), lending support to the involvement of glutamate in the disorder. In rodents, acute administration of the non-competitive NMDA receptor antagonist PCP produces positive and negative symptoms represented as deficits in pre-pulse inhibition (PPI) of the startle response, increases locomotor activity, social withdrawal, and produces cognitive deficits of particular relevance to schizophrenia (Jones et al., 2011). However, sub-chronic PCP treatment in animals has been shown to produce more persistent effects and to produce more enduring cognitive deficits of particular relevance to schizophrenia (Jones et al., 2011). In fact, sub-chronic or chronic PCP administration results in schizophrenia-like pathological changes including a loss of hippocampal and cortical parvalbumin (PV)-containing interneurons (Neill et al., 2010).

However, findings demonstrated that systemic injection of NMDA antagonists at doses that impaired cognitive functions and produced motor stereotypy increase glutamate efflux in the prefrontal cortex (Lorrain et al., 2003). This increase in the extracellular levels of glutamate had functional significance because blockade of 3-hydroxy-5-methyl-4-isoxazolepropionic acid AMPA receptors reduced the motoric and cognitive impairements of NMDA receptor blockade. Thus, NMDA receptor antagonists appeared to increase the release of glutamate at some synapses, which then abnormally increased glutamate neurotransmission at non-NMDA receptors, in particular AMPA receptors, and this mechanism could be involved in mediating cognitive problems in schizophrenia. This finding, therefore, suggested that behavioral consequences of NMDA receptor deficiency is not due to a

generalized "glutamate hypofunction" but dysregulation of glutamate neurotransmission that may potentially involve NMDA receptor hypofunction, but excessive activity of non-NMDA receptors (Moghaddam and Javitt, 2012).

e.GABA: The GABAergic hypothesis of schizophrenia was first suggested as an amended version of the glutamate hypothesis. Olney and Farber (Olney and Farber, 1995) posited that the reduced activity of NMDA receptors located on GABAergic interneurons in the cortex is proposed to decrease the activity of these inhibitory neurons, which in turn causes an impaired feedback in neural rhythmic circuitry (figure 5), downregulation of GABA synthesis, release and reuptake in the cortical inhibitory neurons found in schizophrenia patients (Lewis and Gonzalez-Burgos, 2006). This is then thought to disrupt the inhibitory feedback needed to generate synchronous rhythms, particularly in the gamma and theta bands, resulting in schizophrenia symptomatology.

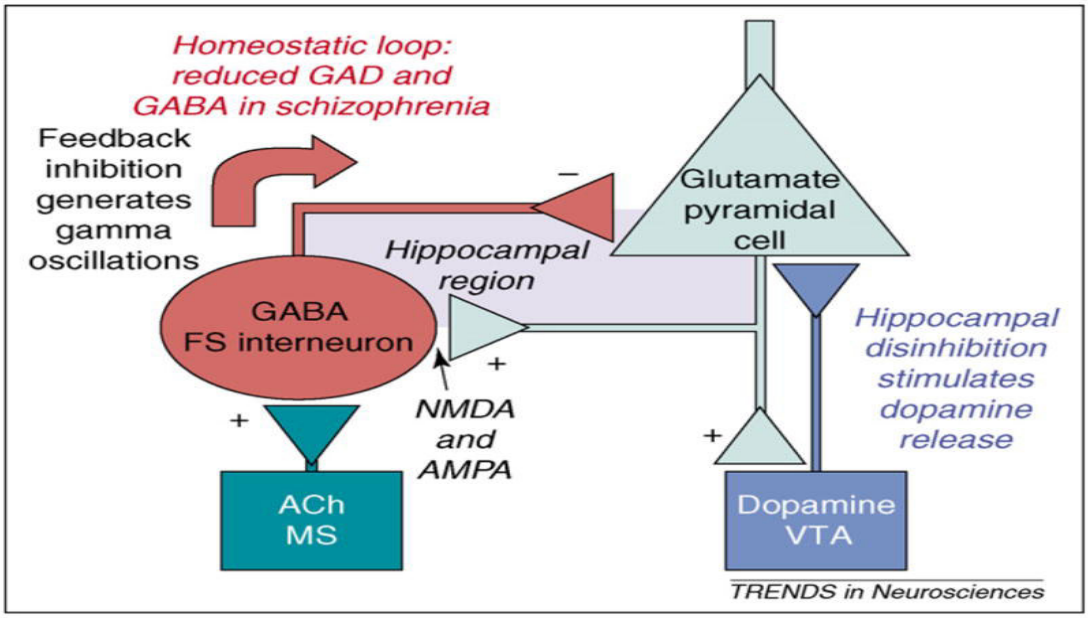


Figure 1: Proposed mechanism by which GABAergic inhibition of glutamatergic pyramidal cells generates oscillatory activity in the cortex and hippocampus.
Dysregulation of the GABAergic system results in disinhibition of this feedback loop and is thought to be responsible for cognitive deficits in schizophrenia (Lisman et al., 2008).

Furthermore, the deficiency of inhibition by fast-spiking GABAergic neurons is also proposed to lead to impairements in cognitive function, due to an absent synchronization of pyramidal neuron activity (Lewis and Moghaddam, 2006). In fact, sub-chronic and chronic administration of NMDA receptor antagonists such as

PCP, which are known to cause schizophrenia-like symptoms, results in decreased expression of parvalbumin in cortical and hippocampal GABAergic cells (Abdul-Monim et al., 2007), (McKibben et al., 2010). Moreover, the hippocampal hyperactivity is believed to result from GABAergic hypofunction supported by findings of a decreased number of GABAergic interneurons in patients with schizophrenia (Benes et al., 1998). Reductions in GABAergic activity in the amygdala have also been suggested by early findings of reduced GABA concentrations (Spokes et al., 1980) and decreases in high affinity GABA uptake sites (Reynolds et al., 1990), (Simpson et al., 1989).

1.5.2.7 Treatment of Schizophrenia

The goals in treating schizophrenia include targeting symptoms, preventing relapse, and increasing adaptive functioning so that the patient can be integrated back into the community. Pharmacotherapy is the mainstay of schizophrenia management, but residual symptoms may persist. For that reason, nonpharmacological treatments, such cognitive behavioral therapy, are also important (Dickerson and Lehman, 2011).

Schizophrenia is treated pharmacologically using a variety of antipsychotic medications. These medications act in ways that are consistent with the theorized neurochemical dysfunctions of the disorder. First antipsychotic medications used to treat schizophrenia were discovered serendipitously. The first antipsychotic, chlorpromazine, was synthesized in 1950 by the French pharmaceutical company Rhône-Poulenc, but was not originally planned to be a psychiatric drug. Its antipsychotic properties were discovered in 1952 and it was first administered to a psychiatric patient as a treatment for schizophrenia (Lehmann and Ban, 1997). Chlorpromazine and various drugs with similar mechanisms are known as neuroleptics or typical antipsychotics (The first generation antipsychotics). In spite of the differences in their structure, all these compounds produce a demonstrable, drug-induced blockade of dopamine D2 receptors in the mesolimbic pathway, and were instrumental in uncovering the role of dopamine in schizophrenia. D2 receptor blockade reduces the dopaminergic hyperactivity in the mesolimbic dopamine

pathway that is believed to cause certain positive symptoms of schizophrenia. Consequently, conventional antipsychotics and neuroleptics cause a reduction in positive symptoms (Lehmann and Ban, 1997).

However, the effects of neuroleptics are not specific to the areas of dopamine hyperactivity. Another common characteristic, shared by all "typical antipsychotics," is a marked blockade of D2 receptors in the nigrostriatal pathways involved in the refinement of movements and motor control. It is the removal of this modulation that is responsible for the debilitating side effects, including tardive dyskinesia and extrapyramidal side effects, associated with the neuroleptic drugs (McWilliam, 2004). Typical antipsychotics and neuroleptics were the common pharmacological treatment of schizophrenia until the introduction of the atypical antipsychotics, which are a new class of medication that are just as effective in treatment as any of the others, but has a considerably lower propensity to induce tardive dyskinesia and extrapyramidal side effects. Typical drugs then fill out of favor, mainly as a result of their many debilitating side effects and difficulty in treating negative symptoms (Lehmann and Ban, 1997).

The first atypical antipsychotic medication was clozapine in the early 1980s, when it was shown to have significantly lower propensity for side effects, equal efficacy in standard schizophrenics, and a higher efficacy in treatment-resistant schizophrenics (Lehmann and Ban, 1997). These effects result from the atypical antipsychotic's higher affinity to mesolimbic than to nigrostriatal D2 receptors, whereas "typical antipsychotics" have higher affinity to nigrostriatal than to mesolimbic D2 receptors. This location-specific effects of atypical antipsychotics help to reduce the number and intensity of negative side effects, although there are still associated side effects (Lehmann and Ban, 1997). Moreover, atypical antipsychotics have antagonistic affinities to both the D2 and the serotonin S2 receptors, whereas "typical antipsychotics" have affinity to the D2 receptor only. Serotonin inhibits dopamine release in the brain, but does so differentially in the various dopamine pathways. Hence, along with the D2 receptor antagonist properties, atypical antipsychotics (the second generation antipsychotics) allow for

greater dopamine availability in areas where dopamine is decreased in schizophrenia, and decrease dopamine availability in areas of dopamine hyperactivity in schizophrenics (McWilliam, 2004). Several new atypical antipsychotics have been introduced since the 1980s and are now considered the first-line medications for schizophrenia, depending on their efficacy and improved side effect profile, but they still induce some side effects; such as weight gain and disregulations in glucose and lipid metabolism (Lehmann and Ban, 1997). Moreover, although both typical and atypical antipsychotics effectively reduce psychotic symptoms, they lack efficacy for negative and cognitive symptoms (Miyamoto et al., 2012).A fact that suggests that alternative treatments should be examined.

Early treatment for schizophrenics is vital. As long as the patient is left without treatment, prognosis gets worsened (Hill et al., 2012). And the most effective treatment is prevention. Several biological, psychological and social changes underpinning the development of schizophrenia are active before the onset of psychosis. Patients already exhibit cognitive and emotional deficits in the pre-psychotic phase. Also, a hyperactivity of hippocampus, manifested as an abnormal increase in cerebral blood volume and hypermetabolism were observed in the hippocampus of at-risk human samples (Schobel et al., 2009), (Schobel et al., 2013). Indeed, it is difficult to diagnose schizophrenia early, but numerous studies have identified some symptoms that are predictive of onset of psychosis later in life, and they demonstrated that anxiety and impaired tolerance to stress in childhood and adolescence are some of these factors that correlate with later onset of psychosis (Owens et al., 2005), (Yung et al., 2005), (Corcoran et al., 2012), (Devylder et al., 2013).

1.5.2.8 PPAR-α and Schizophrenia

PPAR-α is also considered as a good candidate for early neuroprotection in schizophrenia. Prefrontal cortex and basal nuclei are cerebral regions that are both particularly involved in the symptomatology of schizophrenia (Ursu et al., 2011), (Sorg et al., 2013). Interestingly, these two regions are also among those in which the level of expression of both PPAR-α is very important in the brain (Moreno et al.,

2004). And since PPAR-α has shown a potential effect in reducing inflammatory and oxidative processes (Tzani et al., 2018),(Remels et al., 2008), they possess potential features of disease-modifying medication in schizophrenia. The involvement of PPAR-α in regulating hydrogen peroxide H_2O_2-producing and removing enzymes may also be relevant to neurotransmission per se, as H_2O_2 may act as a physiological modulator of glutamate and dopamine release (Chen et al., 2001), (Avshalumov and Rice, 2002). In fact, it has been recently reported that PPAR-α agonist could experimentally reduce the activity of dopaminergic neurons (Melis et al., 2010). This finding may have significant impact on the potential interest of PPARs in schizophrenia, in which dopamine transmission is considered to be a key mechanism underlying the positive symptoms. Despite these perspectives, only few studies have examined the potentiability of PPAR-α on modifying the symptomatology of schizophrenia. Specifically, it has been revealed that PPAR-α activation can improve antipsychotic medication adverse event oral tardive dyskinesia (Grover et al., 2013) and indirectly reduce the activity of dopamine cells in the ventral tegmental area in rodents (Melis et al., 2013b). PPAR-α may also have direct antipsychotic effects by downregulating the dopaminergic system. Another study has demonstrated that after a neonatal lesion inducing delayed PPI anomalies in rats, PPAR-α agonist fenofibrate administration allowed to partially reverse the PPI disruption (Rolland et al., 2012). In this case, the direct action of fenofibrate on the dopaminergic transmission might be the mechanism that could explain such a behavioral effect.

1.6 Modeling anxiety and schizophrenia in rodent models

The use of animals as valid experimental models plays a crucial role for studying human diseases, and has been the foundation for many scientific advances to understand and treat a variety of medical problems. Animal models permit the development of procedures and treatments that would be difficult or prohibited to examine in human samples.

The research of psychiatric and mental disorders often involves the use of valid animal models (Nestler and Hyman, 2010). They constitute a crucial tool for progress in the understanding of neurobiological mechanisms involved in psychiatric diseases and/or symptoms (Río et al., 2014). These models could be used to test the plausibility of (physiological, neurobiological) theories about the origin of the diseases, to explore the mechanisms involved, to investigate therapeutic and adverse effects of the drugs used for treatment, and to develop new potential treatments (Bakshi, 2002).

Since psychiatric disorders are usually highly complex, involving different clusters of symptoms even within the same diagnostic, it is a very different task to mimic all the main features of the disease in one animal model. Thus, these models are either based symptomatically or mechanistically. Symptomatic animal models have features consistent with human disorders and attempt to mimic a specific symptom or symptoms of a disorder, and are often used to identify the anatomical and physiological processes involved in the expression of symptoms (Nestler and Hyman, 2010), (Wilson and Hess, 2013). Mechanistic animal models are animals which are used to evaluate the mechanism of action which underlies an observed abnormal behaviors or symptoms associated with specific disorders (Nestler and Hyman, 2010). The debate is still on about which type of model is better for studying mental disorders, but generally concur that both have played major roles in understanding various conditions.

Rodents have been a favored model in the investigation of neuropsychiatric disorders and behavioral dysfunctions for many years, especially in the field of

psycopharmacology, where it is considered to be of particular importance in drug development programs. Animal studies can control behavioral and environmental factors that are difficult to control in humans, and the innate behavior of rodents is well known. Hence, the chemical modulation of these behaviors has been identified to examine the validity and function of potential drug candidates for treatment of mental illnesses in humans (van der Staay et al., 2009), (Fernando and Robbins, 2011).

Various methodical procedures are employed when designing experiments. These procedures include the environmental condition in which the animals are housed (this should be kept consistent across experiments), food and water access should be *ad libitum*, experimental history of subject, prior test and drug exposure and housing.

1.6.1 Animal models of Anxiety

Typically, anxiety-like behavioral models are conducted on males. A major reason for using male rats is that the cyclic release of female sex hormones, estrogen and progesterone, in female rats produces an unstable endogenous factor in the models that by itself can have a significant outcome on the physiology and behavior of animals.

Rodents possess the same neurotransmitters and brain areas that regulate anxiety in humans. Their innate behavioral drive to explore a new environment can be manipulated using compounds with known anxiogenic or anxiolytic function. For assessment of anxiety-like behaviors, pre-clinical animal models include non-exploration based tests and exploration-based conflict tasks. Non-exploration based tests, e.g. conditioned inhibition; marble burying and acoustic startle response do not rely on exploration and hence allow the measurement of anxiety-like behavior. In contrast, exploration-based conflict tasks, such as the **open-field test**, **elevated plus maze**, and **social interaction test** utilize test apparatuses where the rat's drive to approach is in disagreement with the avoidance of the potential threat. Exploration-based conflict tasks, which are utilized in this thesis, are the most commonly used anxiety-like tests in rodents, and they take advantage of the

competing ethological drives of rats to avoid predation and to explore a novel environment.The aversive subject in such model of anxiety can take various forms; central area of a novel or brightly lit open fields (open-field test), an open, elevated arm (elevated plus maze), and a confrontation with a conspecific in a neutral test environment (social interaction test) (Kim et al., 2019), (Steimer, 2011).

1.6.2 Animal Models of Schizophrenia

Since schizophrenia is a complex heterogeneous psychiatric disorder with a large variety of symptoms, it difficult to be modeled. Some of the core symptoms are of cognitive domains (like thoughts,verbal learning, and memory), which are uniquely human traits, besides to the variable course and outcome, and possible genetic and environmental influences. Therefore, animal models of schizophrenia are constructed principally to mimic specific aspects of the disorder, rather than the entire human condition. Unlike the disorder, the models are derived through a single type of manipulation; environmental, genetic, or pharmacological (Jones et al., 2011).

There are various animal models of schizophrenia that have behavioral phenotype changes that resemble positive, negative or cognitive symptoms of schizophrenia. Environmental models, also referred as neurodevelopmental models, rely on the exposure of the neonates, either during gestation or the perinatal period, to environmental stress, such as maternal separation (Liu et al., 1997) and early social isolation (Geyer et al., 1993). These models replicate the sensorimotor and cognitive deficits that are reported in schizophrenic patients. Schizophrenic animal models can also be derived by genitic manipulations. Knock out technology and selective breeding techniques have produced strains of animals that mimic the physiological and behavioral traits of schizophrenia (Jones et al., 2011). Specific strains of rats (i.e., apomorphine sensitive APO-SUS rats) have been selectively bred to maximize a variety of behavioral and biochemical traits related to schizophrenia (Ellenbroek et al., 1995). Other genetic models of schizophrenia were built with mutations that were produced in the genes that play a role in the pathophysiology of schizophrenia, such as dopamine, adrenergic, or glutamate receptors (Sibley, 1999).

The neurotransmitter systems implicated in schizophrenia disorder can also be manipulated pharmacologically, one of the most frequent techniques for setting up schizophrenic animal models. In this thesis, we used selectively the dopaminergic and glutamatergic drug models.

It is hypothesized that a hyperdopaminergic state resulting from an excess of dopamine in the brain causes for the condition of schizophrenia (Carlsson and Lindqvist, n.d.), (Seeman, n.d.). It was demonstrated that amphetamine administration in psychotic patients stimulates the release more dopamine at the synapse than normal control groups suggesting increased midbrain dopamine activity (Abi-Dargham et al., 2009), inducing the positive symptoms of schizophrenia, but it is not thought to fully resemble the cognitive and negative symptom domains. In rodents, administration of such dopaminergic stimulants has been reported to induce progressive augmentation of locomotor activity, repeated stereotyped behaviors, that may be related to the positive symptoms of psychosis, as well as to impaired prepulse inhibition (PPI), a marker of sensory gating impairment also seen in patients with schizophrenia (Segal and Mandell, 1974).

Another neurochemical model of schizophrenia, was proposed, based on NMDA receptor hypofunction by Olney et al. (Olney et al., 1999). It suggested a dysfunction of the NMDA receptor, which could be reproduced by blocking NMDA receptors pharmacologically with phencyclidine (PCP). Phencyclidine (PCP) is an arylcyclohexamine psychotomimetic drug, originally used as a dissociative anaesthetic, whose use was discontinued after it was found to cause schizophrenia-like symptoms in healthy humans (Collins et al., 1960) as well as exacerbating pre-existing symptoms in patients (Luby et al., 1959). The organization of the glutamatergic system and its important role in synaptic plasticity and cortical processing in the brain, strongly implicates the disruption of the glutamatergic system in the pathophysiology of schizophrenia (Schwartz et al., 2012). PCP treatment also influences oxidative stress (Radonjić et al., 2010), hypofrontality (Weinberger and Berman, 1996) and glucose utilisation (Cochran et al., 2003) in the

areas of the brain associated with neural plasticity and cognition, such as the prefrontal cortex, hippocampus and cerebellum.

Acute, chronic and sub-chronic administration of PCP to rats gives rise to schizophrenia-like positive and negative symptoms represented as deficits in pre-pulse inhibition (PPI) of the startle response, increases locomotor activity,social withdrawal, besides to cognitive deficits in a variety of tests including attentional set-shifting and object recognition memory (Jones et al., 2011). However, sub-chronic administration of PCP is thought to provide a more valid model than acute administration for modelling negative symptoms and cognitive deficits in schizophrenia (Jones et al., 2011).

2. Chapter II: Objectives

Clofibrate is a representative of the fibrate class of medications that is widely prescribed to treat lipid disorders even before its identification as a synthetic PPAR-α agonist (Salakhutdinov and Laev, 2014). Therefore most of the literature focuses mainly on its effect on lipid metabolism and its potential role in the therapy of cardiovascular diseases (Theobald, 2017), (Krasno and Kidera, 1972), (J. B. Arthur et al., 1971). Because of its poor ability to cross the blood-brain barrier, its central effects have always been considered negligible. Therfore, there are only one clinical study that examined the potential effect of clofibrate on neuropsychiatric animal models. Fakhraei et al(Fakhraei et al., 2017) reported that clofibrate may have antidepressant-like effects in depression animal models.

Besides, preliminary studies conducted in our laboratories, not published yet, but are a subject of a previous thesis, report that:

- PPAR-α synthetic agonist, clofibrate (25 mg/kg, i.p), produces antidepressant effect on rats subjected to the forced swimming test;
- this antidepressant effect would seem to be comparable to that induced by the reference antidepressant drug (amitriptyline 15 mg/kg, i.p),
- and significantly reverted by MK886, specific antagonist of the PPARα receptor, underlining a mechanism surely mediated by PPARα receptors.
- clofibrate and the endogeneous PPAR- α agonist; palmitoyethanolamide PEA, maintained an antidepressant effect also after 14 days of chronic treatment (25 mg/kg, 1 mg/kg, i.p respectively) in the forsed swimming test.
- moreover, none of the PPAR-α agonists injected acutely, produced anxiolytic or anxiogenic-like behaviors in the elevated plus maze test, while an anxiogenic profile was observed after acute treatment in the social interaction test
- whereas no anxiogenic or anxiolytic effect was observable after chronic treatment with both clofibrate and PEA.

Thus, we hypothesized that the PPAR-α receptor agonist clofibrate might have effects on psychiatric disease.
To test this hypothesis we decide to study the behavioural effects of clofibrate in animal models of anxiety and schizophrenia to assess the role of clofibrate in regulating emotional responses.
The studies were conducted through a series of experimental tests on adult male Sprague Dawley rats.

- Firstly we analyzed the possible anxiogenic/lytic profile of clofibrate assessed by boththe "social interaction test", and "elevated plus maze test" acutely to confirm and compare our results with that of our previous fingings, and to validate the establishment of the same experimental conditions.

- Then, we further examined the behavioral profile of clute using a different anxiety paradigm, the open field test, via acute, sub-acute, and chronic regimes of treatments, to confirm its effect successively in a wider variety of anxiety models and understand the mode of action upon which clofibrate's behavioral effects rely.

-Next, we evaluated the prospective antipsychotic effect of clofibrate in the phencyclidine and amphetamine animal models of schizophrenia.

- The efficacy of clofibrate in counteracting symptoms induced by acute phencyclidine and amphetamine administration were assessed in a test battery:

1. including the prepulse inhibition (PPI) of the acoustic startle reflex, to appreciate the sensory motor gating;
2. locomotor activity and stereotyped behaviors for the evaluation of psychotomimetic aspects;
3. the novel object recognition (NOR) paradigm, to assess cognitive deficits.

- Furthermore, since extrapyramidal symptoms are one of the principal antipsychotics side effects, we compare, in the bar test for catalepsy, the effect of the classical antipsychotic agent haloperidol with different doses of clofibrate. And finally, to explore the neuropharmacological mechanism, we examined the influence

of acute and chronic effect of clofibrate administration on the serotonin and dopamine contents and their metabolites in discrete brai area such as the prefrontal cortex, nucleus accumbens, striatum, amygdala, hippocampus, and hypothalamus.

3. Chapter III: Materials and Methods

3.1 Experimental animals

Adult male rats of the Sprague Dawley strain (Harlan - Nossan, Italy) were used, weighing 250-300 grams at the time of experimentation. The animals were housed four per cage and kept at a regular light/dark cycle of 12 hours (7.00am - 7.00pm), under standard ambient temperature and humidity conditions (T = 21 ± 2 °C; U = 60%). Food and water were available *ad libitum*. Animals were handled by the experimenters for 1 week prior to testing, and before each test, animals were subjected to acclimatization (1h) of the environmental conditions in the experimentation rooms. Behavioral tests were conducted during the period of light. All the experiments were approved by the Ethics Committee for the Protection of Laboratory Animals and conducted in compliance with the regulations in force on E.C. Regulations for Animal Use in Research (EEC No. 86/609, Decree Law 27.01.1992).

3.2 Drugs used in our behavioral tests

- *Clofibrate (Tocris, UK):* 25 mg/kg dissolved in 10% Tween 80, 20% DMSO and 70% distilled water, administered 1 hour before testing.

- *Phencyclidine hydrochloride (PCP; Sigma-Aldrich, UK):* was dissolved in sterile water.

- *Amphetamine (AMPH; Sigma-Aldrich, UK):* was dissolved in sterile water.

- *Haloperidol (HAL; Tocris, UK):* was dissolved in sterile water

All drugs were freshly prepared on the administration day and were injected intra peritoneally (i. p.) in a volume of 1.0 ml·kg^{-1}.

3.3 Experimental groups and pharmacological treatments

- *Clofibrate* was administered intraperitoneally (i.p.), following 3 different types of treatment:

1. *an acute treatment*, in which a single administration (25 mg·kg^{-1}) of the drug occurred 1 hour before the test.
2. *a sub-acute treatment*; in which a single daily administration (25 mg·kg^{-1}) for a period of 3 consecutive days occurred, and the last administration was 1 hour before the test.
3. *a chronic administration*; in which a single daily administration (25 mg·kg^{-1}) for a period of 14 consecutive days occurred, and the last administration was 1 hour before the test.

- *Amphetamine* was administered acutely in order to induce psychotic-like symptoms, *i.e.* hyperlocomotion, stereotypies and impaired PPI. Animals received a single injection of AMPH (3 mg·kg^{-1}), or saline (SAL, 1 ml) immediately before the beginning of behavioral tests.

-Phencyclidine PCP was administered intraperitoneally (i.p.), following 2 different types of treatment:

1. *acute PCP administration;* in order to induce positive-like symptoms of schizophrenia, *i.e.* hyperlocomotion, stereotypies and impaired PPI, animals received a single i.p. injection of PCP (5 ml·kg^{-1}) or saline (Sal, 1 ml) immediately before the beginning of the behavioral tests.
2. *sub-chronic PCP administration;* to produce cognitive-like symptoms, animals were treated with either PCP (5 ml·kg^{-1}) or saline (Sal, 1 ml) twice a day for 7 days, according to a treatment schedule described by (Redrobe et al., 2012). Later, animals were given a 7-day drug-free period followed by behavioral tests (NOR test). This 1-week period of withdrawal ensured that behavior was not influenced by any residual drug effects (Jentsch et al., 1998).

3.4 Behavioral Tests

3.4.1 Social Interaction Test

A plexiglass arena (60 x 60 cm) not familiar to animals was used. The luminance was 30 lux. Within this arena, the experimental animal was introduced together with an unfamiliar conspecific rat of the same sex and of similar weight (± 5 g). Subsequently, their behaviors were observed for 10 minutes by an external monitoring room, using digital video cameras and a specific software (Anymaze Software, Stoelting).

All the activities of exploration (smelling, following, nibbling), ano-genital inspection, mountaineering, and colluding carried out by the animal being studied against the partner were considered active social interactions.

The parameters evaluated were:

- The number of active social interactions
- Social interaction: the time (sec) spent in active interactions.

Between one session and the next, the apparatus was cleaned with H_2O_2, and the sawdust was replaced in order to eliminate any possible olfactory traces.

3.4.2 Elevated plus maze test

The apparatus consists of two closed arms (50 cm x 10 cm) with walls 40 cm-high, and two open arms (50 cm × 10 cm).The arms extend from a common central platform (10 cm × 10 cm) to form a cross-shaped structure (figure 6). The whole apparatus was elevated 50 cm from the floor, and the luminance was 30 lux. The test began with positioning of each animal in the central area of the apparatus, with the head facing an open arm. The animals were left free to explore the apparatus and their behavior was observed for 5 minutes, from an external monitoring room, through digital cameras and specific software (Anymaze Software, Stoelting). The animals were randomized into the experimental groups and individually tested. When 90% of the animal's body cross the edge of the arm (the entrance), we consider

it as an entry to be counted. Between one session and the other, the apparatus was cleaned with H_2O_2 in order to eliminate any possible olfactory traces. The behavioral conventional parameters recorded are:

- time spent in the open and closed arms (sec);
- number of entries into the open and closed arms;
- total number of entries into the 4 arms.

The values obtained were used to measure the following conventional parameters:

- percentage of time spent in open arms ([time spent in the open arms / total duration of time] x 100);
- number of entries in open arms ([number of entries to the open arms / total number of entries] x 100).

For a better evaluation of the anxiolytic / anxiogenic profile of drugs, the ethological parameters were also evaluated:

- Head-dips: exploratory movements carried out with the head in areas outside the open arms;
- Risk-assessment: scouting movements carried out with the head followed by the repositioning of the animal to the original position without crossing any area of the apparatus.

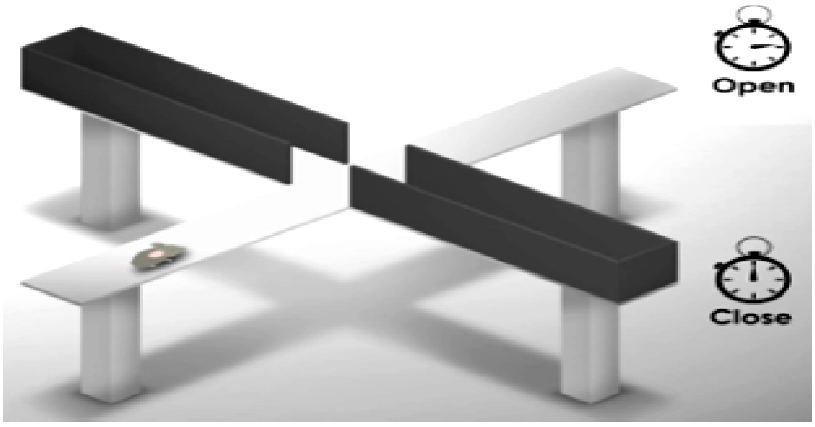


Figure 6: A Schematic representation of an Elevated Plus Maze test

3.4.3 Open Field Test

The Open Field test consists of a 1m x 1m box, separated into 3 zones on the analysis software: the central, peripheral, and corners zone. Illumination intensity is set around 30 lux. The animals were randomized into the experimental groups and individually tested. The test began with positioning of each animal at the center of the arena, and then they are left free to explore the open arena. Their behavior was observed for 10 minutes, from an external monitoring room, through digital cameras and specific software (Anymaze Software, Stoelting). Between one session and the other, the apparatus was cleaned with H_2O_2 in order to eliminate any possible olfactory traces. The behavioral conventional parameters recorded are:

- The number of entries into each of the central, peripheral, and corner zones: with the four paws;
- The duration of time spent in the central, peripheral, and corner zones (sec.);
- Total distance traveled (cm)
- Distance traveled in each of the central and peripheral zones (cm)

The values obtained were used to measure the following parameters:

- ratio of the number of entries into each of the central, peripheral, and corner zones ([number of entries into a specific zone / total number of entries]);
- ratio of time spent in each of the central, peripheral, and corner zones ([time spent in a specific zone / total duration of time]);
- ratio of the distance traveled in each of the central, peripheral, and corner zones ([distance traveled in a specific zone / total distance traveled]).

3.4.4 Spontaneus locomotor activity and stereotyped behaviours

Rats were individually tested for locomotor activity using the Digiscan Animal Activity Analyser (Omnitech Eletronics, USA). Each operant cage (42 x 30 x 60 cm) was fitted with two sets of 16 photocells positioned along the perimeter, which project horizontal infra-red beams spaced 2,5 cm from each other, at 4 cm of height from the cage floor. Further 16 horizontal beams set, adaptable in height depending on size of animals, were allocated above. The test was conducted in a dimly lit room.

Animals were treated with clofibrate or vehicle and habituated for 1 hour to the motility cage. At the end of this period animals were injected with SAL, PCP, or AMPH, and the spontaneous locomotor activity was monitored for further 60 minutes, recording horizontal and vertical activity parameters every 10 min intervals. During the test, stereotyped behaviours were scored by two observers blind to the treatment groups, through the assignment of a numerical value over 15 sec blocks per rat according to the PCP rating scale described by (Sams-Dodd, 1998): (0), Stationary, little or no movement; (1), Active, occasional to frequent movement; (2), Active with episodes of repetitive forward head searching (the rat walked forward in a stereotyped manner along the periphery of the arena without engaging in other behaviors); (3), Continuous forward head searching; (4), Frequent repetitive rearing, side-to side weaving or turning; (5), Episodes of rapid jerky side-to-side, circular or dorsoventral head movements (the rat was usually stationary), or according to the AMPH rating scale described by (Sams-Dodd, 1998): (0), No repetitive head movements; (1), Weak repetitive side-to-side head movements; (2), Strong repetitive side-to-side head movements; (3), Stationary stereotyped behavior with strong side-to-side or circular head movements.

3.4.5 PPI of the acoustic startle reflex

The apparatus utilized for the measurement of the acoustic startle reflex is composed by 4 sound-attenuated and ventilated chambers (Med Associated, VT, USA). Inside each chamber the startle cages are positioned, non-restrictive Plexiglas cylinders (diameter 9 cm), mounted on a piezoelectric accelerometer platform connected to an analog to digital converter. Background noise and acoustic bursts were conveyed through two speakers placed in proximity to the startle cage to produce a maximum variation in sound intensity within 1 dB across it. The experimental protocol utilized for the test was previously described by (Frau et al., 2007). Each rat was placed in the experimental cage for a 5 min acclimatization period with a 70 dB white noise background (continued for the remainder of the session) and was then tested on 3 consecutive trial blocks: the first and the third blocks consisted of 5 pulse-alone trials of 40 ms at 115 dB, while the second block

(test block) was a pseudorandom sequence of 50 trials including 12 pulse-alone trials, 30 pulse trials preceded by 73, 76 or 82 dB prepulses (10 for each level of prepulse loudness), and 8 no-stimulus trials where the only background noise was diffused. The percent (%) PPI was calculated evaluating only the second block values, using the following formula: 100-[(mean startle amplitude for prepulse+pulse trials/mean startle amplitude for pulse-alone trials)×100]. Animals received an injection of clofibrate or vehicle 1 h before the beginning of the test and then were injected with either PCP, AMPH, or saline 10 min prior to being placed into the PPI boxes (Li et al., 2011).

3.4.6 Novel Object Recognition Test (NOR)

Novel object recognition test NOR testing was carried out according to (Ennaceur and Delacour, 1988) with slight modifications.The NOR apparatus consists of open boxes (40, 40, 30 cm). In a dimly illuminated room (50 lux), a camera was attached to frames above the boxes to record the rats' behaviour in each trial. The objects to be discriminated were made of glass, plastic or metal, devoid of any natural significance, and were carefully cleaned with H_2O_2 and water between each trial to avoid olfactory cues. Exploratory behavior was defined as the animal directing its nose toward the object at a distance ≤2 cm and/or touching it with the nose, whereas it was not considered turning around, climbing over or sitting on the object.

-Habituation: Each rat was handled and exposed to the empty NOR arena and testing room for 10 minutes prior to NOR testing. Habituation reduces the level of novelty of the arena itself, therefore increasing focus on the objects during testing.

-Aqcuisition trial: 3 minutes later, each rat was placed into the same box in which two identical objects (F1 and F2, figure 7a) were placed at opposite corners of the arena.The rats were allowed free access to the arena for 10 minutess of exploration.

-Inter-trial interval: Following the 10 minutes acquisition trial, rats were returned to their home cage for 1 hour. The 1 hour inter-trial interval has been shown to be a sufficient for vehicle rats to recall the familiar object, but PCP-treated animals are not able to, based on previous work (Grayson et al., 2007), (Grayson, 2012),

(Neill et al., 2010). During this period, the arena was cleaned with ethanol and water. A triplicate copy of the familiar object (F3) and a novel object (N1) were then placed in the same positions as used in the acquisition trial (figure 7b).

-**Retention trial:** Following the inter-trial interval, rats were then allowed to explore the arena with the novel (N1) and familiar object (F3) for 3 minutes (figure 7b). After the 3 minutes exploration period, rats were returned to their home cage.

The following parameter was examined: total time spent exploring the objects during acquisition and retention phases.

A discrimination index (DI) was calculated for each animal using the formula (N-F)/(N+F) (N=time spent exploring the novel object; F=time spent exploring the familiar one). Rats were PCP sub-chronically treated and on the test day received an injection of clofibrate or vehicle 1 h before the habituation session.

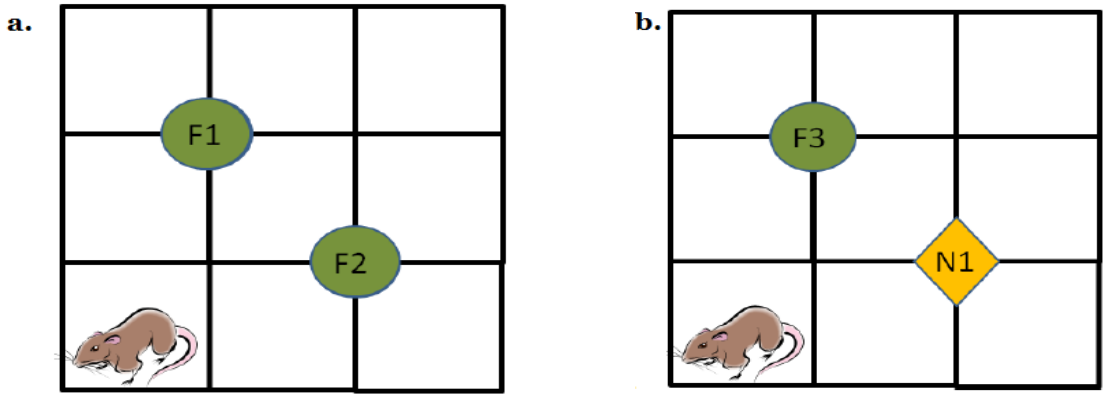


Figure 7: A schematic representation showing the positions of the identical objects during the acquisition (a) and the novel and familiar objects during the retention (b) trial of the NOR test (internet).

3.4.7 Bar test for catalepsy

Catalepsy was measured by means of the bar test (Costall and Olley, 1971). A horizontal metal bar (1 cm) was fixed at 9 cm in height from the working surface. Rats were tested individually, and placed with both forelegs over the metal bar. The descent latency (length of time it retained this position) was recorded for a period of up to 5 min (figure 8). The experiment was conducted in a dimly illuminated room. Animals were tested 60 min after drug administration. Clofibrate (100, 250 e 500 $mg \cdot kg^{-1}$) and vehicle treatments were alternated as well as the sequence of bar tests. Haloperidol (1 $mg \cdot kg^{-1}$) was chosen as reference drug for catalepsy effects. Descent latencies of all animals were averaged for each drug dose and statistically analyzed.

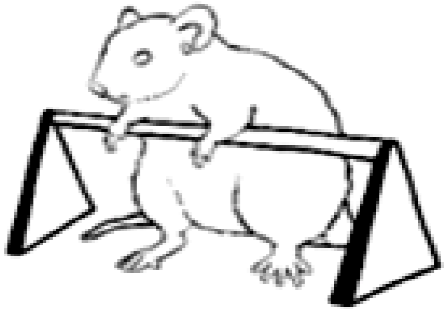


Figure 8: A schematic representation of the bar catalepsy test (internet)

3.5 Sacrifice and collection of brain areas

For neurochemical studies, rats were sacrificed by decapitation. After decapitation, brains were removed carefully from the skull in preparation for dissection. Brain areas of interest were dissected and then immediately frozen by contact with dry ice, and stored at -80° C until the determination of dopamine DA, serotonin 5-HT, as well as their metabolites levels by HPLC. The brain areas collected are the prefrontal cortex, the nucleus accumbens, the dorsal striatum (caudate and putamen), the amygdala, the hippocampus, and the hypothalamus.

3.6 Neurochemical Determination of Dopamine, serotonin and their metabolites

Tissue samples were weighted and homogenized in ice-cold 0.1 M perchloric acid (1:20 weight tissue per solvent volume). After centrifugation (23,000g, 30 min), the supernatants were filtered by 0.22 µm Spin-X Centrifuge Tube Filter (Costar, Corning Incorporated, Corning, NY), and 20µl injected into a High Performed Liquid Cromatography (HPLC) system provided with a C18 column (150 x 4,6 mm, Hichrom, Hichrom Limited, Reading, UK) and Coulochem III detector (ESA Inc., Chelmsford, MA, USA). The mobile phase consisted of 50 mM sodium acetate buffer (pH 4.2), supplemented with 0.07 mM EDTA, 0.35 mM sodium octyl sulfonate, and 10 % methanol. The column temperature was set at 26 °C and the flow rate maintained constant at 1 mL/min. Dopamine (DA), its metabolites [3,4-dihydroxyphenylacetic acid (DOPAC), homovallinic acid (HVA)], serotonin (5-HT), and its metabolite [5-Hydroxyindoleacetic acid (5-HIAA)] were quantified by peak area comparisons with standards, which were processed at the same day of analysis. Data were collected and analyzed using the EZchrom SI 3.2 software. The values obtained were expressed as ng neurotransmitter/mg tissue.

3.7 Statistical analysis

The data represented in this study are expressed as MEAN ± SEM.

The data obtained from the “open field test”, “social interaction test” and "elevated plus maze test” were analyzed using unpaired Student’s t test for the evaluation of the differences between groups.

The analysis of the data related to the locomotor activity tests was carried out by two-way ANOVA (study of the Treatment x Time interaction). In the case of statistical significance, the Turkey’s and Newman Keul’s posthoc test for multiple comparisons was applied. Also the data concerning stereotypy tests were analyzed by two-way ANOVA (phencyclidine/amphetamine x clofibrate interaction interaction), followed by Benferroni and Turkey’s posthoc test. Pre-pulse inhibition and acoustic

strtle test were analyzed as well by two-way Anova (Treatment x Pre-pulse intensity interaction and phencyclidine/amphetamine x clofibrate interaction respectively), and by Turkey's pothoc test. However, regarding the NOR test, the data obtained from acquisition and retention phases were analyzed using unpaired Student's t test, while the discrimination index was analyzed by two-way ANOVA (phencyclidine x clofibrate interaction), followed by Turkey's posthoc test.

For the neurochemical analysis, the obtained data were analyzed using unpaired Student's.

Statistical significance was set to $P < 0.05$. The analyses were conducted with using GraphPad Prism versions 5 and 6.

4. Chapter IV: Results

4.1 Evaluation of the acute treatment with the PPAR-α agonists, clofibrate, in social interaction test

The graphs shown in Figure 9 represent the effect of acute treatment with clofibrate (25mg/kg) on animals' behavior during the social interaction test. As can be seen from the graphs of Figure 12a and 12b, an anxiogenic effect was revealed, observable as a reduction in the number of social interactions (*P<0.05 25 mg/kg clofibrate vs. vehicle; student's t test) and time spent in social interaction among animals in the study (*P<0.05 25 mg/kg clofibrate vs. vehicle; student's t test).

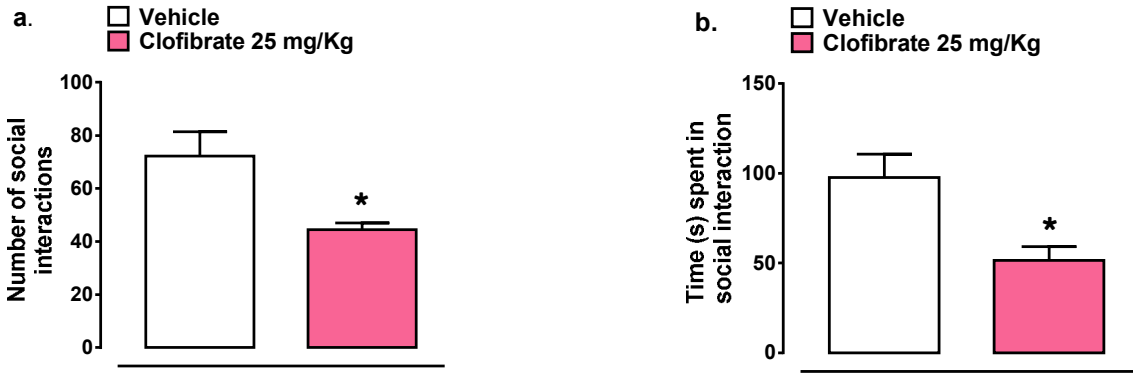


Figure 9: The effect of acute clofibrate treatment (25 mg/kg) in the social interaction test. The values are expressed as mean ± SEM (n = 6 animals per group). **(a) Number of social interaction contacts. (b) Time spent in social interaction.** *P <0.05 clofibrate (25 mg/kg) vs. vehicle; student's t-test.

4.2 *Evaluation of the acute treatment with the PPAR-α agonists, clofibrate, in the elevated plus maze test*

The graphs of figure 10 present the effects of the acute treatment with the synthetic PPAR-α agonist, clofibrate (25mg/kg), on the behavior of rats in the "Elevated Plus Maze" test for assessing the state of anxiety of animals. As we can observe from the graphs, the treatment with clofibrate, at the doses used did not induce anxiogenic nor anxiolytic effects. In fact it didn't modify the parameters considered; both the classic (% number of entries into the open arms, % time spent in the open arms and number of entries into the closed arms) and the ethological parameters (head-dipping, risk-assessment), compared to the control group treated with the vehicle alone.

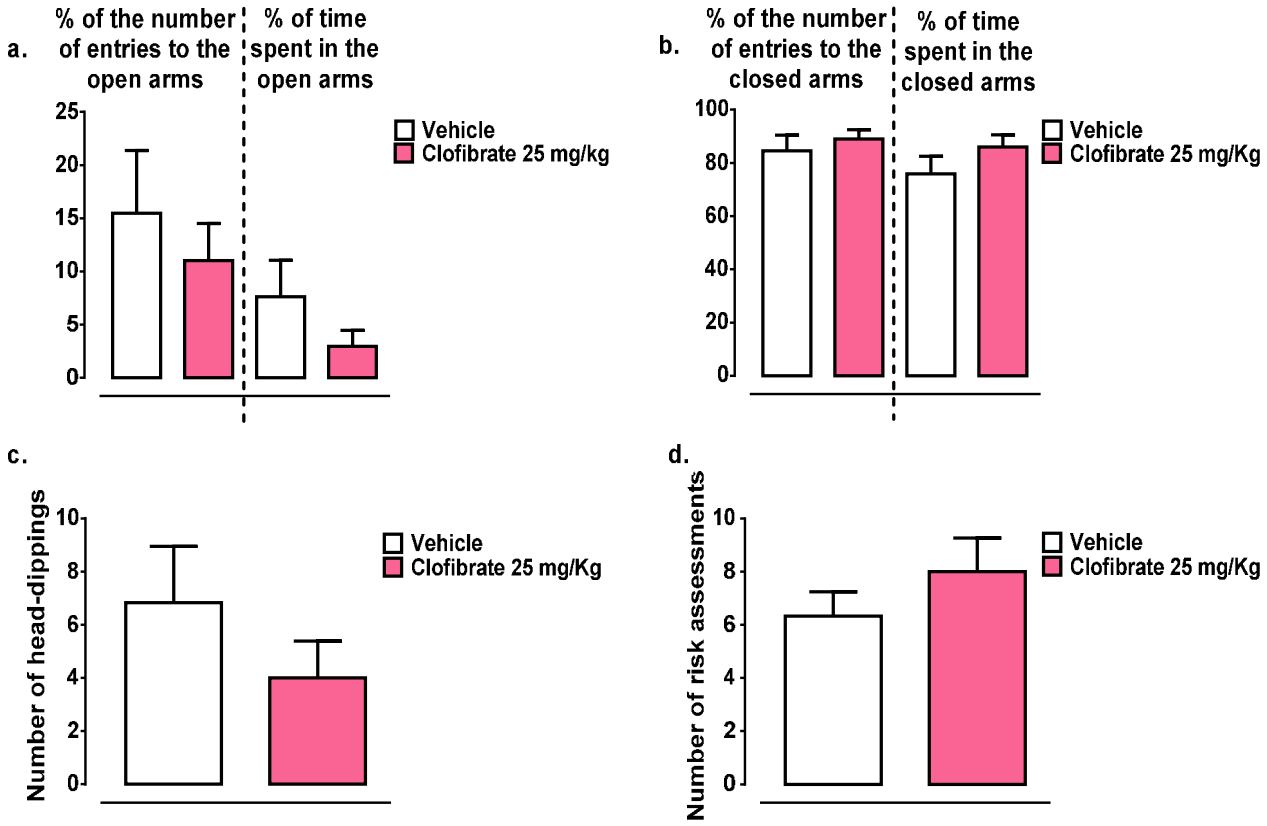


Figure 10: The effect of acute clofibate treatment (25 mg/kg) on the elevated plus maze test. Values are expressed as MEAN ± SEM (n = 6 animals/group). **(a) Percentage (%) of the number of entries and time spent in the open arms. (b) % Number of entries and time spent in the open arms. (c) Number of head-dippings. (d) Number of risk assessments**; Student's t-test.

4.3 Evaluation of the acute treatment with the PPAR-α agonist, clofibrate, in the open field test

The graphs of figure 11 represent the effects of the acute treatment with the PPAR-α agonist, clofibrate (25 mg/kg), on the behavior of rats in the "open field test" for assessing the state of anxiety in animals. As we can notice from the graphs, acute clofibrate treatment, at the dose used, demonstrated an anxiogenic effect in rats, revealed as a statistically significant decrease in the number of entries ratios to the center zones (fig.11a), and increase to the corners zone (fig.11b) compared to vehicle-treated rats (*P<0.05 25 mg/kg clofibrate vs. vehicle; student's t test). Clofibrate reduced as well the ratios of time spent and distance traveled in the center of the testing arena (fig.11 c and e) (**P<0.01 25 mg/kg clofibrate vs. vehicle; student's t test), while increased the ratio of time spent in the corners (fig.11 d) relative to controls (**P<0.01 25 mg/kg clofibrate vs. vehicle; student's t test).

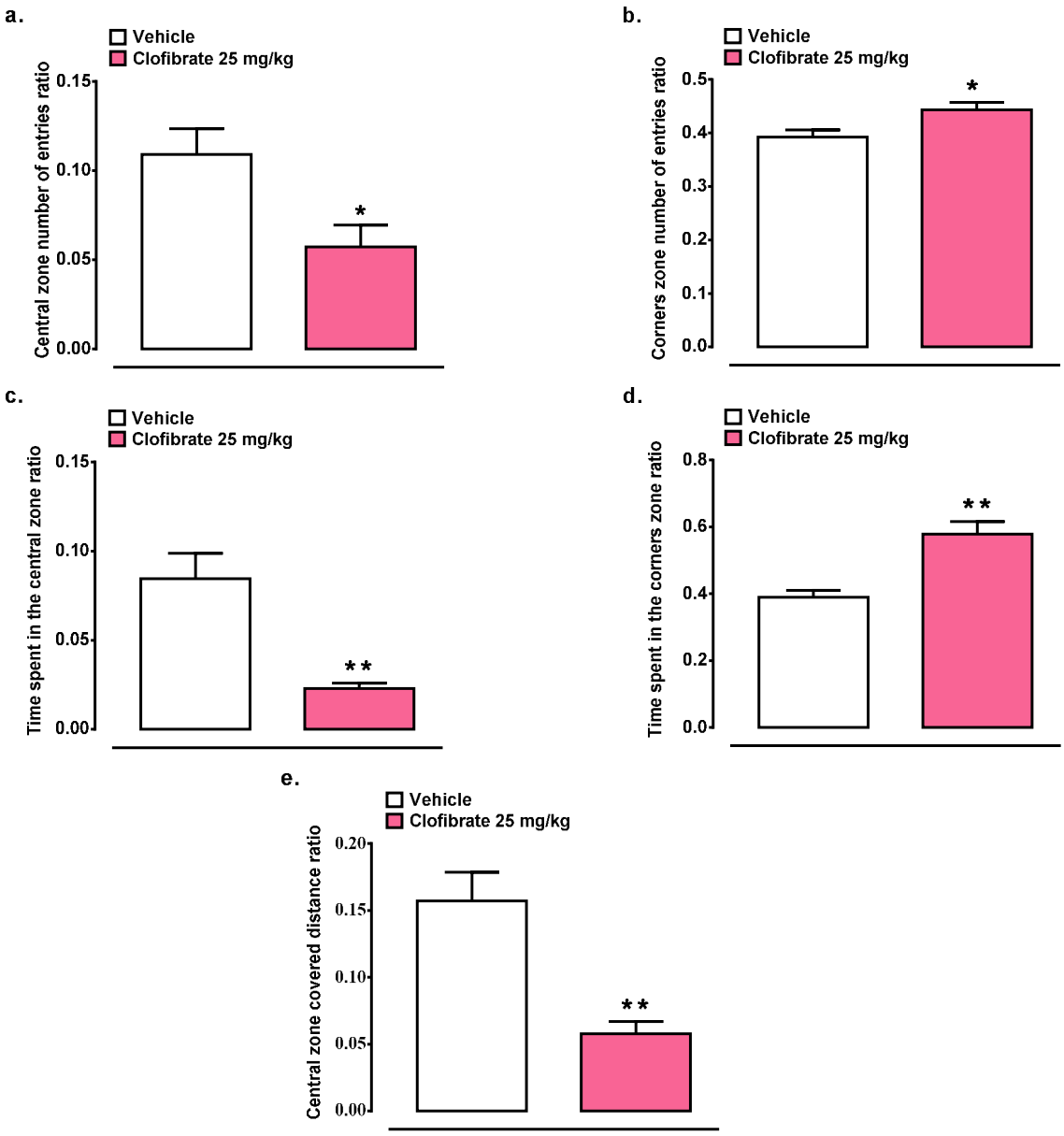


Figure 11: The effect of acute clofibrate treatment (25 mg/kg) on the open field test exploratory behavior. The values are expressed as MEAN ± SEM (n=4-6 animals per group). (**a) Ratio of the number of entries to the central zone**: * P < 0.05 compared with the vehicle control group; unpaired t test. **(b) Ratio of the number of entries to the corners zone**: * P < 0.05 compared with the vehicle control group; unpaired t test. (**c) Ratio of time spent in the central zone:** ** P < 0.01 compared with the vehicle control group; unpaired t test. **(d) Ratio of time spent in the corners**: ** P < 0.01 compared with the vehicle control group; unpaired t test, and (**e) Ratio of distance covered in the central zone**: ** P < 0.01 compared with the vehicle control group; student's t-test.

4.4 Evaluation of the sub-acute treatment of PPAR-α agonist, clofibrate, in the open field test

In the open field test, however, sub-acute administrations of clofibrate (25 mg/kg) neither produced anxiogenic nor anxiolytic effects (graphs of figure 12). In fact, clofibrate treatment didn't demonstrate statistically significant effects on any of the parameters considered: number of entries and time spent ratios in the center and corners zones, as well as the distance traveled in the central zone, compared to vehicle-treated rats.

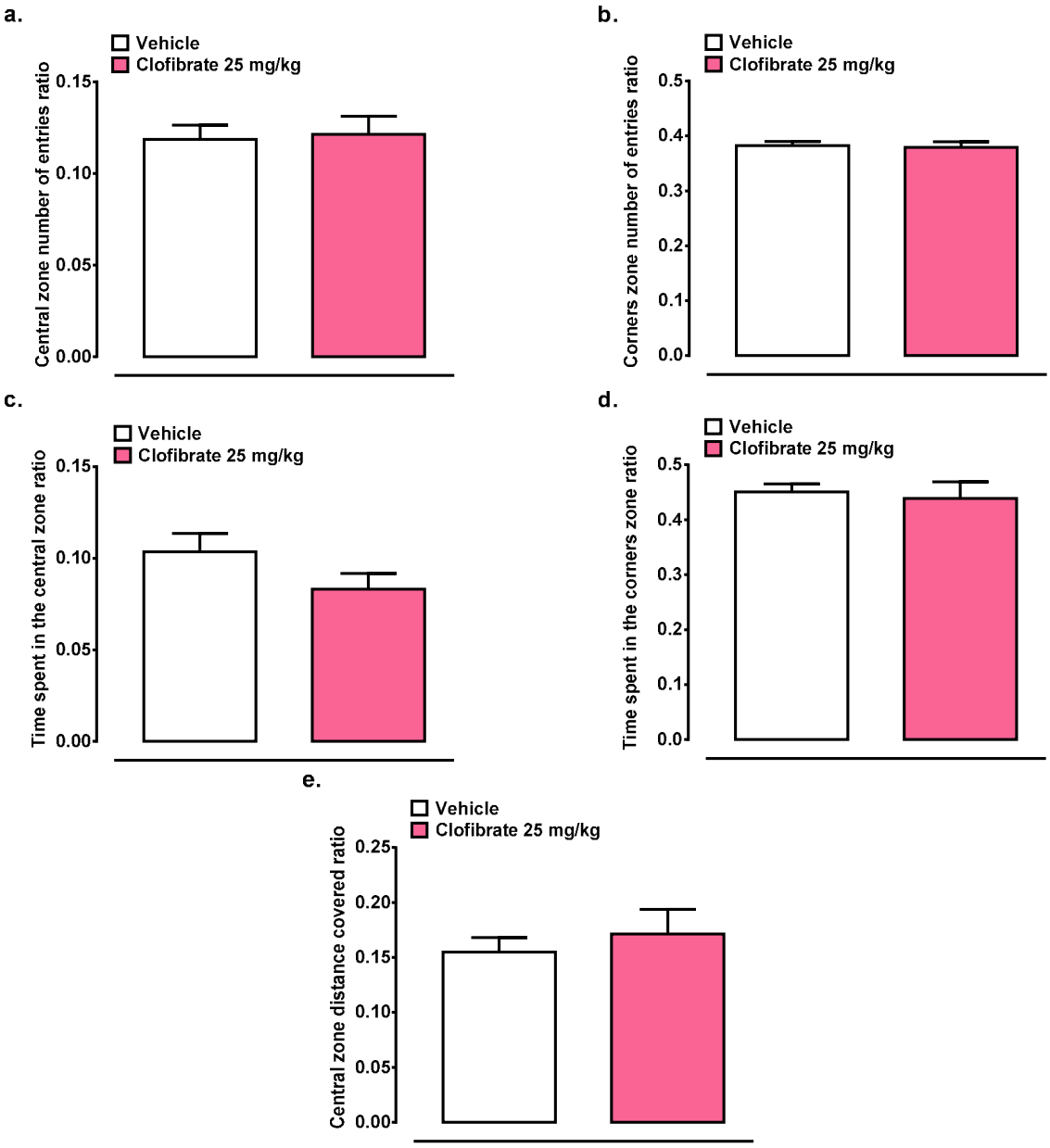


Figure 12: The effect of sub-acute administrations of clofibrate treatment (25 mg/kg) on the open field test exploratory behavior. The values are expressed as MEAN ± SEM (n=8 animals per group). **(a) The ratio of the number of entries to the central zone** and **(b) the corners zone, (c) time spent in the central zone** and **(d) corners,** and **(e)distance covered in the central zone;** student's t-test

4.5 Evaluation of the chronic treatment of PPAR-α agonist, clofibrate, in the open field test

The graphs of figure 13 show the effect of chronic treatment with the synthetic PPAR-α agonist clofibrate (25 mg/kg) on the behavior of rats in the open field test. As shown in the graphs, clofibrate chronic treatment induced an anxiolytic effect in rats, manifested in the central arena as a significant increase in the ratios of number of entries (fig.13a) (**P<0.01 25 mg/kg clofibrate vs. vehicle; student's t test), time spent (fig.13c) (***P<0.001 25 mg/kg clofibrate vs. vehicle; student's t test) and distance travelled in it (fig.13e) (**P<0.01 25 mg/kg clofibrate vs. vehicle; student's t test), accompanied with a significant reduction in the ratios of the number of entries (**P<0.01 25 mg/kg clofibrate vs. vehicle; student's t test) and time spent (*P<0.05 25 mg/kg clofibrate vs. vehicle; student's t test) in the corners (fig.13b and d) relative to the control rats.

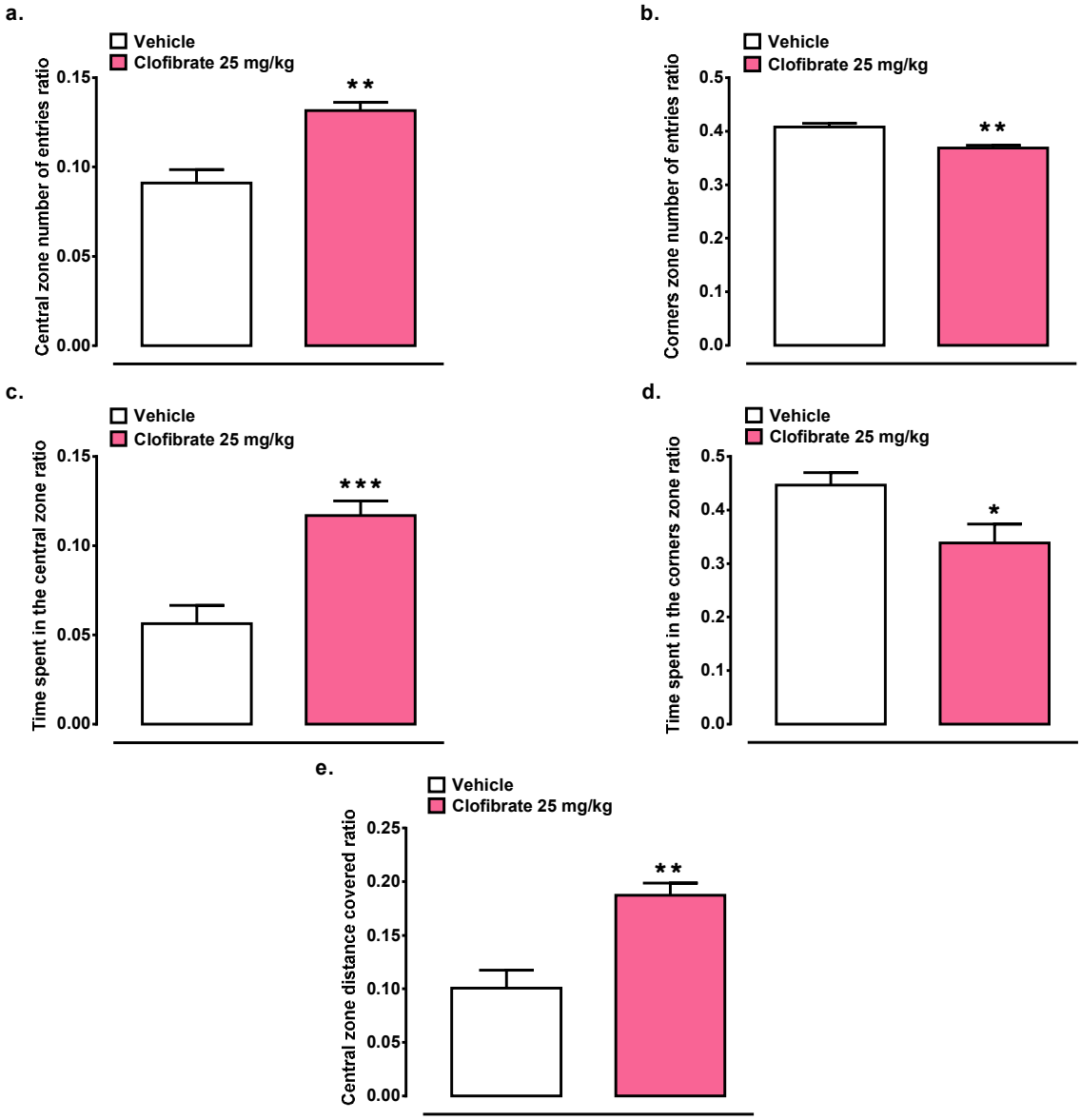


Figure 13: The effect of chronic clofibrate treatment (25 mg/kg) on the open field test exploratory behavior. The values are expressed as MEAN ± SEM (n= 8 animals per group). **(a) The ratio of the number of entries to the central zone:** **p<0.01 compared with the vehicle control group; unpaired t test. **(b) The ratio of the number of entries to the corners zone:** **p<0.01 compared with the vehicle control group; unpaired t test. **(c)Ratio of the time spent in the central zone**: ***p<0.001 compared with the vehicle control group; unpaired t test**. (d) Ratio of time spent in corners:** *p<0.05 compared with the vehicle control group; unpaired t test. **(e) Ratio of distance covered in the central zone:** **p<0.01 compared with the vehicle control group; student's t-test.

4.6 *Effect of PPAR-α agonist, clofibrate, administration on the two schizophrenic animal models: Phencyclidine and Amphetamine models.*

We examined the effect of acute clofibrate administration (25 mg/kg, i.p.) on PCP-induced schizophrenia-like symptoms in rats. Two different paradigms of PCP administration were chosen (Sections 4.6.1): acute PCP to mimic the positive-like signs of schizophrenia and sub-chronic PCP treatment to produce the apparent cognitive deficits.

Then, we examined the effect of acute clofibrate (25 mg/kg, i.p) on amphetamine-induced behavioral alterations. Amphetamine was administered also acutely to induce the positive-like symptoms of schizophrenia (Section 4.6.2).

4.6.1 Effect of clofibrate, PPAR-α agonist, treatment in Phencyclidine animal model

4.6.1.1 Effect of clofibrate, PPAR-α agonist, treatment in rats acutely treated with phencyclidine PCP in locomotor activity test

Figure 14 shows the analysis of locomotor activity reported by the animals after acute administration of the PPAR-α synthetic agonist, clofibrate (25 mg/kg) 1 hour before the test, and acute administration phencyclidine (5 mg/kg) immediately before the beginning of the same test.

Regarding the horizontal activity of rats, evaluated for a total period of 60 minutes, we observe that the activity of clofibrate treated animals did not differ compared to the control, which is consistent with our previous laboratory studies which showed that neither acute nor chronic treatment of clofibrate (25 mg/kg) affect the locomotor activity (figure 14a). However, phencyclidine administration led to an increase in this parameter compared to vehicle treatment [Total distance; Two-way ANOVA: PCP ($F_{1,20}$ = 17.02; ***P=0.0005); clofibrate ($F_{1,20}$ = 0.0007; P = 0.979, PCP x clofibrate interaction ($F_{1,20}$ = 0.6049; P =0.4458); and the horizontal activity following combined treatment of PCP and 25 mg/kg of clofibrate was similar to the PCP-treated animal, demonstrating no effect of clofibrate on PCP-induced hyperlocomotion.

From the analysis of the temporal curve (values of distance travelled at intervals of 10 minutes for a total period of 60 minutes), shown in figure 14b, it has been revealed that the increase of locomotor activity for PCP-treated rats, is significantly point by point starting from the first 10 minutes till the last 50 minutes of the test [Horizontal activity; two-way ANOVA: treatment ($F_{3,21}$ = 6.593; **P =0.0026); Time ($F_{5,105}$ = 6.888; ****P< 0.0001); Treatment x Time interaction ($F_{15, 105}$ = 0.9608; P = 0.5013)], meanwhile combined treatment of PCP and clofibrate (25 mg/kg) did not show a significant effect on the PCP-induced locomotor changes at any point of the test.

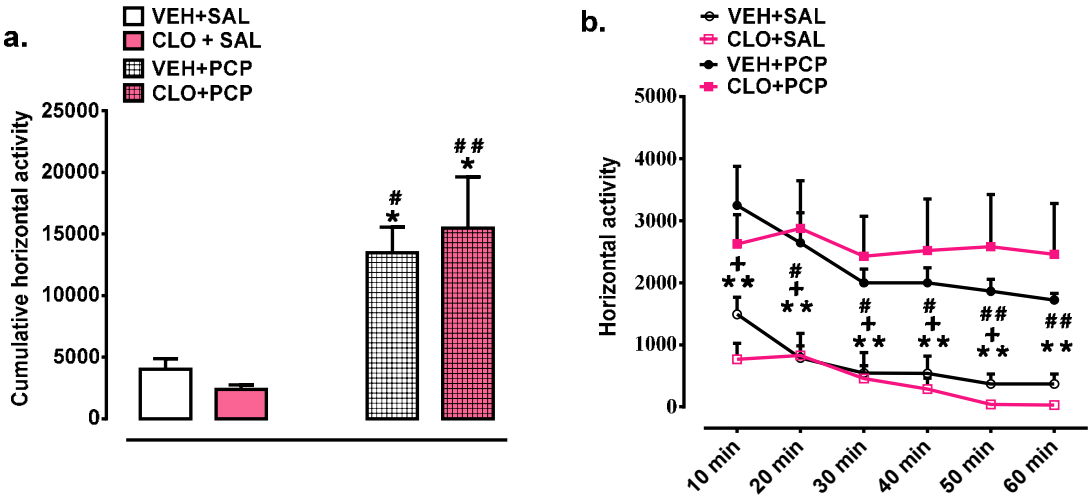


Figure 14: Effect of administration of synthetic PPAR-α agonist, clofibrate (25 mg/kg), and phencyclidine (5 mg/kg) on the horizontal activity in the motor activity test. The graphs represent the effects of clofibrate, phencyclidine, and clofibrate + phencyclidine on the horizontal activity in the locomotor activity test in rats. The values are expressed as mean ± SEM (n = 6/7 animals per group). **(a): cumulative horizontal activity.** *P <0.05 vehicle +PCP and clofibrate + PCP vs. vehicle + saline; #P <0.05; ##P <0.01 vehicle +PCP and clofibrate + PCP vs. clofibrate + saline; Newman Keul's post hoc test. **(b): horizontal activity temporal curve.** +P <0.05 vehicle + PCP vs. vehicle + saline; #P <0.05; ##P <0.001 clofibrate + PCP vs. vehicle + saline; ** P <0.01 clofibrate + PCP vs. clofibrate + saline; Newman Keul's post hoc test.

4.6.1.2 *Effect of clofibrate, PPAR-α agonist, administration in rats acutely treated with phencyclidine PCP in the stereotypy test*

A common phenotype of rat models of schizophrenia is enhanced activity when subjected to a novel open environment. Hyperactivity can be measured by assessing stereotyped behaviors also, which are repetitive and purposeless movements, and this behavior is elevated in people with schizophrenia (Hill, 1974), (Randrup and Munkvad, 1974). We subjected both clofibrate and vehicle-treated rat groups to an open field chamber and recorded stereotyped movements (figure 15). Low doses of NMDA receptor antagonists induce hyperactivity in humans and rodents. Therefore, we tested the effect of PCP administration on stereotyped behaviors in clofibrate rats. As expected, PCP-treated rats exhibited a robust increase in stereotypies relative to controls , as supported by the main effect of PCP treatment [Two-way Anova: PCP ($F_{(1, 17)}$ = 123.7, ****p < 0.0001); Clofibrate ($F_{(1, 17)}$ = 0.507, p =0.486); PCP x clofibrate interaction ($F_{(1,17)}$ = 0.867, p =0.364)], while clofibrate didn't demonstrate any significant stereotypy effect relative to vehicle rats. In particular, Bonferroni's post-hoc test reports a statistically significant effect on PCP ****P <0.0001 PCP+ vehicle and PCP + clofibrate vs. saline + vehicle and saline + clofibrate.

However, clofibrate rats injected with PCP had similar levels of activity compared to PCP-treated rats. Taken together, these data indicate that clofibrate does not affect the PCP-induced stereotyped behavior in rats.

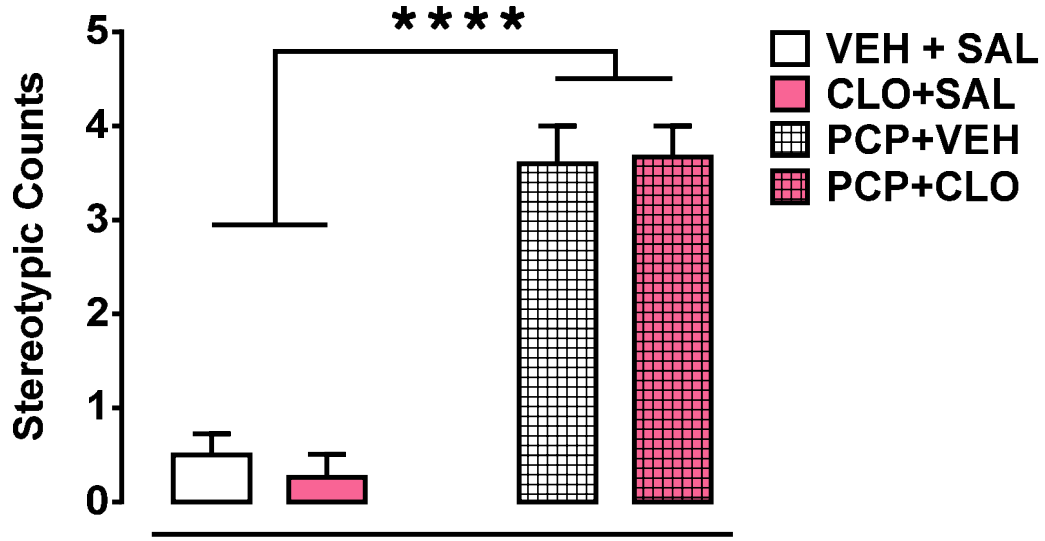


Figure 15: Effect of administration of PPAR-α agonist, clofibrate (25 mg/kg), and phencyclidine (5 mglkg) on the stereotyped behaviors. The graphs represent a comparison of stereotypic counts between clofibrate and vehicle rats pretreated with phencyclidine or saline groups on the stereotypic coounts in rats. The values are expressed as mean ± SEM (n = 4/7 animals per group). ****P <0.0001 PCP vs. saline; Bonferroni's post hoc test.

4.6.1.3 *Effect of clofibrate, PPAR-α agonist, administration in rats acutely treated with phencyclidine PCP in the pre-pulse inhibition PPI test*

Using two-way Anova, we identified a significant effect of treatment, but no interaction between treatment and pre-pulse intensity. [Two-way ANOVA: treatment ($F_{3,57}$ = 39.28; P < 0.0001); pre-pulse intensity ($F_{2,57}$ = 0.6179; P = 0.5427); Treatment x Pre-pulse intensity interaction ($F_{6,57}$ = 0.1793; P = 0.9814)]. Post-hoc analysis revealed a significant reduction in PPI following PCP treatment for each tested pre-pulse intensity compared to vehicle (74 dB: 21.733 ± 10.125%, ***p<0.001; 78 dB: 17.351 ± 10.56%, ***p<0.001; 86 dB: 23.108 ± 16.617%, ***p<0.001) (figure 16a).Clofibrate treatment at 25 mg/kg had no effect on pre-pulse inhibition PPI compared to vehicle. In addition, PPI following combined treatment of PCP with 25 mg/kg clofibrate did not differ significantly for any pre-pulse intensity to PCP-only treatment.

Analysis of the effect of clofibrate on startle amplitude revealed no main effects of clofibrate treatment and no interactions with PCP [Two-way ANOVA: PCP ($F_{1,19}$ = 7.33; *P=0.014); clofibrate ($F_{1,19}$ = 0.8494; P = 0.3683, PCP x clofibrate interaction ($F_{1,19}$ = 9.275 x 10^{-5}; P = 0.9924)] (figure 16b).

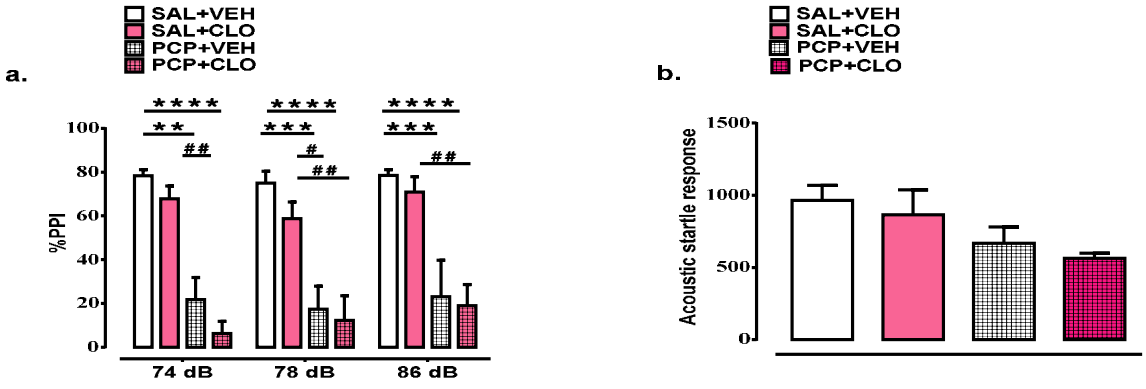


Figure 16: Effect of administration of PPAR-α agonist, clofibrate (25 mg/kg), and phencyclidine (5 mg/kg) on the pre-pulse inhibition intensity PPI (%) and startle amplitude (arbitrary units). The graphs represent the effects of clofibrate, phencyclidine, and clofibrate + phencyclidine on the PPI and startle amplitude response in rats. The values are expressed as mean ± SEM (n = 5/7 animals per group). (a): **pre-pulse inhibition intensity PPI (%).** *** P <0.001 vs. saline + vehicle; **** P <0.0001 vs. saline + vehicle; # P <0.05 vs. PCP + vehicle; ## P <0.01 vs. PCP + vehicle; Turkey's post hoc test. (b): **acoustic startle response (a.u).**

4.6.1.4 *Effect of clofibrate, PPAR-α agonist, administration in rats sub-cronically treated with phencyclidine PCP in novel object recognition NOR test*

Figure 17 depicts the effect of clofibrate on the cognitive impairment induced by sub-chronic PCP pretreatment in the novel object recognition NOR test. Unpaired student t-test statistical analysis revealed that administration of clofibrate (25 mg/kg), PCP (10 mg/kg) or clofibrate (25 mg/kg) + PCP (10 mg/kg) had no significant effect on object exploration in the acquisition trial of the NOR test ($F_{3,3}$= 1.363, NS; Figure 17a). Rats from all of the treatment groups spent similar times exploring both of the right and left objects.

In the retention phase, saline-groups rats treated with vehicle or clofibrate spent significantly (vehicle: **p< 0.01 novel object vs. familiar object; clofibrate: *p< 0.05 novel object vs. familiar object) longer time exploring the novel object compared with the familiar object (figure 17b). The ability to discriminate familiar and novel objects was abolished following sub-chronic PCP treatment, whereby there was no significant difference in exploration of the novel and familiar object. Acute treatment with clofibrate significantly attenuated the sub-chronic PCP induced impairment such that a significant increase in time spent exploring the novel compared with the familiar object was again observed (**p< 0.01 novel object vs. familiar object). In addition, sub-chronic PCP significantly impaired recognition memory, as indicated by a significant reduction in the discrimination index of more than 50% compared with controls [Two-way ANOVA: PCP ($F_{1,13}$ = 7.897; *P=0.0147); clofibrate ($F_{1,13}$ = 5.891; *P = 0.0305, PCP x clofibrate interaction ($F_{1,13}$ = 3.472; P = 0.0852)]. Post-hoc test revealed that clofibrate administration reversed the sub-chronic PCP-induced reduction in discrimination index (*p< 0.05 PCP + vehicle vs. vehicle + saline; *p< 0.05 clofibrate + PCP vs. PCP + vehicle). (Figure 17c)

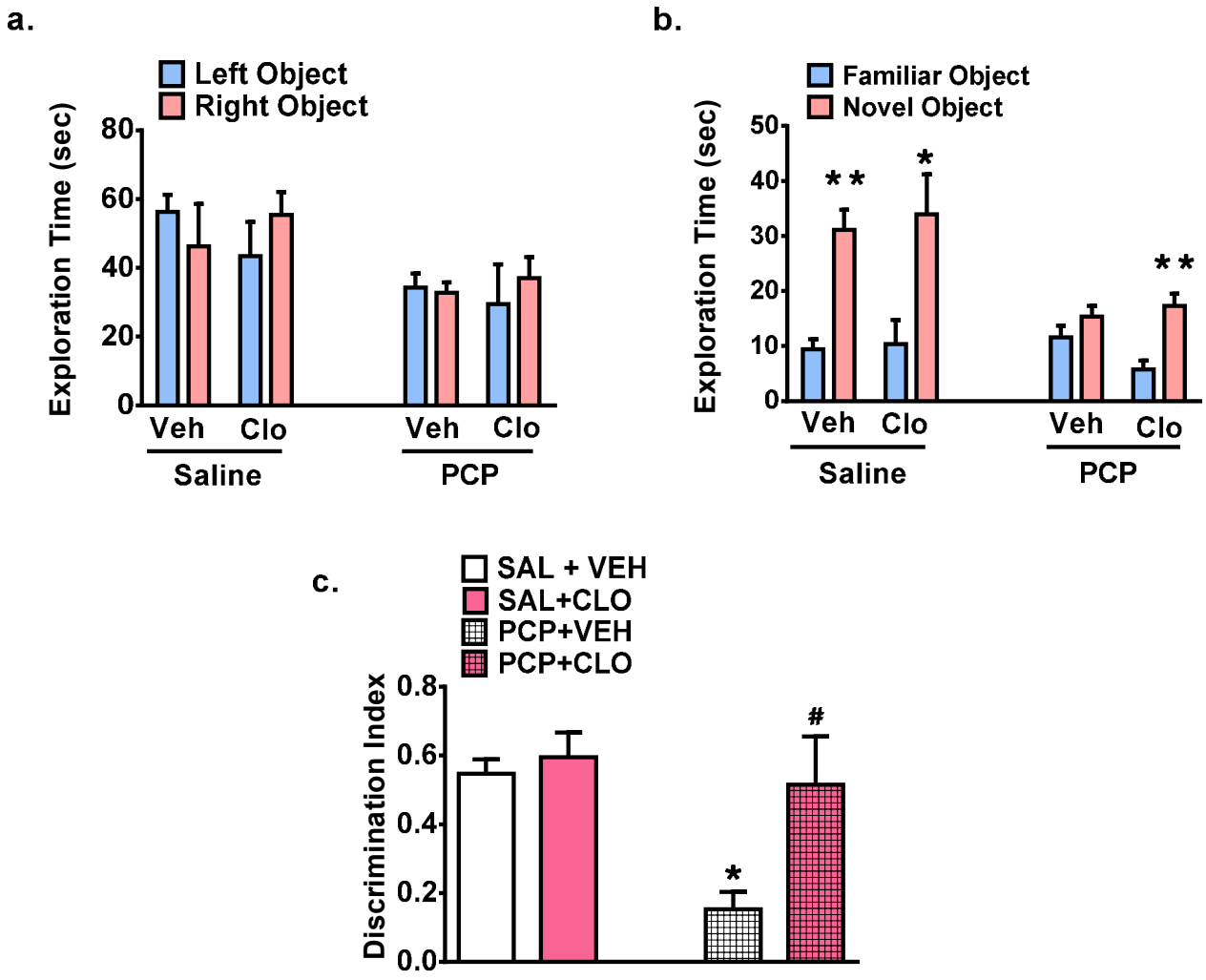


Figure 17: Effect of administration of PPAR-α agonist, clofibrate (25 mg/kg), and phencyclidine-induced cognitive dificits in the novel object recognition (NOR) test. The graphs represent the effects of saline, clofibrate, phencyclidine, and clofibrate + phencyclidine on the exploration time and discrimination index in rats. The values are expressed as mean ± SEM (n = 5 animals per group). **(a): Left object vs. right object acquisition trial**; Unpaired student t test for each experimental group**. (b): Familiar object vs. novel object retention phase.** *P <0,05 novel object vs respective familiar object, ** P<0,01 novel object vs respective familiar object; Unpaired student t test for each experimental group. **(c): Discrimination index.** *P<0,05 PCP + veh vs. SAL + VEH, #P < 0.05 CLO + PCP vs. PCP + VEH, Turkey's pot-hoc test.

4.6.2 Effect of clofibrate, PPAR-α agonist, treatment in Amphetamine animal model

4.6.2.1 Effect of clofibrate, PPAR-α agonist, administration in rats acutely treated with amphetamine Amph in locomotor activity test

In figures 18, 19, and 20, it is shown the analysis of locomotor activity reported by the animals after acute administration of the PPAR-α synthetic agonist, clofibrate (25 mg/kg) 1 hour before the test, and acute administration of amphetamine (3 mg/kg) immediately before the beginning of the same test.

Regarding the total distance, horizontal and vertical activities, evaluated for a total period of 60 minutes, we observed that the activities of clofibrate treated animals did not differ compared to the control, which is consistent with our previous results (figures 18a, 19a, and 20a). However, amphetamine administration led to an increase in all studied parameters compared to vehicle treatment [Total distance; Two-way ANOVA: Amph ($F_{1,20}$ = 15.52; ***P=0.0008); clofibrate ($F_{1,20}$ = 0.0643; P = 0.802), Amph x clofibrate interaction ($F_{1,20}$ = 0.03414; P =0.8553); Horizontal activity; Two-way ANOVA: Amph ($F_{1,20}$ = 35.86; ****P<0.0001); clofibrate ($F_{1,20}$ = 0.1121; P = 0.07413, Amph x clofibrate interaction ($F_{1,20}$ = 0.067; P =0.7979) ; Vertical activity: Two-way ANOVA: Amph ($F_{1,20}$ = 47.13; ****P<0.0001); clofibrate ($F_{1,20}$ = 0.1144; P = 0.7387, Amph x clofibrate interaction ($F_{1,20}$ = 0.1496; P =0.7030)], and the locomotor activity following combined treatment of amphetamine and 25 mg/kg of clofibrate was similar to that of amphetamine-treated animals, demonstrating no effect of clofibrate on amphetamine-induced hyperlocomotion.

From the analysis of the temporal curve (values of motor activity collected at intervals of 10 minutes for a total period of 60 minutes), shown in figures 18b, 19b,and 20b, it has been revealed that the increase of total distance travelled, horizontal and vertical activities for amphetamine-treated rats, is significantly point by point starting from the first 10 minutes till the end of the test [Total distance;

Two-way ANOVA: [treatment ($F_{3,15}$ = 7.973; **P=0.0021); time ($F_{5,25}$ = 2.019; P = 0.1106, treatment x time interaction ($F_{15,75}$ = 1.049; P =0.4175)]; Horizontal activity; two-way ANOVA: [treatment ($F_{3,20}$ = 12.01; ****P =0.0001); Time ($F_{5,100}$ = 1.61; P =0.1649); Treatment x Time interaction ($F_{15,\ 100}$ = 0.95; P = 0.5169)], Vertical activity; two-way ANOVA: [treatment ($F_{3,18}$ = 44.8; ****P <0.0001); time ($F_{5,90}$ = 18.68; ****P <0.0001); Treatment x Time interaction ($F_{15,90}$ = 8.79;****P <0.0001)], meanwhile combined treatment of amphetamine and clofibrate (25 mg/kg) did not show a significant effect on the amphetamine-induced locomotor changes at any point of the test.

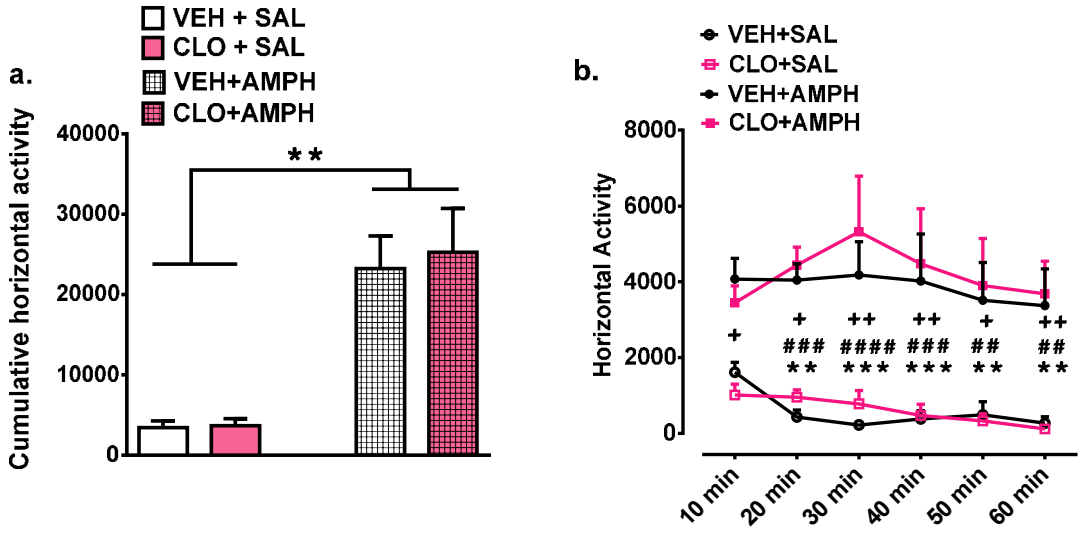


Figure 18: Effect of administration of PPAR-α agonist, clofibrate (25 mg/kg), and amphetamine (3 mg/kg) on the horizontal activity in the motor activity test. The graphs represent the effects of clofibrate, amphetamine, and clofibrate + amphetamine on the horizontal activity in the locomotor activity test in rats. The values are expressed as mean ± SEM (n = 6 animals per group). (a): **cumulative horizontal activity.** **P <0.01 amph vs. saline; Turkey's post hoc test. **(b): horizontal activity temporal curve**. $^{+}$P <0.05; $^{++}$P <0.01 vehicle + amph vs. vehicle + saline; $^{\#\#}$P <0.01; $^{\#\#\#}$P <0.001; $^{\#\#\#\#}$P <0.0001 clofibrate + amph vs. vehicle + saline; ** P <0.01; *** P <0.001 clofibrate + amph vs. clofibrate + saline; Turkey's post hoc test.

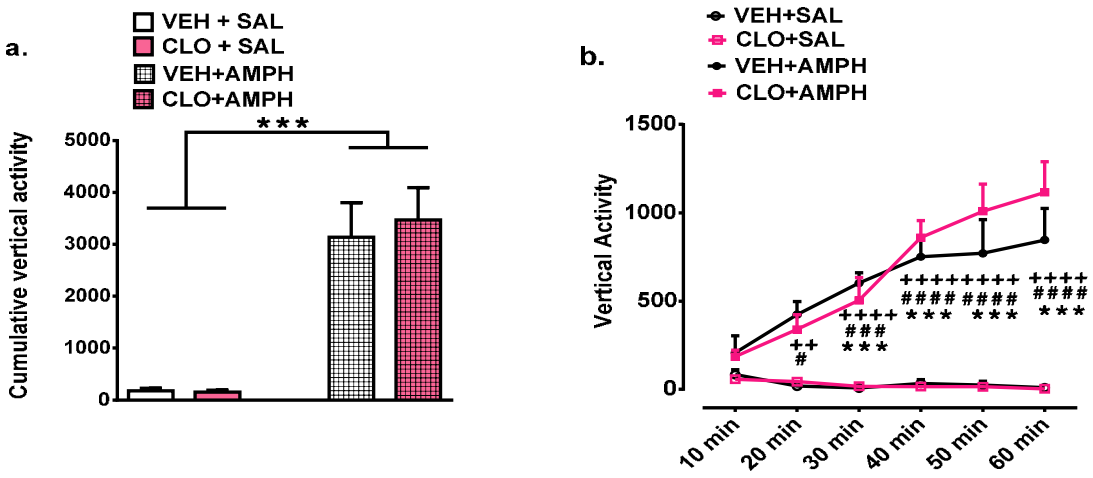


Figure 19: Effect of administration of PPAR-α agonist, clofibrate (25 mg/kg), and amphetamine (3 mg/kg) on the vertical activity in the motor activity test. The graphs represent the effects of clofibrate, amphetamine, and clofibrate + amphetamine on the vertical activity in the locomotor activity test in rats. The values are expressed as mean ± SEM (n = 6 animals per group). **(a): cumulative vertical activity.** **P<0.01 vehicle+saline vs. vehicle+amph and clofibrate+ amph; ##P<0.01 clofibrate +saline vs. vehicle+amph and clofibrate+amph; Turkey's post hoc test. **(b): vertical activity temporal curve.** ++P <0.01; ++++P <0.01 vehicle + amph vs. vehicle + saline; #P <0.05; ###P <0.001; ####P <0.0001 clofibrate + amph vs. vehicle + saline; ***P <0.001; **** P <0.0001 clofibrate + amph vs. clofibrate + saline; Turkey's post hoc test.

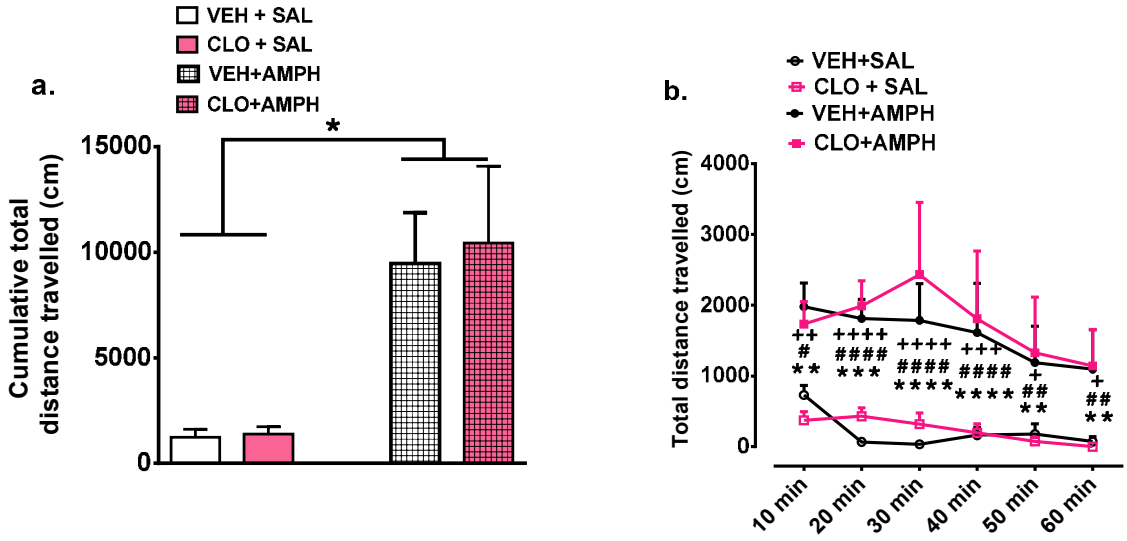


Figure 20: Effect of administration of PPAR-α agonist, clofibrate (25 mg/kg), and amphetamine (3 mg/kg) on the total distance travelled in the locomotor activity test. The graphs represent the effects of clofibrate, amphetamine, and clofibrate + amphetamine on the distance travelled in the locomotor activity test in rats. The values are expressed as mean ± SEM (n = 6 animals per group). **(a): cumulative total distance.** *P<0.05 amph vs. saline; New-man Keul's post hoc test. **(b): total distance temporal activity.** +P <0.05; ++P <0.01; +++P <0.001; ++++P <0.01 vehicle + amph vs. vehicle + saline; #P <0.05; ##P <0.01; ####P <0.0001 clofibrate + amph vs. vehicle + saline; **P <0.001;***P <0.001; **** P <0.0001 clofibrate + amph vs. clofibrate + saline; Turkey's post hoc test.

4.6.2.2 *Effect of clofibrate, PPAR-α agonist, administration in rats acutely treated with amphetamine Amph in stereotypy test*

In parallel to the locomotor activity, stereotypy scores increased also in animals treated with amphetamine, both in the group treated with saline and group pretreated with clofibrate compared to controls [Two-way Anova: Amphetamine ($F_{(1, 20)}$ = 176.4, ****p < 0.0001); Clofibrate ($F_{(1, 20)}$ = 0.0, p <0.999); Amphetamine x clofibrate interaction ($F_{(1, 20)}$ = 0.0, p <0.999)], while clofibrate didn't demonstrate any significant stereotypy effect relative to vehicle rats. In particular, Turkey's post-hoc test reports a statistically significant effect on Amph ****P <0.0001 Amph+ vehicle and Amph + clofibrate vs. saline + vehicle; ####P <0.0001 Amph + vehicle and Amph + clofibrate vs. saline + clofibrate. Thus, Clofibrate failed to block the development of psychomotor sensitization seen with amphetamine treatment regimen. (Figure 21)

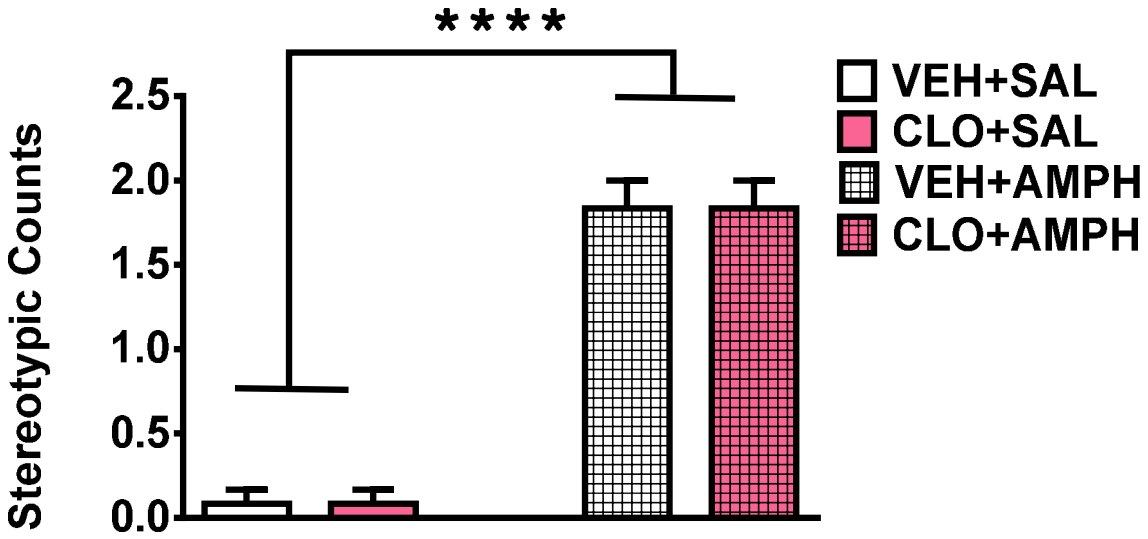


Figure 21: Effect of administration of PPAR-α agonist, clofibrate (25 mg/kg), and amphetamine (3 mg/kg) on the stereotyped behaviors. The graphs represent a comparison of stereotypic counts between saline, clofibrate, amphetamine, and clofibrate + amphetamine groups on the stereotypic coounts in rats. The values are expressed as mean ± SEM (n = 6 animals per group), one-way anova. ***P <0.001 Amph vs. saline; Turkey's post hoc test.

4.6.2.3 *Effect of clofibrate, PPAR-α agonist, administration in rats acutely treated with amphetamine Amph in pre-pulse inhibition test*

Regarding the pre-pulse inhibition test, we identified a significant effect of treatment using two-way ANOVA, but no interaction between treatment and pre-pulse intensity. [Two-way ANOVA: treatment ($F_{3,54}$ = 24.2; ****P < 0.0001); pre-pulse intensity ($F_{2,54}$= 1.357; P= 0.2662); Treatment x Pre-pulse intensity interaction ($F_{6,54}$= 0.2636; P= 0.9514)]. Post-hoc analysis revealed a significant reduction in PPI following amphetamine treatment for each tested pre-pulse intensity compared to vehicle (74 dB: 49.325 ± 6.821 %, *p<0.05; 78 dB: 41.227 ± 5.536%, *p<0.05; 86 dB: 43.822 ± 9.372%, *p<0.05)[figure 22a].Clofibrate treatment at had no effect on pre-pulse inhibition PPI compared to vehicle. In addition, PPI following combined treatment of PCP with 25 mg/kg clofibrate did not differ significantly for any pre-pulse intensity to PCP-only treatment.

Analysis of the effect of clofibrate on startle amplitude revealed no main effects of clofibrate and amphetamine treatments and no interactions between them [Two-way ANOVA: Amphetamine ($F_{1,17}$ = 2.897; P=0.1069); clofibrate ($F_{1,17}$ = 0.3307; P = 0.5728, amphetamine x clofibrate interaction ($F_{1,17}$= 3.345; P= 0.085)](figure 22b).

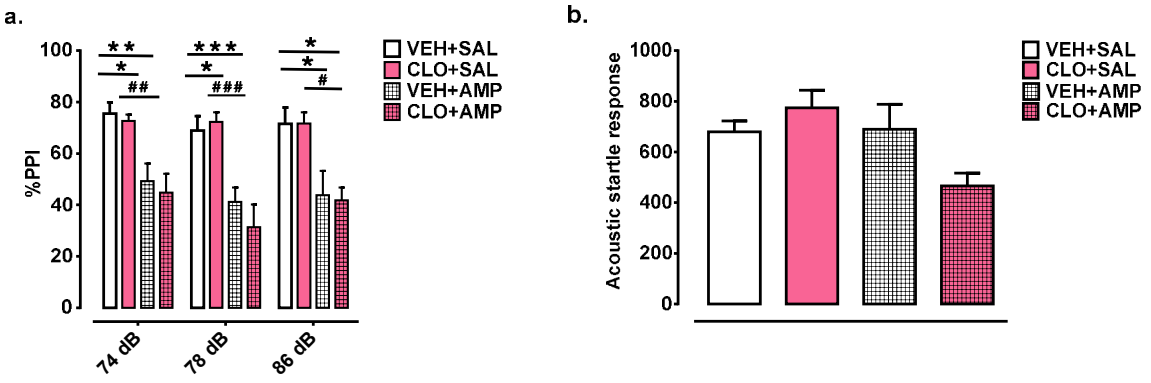


Figure 22: Effect of administration of PPAR-α agonist, clofibrate (25 mg/kg), and amphetamine (3 mg/kg) on the pre-pulse inhibition intensity PPI (%) and startle amplitude (arbitrary units). The graphs represent the effects of clofibrate, amphetamine, and clofibrate + amphetamine on the PPI and startle amplitude response in rats. The values are expressed as mean ± SEM (n = 5/6 animals per group). **(a): pre-pulse inhibition intensity PPI (%).***P <0.05 vs. saline + vehicle; ** P <0.01 vs. saline + vehicle ; *** P <0.001 vs. saline + vehicle; #P <0.05 vs. PCP + vehicle; ##P <0.01 vs. PCP + vehicle; ###P <0.001 vs. PCP + vehicle; Turkey's post hoc test. **(b): acoustic startle response (a.u).**

4.6.3 *Effects of clofibrate, PPAR-α agonist, administration versus haloperidol on catalepsy bar test*

As shown in figure 23, acute intraperitoneal administration of clofibrate at any dose (100–500 mg/kg) did not alter the motoric activity; as indicated by decreased descent latency in the bar catalepsy test relative to control group in rats. Further, we have employed haloperidol (1 mg/kg, i.p.) as a standard cataleptic agent which exhibited catalepsy in rats as compared to control group [One-way ANOVA ($F_{4,31}$ =118.6; ****P<0.0001), and suggesting evidence for normal motor coordination and thus, lack of extrapyramidal side effects for clofibrate.

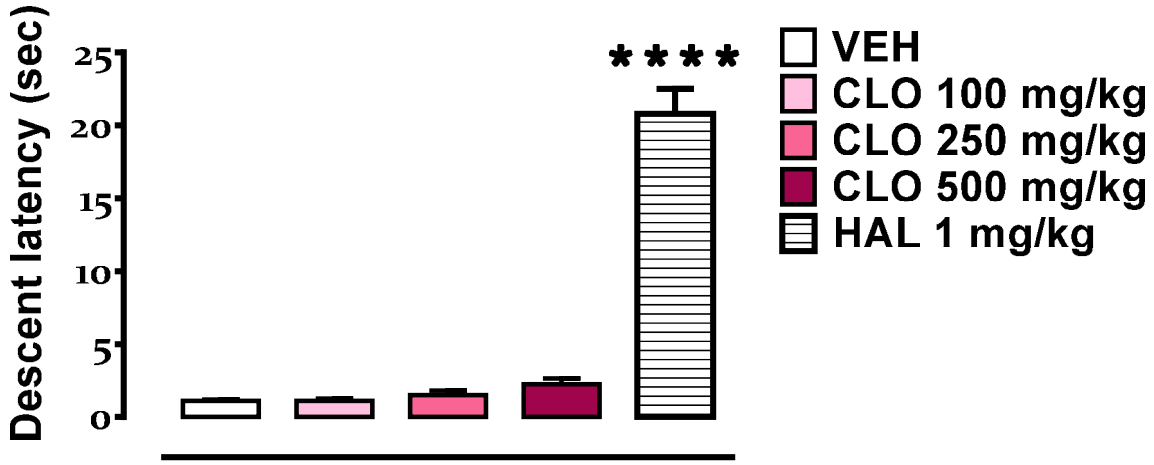


Figure 23: Effect of administration of PPAR-α agonist, clofibrate, on haloperidol-induced catalepsy. The graph represents a comparison of descent latency in the bar catalepsy test between vehicle, clofibrate (100, 250, 500 mg/kg), and haloperidol (1 mg/kg) in rats. The values are expressed as mean ± SEM (n = 6/8 animals per group). ****P<0.0001 HAL vs. vehicle; Bonferroni post-hoc test.

4.7 *Effect of acute administration of clofibrate, PPAR-α agonist, on dopamine, serotonin, and their metabolites levels in different brain areas*

Measurements of dopamine and serotonin monoamines and their metabolites (ng/mg tissue) were presented after acute intraperitoneal clofibrate administration, at a dose of 25 mg/kg, in the prefrontral cortex, nucleaus accumbens, striatum, amygdale, hippocampus and hypothalamus (figures 24, 25, 26, 27, 28, 29). In fact, clofibrate treatment didn't demonstrate statistically significant effects on any of the parameters measured; neither dopamine nor serotonin or their metabolites contents varied significantly compared to their control at any studied brain site.

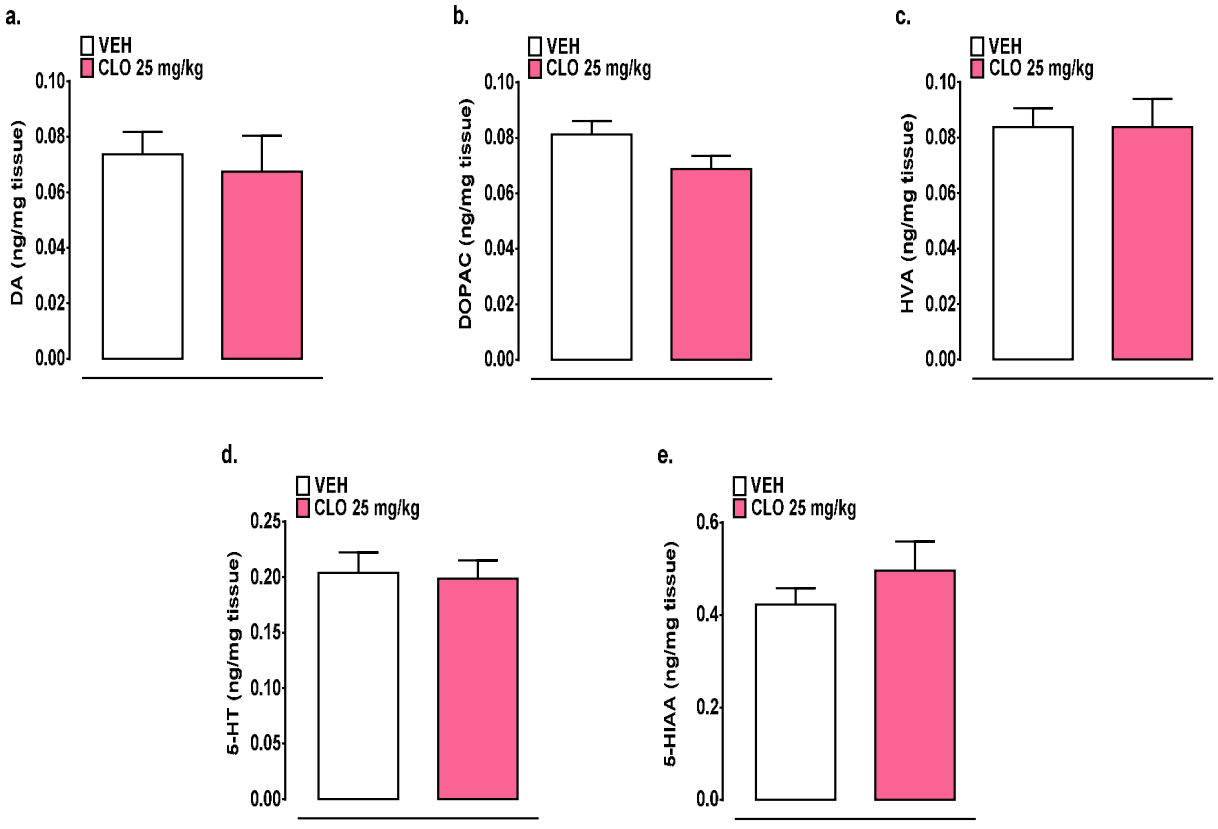


Figure 24: Effect of acute administration of PPAR-α agonist, clofibrate (25 mg/kg), on DA (a), DOPAC (b), HVA (c), 5-HT (d) and 5-HIAA (e) contents in the pre-frontral cortex of rats. The values are expressed as mean ± SEM (n = 8 animals per group).

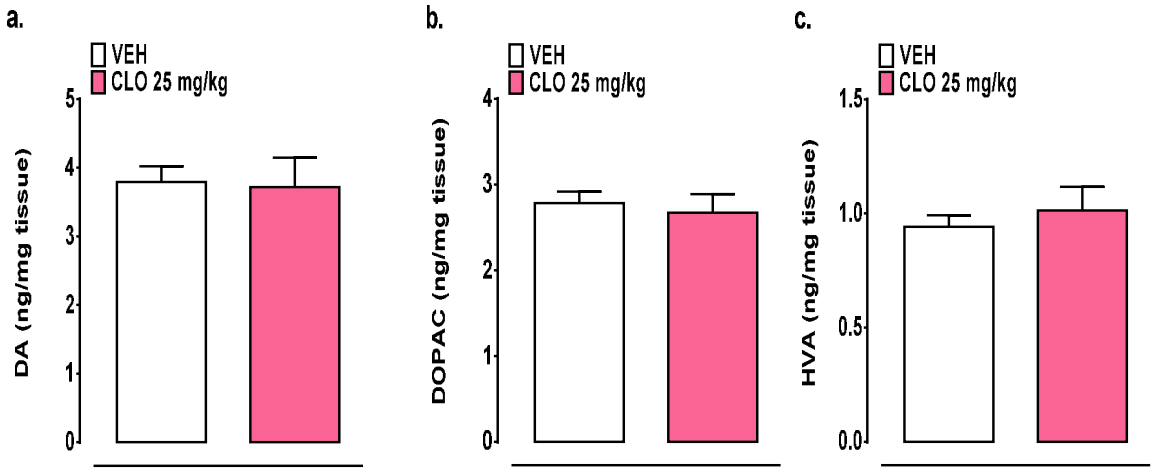


Figure 25: Effect of acute administration of PPAR-α agonist, clofibrate (25 mg/kg), on DA (a), DOPAC (b), and HVA (c) contents in the nucleus accumbens of rats. The values are expressed as mean ± SEM (n = 8 animals per group).

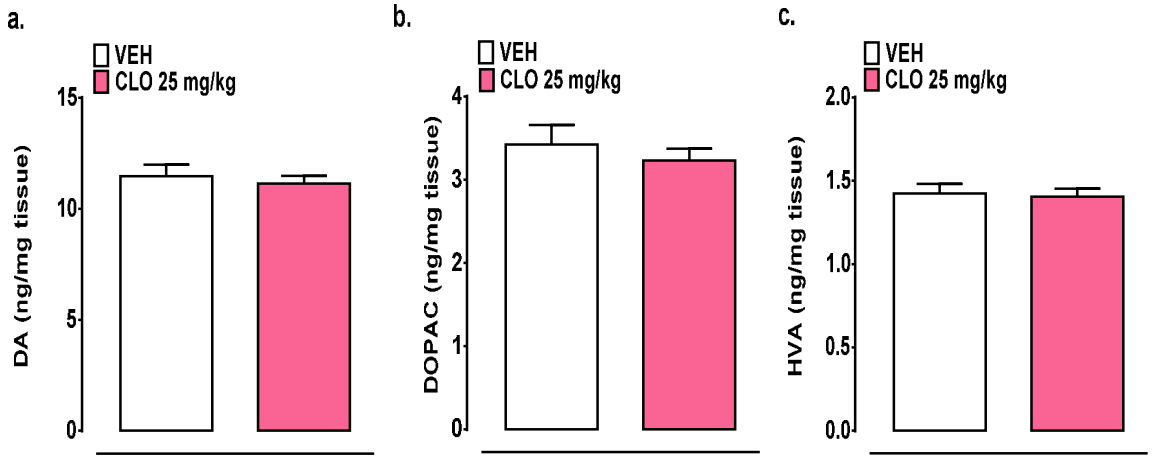


Figure 26: Effect of acute administration of PPAR-α agonist, clofibrate (25 mg/kg), on DA (a), DOPAC (b), and HVA (c) contents in the striatum of rats. The values are expressed as mean ± SEM (n = 8 animals per group).

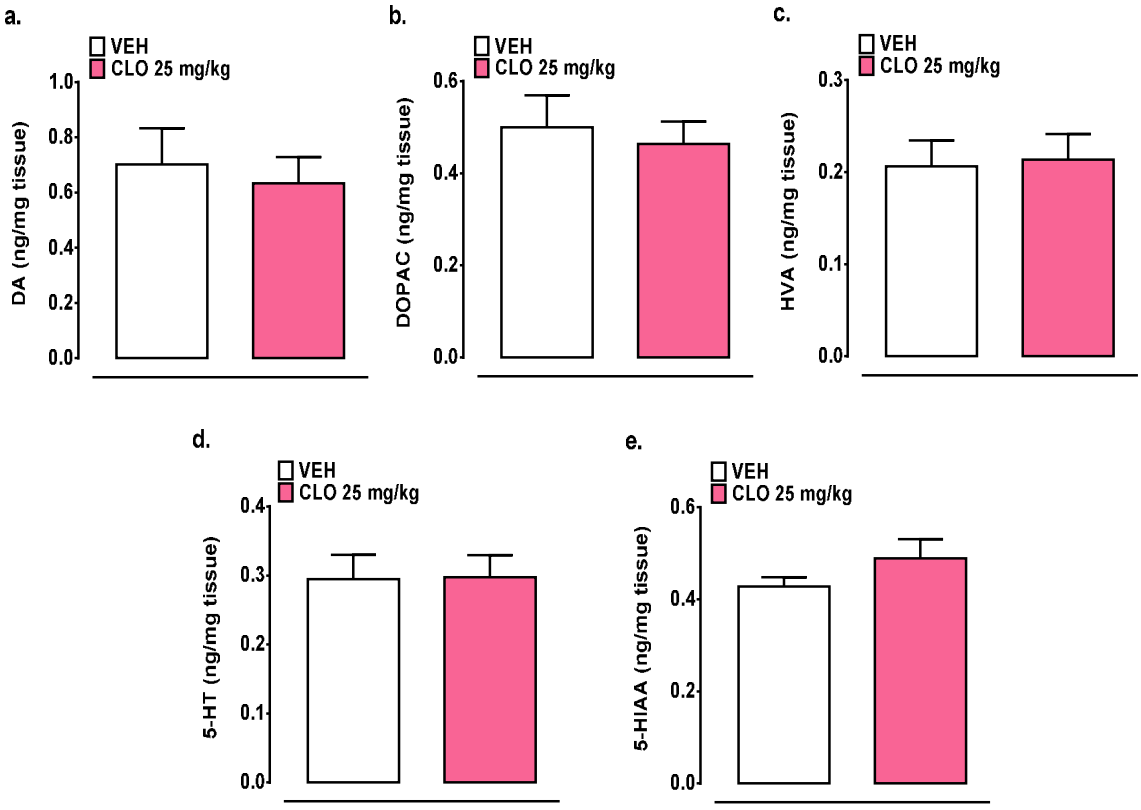


Figure 27: Effect of acute administration of PPAR-α agonist, clofibrate (25 mg/kg), on DA (a), DOPAC (b), HVA (c), 5-HT (d) and 5-HIAA (e) contents in the amygdala of rats. The values are expressed as mean ± SEM (n = 8 animals per group).

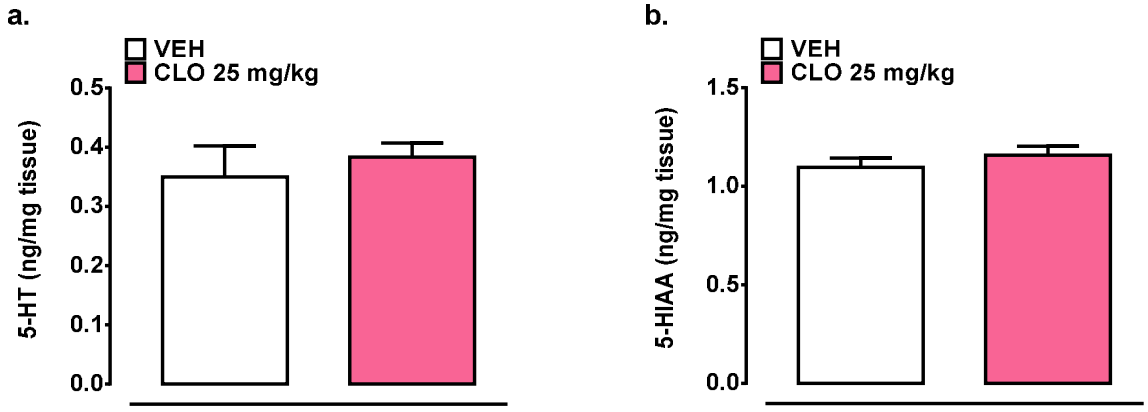


Figure 28: Effect of acute administration of PPAR-α agonist, clofibrate (25 mg/kg), on 5-HT (a) and 5-HIAA (b) contents in the hippocampus of rats. The values are expressed as mean ± SEM (n = 8 animals per group).

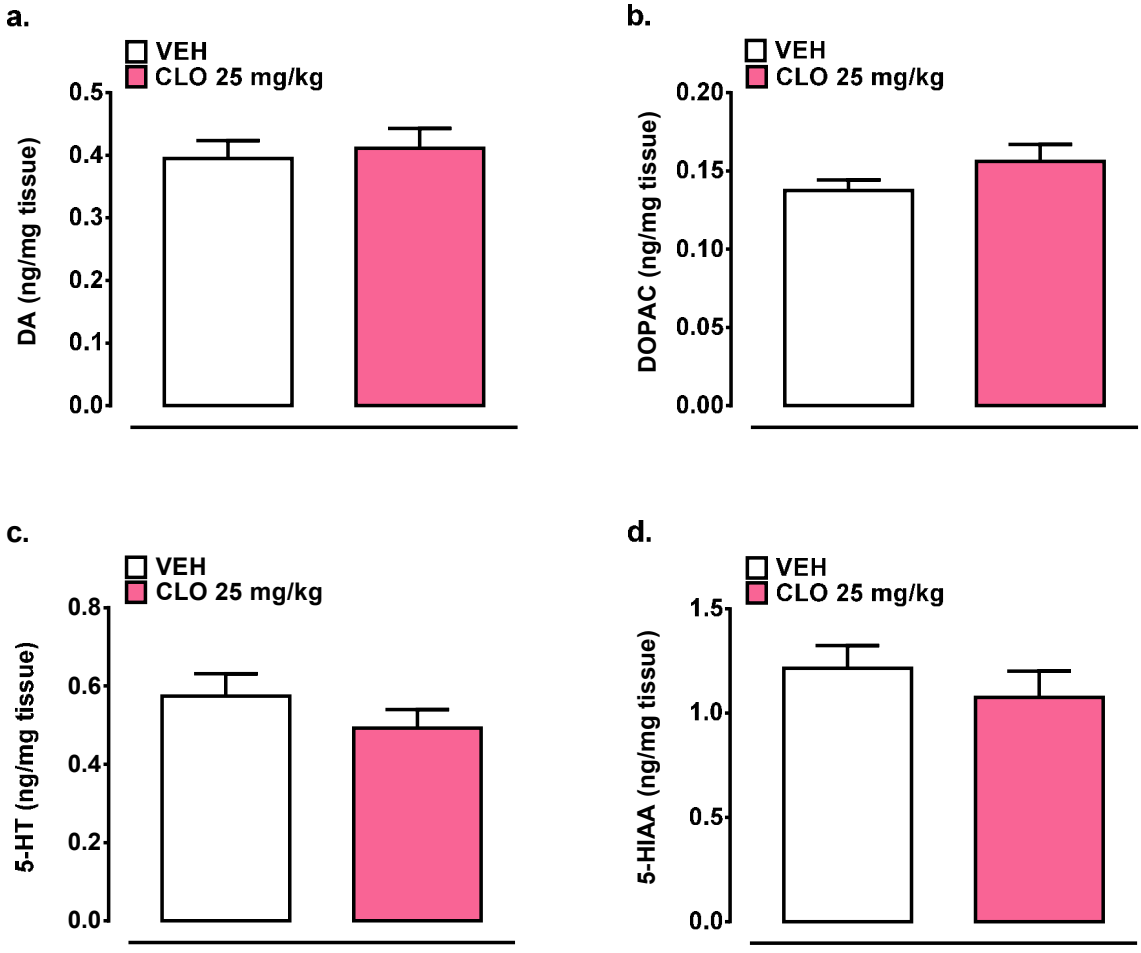


Figure 29: Effect of acute administration of PPAR-α agonist, clofibrate (25 mg/kg), on DA (a), DOPAC (b), 5-HT (c), and 5-HIAA (d) contents in the hypothalamus of rats. The values are expressed as mean ± SEM (n = 8 animals per group).

4.8 Effect of chronic administration of clofibrate, PPAR-α agonist, on dopamine, serotonin, and their metabolites in different brain areas

Figures 30, 31, 32, 33, 34, and 35 represent the effects of the chronic treatment with the PPAR-α agonist, clofibrate (25 mg/kg), on dopamine, serotonin and their metabolites contents in prefrontral cortex, nucleaus accumbens, striatum, amygdale, hippocampus, and hypothalamus. As we can notice from the graphs of figure 30(b,c, d), chronic clofibrate treatment, at the dose used, demonstrated a significant decrease of dopamine metabolites DOPAC and HVA and serotonin metabolite 5-HIAA in the prefrontral cortex compared to vehicle-treated rats (figure 30b, 30c, 30d) (DOPAC and HVA: (**P<0.01 25 mg/kg clofibrate vs. vehicle; 5-HIAA: *P<0.05 25 mg/kg clofibrate vs. vehicle; student's t test). Clofibrate reduced as well dopamine and its metabolites; DOPAC ad HVA, in the amygdala (figure 33b and c) (DOPAC: P<0.05 25 mg/kg clofibrate vs. vehicle; HVA: **P<0.01 25 mg/kg clofibrate vs. vehicle; student's t test), while in the hippocampus, serotonin metabolite 5-HIAA (figure 34c) relative to controls (*P<0.05 25 mg/kg clofibrate vs. vehicle; student's t test). Concernin the other brain sites; nucleas accumbens, striatum and hypothalamus, we didn't obtain any significant variety between the studies monoamine contents or their metabolites compared to controls (figures 31, 32, 35).

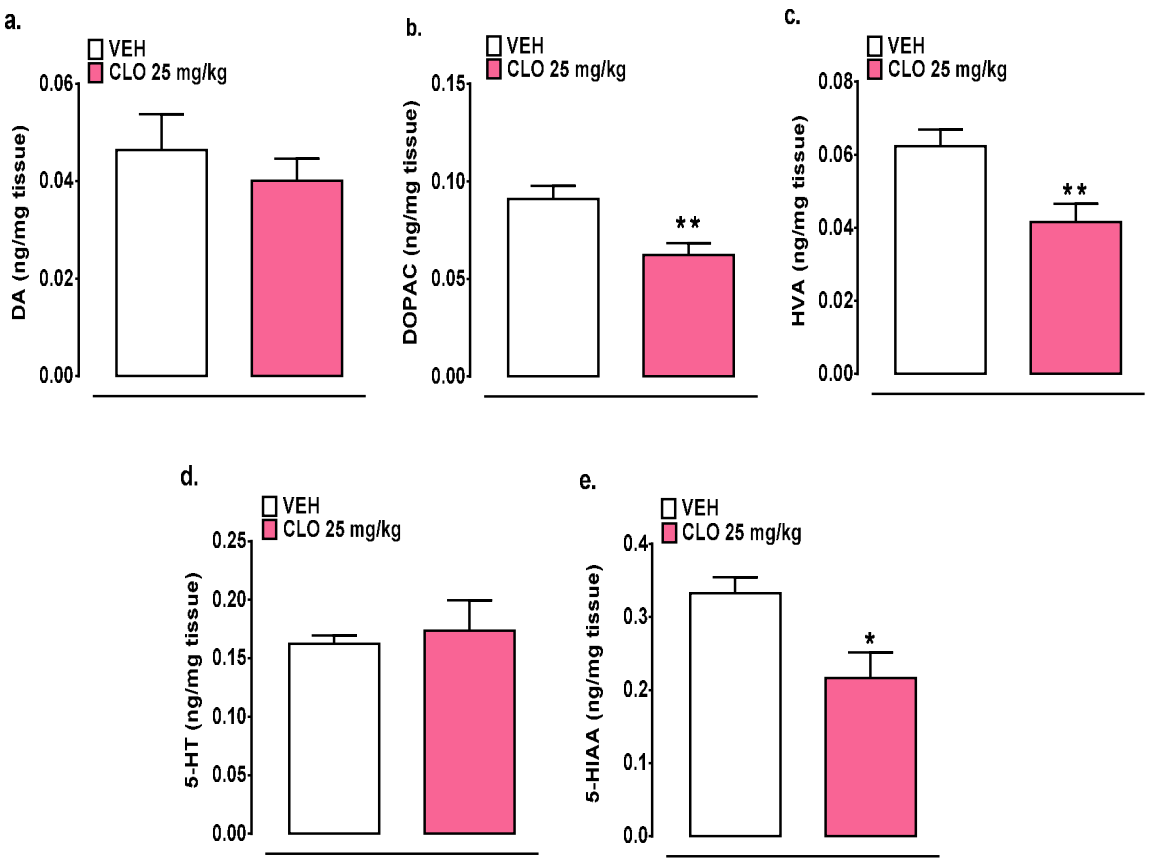


Figure 30: Effect of chronic administration of PPAR-α agonist, clofibrate (25 mg/kg), on DA (a), DOPAC (b), HVA (c), 5-HT (d) and 5-HIAA (e) contents in the pre-frontral cortex of rats. The values are expressed as mean ± SEM (n = 8 animals per group). **p< 0.01 and *p < 0.05 clofibrate vs. vehicle, student's t test.

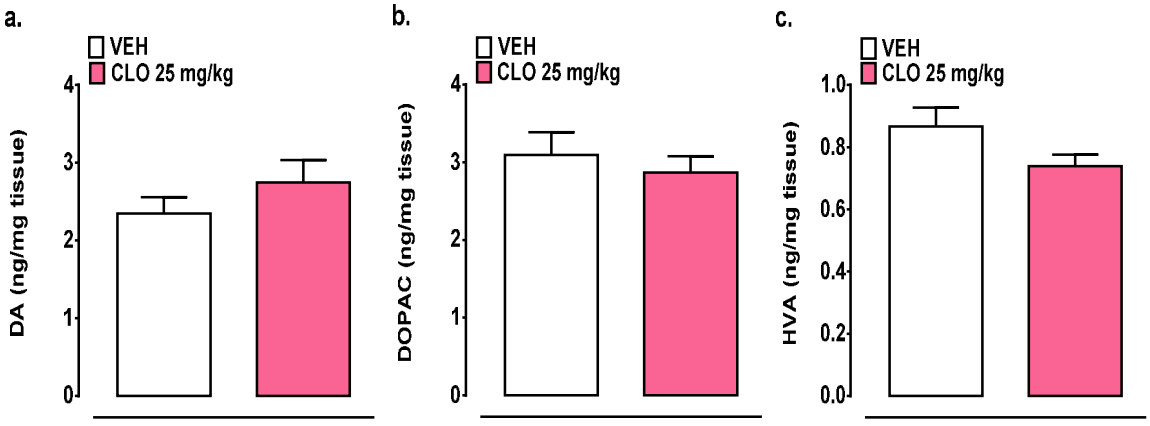


Figure 31: Effect of chronic administration of PPAR-α agonist, clofibrate (25 mg/kg), on DA (a), DOPAC (b), and HVA (c) contents in the nucleus accumbens of rats. The values are expressed as mean ± SEM (n = 8 animals per group).

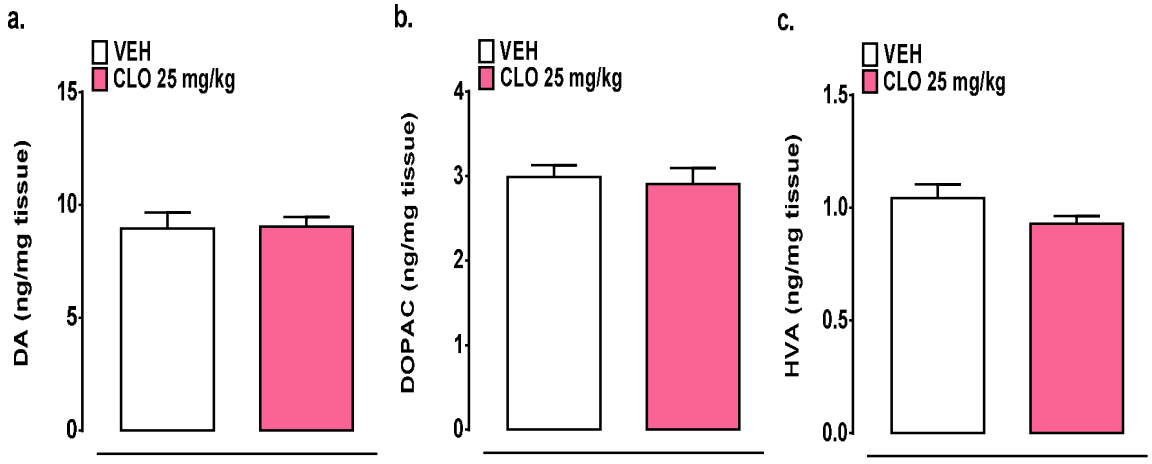


Figure 32: Effect of chronic administration of PPAR-α agonist, clofibrate (25 mg/kg), on DA (a), DOPAC (b), and HVA (c) contents in the striatum of rats. The values are expressed as mean ± SEM (n = 8 animals per group).

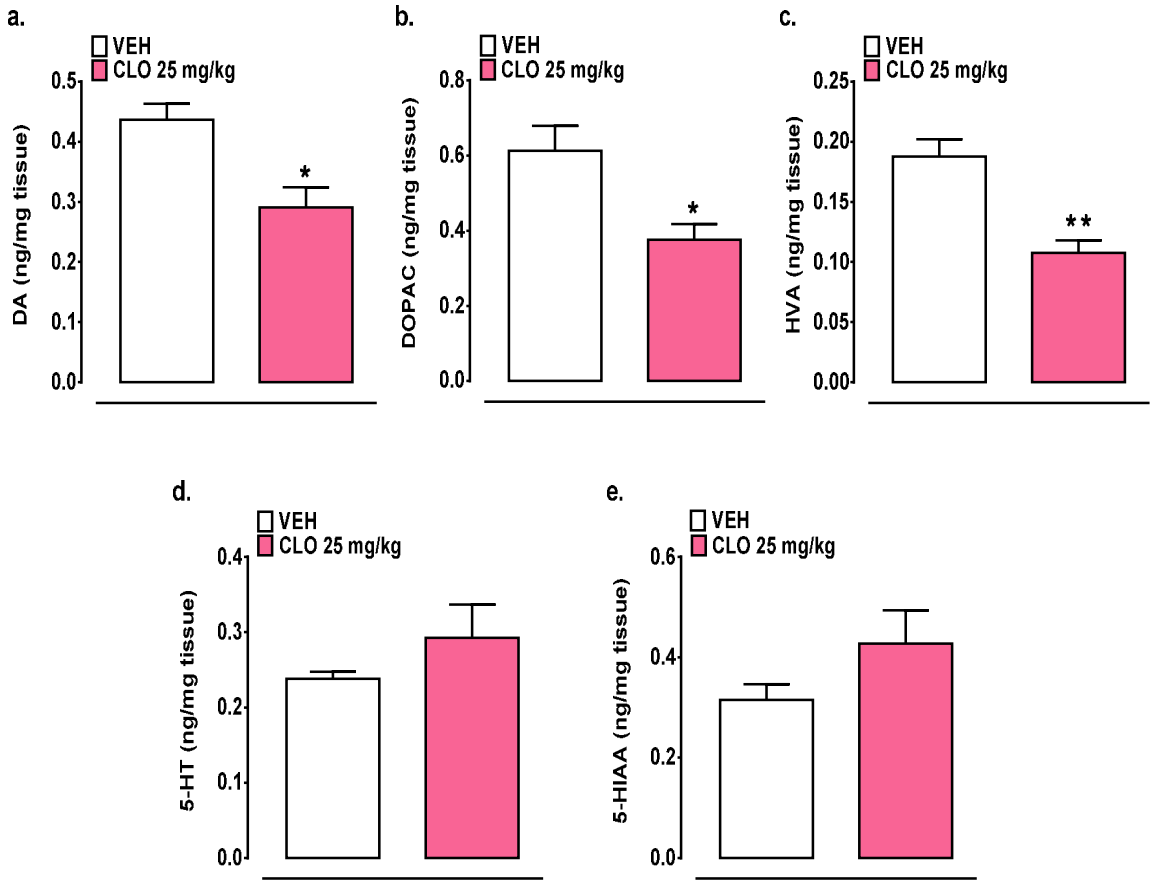


Figure 33: Effect of chronic administration of PPAR-α agonist, clofibrate (25 mg/kg), on DA (a), DOPAC (b), HVA (c), 5-HT (d) and 5-HIAA (e) contents in the amygdala of rats. The values are expressed as mean ± SEM (n = 8 animals per group). **p< 0.01 and *p < 0.05 clofibrate vs. vehicle, student's t test.

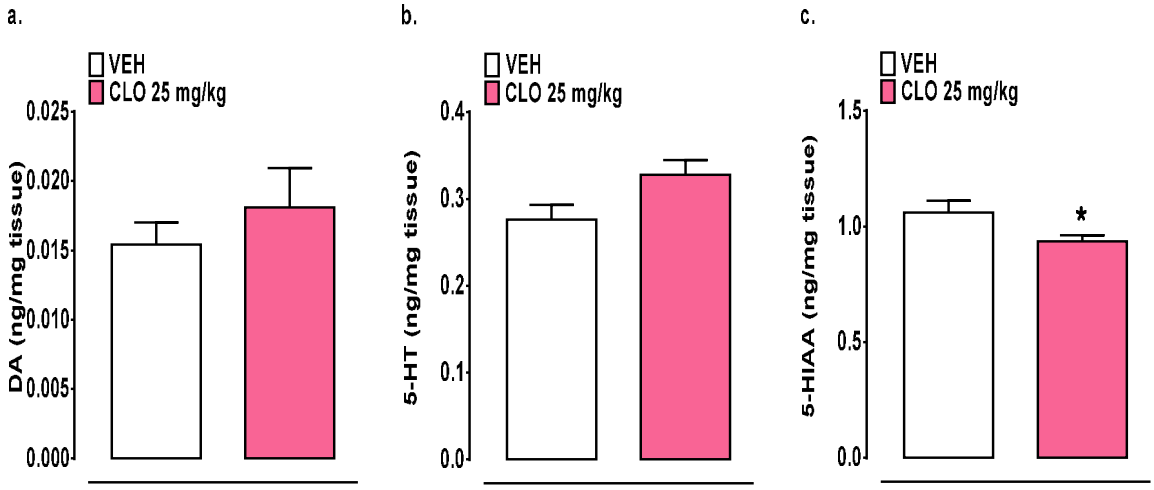


Figure 34: Effect of chronic administration of PPAR-α agonist, clofibrate (25 mg/kg), on DA (a), 5-HT (b) and 5-HIAA (c) contents in the hippocampus of rats. The values are expressed as mean ± SEM (n = 8 animals per group). *p < 0.05 clofibrate vs. vehicle, student's t test.

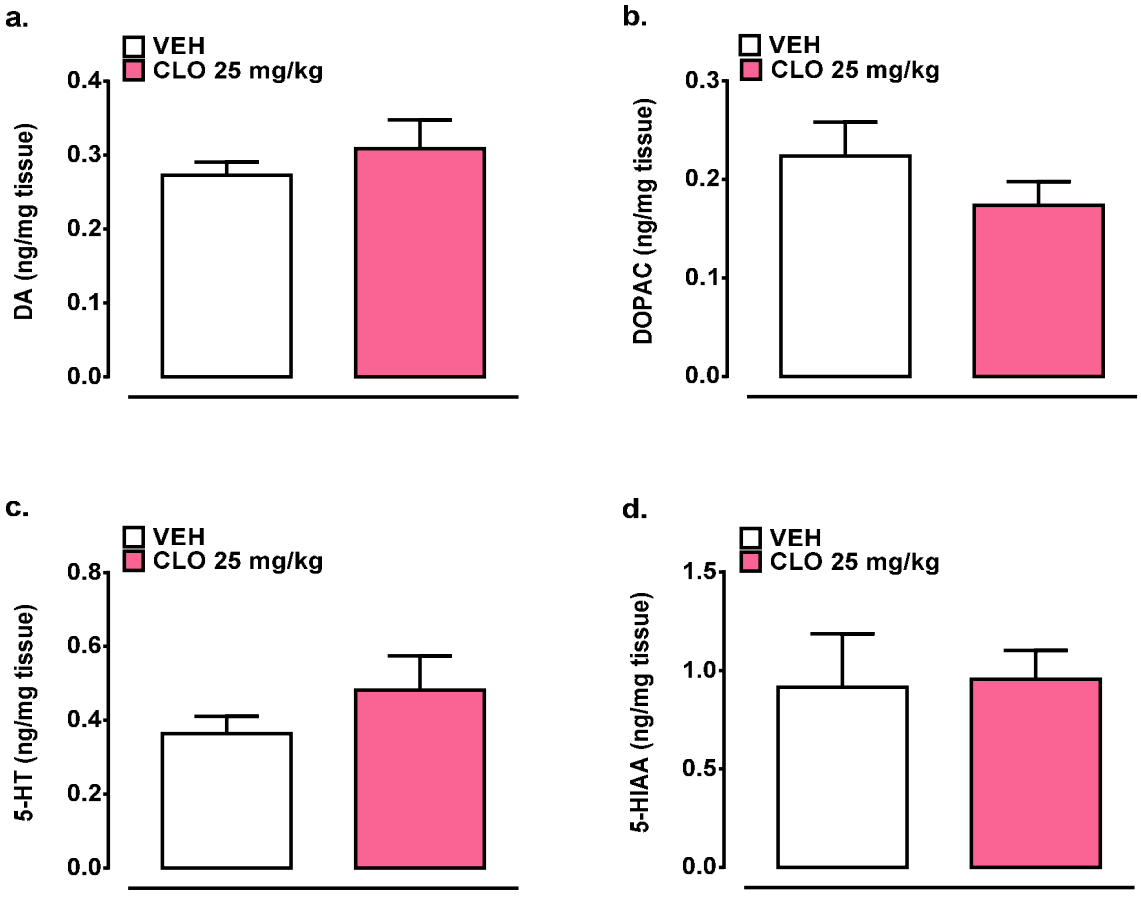


Figure 35: Effect of chronic administration of PPAR-α agonist, clofibrate (25 mg/kg), on DA (a), DOPAC (b), 5-HT (c), and 5-HIAA (d) contents in the hypothalamus of rats. The values are expressed as mean ± SEM (n = 8 animals per group).

5. Chapter V: Discussion

Clofibrate as reported by Thorp and Waring since 1962, was the most effective compound among a series of α-aryloxyisobutanoic acid derivatives at lowering the concentration of cholesterol and total lipid in rat serum and liver (Thorp and Waring, 1962). In 1965, clofibrate became the first PPAR-α agonist to be used in clinical therapy in the treatment of dyslipidemia (Salakhutdinov and Laev, 2014). Despite the accumulated evidences about the psychotherapeutic potential effect of PPAR-α agonists, the potential outcomes of clofibrate on psichiatric disorders are poorly understood. Only one recent paper has demonstrated the effects of clofibrate on behavioral despair in animals (Fakhraei et al., 2017). To the best of our knowledge, our study is the most comprehensive study showing that clofibrate could has beneficial effects against anxiety and schizophrenia

The goal of this doctoral thesis was to investigate the potential anxiolytic-like and anti-schizophrenic effects of clofibrate after intraperitoneal administration in different treatment regime in rats. In addition, we evaluated the effects of clofibrate on serotonin and dopamine levels in different brain areas of rats.

Three separate set o experiments were conducted to address these goals.

1. Experiments set #1 examined the effect of clofibrate on anxiety-like behaviors in the open field test. We have reated experiment already done in our laboratories using the social interaction test and the elevate plus maze test to confirm the previuos experimental conditions applied.
2. Experiments set #2 studied the effects of clofibrate on schizophrenic-like behaviors in both dopaminergic and glutamatergic animal models of schizophrenia, in rats. In addition we examined if clofibrate can induce cataleptic effects by the bar test.
3. Experiments set #3 examined the effects of clofibrate on serotonin, dopamine, and their metabolites contents in brain tissues.

-Discussion #1

The present study demonstrates for the first time the role of the PPAR-α agonist, clofibrate, in modulating anxiety behavior in rats. Clofibrate was investigated in three well-characterized anxiety paradigms, namely the social interaction test (File and Hyde, 1978), elevated plus maze test (Carobrez and Bertoglio, 2005) and the open field test (Seibenhener and Wooten, 2015).

The acute administration of clofibrate (25 mg/kg) at a dose which does not influence the locomotor activity of animals neither acutely nor chronically, significantly modify the emotional avoidance response towards novel places as animals markedly reduced exploratory variables such as time spent, number of entries, and duration covered by rats in the central compartment of the open field test arena. On the other hand, repeated treatment (25 mg/kg, once daily, 3 days) with clofibrate produced a loss of the anxiogenic-like acute effects induced by this drug in the open field test. Clofibrate treated group of rats demonstrated the same level of performance as control group. In line with Fakhraei et al (2017), a sub-chronic administration of clofibrate (3 times during 24 hours) didn't induce any significant change in the number of entries to the central arena in the open field test. On the contrary, more evident was the shift observed following chronic administration (25 mg/kg, once daily, 14 days), after which clofibrate displayed an anxiolytic-like profile with a significant increase in the duration of time spent, number of entries, and duration covered in the central region of the field: This effect is in accordance with the anxiolytic effect reported after the chronic administration of the the PPAR-α, palmitoylethanolamide PEA natural agonist, in the open field test (Crupi et al., 2013).

We also demonstrated the anxiogenic effect of clofibrate after acute administration by means of the social interaction test in rats. Our data indicate again that clofibrate administered acutely at a dose of 25 mg/kg reduced the number of contacts and duration of time spent in social interaction In agreement with us a previous study (Lapin, 1990) demonstrated that the acute administration of PEA reduced both the number and duration of contacts in a dose-dependent manner in social interaction test.

In contrast, the acute administration of clofibrate at the same dose (25 mg/kg) in the plus maze test did not exert any anxiolytic or anxiogenic effects on both classical and ethological parameters. These data are consistent with what was reported in our laboratories (personal communication) and about another endogeneous PPAR-α agonist, OEA by Campolongo et al, (2009). Since the clofibbrate dose tested in each behavioural maze tested (open field, social interaction and elevated plus maze) did not influence the locomotor activity of animals, neither acutely nor chronically we can conclude that behavioral effects of clofibrate observed were not due to its stimulant or depressant action.

The data observed after the acute administration of clofibrate, are opposite to those of anxiolytic-like properties of minor tranquilizers in animals, and resemble those observed after administration of some antidepressants such as serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors (SNRIs) (Bandelow et al., 2017). These effects, except those of the plus maze test, are interpreted as reflecting the anxiogenic effects of the PPAR-α synthetic agonist clofibrate when administred acutely. Conversely, the sub-acute administration of clofibrate normalized the anxiogenic-like effects as observed in the open field test and then elicted an anxiolytic-like behavior after chronic administrationupon. It is worthy to note that Jiang et al (Jiang et al., 2017) also demonstrated that the chronic administration of fenofibrate, another synthetic PPAR-α ligand, reversed the decreaseinduced by the chronic social defeat stress- in social interaction test. This effect was blocked by the selective PPAR-α inhibitor GW6471, confirming the fact that this effect was mediated by PPAR-α receptors.

The behavioral results obtained after the acute administration of clofibrate raise the question on the discrepancy between these behavioral tests to study anxiety-like behaviors in animal... Contradictory results have been reported both in the open field test and inn the social interaction test as well as in the elevated plus maze test. For example, same rat or mouse strains were defined as anxious by one model of anxiety, but non-anxious by other models (Trullas and Skolnick, 1993), (Rogers et al., 1999), (Ramos et al., 1997) indicating that anxious behaviors, due to their complexity, can vary in their biological significance among different strain of

animals . A different explanation could be that the elevated plus maze, open field, and social interaction tests may measure different aspects of anxiety.

In the social interaction test are not introduced aversive conditions and the test is designed for contrasting the tendency of rats to engage in social investigation upon introducing naïve rats in the arena of a resident one (Bailey and Crawley, 2009).

in the open field test aversive stress is mainly represented by the novelty of the new environment for the animal, whereas aversive stress in the elevated plus maze is due to novelty and the height of the maze(Rodgers, 1997)

In the elevated plus maze, the test is initiated by placing the animals at the center of the plus maze where animals initially engage in high level of risk assessment, therefore, the design of the elevated plus maze offers more choices and causes a higher level of stress to the animals as compared to the open field test. Then the differences in the stressfulness between social interaction, open field and elevated plus maze tests may contribute to the different results observed. It has been suggested that the social interaction test is a useful animal model for evaluating social anxiety, social phobia, social failure/impairments, aggressiveness and emotional immaturity (Nakamura and Kurasawa, 2001),while the open field test would be a better measure of passive coping, and the elevated plus maze would be a more sensitive measure of active coping in response to stress (Nosek et al., 2008). The opposite aspects of active and passive coping can be observed as a considerable excitation when the animal faces stress initially, but if the stressor might persist without successful active coping, a following period could be observed with the animal behaving in a very passive fashion (Anisman, 1975),(Matheson and Anisman, 2003),(Glavin, 1985). Hence, the different behavioral outcomes observed in these tests in the animals trated with clofibrate may suggest a different stress response, manifesting itself as an anxiogenic-like and reduced social behavior that doesn't cope to stress neither actively nor passively in acute treatment, whereas chronic administration tends to induce an anxiolytic-like behavior at the passive coping phase of stress.Our results support the notion that the chronic administration of the PPAR-α agonist, clofibrate, reverses the anxiogenic phenotype and this is in accordance with what was reported by (Crupi et al., 2013) about the potential

anxiolytic effects of PEA another PPAR-α agonist, , in the open field test when administred chronically. The latter correlated these behavioral responses with proliferation of new neurons in the hippocampus, increasing the dendritic spine density in the dentate gyrus and anti-apoptotic factors in the brain, besides to elevating the brain derived neurotrophic factor “BDNF” level in the hippocampus. In addition other papers support the role of BDNF growth factor in the hippocampus as being an active modulator of emotional behavior. Interestingly, results obtained after acute BDNF injection in the hippocampus of rats, a paradoxical anxiogenic/antidepressant activity was displayed (Casarotto et al., 2012), (Hoshaw et al., 2005), (Shirayama et al., 2002).. Previous experiments performed in our laboratries had demonstrated a possible antidepressant effect of clofibrate in rats after both acute and chronic regimes (personal communication).It is possible to postulate that the clofibrate acute and chronic profile was generated by an upregulation of BDNF levels in the hippocampus. In fact BDNF was reported to be elevated in the hippocampus after chronic administration the PPAR-α agonist, PEAthat also indiucede an anxiolytic effect. Further examinations should be conducted to ascertain this hypothesis.

-Discussion #2

Recent epidemiological studies showed that anxiety symptoms are highly prevalent in schizophrenia when compared to the general population (Achim et al., 2011). Evidence suggests that comorbid anxiety disorders may worsen schizophrenics' functioning and negatively impacts treatment compliance. Then the presence of anxious symptomatology needs to be considered when developing and prescribing treatments for schizophrenia disorders. Some studies have demonstrated that certain antipsychotic medications may produce symptoms of anxiety or aggravate it, in addition to causing a variety of other undesirable side effects (Srivastava and Soni, 2007). Other evidence have reported that the anxiety symptoms associated with schizophrenia can be medicated using anxiolytic drugs (Kahn et al., 1988),(Csernansky et al., 1984), (Wolkowitz et al., 1986), (Braunstein-Bercovitz, 2000),(Braunstein-Bercovitz et al., 2002). Then alternative treatments for schizophrenia that address the issues of unpleasant side effects and low rates of compliance are needed. Hence, we examined the effects of clofibrate on two different model of schizophrenia in animal . To model the different human symptoms of schizophrenia in animals we can used drugs acting on different e neurotransmitter system (Steeds et al., 2015). In this thesis we used selectively the amphetamine and phencyclidine animal model of schizophrenia .d.

The amphetamine animal model of schizophrenia is based on dopamine hyperfunction. It was theorized that dopamine dysregulation with hyperfunction of the mesolimbic dopamine system underlies the basis of schizophrenia (Murray et al., 2008). It was demonstrated that amphetamine administration in psychotic patients stimulates the release of dopamine at the synapse than in normal control groups suggesting an increased midbrain dopamine activity (Abi-Dargham et al., 2009) inducing the positive symptoms of schizophrenia. Theses results it are not thought to fully resemble the cognitive and negative symptom of schizophrenia . In rodents, administration of amphetamine has been reported to induce progressive augmentation of locomotor activity, repeated ('stereotyped') behaviours, that may be related to the positive symptoms of psychosis. At the same time as amphetamine

administration impaired prepulse inhibition (PPI),that is a marker of sensory gating impairment also presents in patients with schizophrenia (Segal and Mandell, 1974).

By using the amphetamine animal model of schizophrenia, the acute administration of clofibrate (25 mg/kg) had no effect on hyperlocomotion and stereotyped behavior induced by the drug in rats. Administration of clofibrate (25 mg/kg) didn't attenuated the amph-induced disruptionsof PPI ,in rats relative to saline-treated controls . Hence, our findings do not support a beneficial effect of clofibrate treatment on positive symptoms of schizophrenia.

Increasing evidence supports the idea that dysfunction of the glutamatergic system is a primary pathophysiological change seen in schizophrenia (Konradi and Heckers, 2003), (Coyle et al., 2003). Pharmacological evidence for the role of glutamate in schizophrenia centres on findings that the blockade of the NMDA receptor by non-competitive antagonists, such as phencyclidine PCP, induces delusions and hallucinations in healthy subjects, symptoms commonly seen in schizophrenia (Cohen et al., 1962), (Krystal et al., 1994). In rodent, acute PCP administration causes both positive and negative symptoms of schizophrenia presented as hyperlocomotion and increased stereotypies (Kalinichev et al., 2008), social withdrawal (Sams-Dodd, 1995), and impairment of both pre-pulse inhibition PPI (Mansbach and Geyer, 1989) and cognition deficits (Egerton et al., 2005), while the chronic treatment with PCP has been shown to produce more persistent effects and more enduring cognitive deficits of particular relevance to schizophrenia (Jentsch and Roth, 1999).

By using the PCP animal model of schizophrenia , our results showed that clofibrate has no significant impact on the positive symptoms of schizophrenia produced by the acute PCP (5 mg/kg) treatment regime. Neither locomotor activity nor stereotypic behavior or PPI experimental results revealed any significant differences between control and clofibrate-treated animal groups. This findings suggest that clofibrate does not significantly disrupt or affect normal locomotion activity or sensorimotor gating, and they are consistent with previous studies that

demonstrated that WY14643 and simvastatin, which are both PPAR-α ligands, didn't alter the stereotypic behavior in rats (Mazzola et al., 2009), (Roy et al., 2015).

On the contrary, clofibrate (25 mg/kg) revealed significant rescue of the chronic PCP-induced cognitive disruptions in the novel object recognition test NOR (Ennaceur and Delacour, 1988), in which the spontaneous exploratory activity toward a novel and a familiar object is measured. This test does not involve rule learning or reinforcement and is thought to evaluate working and visual memory and it has many useful applications to study the neurobiological mechanisms of learning and memory.

It is note that schizophrenic patients demonstrate impaired recognition of visually-presented objects (Calkins et al., 2005). Our results showed that clofibrate by itself has no direct action on the cognitive performance in normal rats, whereas the PCP-induced cognitive deficit was reversed by clofibrate (25 mg/Kg) in the PCP animal model of schizophrenia. Consistent with these results, investigations employing PPAR-α null mice demonstrated theinvolvement of PPAR-α receptors -in spatial learning and memory, through regulation of cyclic AMP response element binding (CREB) and hippocampal plasticity-related genes (Roy et al., 2013). Other evidences showed that the PPAR-α agonist fenofibate prevented the cognitive poststroke consequences in mice (Ouk et al., 2014) and reversed 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine MPTP-induced cognitive impairements by protecting against MPTP-generated oxidative stress and neuroinflammation (Uppalapati et al., 2014). Similarly, the PEA PPAR- α agonist protects against β-amyloid-induced learning and memory impairment (Fidaleo et al., 2014), and OEA PPAR- α agonist ameliorated the cognitive deficits induced by 3,4-Methylenedioxymethamphetamine amphetamine derivative MDMA by protecting against MDMA-induced oxidative damage (Plaza-Zabala et al., 2010).

We believe that the present study was the first experiment to examine the potential cognitive benefit of clofibrate in a nimal model of schizophrenia schizophrenia. In this study, clofibrate treatment (25 mg/kg) had no significant beneficial effect on the positive effects of schizophrenia. In fact it did not prevent the

acute PCP and AMPH-induced increase in the locomotor activity, PPI deficits or increased stereotypy, however, acute clofibrate administration prevented the chronic PCP-induced cognitive impairment. These data suggest that pretreatment with clofibrate can modulate the cognitive deficits through a specific mechanism that allows it to reverse the chronic PCP effect.

The first hypothesis can be that clofibrate, as like as fenofibrate and many other PPAR-α agonists, could be neuroprotective and improve PCP- cognitive impairements, by protecting against the oxidative stress induced by PCP (Shirai et al., 2015).

Furthermore, there is a growing body of evidence for the dysfunction of the GABA system in schizophrenia (Steeds et al., 2015). Numerous post-mortem studies have emerged reporting deficits relating to interneurons that contain GABA as their neurotransmitter (Blum and Mann, 2002). More recently, researchers have taken advantages of the availability of antibodies against a number of calcium binding proteins (CBP). These CBPs, namely parvalbumin, calbindin and calretinin have been used as markers of specific subpopulations of nonoverlapping GABAergic interneurons in the brain (Neill et al., 2010). Deficits in paravalbumin PV immunoreactive cells have been reported in both the prefrontal cortex and hippocampus in post-mortem brain tissue from patients diagnosed with schizophrenia (Neill et al., 2010). In addition, Hashimoto et al. (Hashimoto et al., 2003) reported that, at the cellular level, a decrease in signal intensity for PV mRNA was attributable principally to a reduction in PV mRNA expression per neuron rather than by a decreased density of PV mRNA-positive neurons. And one of the most important findings is that both GABA synthesis and reuptake appear to be altered at the level of gene expression in schizophrenic brain tissues, specifically only in the PV subset of GABA neurons (Neill et al., 2010), and the resulting changes in GABA neurotransmission may contribute to the cognitive deficits in schizophrenia (Lewis et al., 2005).

Employing the NMDA receptor antagonist PCP model, numerous studies have reported deficits in PV-immunoreactive neurons in the cortex and

hippocampus in rats (Neill et al., 2010).Acute administration ofPCP has been found to produce deficits in PV mRNA in the reticular thalamus with no change in the prefrontal cortex. These pathological deficits are accompanied by deficits in a perceptual set shifting task, comparable to an aspect of executive dysfunction in schizophrenia (Egerton et al., 2005). However using a regime of sub-chronic exposure to PCP, it has been reported deficits in PV-immunoreactive neurons in the prefrontal cortex and hippocampus of adult rats, resulting in dysinhibition of pyramidal cells (Neill et al., 2010), (Abdul-Monim et al., 2007), (McKibben et al., 2010), in addition to reduction in BDNF mRNA levels (Snigdha et al., 2011) and dendritic spine density (Hajszan et al., 2006). These pathological changes occurred alongside cognitive and behavioral alterations(Jenkins et al., 2008), and are very similar to the changes seen in post-mortem studies of schizophrenia patients including reduced prefrontal cortical dendritic spine density (Glantz and Lewis, 2000), (Kolluri et al., 2005), decreased levels of prefrontal BDNF mRNA (Snigdha et al., 2011), and decreased levels of parvalbumin-positive interneurons (Beasley and Reynolds, 1997), (Lewis et al., 2001).

Using the PCP animal model of schizoprenia, our results showed that clofibrate revealed a disease-modifying action on the chronic PCP-induced cognitive disruptions. The PCP-induced cognitive deficit was reversed by clofibrate. In support to our results, D'Agostino et al. (D'Agostino et al., 2015) demonstrated that PPAR-α receptor is required for cognitive flexibility by playing an instrumental role in the organization and orchestration of PV interneuron-pyramidal neuron cortical microcircuitry, and synchronization of the neural activity. Besides, PPAR-α receptor absolutely contributes to improve the cognitive function in NMDA receptor antagonist models by protecting the structural morphology and functional integrity of PV- GABAergic interneurons in the prefrontal cortex and the hippocampus (D'Agostino et al., 2015). According to what mentioned above, we can hypothesize that the ability of clofibrate to reverse the cognitive deficit in the NOR task may be attributed to its ability to compensate for the sub-chronic PCP-induced reduction in parvalbumin.

Another hypothesis can also be postulated from the observations of the BDNF gene. BDNF is a neuronal transcription factor which is highly expressed in the

frontal cortex and hippocampus that has also been implicated in the formation of short- and long-term memory (Alonso et al., 2002), making it a plausible target for both the cognitive and transcriptional effects of PCP. Sub-chronic PCP regime has been shown to cause a reduction in frontal cortical BDNF mRNA levels in rats (Snigdha et al., 2011). BDNF binds to the Tropomyosin receptor kinase B TrkB receptor, which auto-phosphorylates and induces the transcription of genes containing a CREB promotor site (Minichiello et al., 2002), (Gupta et al., 2013), such as parvalbumin gene and BDNF genes (Cohen et al., 2016), (Lopez-Munoz and Alamo, 2011), (Yasuda et al., 2007), (Hashimoto et al., 2005). PCP-mediated reductions in BDNF levels in parvalbumin-positive interneurons would therefore further reduce the transcription of genes with a CREB promotor sequence, such as the paravalbumin gene, as well as reducing auto-activation of BDNF gene transcription. Reduced TrkB signalling due to a reduction in BDNF levels would further impair NMDA receptor mediated signalling, as TrkB receptors have been shown to induce the phosphorylation of the NMDA receptor subunits (Yamada et al., 2002). This would exacerbate the antagonistic effects of PCP. On the other side, the observation that was reported by Crupi et al. (Crupi et al., 2013) about the potentialiaty of PPAR-α agonist PEA to elevate BDNF levels can postulate the involvement of BDNF in reverting cognitive deficits induced by PCP. Absolutely further experimental studies are required to be conducted to support our hypothesis.

Looking to our experimental results in which PPAR-α agonist clofibrate treatment improves behavior in a chronic-PCP pharmacological animal model of schizoprenia, we can suggest that to prescribe clofibrate beside antipsychotic medication in patients with schizophrenia to improve dyslipidemia may show a greater benefit in cognitive symptom . A further investigation is required in patient population to assess this hypothesis. If this were the case, it would have the added benefit of overcoming the metabolic disturbance associated with many current antipsychotic medications (Melkersson and Dahl, 2003), (Atmaca et al., 2003), (Koro et al., 2002). It is worthy to note that the loss of function of PPAR-α receptor results in middle age-onset obesity/weight gain (Knauf et al., 2006b). Thus,

clofibrate may serve as further metabolic-protective role in schizophrenic patients.

Acute dystonia, parkinsonism and akathisia are distressing movement disorders, collectively known as extrapyramidal syndromes (EPS), that occur frequently during chronic treatment with first or second generation antipsychotics (Miller et al., 2008), (Bishnoi et al., 2008)

These adverse effects involve multiple causes including neurotransmitters disbalance, oxidative stress and neuroinflammation. Haloperidol, a non-selective dopamine D2 blocker, induces catalepsy by inhibiting the dopamine D2 receptors in the striatum (Boulay et al., 2000). Catalepsy animal experimental test consists of putting a rodent in an unusual, superimposed posture and measuring the descent time needed for the animal to initiate the movement to shift down , and it is often employed to assess a potential of a compound to induce extrapyramidal side effects in humans (Wadenberg, 1996), (Sanberg et al., 1988). In the present study, haloperidol was used as a positive control that produce catalepsy at a dose of 1 mg/kg. However, in our experiments clofibrate didn't produce any cataleptic effect in rats at any of thedoses tested. It is worthy to note that this effect can sustain our hypothesis about the potential role of the PPAR-α agonist clofibrate in protecting the GABAergic interneurons from the NMDA receptor antagonist negative effect. Several reports showed that GABAergic drugs diminish both the extrapyramidal side effects of antipsychotics and ameliorate the cognitive impairment associated with schizophrenia (Keverne, 1999),(Benes and Berretta, 2001), (Fatemi et al., 2005), (Lewis et al., 2005), (Wassef et al., 2003), (Guidotti et al., 2005), (Ferguson and Gao, 2018). Moreover, previous reports support our data by demonstrating that fenofibrate significantly attenuated haloperidol-induced catalepsy (Grover et al., 2013). Esposito et al. revealed also that PEA significantly reduced MPTP-induced catalepsy, an effect that was absent in PPAR-α knock out mice (Esposito et al., 2012). It has been reported that fenofibrate and PEA, significantly attenuated haloperidol and MPTP-induced catalepsy respectively through their antioxidant and anti-inflammatory effects (Grover et al., 2013), (Esposito et al., 2012). This fact

suggests that clofibrate *per se* may have a neuroprotective role against cataleptic effects of antipsychotic and other inflammatory diseases

Hence, our findings disclose a previously unknown role for clofibrate in cognitive function in rats. It suggests that clofibrate may represent a target for the pharmacological amelioration of neurological conditions associated with cognitive deficits, possibly without producing any extrapyramidal side effects. Again further studies are required to elucidate the mechanisms underlying the ability of the PPAR alpha agonist clofibrate to reverse the deficits induced by sub-chronic PCP administration.

-Discussion #3

The literature has not reported yet the effects of clofibrate on the serotonin and dopamine levels and their metabolites in the different brain areas. In the present work, the effec of clofibrate (25 mg/kg) was studied by determining the levels of dopamine, serotonin and and their metabolites in the prefrontal cortex, nucleus accumbens, striatum, amygdala, hippocampus and hypothalamus of rats, following acute and chronic regimes.

Our data showed that no significant alterations in dopamine, serotonin, and metabolites in all brain areas were revealed after acute administration of clofibrate (25 mg/kg). This is consistent with our results which showed that acute clofibrate treatment wasn't able to reverse hyperlocomotion, stereotypy, and sensory gating impairements in the amphetamine animal model of schizophrenia.. In contrast, the chronic administration of clofibrate showed some significant alterations in selected neurotransmitters and metabolites in the prefrontal cortex, amygdala, and hippocampus.

The dopaminergic and serotonergic systems are considered crucial neurotrasmitters in anxiety disorders. The prefrontal cotex, amygdala, and hippocampus, both as dopaminergic and serotoninergic projections, regulate anxiety-like behaviors (Zarrindast and Khakpai, 2015), (Forster et al., 2012), (González-Burgos and Feria-Velasco, 2008), (Vidal et al., 2007). In the amygdala, aversive stimuli and anxiogenic drugs markedly increase dopamine release in normal rats, whereas anxiolytics completey inhibit this changes and decrease dopamine release and activity (Liu et al., 2011), (Forster et al., 2012). The present results are consistent with these studies. In fact clofibrate significantly reduced the dopamine concentration in the amygdala. The levels of DOPAC and HVA, the major metabolites of dopamine, were also significantly decreased. So as long as clofbrate significantly reduced the levels of dopamine and its metabolites DOPAC and HVA in the amygdala, it is probable that clofibrate affects the synthesis or release of dopamine in this brain area. Since the administration of dopamine receptor antagonist drugs, such as buspirone, that reduce the level of dopamine, play a role

in anti-anxiety effects (McMillen et al., 1983), the down-regulation of dopamine in the amygdala e may be responsible for the anxiolytic effect of clofibrate. Melis el al. (2008) found also that the intracerebroventricular injection of the PPAR-α endogeneous agonists OEA and PEA suppresses nicotine-induced increase in dopamine neuron firing rate in the ventral tegmental area of the brain. However, it should be noted that the roles of dopamine in the brain in anxiety disorders are multiple and subtle, strongly depending on the dopamine receptor subtypes modified or involved, brai area analyzed and behavioral phenotypes considered (Zarrindast and Khakpai, 2015). Further studies need to be performed before a definite conclusion can be reached about the role of dopamine in the pharmacological mechanism underlying the chronic anxiolytic properties of clofibrate.

There could be other possible anxiolytic mechanisms of clofibrate. For instance, monoamine oxidases (A and B) aid the degradation of serotonin and dopamine, and monoamine oxidase inhibitors have been found to be effective in reducing anxiety (Tyrer and Shawcross, 1988), (Westenberg, 2009). It can be speculated that the inhibition of monoamine oxidases is another candidate way underlying the anxiolytic mechanism of clofibrate, since the chronic administration of clofibrate (25 mg/kg) significantly reduced the level of 5-HIAA in both the prefrontal cortex and the hippocampus, and the level of DOPAC and HVA in the prefrontal cortex. Regarding dopamine and serotonin, reduced turnover for this neurotransmitter could be expected to increase cytosolic dopamine and serotonin which, in turn, might be capable to inhibit tyrosine hydroxylase and tryptophan hydroxylase activities in these sites, possibly maintaining its basal level unchanged (Kumer and Vrana, 1996), (Mandell, 2012). Since this study measure the concentrations in the brain tissue "*as a whole*", we cannot be certain that there is no difference in just the "extracellular" monoamine levels between control and treated-rats groups. Hence even if we haven't demonstrated a significant difference among dopamine and serotonin levels in the prefrontal cortex and hippocampus, the significant reduced levels of their metabolites may indicate an inhibition or reduction in serotonin and dopamine transporters. Monoamine transporters are responsible for the serotonin and dopamine reuptake into neurons, after their

release. Previous studies demonstrated anxiolytic effects of dopamine reuptake inhibitors such as bupropion (Tanyeri et al., 2016), and serotonin reuptake inhibitors represent currently the most common pharmacological treatment for depression and anxiety (Bandelow et al., 2017). Interestingly, these findings were also demonstrated in the hippocampus and prefrontal cortex, which are considered as regions of interest in anxiety disorders (Martin et al., 2009), (Canteras et al., 2010), (Etkin, 2010), (Shin and Liberzon, 2010), whereas increased 5-HIAA in the hippocampus is associated with increased anxiety (Macbeth et al., 2008), (Davies et al., 2016).

6. Chapter VI: Conclusion

In conclusion, clofibrate, a synthetic PPAR-α agonist and an already clinically used hypolipidemic agent, exhibited anxiogenic effects when given acutely in the open field and social interaction tests. While concerning the elevated plus maze test, neither anxiogenic nor anxiolytic effects were produced by acute clofibrate treatment, suggesting different behavioral stress responses between experimental animal tests of anxiety. In contrast, after chronic treatment with clofibrate an anxiolytic effects appeared in the open field test,. In fact, the anxiogenic effects were normalized after only 3 repeated administrations of clofibrate (once daily over 3 days) in the open field test, and therefore further studies are recommended to examine whether the same short period and mode of administration is sufficient for normalizing the anxiogenic effects in the social interaction test. These results are consistent with our neurochemical data. Chronic clofibrate treatment significantly reduced the levels of dopamine and its metabolites: DOPAC and HVA, in the amygdala, the levels of DOPAC and HVA in the prefrontal cortex, and the level of the serotonin metabolite 5-HIAA in both the prefrontal cortex and the hippocampus, whereas the acute administration of clofibrate didn't induce any neurochemical changes. Taking into consideration that the most commonly used therapeutic drugs of anxiety, selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) (Bandelow et al., 2017), require usually a period of 2-6 weeks of treatments before therapeutic effects develop, and that the emergence of these effects is usually preceded by an episode of anxiety, our findings shed the light about the rapid anxiolytic properties of clofibrate. Co-administration of clofibrate may potentially accelerate the onset as well as the therapeutic potential of the anxiolytic agents.

Moreover, using both glutamatergic and dopaminergic models, we found that an acute injection of clofibrate, at dose that by itself does not affect spontaneous locomotor activity (25 mg/kg), was unable to revert the positive symptoms of schizophrenia such as hyperlocomotion, stereotypies and impaired PPI induced by the acute injections of phencyclidine (5 mg/kg) or amphetamine (3 mg/kg).

However, when we used the sub-chronic treatment of PCP (5 mg/kg i.p. twice day for 7 consecutive days) that induced cognitive deficits in the novel object recognition (NOR) test, acute clofibrate (25 mg/kg i.p.) that by itself does not affect recognition memory in NOR paradigm, was able to significantly attenuate the cognitive deficits. Besides, clofibrate did not induce catalepsy in the bar test at any dose tested compared to haloperidol.

Overall, these results provide evidence that the synthetic PPAR-α agonist, clofibrate, may be useful for the treatment of anxiety and cognitive dysfunctions in schizophrenia, without having undesirable central nervous system side effects.

7. Chapter VII: Future Directions

Further studies should be planned to clarify the mechanism of action of clofibrate in regulating the anxiety and schizophrenic-like behaviors in rats.First of all, clofibrate should be further tested sub-acutely and chronically in each of social interaction and elevated plus maze tests. Then, the expression level of certain molecular factors', such as BDNF and CREB, mRNA and protein in the hippocampus and other brain sites should be examined to detect whether the different cognitive and behavioral profiles of clofibrate are really regulated by these molecular changes. In addition, the capacity of clofibrate to protect against oxidative stress induced by phencyclidine can be demonstrated by examining the activity and expression of several enzymes related related to oxidative process, such as copper- and zinc-superoxide dismutase, and which may in turn contribute to reverse the PCP-induced cognitive deficits. Also, the ability of clofibrate to compensate for the sub-chronic PCP-induced reduction in parvalbumin mRNA, and acute-PCP negative symptoms, must be further investigated. In addition, the effect of clofibrate on different neurotransmitters; such as GABA and gluatamate, and their metabolites could be evaluated. Besides, the evaluation of tyrosine hydroxylase, tryptophan hydroxylase, and dopamine and serotonin transporters, in the rats' brains, by immunohistochemical assays would unravel the neurobiological mechanism of clofibrate in modulating its behavioral and cognitive profile.

8. Chapter VIII: References

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