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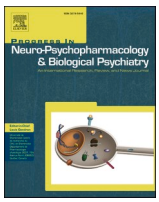

Adolescent stress differentially modifies dopamine and norepinephrine release in the medial prefrontal cortex of adult rats

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ABSTRACT

Adolescent stress (AS) has been associated with higher vulnerability to psychiatric disorders such as schizophrenia, depression, or drug dependence. Moreover, the alteration of brain catecholamine (CAT) transmission in the medial prefrontal cortex (mPFC) has been found to play a major role in the etiology of psychiatric disturbances. We investigated the effect of adolescent stress on CAT transmission in the mPFC of freely moving adult rats because of the importance of this area in the etiology of psychiatric disorders, and because CAT transmission is the target of a relevant group of drugs used in the therapy of depression and psychosis. We assessed basal dopamine (DA) and norepinephrine (NE) extracellular concentrations (output) by brain microdialysis in in the mPFC of adult rats that were exposed to chronic mild stress in adolescence. To ascertain the role of an altered release or reuptake, we stimulated DA and NE output by administering either different doses of amphetamine (0.5 and 1.0 mg / kg s.c.), which by a complex mechanism determines a dose dependent increase in the CAT output, or reboxetine (10 mg/kg i.p.), a selective NE reuptake inhibitor. The results showed the following: (i) basal DA output in AS rats was lower than in controls, while no difference in basal NE output was observed; (ii) amphetamine, dose dependently, stimulated DA and NE output to a greater extent in AS rats than in controls; (iii) reboxetine stimulated NE output to a greater extent in AS rats than in controls, while no difference in stimulated DA output was observed between the two groups. These results show that AS determines enduring effects on DA and NE transmission in the mPFC and might lead to the occurrence of psychiatric disorders or increase the vulnerability to drug addiction.

1. Introduction

An inappropriate stress response can be a major contributor to the development of numerous diseases affecting the cardiovascular, immune, and central nervous systems. The “stress response” involves a rapid activation of the sympathetic nervous system, which engages the release of epinephrine and adrenal glucocorticoids in the blood stream. Corticosteroid hormones act as transcriptional regulators in the brain, leading to stress related brain diseases in genetically predisposed individuals (de Kloet et al., 2005; Sanacora et al., 2022). Among the brain areas, in which the glucocorticoids can produce a detrimental effect that may contribute to the appearance of psychiatric disorders, such as depression or schizophrenia, the prefrontal cortex (PFC) is the most sensitive, and either acute or prolonged stress can cause damage that ranges from a decline in cognitive activities, to architectural changes (Arnsten, 2009). Corticotropin releasing factor (CRF) is a pivotal player in mediating stress consequences that encompass PFC functions such as sustained attention, working memory, but also in cognitive flexibility and decision making; this feature supports its potential involvement in the appearance and development of psychiatric disorders, but also in potential therapeutic interventions (Hupalo et al., 2019).

The outcomes of stress exposure depend on its intensity (mild,

Abbreviations: ACC, anterior cingulate cortex; AS, adolescent stress; BLA, basolateral amygdala; CAT, catecholamines; CUMS, chronic unpredictable mild stress; DA, dopamine; DAT, dopamine transporter; DRN, dorsal raphe nuclei; HPA, hypothalamic-pituitary-adrenal; ILCx, infralimbic cortex; LC, locus coeruleus; LHb, lateral habenula; mPFC, medial prefrontal cortex; NE, norepinephrine; NET, norepinephrine transporter output: extracellular concentration; PFC, prefrontal cortex; PLCx, prelimbic cortex; PND, post-natal day; PTSD, post-traumatic stress disorder; VTA, ventral tegmental area.

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moderate, intense), duration (acute or chronic) and especially, on the life period of exposure (prenatal, post-natal, adolescent, adult) (Musazzi et al., 2017; Macht and Reagan, 2018). In particular, the exposure to stress during adolescent life represents an important risk factor for the development of psychiatric pathologies that may persist throughout adult life (Burke et al., 2017; Sisk and Gee, 2022). Acute and intense levels of stress can trigger relatively low prevalence disorders such as post-traumatic stress disorder (PTSD) (Harnett et al., 2020), whereas chronic moderate stress can trigger a wide range of high occurrence disorders such as anxiety, psychosis, and substance abuse disorders (Macht and Reagan, 2018; Vargas et al., 2020; Munshi et al., 2021; Woo et al., 2021). Among the diverse responses to stress, exposure to acute uncontrollable stress increases CAT release in the PFC, impairing the expression of high cognitive function such as goal directed behaviour (Arnsten, 2015) or altering the crucial role of DA in balancing inhibition/excitation in the mPFC to produce normal, functioning working memory (Arnsten, 2015; Mizoguchi et al., 2000; Murphy et al., 1996; Lee and Goto, 2015). It is interesting to note that the effects of acute stress can be very different from those of chronic stress, both in terms of the brain area involved, release of neuromediators (e.g. BDNF), or gender (Conoscenti et al., 2024; Choi et al., 2008; Lakshminarasimhan and Chattarji, 2012; Zavala et al., 2011). In this study we will only evaluate the long-term effects of chronic stress. The effects of chronic unpredictable mild stress (CUMS) have been widely investigated since it was first proposed as an animal model of depression (Willner, 2016; Antoniuk et al., 2019). Catecholaminergic transmission in the PFC is closely connected with excitatory and inhibitory transmission. Moreover, it undergoes complex changes during adolescence and is directly involved in the effects of stress in this critical developmental period (Perica and Luna, 2023). Exposing juvenile male rats to repeated stress significantly reduced AMPA and NMDA receptor mediated transmission in the PFC and impaired temporal order recognition memory (Yuen et al., 2012). Furthermore, it has been reported that adolescence chronic stress impaired cognitive flexibility and dysregulated the expression of certain GABAergic system markers that contributes to adolescent PFC GABAergic maturation, in Npas4 (neuronal Per-Arnt-Sim domain 4) deficient male mice (Page et al., 2018). Additionally, DA and NE transmission interact profoundly in the PFC (Carboni and Carta, 2009; Xing et al., 2016) and although the effect of stress can affect these two systems in a peculiar manner, the acute and delayed consequences of stress can exacerbate a genetic predisposition leading to profoundly different disorders such as schizophrenia or depression (Hammen, 2005; Krishnan and Nestler, 2008; Howes et al., 2017; Price and Duman, 2020). In view of the fact that chronic stress has a significant role in depression (Hammen, 2005), NE has a pivotal role in the modulation of stress circuits in CNS (Morilak et al., 2005), and DA transmission has a crucial role in the occurrence of psychiatric disorders (Yan and Rein, 2022; Anderson et al., 2019a), this study aims to evaluate basal and stimulated NE and DA transmission in the PFC of adult rats that have been exposed to CUMS in adolescent age, i.e. from post-natal day (PND) 32 to 41. The results could provide hints to understanding the deleterious effects of stress on mPFC CAT transmission and may well contribute to the development of new therapeutically active tools for treating psychiatric disorders.

2. Materials and methods

2.1. Animals

This study was conducted on male rats bred in our facility to avoid any effects of transport-related stress. Male and female Sprague-Dawley rats from Harlan (S. Pietro al Natisone, Italy) were used as breeders. Each male rat was paired with two females, housed in a medium cage for 5 days and then removed. The two female rats were housed together for two weeks and then individually until parturition, under standard conditions of humidity (60%), temperature (22 °C) and artificial light (light, 8 A.M. to 8 P.M.). Food and water were available ad libitum. After birth, the litter was weaned on PND 21, and rats were randomly assigned to the control and stress groups. The rats were housed in groups of three per cage taking care to allocate the members of the same household evenly between the two groups.

2.2. Drugs

D-Amphetamine Sulfate (obtained from Sigma-Aldrich, Milan, Italy) was dissolved in saline and administered (0.1 ml/100 g) subcutaneously (s.c.). Reboxetine was a gift from Pharmacia Upjohn (Milan, Italy). It was dissolved in saline and administered (0.3 ml/100 g) intraperitoneally (i.p.).

2.3. Chronic unpredictable mild stress procedure

The CUMS procedure used is based on the one originally proposed by Willner (2005), suitably adapted for use in adolescent rats (Reich et al., 2013). The stresses used were not per se severe, but the unpredictability of their application is an additional stress. The CUMS protocol is based on the application of 3 stresses per day for 10 consecutive days, starting after PND 32. The order of execution of the stresses was randomly chosen from 7 different types and performed at randomly chosen times; the same stress was never repeated twice in a row. The types of stress performed were: 1) 60 min tube restrain in a novel room environment; 2) 5 min swim stress in water at 25 °C; 3) 30 min vibration in a laboratory shaker at 60 oscillations per min. 4) 12 h dark/light cycle inversion in a novel environment; 5) 18 h food and water deprivation; 6) 18 h social isolation in small cages; 7) the rats were housed for 18 h in their cages in which sawdust was liberally soaked. Controls were handled daily for 5 min near their home cage at 12 a.m. From PND 42, the rats were left undisturbed in their cages, under standard conditions until the day of surgery. At PND 42 the weight of the control rats was 197.7 ± 12.5 g, while that of the AS group was 162.8 ± 10.0 (mean ± S.D.; $n = 22$ for each group). This difference was found to be statistically significant (df = 42, Fr = 1.56; $p < 0.00001$).

From 65 PND and before 75 PND, rats underwent the microdialysis probe implantation procedure. The weight of control rats at the day of surgery was: 351.7 ± 27.3 g, while that of the AS group was 339.9 ± 29.4 (mean ± S.D.; $n = 22$ for each group). This difference was not statistically significant (df = 42, Fr = 1.15; $p = 0.172$).

All animal experimentation was conducted in accordance with the guidelines for care and use of experimental animals as specified by the European Community Council (2010/63/UE L 276 20/10/2010) and by Italian law (DL 04/03/2014 n° 26). This study was approved by the Organization for Animal Care of the University of Cagliari (OPBA-UniCA) and by Ministry of Health, aut. # 352/215-PR and 353/2015 PR (11/05/2015). Every effort was made to minimize suffering and reduce the number of animals used.

2.4. Probes and surgery

Concentric microdialysis probes were house constructed, as previously described (Silvagni et al., 2008). We used AN 69 (sodium methallyl sulphate copolymer) dialysis fiber, (0.310 and 0.220 μm, outer and inner diameter, respectively), cut-off 40.000 Da (Hospal-Dasco, Bologna, Italy), active-membrane length = 3 mm. The rats were anaesthetized with ketamine (80 mg/kg, i.p.)/xylazine (10 mg/kg, i.p.) and placed in stereotaxic apparatus (Kopf, Germany). A small hole was drilled on the side of the exposed skull (the right side is usually preferred) and a microdialysis probe was implanted in the mPFC according to the following coordinates: AP + 3.5 and L ± 0.8; V -4.0 from dura mater; coordinates (AP, L) are in mm, from bregma, according to the Paxinos and Watson (2007). Probes were then fixed to the skull with dental cement (Shofu CX-Plus, GmbH, Ratingen, Germany) and the skin sutured. The rats were individually housed with food and water

available in transparent plexiglass hemispheres, covered with a top hemisphere with sawdust on the bottom.

2.5. Dialysis experiments

Experiments were performed on freely moving rats 48 h after the probe implantation. On the day of the experiment, the implanted probes were connected to a microinjection pump (World Precision Instruments) and a Ringer's solution (NaCl 147 mM; $CaCl_2$ 2.2 mM; KCl 4 mM, pH 6.5) was forced through the dialysis probe at a constant flow rate of 1 μL/min. Dialyzed samples (20 μL) were collected every 20 min and immediately injected unpurified into a HPLC system equipped with reversed-phase column (C-18, 15 cm × 4.6 mm, 3.5 mm Supelco, Milan, Italy) and a coulometric detector (ESA Coulochem II, Bedford, MA, USA; oxidation +125 mV, reduction −175 mV). The mobile phase composition was 0.1 M sodium acetate, 0.3 mM Na_2EDTA, 1.8 mM octanesulfonic acid, 120 ml/L methanol, buffered at pH 5.4. The sensitivity of the assay allowed for the detection of 5 fmoles of NE and DA in the same dialysate sample. Approximately three hours after the start of the probe perfusion, when the basal NE and DA output reached stable values (a mean of three consecutive samples differing <10% from the mean of the previous three samples), the rats were given a single acute administration of the tested drug or saline. Each implanted rat was administered with a test drug once only. Equal numbers of AS and control rats were used in each experiment.

2.6. Histology

Histological analysis was performed in order to locate the position of the fiber. On conclusion of the experiment, rats were anaesthetized with chloral hydrate (1 g/kg, i.p.) and killed; their brains were removed and stored in formaldehyde (10%). The brains were then cut on an oscillating microtome, (Campden Instruments, Lafayette, IN, USA) producing consecutive coronal slices containing the region of interest, in accordance with the coordinates of the Paxinos and Watson (2007). Results from rats implanted outside the PFC were discarded. A schematic representation of the traces left by the probes implanted in the mPFC is shown in Fig. 1. To avoid trace overlapping only 50% of the traces were represented in each section.

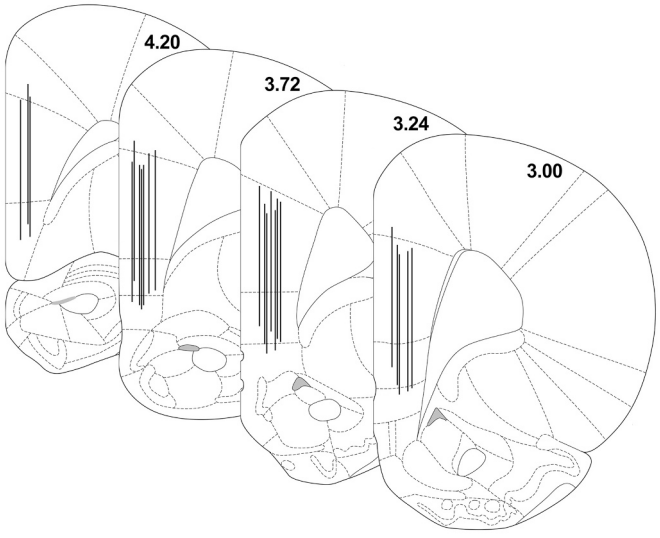

Fig. 1. Schematic representation of the brain area investigated by a succession of coronal section at the level of the prefrontal cortex. Vertical lines have been drawn in each section representing a balanced 50% of the traces left by the fibers implanted, as observed by histological examination. The number in each section represents the anteriority from bregma according to the atlas of Paxinos and Watson (2007).

2.7. Statistics

Statistical analysis was carried out by STATISTICA (Statsotf, Tulsa, OK, USA). One-way or two-way or three-way analysis of variance (ANOVA) for repeated measures was applied to the data expressed as a percentage of basal NE and DA concentration. Considering that basal DA levels in AS rats were significantly lower than in controls, the effect of amphetamine and reboxetine on DA output was analysed and reported in absolute fmoles as well (Panels B in Figs. 3, 4 and 5). Results from treatments showing significant overall changes were subjected to post hoc Tukey's tests with significance attributed where $p < 0.05$.

3. Results

3.1. Effect of adolescent stress on basal output

Fig. 2 shows that the AS reduces the basal DA output by 38.7% but does not affect NE output. DA output was 13.09 ± 1.38 in AS rats and 21.34 ± 2.61 in controls (fmol/μL sample ± SE). One-way ANOVA of DA estimation showed a significant stress effect ($F_{1,42} = 8.48$, $P < 0.01$). Post-hoc analysis (Tukey) showed that DA output in AS rats was significantly lower than in controls ($P < 0.01$). NE output was 34.96 ± 3.40 in AS rats and 33.26 ± 2.95 in controls (fmol/μL sample ± SE). One-way ANOVA of DA estimation showed no significant stress effect ($F_{1,42} = 0.16$, $P = 0.69$).

3.2. Effect of amphetamine on dopamine output

3.2.1. Percentage of basal levels

Figures. 3A and 4A show that amphetamine (0.5 and 1 mg/kg), significantly increased DA output in AS and control rats, dose dependently. Amphetamine (0.5 mg/kg s.c.) maximally increased DA output by 136% and by 75% above basal, in AS and control rats respectively (Fig. 3A), as recorded 40 min after treatment. Overall analysis (Three-way ANOVA) of amphetamine treatment results showed a significant stress effect ($F_{1,16} = 5.97$, $P < 0.05$), treatment effect ($F_{1,16} = 44.32$, $P < 0.001$), time effect ($F_{8,128} = 107.82$, $P < 0.001$), and stress-treatment interaction ($F_{1,16} = 4.71$, $P < 0.05$). Post-hoc analysis (Tukey) showed

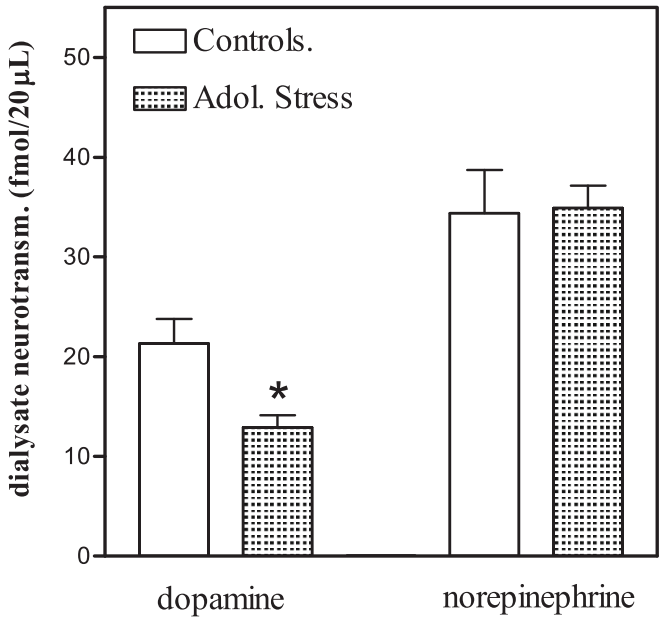

Fig. 2. Basal extracellular concentration of dopamine and norepinephrine in the medial prefrontal cortex of adult rats exposed to adolescent stress and relative controls. Each column is the mean (± SE) of 22 determinations for each of the two experimental groups. * $P \leq 0.05$ from relative control.

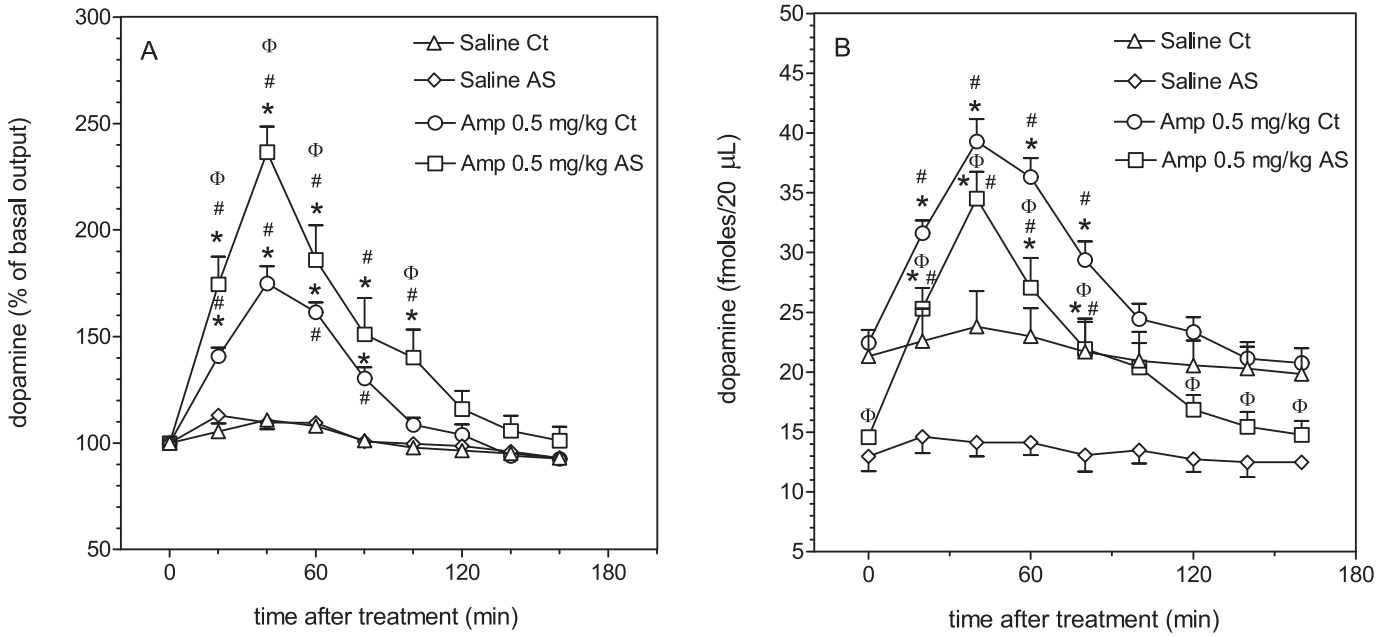

Fig. 3. Effect of amphetamine (0.5 mg/kg s.c.) and saline on dialysate dopamine expressed as a percentage of basal output (A) or as fmoles/20 µL (B), from the medial prefrontal cortex of adult rats exposed to adolescent stress. Each point is the mean (± SE) of at least five determinations. * $P < 0.05$ from basal values; # $P < 0.05$ from the corresponding time point of saline in the same experimental group. Φ $P < 0.05$ versus the corresponding time point of amphetamine in controls.

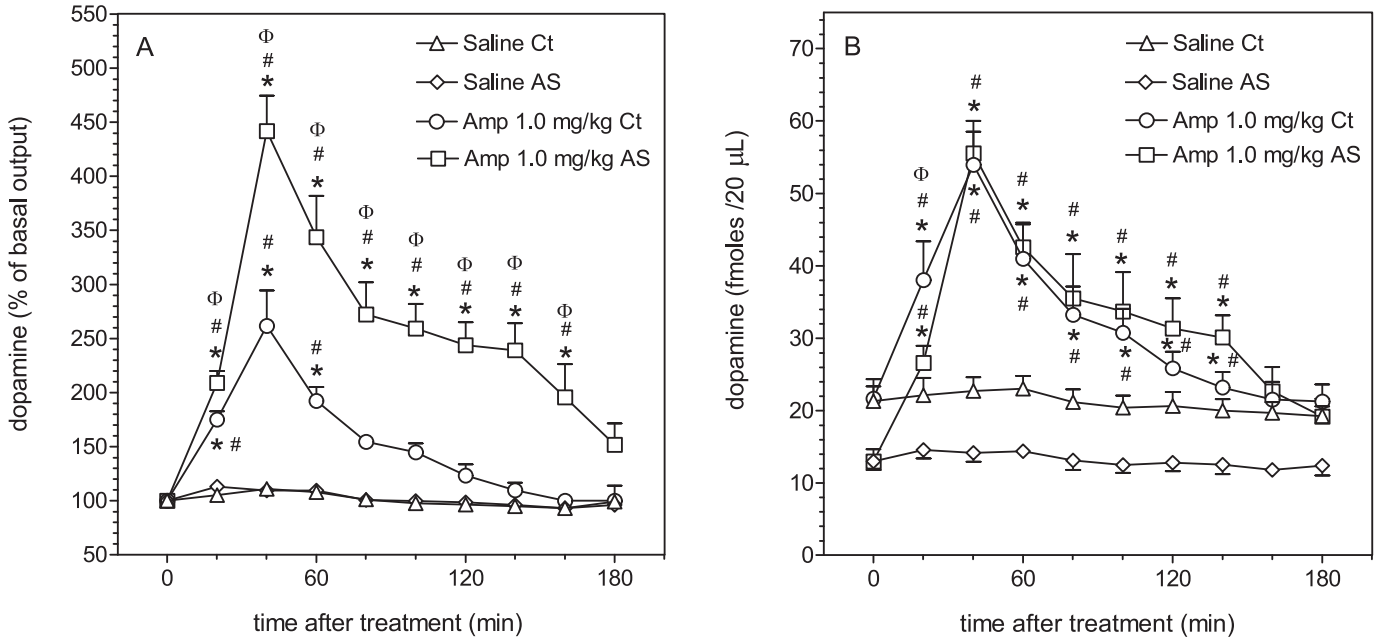

Fig. 4. Effect of amphetamine (1.0 mg/kg s.c.) and saline on dialysate dopamine expressed as a percentage of basal output (A) or as fmoles/20 µL (B), from the medial prefrontal cortex of adult rats exposed to adolescent stress. Each point is the mean (± SE) of at least five determinations. * $P < 0.05$ from basal values; # $P < 0.05$ from the corresponding time point of saline in the same experimental group. Φ $P < 0.05$ versus the corresponding time point of amphetamine in controls.

that DA output was significantly higher in adult AS than in controls at 20, 40, 60 and 100 mins after amphetamine administration.

Amphetamine (1.0 mg/kg s.c.) maximally increased DA output by 342% and by 162% above basal in AS and control rats respectively, as recorded 40 mins after treatment (Fig. 4A). Overall analysis (Three-way ANOVA) of amphetamine treatment results, showed a significant stress effect ($F_{1,16} = 29.85$, $P < 0.001$), treatment effect ($F_{1,16} = 107.37$, $P < 0.001$), time effect ($F_{9,144} = 44.35$, $P < 0.001$), and stress-treatment interaction ($F_{1,16} = 28.08$, $P < 0.001$). Post-hoc analysis (Tukey) showed that DA output was significantly higher in adult AS than in control rats in the time interval between 20 and 160 mins after amphetamine administration.

3.2.2. *Absolute basal levels*

Figure 3B shows that amphetamine (0.5 mg/kg, s.c.) significantly increased DA absolute output in AS and control rats. Overall analysis (Three-way ANOVA) of amphetamine treatment results, showed a significant stress effect ($F_{1,16} = 22.00$, $P < 0.01$), treatment effect ($F_{1,16} = 19.97$, $P < 0.01$), time effect ($F_{8,128} = 95.58$, $P < 0.001$), but not stress-treatment interaction ($F_{1,16} = 0.33$, $P = 0.57$). Post-hoc analysis (Tukey)

showed that DA output was significantly higher in adult AS than in controls in the time interval between 20 and 80 mins after amphetamine administration.

Figure 4B shows that amphetamine (1.0 mg/kg, s.c.) significantly increased DA absolute output in AS and control rats. Overall analysis (Three-way ANOVA) of amphetamine treatment results showed no significant stress effect ($F_{1,16} = 22.00$, $P = 0.20$) or stress-treatment interaction ($F_{1,16} = 1.70$, $P = 0.21$). Fig. 4B shows a significant treatment effect ($F_{1,16} = 36.60$, $P < 0.001$) and time effect ($F_{9,144} = 56.52$, $P < 0.001$). Post-hoc analysis (Tukey) showed that DA absolute output was significantly higher in adult control than in AS rats only at 20 mins after amphetamine administration.

3.3. Effect of reboxetine on dopamine output

3.3.1. Percentage of basal levels

Figure 5A shows that reboxetine significantly increased DA output in AS and controls. Reboxetine (10 mg/kg i.p.) maximally increased DA output by 100% above basal, in both AS and controls, as recorded 60 and 80 mins after treatment, respectively. Overall analysis (Three-way ANOVA) of reboxetine treatment results showed no significant stress effect ($F_{1,20} = 0.03$, $P = 0.85$) or stress-treatment interaction ($F_{1,20} = 0.02$, $P = 0.88$); a significant treatment effect ($F_{1,20} = 140{,}59$, $P < 0.001$) and time effect ($F_{9,180} = 14.40$, $P < 0.001$) was observed.

3.3.2. Absolute levels

Figure 5B shows that reboxetine significantly increased DA output in AS and controls. Overall analysis (Three-way ANOVA) of reboxetine treatment results showed a significant stress effect ($F_{1,20} = 41.13$, $P < 0.001$), treatment effect ($F_{1,20} = 39.51$, $P < 0.001$), time effect ($F_{9,180} = 14.38$, $P < 0.001$), but not stress-treatment interaction ($F_{1,20} = 1{,}74$, $P = 0.20$). Post-hoc analysis (Tukey) showed that DA absolute output was significantly lower in adult AS than in controls in the time interval between 40 and 120 mins after amphetamine administration.

3.4. Effect of amphetamine on norepinephrine output

Figures 6 and 7 show that amphetamine dose dependently (0.5 end 1 mg/kg) significantly increased NE output in AS and control rats. Amphetamine (0.5 mg/kg s.c.) maximally increased NE output by 138% and by 59% above basal, in AS and control rats respectively, as recorded 40 mins after treatment (Fig. 6). Overall analysis (Three-way ANOVA) of amphetamine treatment results showed a significant stress effect ($F_{1,16} = 16.40$, $P < 0.001$), treatment effect ($F_{1,16} = 85.51$, $P < 0.001$), time

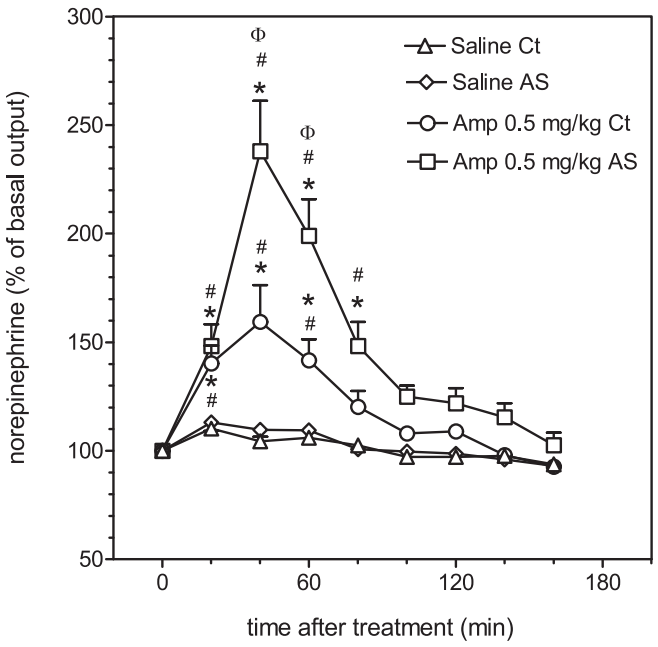

Fig. 6. Effect of amphetamine (0.5 mg/kg s.c.) and saline on dialysate norepinephrine expressed as a percentage of basal output, from the medial prefrontal cortex of adult rats exposed to adolescent stress. Each point is the mean (± SE) of at least five determinations. * $P < 0.05$ from basal values; # $P < 0.05$ from the corresponding time point of saline in the same experimental group. Φ $P < 0.05$ versus the corresponding time point of amphetamine in controls.

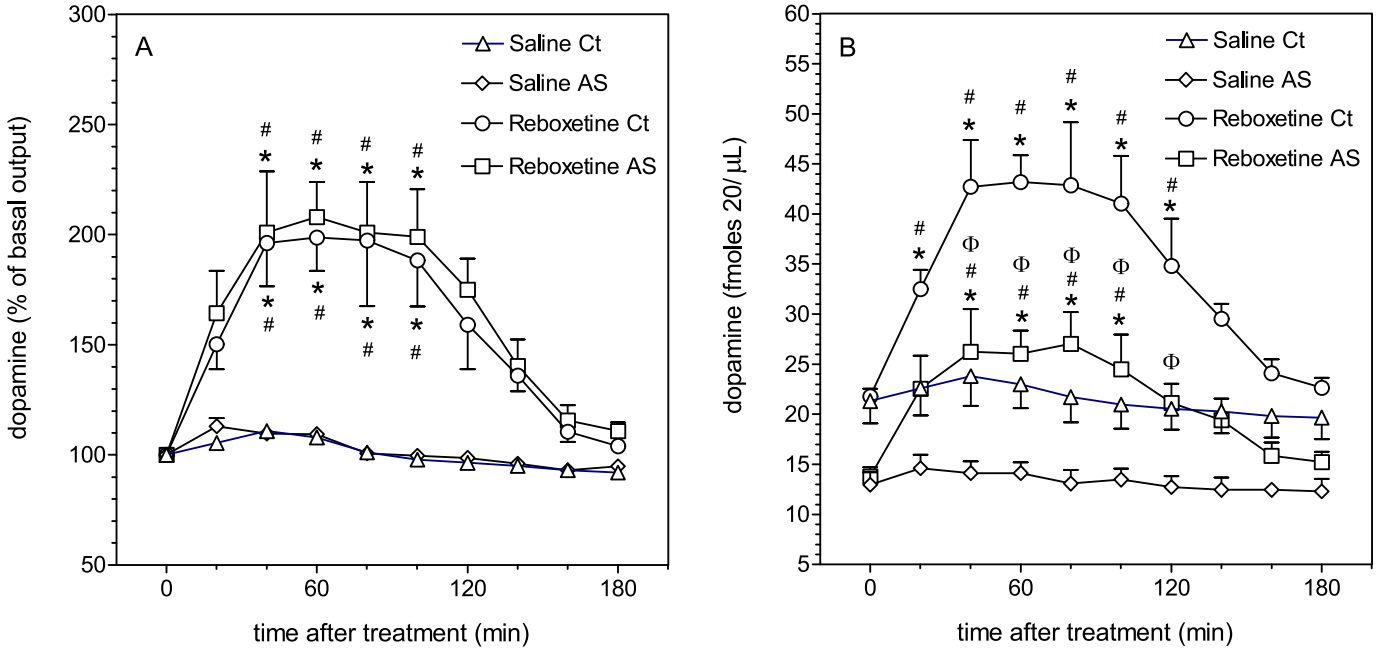

Fig. 5. Effect of reboxetine (10 mg/kg i.p.) and saline on dialysate dopamine expressed as a percentage of basal output (A) or as fmoles/ 20 µL (B), from the medial prefrontal cortex of adult rats at adolescent stress. Each point is the mean (± SE) of at least five determinations. * $P < 0.05$ from basal values; # $P < 0.05$ from the corresponding time point of saline in the same experimental group. Φ $P < 0.05$ versus the corresponding time point of reboxetine in controls.

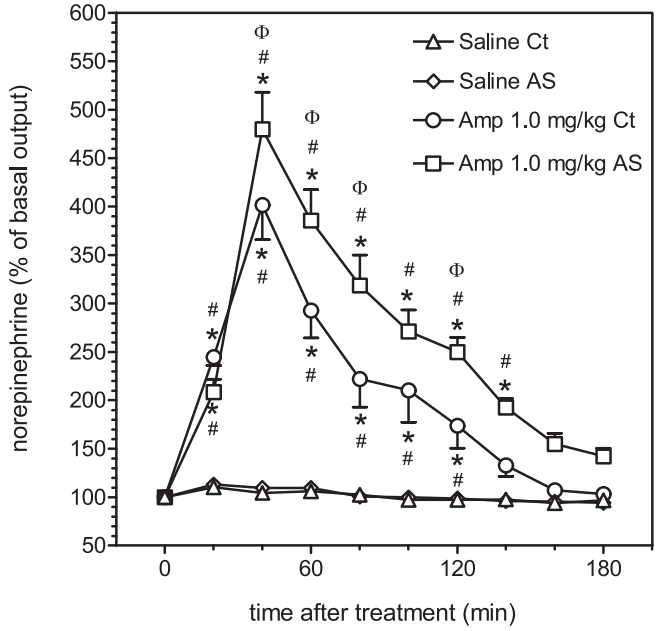

Fig. 7. Effect of amphetamine (1.0 mg/kg s.c.) and saline on dialysate norepinephrine expressed as a percentage of basal output, from the medial prefrontal cortex of adult rats exposed to adolescent stress. Each point is the mean (± SE) of at least five determinations. * $P < 0.05$ from basal values; # $P < 0.05$ from the corresponding time point of saline in the same experimental group. Φ $P < 0.05$ versus the corresponding time point of amphetamine in controls.

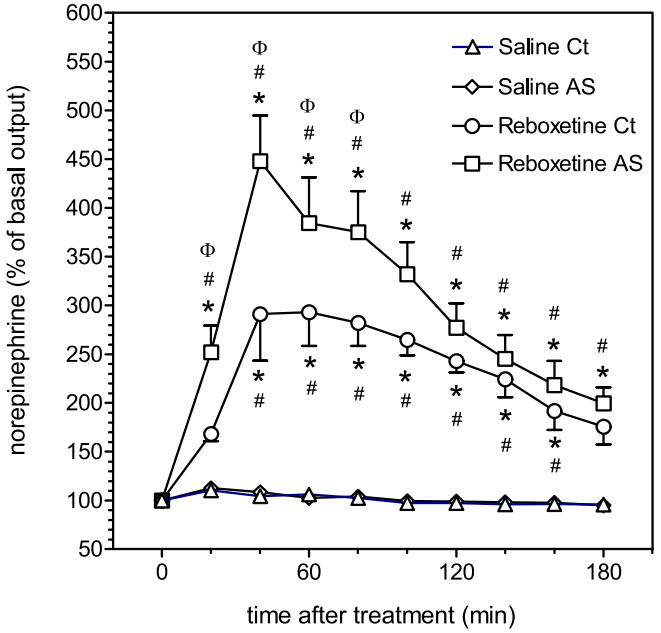

Fig. 8. Effect of reboxetine (10 mg/kg i.p.) and saline on dialysate norepinephrine expressed as a percentage of basal output, from the medial prefrontal cortex of adult rats exposed to adolescent stress. Each point is the mean (± SE) of at least five determinations. * $P < 0.05$ from basal values; # $P < 0.05$ from the corresponding time point of saline in the same experimental group. Φ $P < 0.05$ versus the corresponding time point of reboxetine in controls.

effect ($F_{8,128} = 35.65$, $P < 0.001$), and stress- treatment interaction ($F_{1,16} = 13.54$, $P < 0.005$). Post-hoc analysis (Tukey) showed that NE output was significantly higher in adult AS than in control rats at.

40 and 60 mins after amphetamine administration. Amphetamine (1.0 mg/kg s.c.) maximally increased NE output by 379% and by 301% above basal in AS and control rats respectively, as recorded 40 mins after treatment (Fig. 7). Overall analysis (Three-way ANOVA) of amphetamine treatment results showed a significant stress effect ($F_{1,16} = 7.14$, $P < 0.05$), treatment effect ($F_{1,16} = 157.47$, $P < 0.001$), time effect ($F_{9,144} = 77.08$, $P < 0.001$), and stress-treatment interaction ($F_{1,16} = 6.55$, $P < 0.05$). Post-hoc analysis (Tukey) showed that NE output was significantly higher in adult AS than in control rats 40, 60, 80, and 120 mins after amphetamine administration.

3.5. Effect of reboxetine on norepinephrine output

Figure 8 shows that reboxetine (10 mg/kg, i.p.) significantly increased NE output in AS and control rats. Reboxetine maximally increased NE output by 348% and by 193% above basal, in AS and control rats respectively, as recorded 40 and 60 mins after treatment.

Overall analysis (Three-way ANOVA) of reboxetine treatment results showed a significant stress effect ($F_{1,20} = 6.41$, $P < 0.05$), treatment effect ($F_{1,20} = 162.93$, $P < 0.001$), time effect ($F_{9,180} = 24.83$, $P < 0.001$), and stress-treatment interaction ($F_{1,20} = 5.97$, $P < 0.05$). Post-hoc analysis (Tukey) showed that NE output was significantly higher in adult AS than in control rats in at 20, 40, 60 and 80 mins after reboxetine administration.

4. Discussion

4.1. Major findings

Among the major findings of this study is the significant reduction of basal DA output in the mPFC of adult rats exposed to CUMS at adolescent age; we also observed that the NE reuptake (NET) blocker reboxetine, administered systemically, significantly increased NE and DA output. Reboxetine showed a higher efficacy in blocking the NE reuptake in the mPFC of AS rats, as compared with controls, suggesting that both, NE release and reuptake, were increased in AS rats. Furthermore, we observed that amphetamine-stimulated NE and DA output in the mPFC of adult rats, exposed to AS, was significantly higher than that observed in the relative controls suggesting that NE and DA transmission was increased in AS rats.

4.2. Adolescence stress and mPFC

The literature on the effects of adolescent stress is very diverse, making it difficult to make translational conclusions because of the many variables involved in the study of this topic (e.g., species, sex, age of stress exposure, intensity and duration of stress, type, and time of observation of effects. Despite this, the necessity to study the AS is paramount due to the crucial impact that adolescence has on adult life in humans. AS can in fact have significant repercussions on major psychiatric illnesses such as depression, anxiety, PTSD and substance use disorder. (Carr et al., 2013; Casement et al., 2015); AS can also facilitate the onset of schizophrenia in predisposed individuals (Germann et al., 2021). Stress exposure can imbalance the capacity to regulate impulsivity and alter the sensation seeking interval in adolescence but can also influence the permanence of impulsivity and sensation seeking in early adulthood (Wasserman et al., 2023).

As far as experimental animals are concerned, adolescent social stress can lead to the development of anxiety and depression behaviours, as well as intensified drug use in adulthood (Burke et al., 2017). Chronic AS can lead to circuit deficits that recapitulates schizophrenia (Gomes and Grace, 2017), whereas adult stress can trigger a depression-like hypodopaminergic state in rats (Gomes et al., 2020). Early repeated AS functionally impairs brain subregions involved in emotion and cognition, resulting in a PTSD-like condition in rats (Zhao et al., 2020, 2022). Moreover, AS increases amphetamine and ethanol stimulated locomotion and self-administration under many conditions and reduces

levels of meso-cortical dopamine in rats (Burke et al., 2013; Burke and Miczek, 2014.

The evaluation of the AS effects on brain functioning is somewhat complex because stress may interfere with the remodelling of neuronal circuits that occurs during adolescence (Spear, 2000; Larsen and Luna, 2018) and heavily involves the CAT innervation of the PFC (Reynolds and Flores, 2021; Hoops and Flores, 2017). In fact, during adolescence, the brain DA system goes through a complex process of receptor pruning (Drzewiecki et al., 2016; Delevich et al., 2018; Germann et al., 2021), characterized by synaptic contact elimination or strengthening, that is functional for the maturation of goal-directed behaviour (Selemon, 2013; Shapiro et al., 2017).

Besides synaptic pruning, the DA fiber density and tissue content increase dramatically in the mPFC in early adolescence (Naneix et al., 2012), while in late adolescence, a decrease in mPFC receptor expression coincides with the highest spontaneous firing of DA cell (McCutcheon and Marinelli, 2009; Reynolds and Flores, 2021), as if exposure to high concentrations of DA could contribute to down-regulate DA receptor expression. In this context, it is likely that exposure to AS could profoundly alter this delicate process involving DA's relationship with pyramidal and inhibitory PFC neurons. Thus, the excessive DA stimulation that occurs in AS may alter the development of the correct balance between GABA inhibition and glutamate excitation in the mPFC with the consequence of creating a predisposition to psychiatric illness (Arnsten, 2015).

Besides DA innervation, adolescence also shapes mPFC NE innervation, although the knowledge of the developmental trajectory of this system is scarce (Mokler et al., 2017); in particular, NET density in the prelimbic cortex (PLCx), declines through PND 40 to PND 60 (Bradshaw et al., 2016), and the locus coeruleus (LC) respond to stress insults in a different manner, depending on the PND of stress application (Bingham et al., 2011; Zitnik et al., 2016). The NE innervation of PFC originates from LC, a heterogenous and complex structure that in turn receives excitatory inputs from the same PFC, together with other brain structures that are involved in producing stress outcomes on behavioural output (Cardenas et al., 2021; Barcomb et al., 2022). NE release rises and falls across behavioural states and plays complex roles in the modulation of working memory and attention; it has a neuro-modulatory type action with a long onset and protracted effect. In particular, the interaction between NE and DA innervation and with PFC pyramidal neurons results in an inhibition of background discharge, increasing the signal–to-noise ratio that helps to filter irrelevant stimuli while enhancing behaviourally significant stimuli (Stahl, 2009; Mather et al., 2016). NE release in the PFC is strictly related to stress, as LC neurons are stimulated by CRF receptors that are activated by amygdala innervation (Van Bockstaele et al., 1998; Nakane et al., 1994). In turn, the mPFC has been hypothesized to inhibit hypothalamic-pituitary-adrenal (HPA) responses to emotional stress, via influences on the paraventricular hypothalamic nucleus (Radley et al., 2008).

Although a comparison between the mPFC of humans and rodents is difficult to make, it has been suggested that the rat mPFC combines elements of the primate anterior cingulate cortex (ACC) and the dorsolateral PFC at undeveloped level (Seamans et al., 2008). Furthermore, it is has been postulated that the rodent PLCx could correspond to the pregenual ACC), whereas the rodent infralimbic cortex (ILCx) may be akin to the human equivalent of the subgenual ACC), (aan het Rot et al., 2009; Bicks et al., 2015; Ko, 2017; Laubach et al., 2018; Bittar and Labonté, 2021). The microdialysis probe used in our study monitored the release of CAT, almost exclusively in the PLCx and ILCx (Fig. 1); therefore, the changes in CAT transmission that occur in rats exposed to AS can be cautiously referred to as an alteration of function of pACC and sACC in primates. Interestingly, psychosocial stress stimulates DA release "in vivo" in the dorsomedial PFC of young healthy volunteers (Nagano-Saito et al., 2013).

4.3. Basal levels

This study shows that AS differentially affects basal NE and DA output, in the mPFC of adult rats. Interestingly, the DA and NE innervations of mPFC are heterogenous; in fact, LC NE innervation concentrates mainly in layers I and II/III, where the pyramidal neurons are located. They project to the nucleus accumbens, dorsal striatum, basolateral amygdala (BLA) and contralateral PFC. On the other hand, although distributed in the entire PFC, DA nerve terminals from the ventral tegmental area (VTA), (Sesack et al., 1995; Hoops and Flores, 2017) normally reach layers V and VI, where pyramidal neurons that project to BLA, VTA, thalamus and brainstem nucleus are located (Vander Weele et al., 2018; Quessy et al., 2021; Bittar and Labonté, 2021).

The size of the implanted probe means it is not possible to assess DA and NE output in a specific layer, but the different target of the DA and NE innervation does enable us to consider it plausible that DA output is significantly reduced by AS while NE output is not. Therefore, the neuronal circuit that involves VTA and layers V and VI and its output appear to be more sensitive to the effects of AS. It is hard, however, to identify the real cause of the significant DA output reduction in the mPFC. The most immediate explanations may be: i) AS determines a long-term reduction of VTA neuronal firing and consequently a reduced release; ii) an increased reuptake, not supported by an increased firing and DA release, can produce a reduced output; iii) the developmental changes and the progressive increase of DA output that occurs during adolescence is counteracted by a circuit that is used to handle the high concentration of CAT released in PFC by stress, through a long-term reduction of mPFC DA output. Clearly, all three of these possibilities can occur concurrently. The reduction of mPFC DA transmission has been observed previously in different models of stress. VTA DA neurons projecting to the mPFC have been involved in the regulation of anxiety and social behaviours that are encompassed in emotional stress response (Friedman et al., 2014; Liu et al., 2020) and in aversive stimuli processing (Gunaydin et al., 2014; Lammel et al., 2014). Of great significance is the reduction of DA axon terminals in the mPFC of male and female mice, subjected to chronic social defeat stress (Quessy et al., 2021). Additionally, in a model of depression spawned by social defeat stress in susceptible mice, the repeated optogenetic stimulation of VTA neurons that project to mPFC, reversed depressed-related behaviours (Friedman et al., 2014). In addition, it has been reported that juvenile stress impairs working memory in adulthood, along with decreased mPFC dopamine activity that results from increased DAT function (Novick et al., 2015).

The long-term effects of AS on DA release in the mPFC involve the reciprocal interaction between DA neuronal innervation of mPFC, and glutamate innervation of VTA. In fact, DA neurons which in rodents originates mostly from the VTA and terminates in the prelimbic and infralimbic areas (Berger et al., 1976; Van Eden et al., 1987), interact with PFC glutamate neurons that can control cortical DA release by acting either at the VTA level (Chergui et al., 1993; Wang and French, 1993, 1995; White, 1996) or at the PFC level (Jedema and Moghaddam, 1994). In particular, the tonic activation of AMPA and NMDA glutamate receptors at VTA level contributes to the basal output of DA neurons in the PFC (Takahata and Moghaddam, 1998). It is important to remember that only a small population of glutamate neurons that innervate VTA will target DA neurons (Carr and Sesack, 2000), thereby suggesting that the regulation of cortical DA release by VTA neurons involves other brain structure such as the BLA and most likely the output of both superficial and deep layers of mPFC (Bittar and Labonté, 2021). Additionally, adolescent social isolation stress increased aggression and determined mPFC hypo functioning and BLA principal neuron hyperactivity in male mice (Tan et al., 2021). Interestingly, stress determines an increase in the brain derived neurotrophic factor (BDNF) in the BLA, lasting up to 21 days after the termination of stress (Lakshminarasimhan and Chattarji, 2012), and can be involved in the activation of a

depression circuit (Carboni and Carta, 2022). Considering the deleterious effects of lateral habenula (LHb) on DA neurons of VTA, and in turn on depression-like behaviours in rodents, and that mPFC sends projections to the LHb (Kim and Lee, 2012), it cannot be excluded that AS produces its effects on mPFC DA output through a brain circuit that also involves the LHb (Simmons et al., 2020; Shabel et al., 2019; Yang et al., 2018; Carboni and Carta, 2022; Cerniauskas et al., 2019).

To better understand the long-term effects of AS on mPFC CAT transmission, we could also consider its impact on the delicate process of DA receptor pruning and circuitry remodelling that occurs in adolescence in the mPFC (Shapiro et al., 2017; Selemon, 2013). This peculiarity makes it somewhat difficult to compare the effects of CUMS in adults with those of CUMS in adolescent rats, although some effects, such as depressive-like behavioural effects may overlap, regardless of whether they are generated by adolescent or adult stress. (Willner, 2016; Morilak et al., 2005; Takaba et al., 2022; Page and Coutellier, 2018; Suo et al., 2013). In this context, the robust initial stress-induced increase in DA and NE production, which also occurs in humans (Nagano-Saito et al., 2013), can be considered a common basis for both experimental models. (Del Arco et al., 2007; Kao et al., 2015; Enrico et al., 1998; Kawahara et al., 1999; Feenstra, 2000;Gresch et al., 1994; Takahata and Moghaddam, 1998). In particular, the repeated exposure to an elevated CAT output can interfere with the dopamine D1receptors (D1R) pruning that occurs in adolescence.

Furthermore, exposure to adolescent defeat caused a greater decrease in DA output, upon local infusion of the D2 agonist quinpirole, resulting in greater D2 autoreceptor function (Weber et al., 2018). In addition, it has been reported that short-term repeated juvenile stress (PND 27–29) in male and female rats increased TH-immunoreactivity in mPFC but not in the dorsal striatum or in the nucleus accumbens (Harris et al., 2022); the authors suggest that juvenile stress determines an alteration of CAT innervation of mPFC, which could be involved in the alteration of escape-oriented strategies in the forced swim test (FST), but has no effect on either adult anxiety-like behaviour or locomotor activity in the open field. Considering that tyrosine hydroxylase increase was detected in layers 1 and 2 of the PLCx and ILCx, we can assume that it reflects NE innervation (Harris et al., 2022). Although the application of stress (PND 27–29) does not overlap our protocol (PND 29–42 PND), these data are somehow in agreement with our observation of an increased NE release and reuptake in the PLCx and ILCx of adult rats exposed to AS. Curiously, in a mouse model of schizophrenia, reduced DA content and elevated NET expression were observed, with increased NE levels in the mPFC (Siuta et al., 2010); these authors hypothesized that rictor-null (KO) mice accumulate both NE and DA within the noradrenergic neuron; a subsequent conversion of DA to NE would determine an increase of NE tissue content and release associated with a decrease of DA. Furthermore, in these animals the reuptake of ^{3}H-NE and ^{3}H-DA in cortical synaptosomes was increased by 100 and 60% respectively (Siuta et al., 2010). Although not in a direct manner, the condition observed in our model resembles that described by Siuta and collaborators and is compatible with a condition of cortical hypodopaminergia, which is thought to be associated with both the cognitive deficits and the negative symptoms of schizophrenia. In addition, the DA transmission plays a key role in the dorsolateral PFC, contributing to the correct functioning of working memory. Thus, a hypodopaminergic state in this area can render glutamatergic activity unstable, producing a dysfunction that has common traits with those observed in schizophrenia (Tanaka, 2006).

4.4. Reboxetine effect

This study shows that reboxetine, as compared with saline, significantly increased DA and NE output in the mPFC of both the adult rats exposed to AS and their controls; also worth noting is that NE output increase was significantly greater in the former. Reboxetine is a rather selective NET blocker, being Ki (nM) 13.4, 273.5 and higher than 10.000 for NET, serotonin transporter (SERT) or dopamine transporter (DAT), respectively (Wong et al., 2000; Hajós et al., 2004). When administered systemically, it significantly increased DA output (in addition to NE output), most likely because in the mPFC, DA is taken up by the NET of the NE terminals (Carboni et al., 1990; Linnér et al., 2001; Carboni et al., 2006;). Although the effect of reboxetine on DA output, expressed as a % of basal, was similar in AS and control rats (Fig. 5A), its effect in the mPFC of AS rats was reduced by half, if DA output was expressed in absolute values (fmoles/mL) and compared with controls. This result suggests that in AS rats a smaller amount of DA was captured by NET, as compared with controls. We can thus hypothesize that the increased NET function in AS rats does not contribute to the reduction of DA basal output in the mPFC. This conclusion is further supported by the observation that an increased NE output (see below) would compete with DA for the NET site, eventually increasing DA output instead of decreasing it.

It is well-known that brain circuits change following acute or chronic stressful events; in particular, the noradrenergic innervation originating in the LC and innervating the mPFC, plays a key role in the circuitry that mediates the HPA activation induced by emotional stress (Urry et al., 2006; Radley et al., 2008). Additionally, the effect of stress on LC function is mediated by a direct action of CRF (Curtis et al., 1997; Valentino and Wehby, 1988) and a local blockade of CRF1 receptors prevents the stress-induced changes in LC activity (Curtis and Valentino, 1994; Valentino and Wehby, 1988; Valentino et al., 1991). Additionally, administering CRF directly into the LC mimics the effect of stress and increases electroencephalogram (EEG) activity in the arousal state (Curtis et al., 1997). Therefore, it can be assumed that stress can increase NE release and EEG activity in the mPFC by activating CRF receptors at LC level (Kawahara et al., 2000; Page et al., 1993; Smagin et al., 1997). Given such premises, the long-term effect of AS on NE uptake in the mPFC of adult rats cannot be considered surprising.

Since AS did not modify the basal NE output in the mPFC of adult rats, we can hypothesize that the observed higher NET function in AS rats (Fig. 8) could play a role in counteracting the increased synaptic concentration of NE triggered by stress, thus keeping mPFC basal NE output at proper concentrations. An optimal CAT concentration is indeed required for maintaining an appropriate PFC function (Arnsten, 2007). In fact, besides arousal, attention, cognitive flexibility, decision making, LC activity is known to be involved the control of anxiety-like behaviours (Nestler et al., 1999; Benarroch, 2009; Hirschberg et al., 2017).

Although it is plausible to think that CUMS can cause an increase of NET function in the mPFC, it remains unclear why this increase is maintained even after CUMS exposure ends. In this context, we can speculate that upon the cessation of CUMS exposure, the presence of an elevated NET function in the mPFC could lead to an excessive reduction of NE output; this reduction, in turn, could trigger a stimulation of LC neurons, with the purpose of maintaining an optimal NE synaptic concentration. Considering the complexity of cortex pyramidal neuronal activity, it is hard to hypothesize how NE firing stimulation is achieved. Among the possible mechanisms involved, the following are conceivable: i) the involvement of pyramidal neurons projecting to the LC, (Jodo et al., 1998; Kawahara et al., 2000); ii) the LC-BLA circuitry activated by stress (Giustino et al., 2020; Borodovitsyna et al., 2020); iii) a desensitization of α2 receptor at LC level (Benarroch, 2009); iv) a desensitization of α2 NE autoreceptors that control NE release at mPFC level (Florin et al., 1994; Garcia et al., 2004). The results obtained administering reboxetine to AS and control rats thus suggests that AS has likely determined an upregulation of NET function in the mPFC, and it is maintained well after CUMS application ceases, although the mechanism of this biochemical adaptation remains to be clarified.

4.5. Amphetamine effect

In this study we have shown that the effect of amphetamine on DA

output was significantly higher in AS rats than in controls, when DA output was expressed as a % of basal output. When DA output was instead expressed in absolute amount (fmoles/20 mL), it was significantly lower in AS rats compared with controls. This difference was observed only when the lower dose of amphetamine was administered, whereas no significant difference was observed when the higher dose was administered. In other words, amphetamine determined a stronger increase of DA output in AS rats, but since the basal DA output was lower in AS rats, their synaptic DA concentration, after amphetamine, did not exceed that of controls. Furthermore, at both dose levels, amphetamine produced a stronger effect on NE output in AS rats compared with controls.

Amphetamine has a complex mechanism of action and can increase DA and NE output through different dose dependent mechanisms: i) at low doses, amphetamine enters in the presynaptic terminal through the neuronal transporters DAT and NET and as it competes for the transporter, raises DA and NE synaptic concentrations; ii) once in the cytosol, amphetamine competes with monoamines for the vesicular monoamine transporter 2 (VMAT2), increasing their cytosol concentration sufficiently to trigger DA and NE release though a reversal of DAT and NET flow direction; iii) when administered at higher doses, amphetamine can pass through the plasmalemma membrane because of its lipophilicity properties, thereby reaching high cytosol concentration and triggering a massive, firing independent release of monoamine in the synaptic space, through the reversal of the DAT and NET function. (Heal et al., 2013; Fleckenstein et al., 2007, 2009; Robertson et al., 2009; Sulzer et al., 2005; Carboni and Silvagni, 2004). To detect subtle differences in the output of DA and NE, between AS rats and relative controls, we used low doses of amphetamine, as they should interact mainly with the DA and NE reuptake (Freyberg et al., 2016; Florin et al., 1994; Silvagni et al., 2008; Carboni et al., 2010;). As previously reported, DA can be captured by NET in the mPFC (Carboni et al., 2006), so any increase of DA output, due to amphetamine, could be due to an altered reuptake in both DA and NE terminals (Shoblock et al., 2004).

It seems likely that the higher effect of amphetamine in AS rats reveals a higher availability of vesicular DA and NE (Freyberg et al., 2016; Carboni et al., 2003). Such a condition could be associated to an increased synthesis and an increased release, sustained by increased neuronal firing. Considering that we did not observe an increased NE basal output in AS rats, and their DA output was lower than in control rats, we could suppose that NE and DA reuptake was also increased in AS rats. This result is also supported by the higher reboxetine effect in AS rats and although DA and NE transmission in the mPFC is under a direct mPFC-VTA or mPFC-LC influence, an involvement of a broader circuitry in AS effects is more than likely.

It has been frequently reported that stress sensitizes to the locomotor effect of amphetamine in various experimental models that include adolescent and adult stress (Toledano et al., 2013; Cruz et al., 2012). Adolescent physical stress, but not social stress, induced a robust amphetamine behavioural sensitization (Kabbaj et al., 2002). Repeated i.c.v., but not peripheral administration of CRF, can determine a long-lasting sensitization to amphetamine induced locomotion (Cador et al., 1993). In addition, stress can sensitize to the stimulant effect of amphetamine on DA and NE release in different brain areas (Burke et al., 2010; Cadoni et al., 2003), suggesting that AS could signal a predisposition to higher psychostimulant abuse vulnerability. Additionally, adolescent amphetamine exposure leads to an enhanced response to amphetamine during adulthood, suggesting that there is cross sensitization between stress and amphetamine adolescent exposure, likely mediated by an enduring adaptation of the DA system in the mPFC (Sherrill and Gulley, 2018). The interaction between either stress or amphetamine sensitization with the VTA-mPFC DA circuit could involve a long-lasting modification of the excitatory transmission at level of VTA, resembling hippocampal long-term potentiation (Clark and Overton, 1998). Interestingly, a sensitizing regimen of amphetamine, that somehow resembles AS due to the repeated exposition of the mPFC to elevated CAT synaptic concentrations, decreased spine density on pyramidal cells, and had detrimental long-term effects on working memory performance (Selemon et al., 2007; Anderson et al., 2019b). In conclusion, the enhanced effect of amphetamine on DA and NE output in adult rats exposed to AS, confirms that AS produces a long-term alteration of CAT transmission in the mPFC.

4.6. Overall considerations

The rodent mPFC is made primarily of glutamatergic pyramidal neurons (80–90%) and by inhibitory GABAergic cells (10–20%), (Nieuwenhuys, 1994; Rudy et al., 2011) that are differently located in 5 layers. The mPFC is innervated by glutamate neurons from the hippocampus, amygdala and thalamus and receives dopaminergic innervation from the VTA, noradrenergic innervation from the LC and serotonergic projections from the dorsal raphe nuclei (DRN). It sends glutamatergic projections back to VTA, DRN, LC and other brain areas as elegantly described in the review by Bittar and Labonté (2021). Through these functional connections, the mPFC is involved in several complex functions that can be damaged by stress, including attention (Jezierski et al., 2007), emotion, social cognition and inhibitory control (Hiser and Koenigs, 2018; Liu et al., 2020), working memory (Mika et al., 2012; Woo et al., 2021), decision making and long-term memory (Bechara et al., 2000; Euston et al., 2012).

5. Conclusion

The results of this study show that AS produces a long-lasting alteration of DA and NE transmission in the mPFC of male adult rats. A reduction of basal DA output and an increased response to amphetamine and to reboxetine has been observed. On the basis of our results and considering the connections and the functions of the mPFC, we suggest that by altering these functions, AS is highly likely to be involved in the expression of psychiatric disorders such as depression, schizophrenia and drug abuse disorders (Keedwell et al., 2005; Arnsten, 2011; Page and Coutellier, 2018; Anderson et al., 2019a).

Ethical statement

On the behave of all authors I declare that all animal experimentation was conducted in accordance with the guidelines for care and use of experimental animals as specified by the European Community Council (2010/63/UE L 276 20/10/2010) and by Italian law (DL 04/03/2014 n° 26). This study was approved by the Organization for Animal Care of the University of Cagliari (OPBA-UniCA) and by Ministry of Health, aut. # 352/215-PR and 353/2015 PR (11/05/2015). Every effort was made to minimize suffering and reduce the number of animals used.

CRediT authorship contribution statement

Ezio Carboni: Writing – review & editing, Writing – original draft, Validation, Supervision, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Marcello Ibba:** Investigation, Formal analysis, Data curation. **Elena Carboni:** Writing – original draft, Conceptualization. **Anna R. Carta:** Writing – review & editing.

Declaration of competing interest

On the behave of all authors I declare that all authors have no conflict of interest or any financial and personal relationships with other people or organizations that could inappropriately influence (bias) our work.

Data availability

Data will be made available on request.

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