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REVIEW

The process of angiogenesis in neurodegeneration—pathomechanisms and new therapeutic interventions

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Abstract

Objective Neurodegenerative diseases are a leading cause of disability worldwide, and recent evidence highlights the role of angiogenesis in their pathophysiology. This review aimed to explore molecular and metabolic links between neurodegeneration and angiogenesis, and to assess the potential of antiangiogenic drugs as therapeutic agents.

Methods A targeted literature search of experimental and clinical studies was performed, focusing on angiogenesis-related mechanisms in neurodegeneration and the effects of antiangiogenic compounds on neuronal and vascular function.

Results Antiangiogenic agents have been shown to promote synaptic plasticity, enhance neurotransmission, and exert anti-inflammatory effects. They also modulate vascular remodeling, which supports optimal cerebral blood flow and nutrient delivery to neurons. These actions may counteract key pathological processes in neurodegenerative diseases and help preserve cognitive and motor function.

Conclusions Modulation of angiogenesis represents a promising therapeutic approach in neurodegenerative disorders. Antiangiogenic drugs may address both vascular and neuronal dysfunction, offering a potential avenue for disease-modifying treatments. Further preclinical and clinical research is needed to validate their safety, efficacy, and long-term benefits.

Keywords Neurodegenerative diseases · Angiogenesis · Inhibitors of angiogenesis

Neurodegenerative diseases are a leading cause of physical and cognitive disability worldwide. It is estimated that the burden will double over the next two decades (Checkoway et al. 2011). They are characterized by a progressive loss of sensitive neuronal populations (Checkoway et al. 2011; Dugger and Dickson 2017).The group of neurodegenerative diseases includes a significant number of conditions, and Alzheimer's disease (AD), Parkinson's disease (PD), Multiple Sclerosis (MS), Amyotrophic Lateral Sclerosis (ALS) and Spinal Muscular Atrophy (SMA) are the main ones (Checkoway et al. 2011; Vaquer-Alicea and Diamond 2019). The pathomechanisms of these diseases are multifactorial (Fig. 1) but the detailed mechanisms of their development have not yet been sufficiently explained, which is one of the main reasons for the lack of effective and safe therapies. Most neurodegenerative diseases are characterized by the deposition of misfolded proteins (e.g., α-synuclein, β-amyloid, huntingtin) and degeneration of brain networks (Vaquer-Alicea and Diamond 2019). However, there is ample evidence to suggest that the environmental factors and gene-environment interactions may be important causes of neurodegenerative diseases. Other common causes of these conditions include aging and oxidative stress (Wu et al. 2019). In recent years, oxidative stress has been recognized as one of the main pathomechanisms of AD, since this phenomenon is closely related to some key events in neurodegeneration, such as mitochondrial dysfunction, inflammation, metal-induced toxicity, and protein misfolding (Nunomura and Perry 2020).

In recent years, special attention has turned to the cerebrovascular system, and in particular, to the blood–brain barrier (BBB) and angiogenesis, as emerging components of the neurodegenerative process. The central nervous

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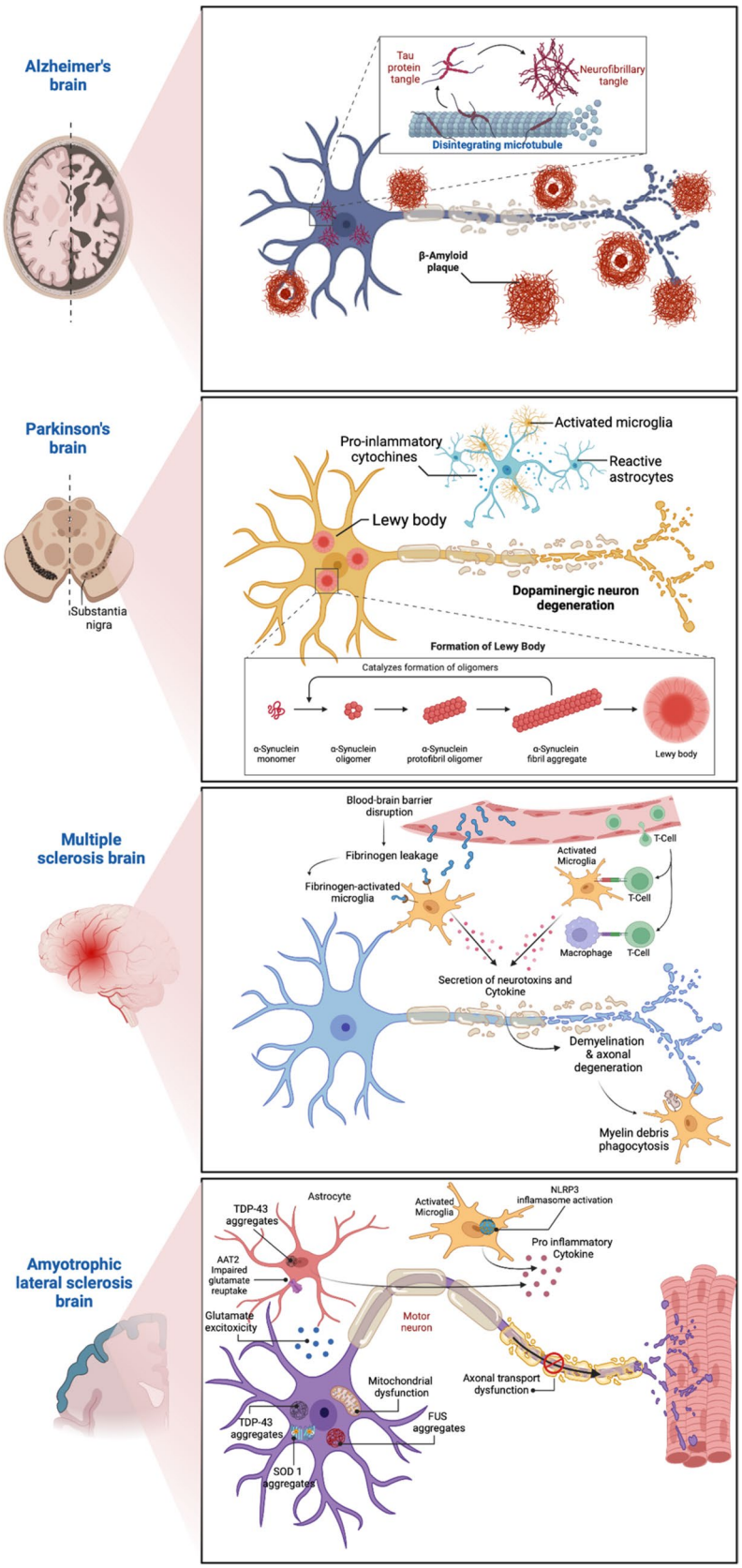

Fig. 1 Pathological mechanisms in neurodegenerative diseases: The figure highlights the molecular and cellular mechanisms that are thought to underlie four major neurodegenerative diseases. Alzheimer's disease: deposition of β-amyloid plaques and tau protein tangles lead to synaptic dysfunction, neuronal death, and cognitive decline. Parkinson's disease: α-synuclein aggregates form Lewy bodies, causing the degeneration of dopamine neurons in the *substantia nigra pars compacta*, exacerbated by reactive astrocytosis and microgliosis. Multiple sclerosis: disruption of blood–brain barrier facilitates fibrinogen leakage, activating microglia and triggering demyelination and axonal degeneration. Amyotrophic Lateral Sclerosis: transactive response DNA binding protein of 43 kDa (TDP-43), fused in sarcoma (FUS) and superoxide dismutase 1 (SOD1) protein aggregates lead to motor neuron degeneration, glutamate excitotoxicity, mitochondrial dysfunction, and axonal transport defects. All these processes are driven by pro-inflammatory cytokines, oxidative stress, and dysregulation of protein homeostasis, contributing to progressive neurodegeneration. Created with Biorender

system (CNS) has uniquely specialized vasculature due to its high metabolic demands and the necessity of tightly controlled transport mechanisms. The cerebral vasculature are formed exclusively due to the angiogenic sprouting of vessels from the perineural vascular plexus, so the process of angiogenesis plays a special and important role in the development and functioning of the CNS (Sajib, et al. 2018; Qiang et al. 2020). While angiogenesis in the adult brain is classically considered quiescent under physiological conditions, mounting evidence from pathological contexts—such as stroke, trauma, glioma, and multiple sclerosis—demonstrates that angiogenic reactivation can occur in response to stress or injury (Thomsen et al. 2025). However, in neurodegenerative diseases, the extent and functional relevance of such reactivation remain ambiguous. Changes often interpreted as angiogenesis may instead reflect alternative vascular phenomena such as remodeling, pericyte dropout, thickening of the basement membrane, or BBB disruption without true neovascularization (Sweeney et al. 2018b). Experimental models continue to shed light on this complex relationship, albeit with contrasting findings. In a model of chronic neurodegeneration, Thomsen et al. (2025) utilized ibotenic acid—a neurotoxin that selectively ablates neuronal populations while sparing the cerebral vasculature—to study neuroinflammation in the absence of overt vascular damage. Intriguingly, despite robust inflammatory activation, they reported no changes in the expression of canonical tight junction proteins (e.g., Cldn5), adherens junction molecules (e.g., Cdh1), or components of the basal lamina across both early and late phases of the disease model. These findings challenge the commonly held assumption that neuroinflammation necessarily leads to BBB breakdown. Instead, they suggest that under some chronic neurodegenerative conditions, the BBB may maintain its structural and functional integrity. Furthermore, the lack of molecular indicators of angiogenesis or barrier compromise in this model raises compelling questions about the molecular thresholds and contextual signals required to initiate vascular changes during progressive neuronal loss (Thomsen et al. 2025).

In contrast, Carvey et al. (2005) provided compelling evidence for BBB disruption in an acute dopaminergic injury model. Following unilateral intrastriatal or medial forebrain bundle injection of 6-hydroxydopamine (6-OHDA)—a classical neurotoxin used to mimic parkinsonian neurodegeneration—they observed pronounced leakage of FITC-labeled albumin and horseradish peroxidase into the ipsilateral striatum and substantia nigra at both 10 and 34 days post-lesion. This breakdown of the BBB coincided with extensive microglial activation, dopaminergic neuronal degeneration, and upregulation of P-glycoprotein and β3-integrin—changes suggestive of a compensatory and potentially angiogenic response. Most notably, domperidone—a dopamine receptor antagonist that does not typically cross an intact BBB—was found to exert central behavioral effects in lesioned animals, indicating a functional breach of the barrier (Carvey et al. 2005).Taken together, these divergent findings underscore a critical and unresolved question: Can neurodegeneration proceed independently of BBB disruption, or is barrier compromise a central driver that facilitates the progression of neurodegenerative pathology?

It therefore seems crucial to consider this special role of angiogenesis in developing therapeutic solutions for neurodegenerative diseases about their pathomechanisms. Despite extensive research on the explanation of the role of angiogenesis in neurodegeneration and the potential use of drugs based on this process, there is no comprehensive study in this field in the scientific literature. This review aims to summarize the metabolic and molecular connections between neurodegenerative diseases and the process of angiogenesis. This work also discusses the potential role of antiangiogenic drugs in developing new therapeutic strategies for neurodegenerative diseases. A thorough analysis of the literature will allow for determining future directions of research in the search for more effective therapies aimed at the pathomechanisms of these diseases.

Angiogenesis

Angiogenesis, the intricate process of generating new blood vessels from pre-existing ones, plays a pivotal role in various physiological phenomena (Sajib, et al. 2018; Qiang et al. 2020). Among its beneficial roles are wound healing, the establishment of the BBB, and embryonic development. However, its involvement extends to pathological conditions such as cancer, retinopathy, inflammation, atherosclerosis, and psoriasis. Angiogenesis consists of several stages—including endothelial cell proliferation, cell migration, vascular lumen formation, differentiation, and maturation (Sajib, et al. 2018). (Fig. 2). The course of angiogenesis, which is a tightly regulated response of the endothelium, requires many molecules modulating individual stages of this process (Chen et al. 2013). These include pro-angiogenic molecules: growth factors, including vascular endothelial growth factor (VEGF), hypoxia-inducible factor 1-alpha transcription factor (HIF-1α), platelet-derived growth factor (PDGF-B), transforming growth factor (TGF-β), fibroblast growth factor, placental growth factor (PlGF), interleukins, as well as anti-angiogenic factors: angiostatin, endostatin, thrombospondins 1 and 2 (Qiang et al. 2020; Claire and Larrivée 2017). VEGF stands as a pivotal driver behind the genesis of fresh blood vessels through both vasculogenesis and angiogenesis, exerting a profound influence on endothelial proliferation (McConnell et al. 2019).

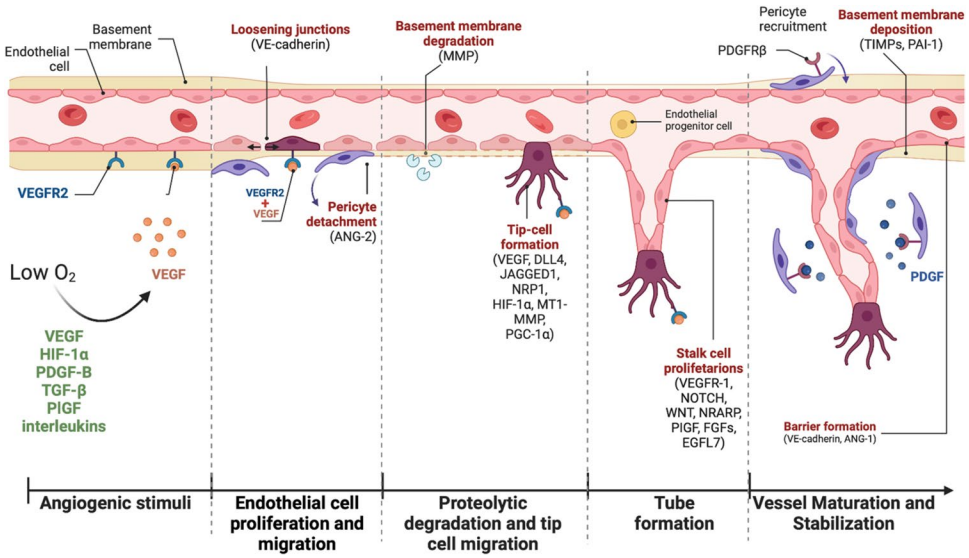

Fig. 2 Angiogenesis and its mechanisms: (**A**) Angiogenesis may be initiated by several processes such as hypoxia (low O_2), which stimulates the release of angiogenic factors: vascular endothelial growth factor (VEGF), hypoxia-inducible factor 1-alpha (HIF-1α), platelet-derived growth factor B (PDGF-B), transforming growth factor-beta (TGF-β), placental growth factor (PlGF), and interleukins. (**B**) The signal mediated by the angiogenic factors, for example by activating the vascular endothelial growth factor receptor 2 (VEGFR2), triggers the recruitment of other molecules such as vascular endothelial (VE)-cadherin and angiopoietin-2 (ANG-2) that cause loosening of junctions and pericyte detachment, respectively, culminating in the proliferation and migration of endothelial cells. (**C**) This event is followed by the proteolytic degradation of the basement membrane by matrix metalloproteinases (MMPs), and by the formation of tip cells, led by VEGF, delta-like ligand 4 (DLL4), jagged canonical notch ligand 1 (JAGGED1), and neuropilin-1 (NRP1), which guide the direction of new vessel growth. (**D**) Signaling from VEGFR1, notch receptors, Wnt proteins, NRARP (Notch-regulated ankyrin repeat protein), PlGF, fibroblast growth factors (FGFs), and endothelial growth factor-like domain 7 (EGFL7) triggers the proliferation of stalk cells to elongate the newly formed vessels. (**E**) In the later stages, endothelial progenitor cells and pericytes are recruited by PDGF to stabilize the vessel. The basement membrane is then redeposited by tissue inhibitors of metalloproteinases (TIMPs) and plasminogen activator inhibitor-1 (PAI-1), ensuring vessel maturation. Finally, the formation of tight junctions (VE-cadherin) and angiopoietin-1 (ANG-1) contributes to barrier formation, stabilizing the vessel and creating a fully functional vascular network. Created with Biorender

Its multifaceted role encompasses not only the regulation of vascular permeability and dilation but also extends to beneficial aspects such as enhancing neuronal access to vital nutrients, orchestrating cytoskeletal rearrangements, and promoting cell migration (McConnell et al. 2019). Unfortunately, VEGF can also be detrimental because its overexpression can cause inflammation in the nervous system, which in turn can lead to BBB leakage, promote the production of pro-inflammatory cytokines and the occurrence of neurodegeneration (Claire and Larrivée 2017; McConnell et al. 2019). Overexpression of VEGF is observed in certain neurodegenerative diseases such as AD, PD, ALS, and MS. Factors influencing VEGF expression include glucose deficiency and hypoxia (McConnell et al. 2019). Cells in response to glucose deficiency and hypoxia produce factors that stimulate angiogenesis (McConnell et al. 2019). However, an excess of pro-angiogenic factors such as VEGF can trigger the production of pro-inflammatory cytokines and neuroinflammation, potentially contributing to neurodegeneration (McConnell et al. 2019). Within the VEGF family, there are distinct isoforms binding to VEGF receptors (VEGFR1-3) and neuropilin coreceptors (Nrp-1, Nrp-2), including VEGF-A, VEGF-B, VEGF-C, VEGF-D, and Placental Growth Factor (PlGF). The signaling cascade initiated by VEGF, particularly through the VEGF/Nrp-1 pathway, holds paramount importance for angiogenesis within the CNS. Many studies indicate an association between increased VEGF expression in the brain, brain hypoperfusion, and increased BBB permeability, which increases unwanted angiogenesis, and may favor the occurrence of neurodegenerative diseases (Chen et al. 2013). When combined with fibroblast growth factors (FGFs), which bind to receptors in the presence of heparin, causing endothelial cell migration, VEGF-A levels increase, leading to stabilization and growth of new vessels (Claire and Larrivée 2017; McConnell et al. 2019). Furthermore, the cooperative interplay of VEGF with PIGF enhances angiogenesis, causing in intensified vascularization and the enlargement of blood vessels. In the brain increased VEGF activity is noted after damage or trauma, which increases angiogenesis [12, 143]. As mentioned above, on the one hand, increased VEGF activity is beneficial because it increases the amount of nutrients from the blood for neurons; on the other hand, increased levels of VEGF-A in the brain may lead to the production of pro-inflammatory cytokines, neuroinflammation and BBB stratification.

Substances that increase VEGF-A levels include β-amyloid, a protein whose mutation is implicated in AD, as well as L-3,4-dihydroxyphenylalanine (L-DOPA), the drug of choice in the treatment of PD (Ouellette et al. 2020). Increased expression of VEGF stimulates angiogenesis, acting on dopamine D1 receptors, and may cause, among other things, dyskinesia, a major side effect of L-DOPA, which may further reduce the quality of life of PD patients under L-DOPA medication (Veith and Henderson 2019) Increased VEGF expression has been also documented in astrocytes, endothelial cells (ECs), and monocytes of MS patients, potentially contributing to BBB permeability and the onset of MS. Escalations in molecules like basic fibroblast growth factor, intricately involved in angiogenesis, have also been noted in MS patients (Sharma and Brown 2021; Callahan et al. 2020; Cąkała and Strosznajder 2010).

The role of angiogenesis in neurodegeneration

Angiogenesis in the CNS is a natural process, a physiological reaction, or as a pathological progression of disease (Vallon and Chang 2014) (Fig. 3). The induction of angiogenesis in the CNS has been reported to promote pathological conditions such as brain tumor growth, and sterile-venous malformations (SVM) (Vallon and Chang 2014). On the other hand, angiogenesis in the CNS is also essential for

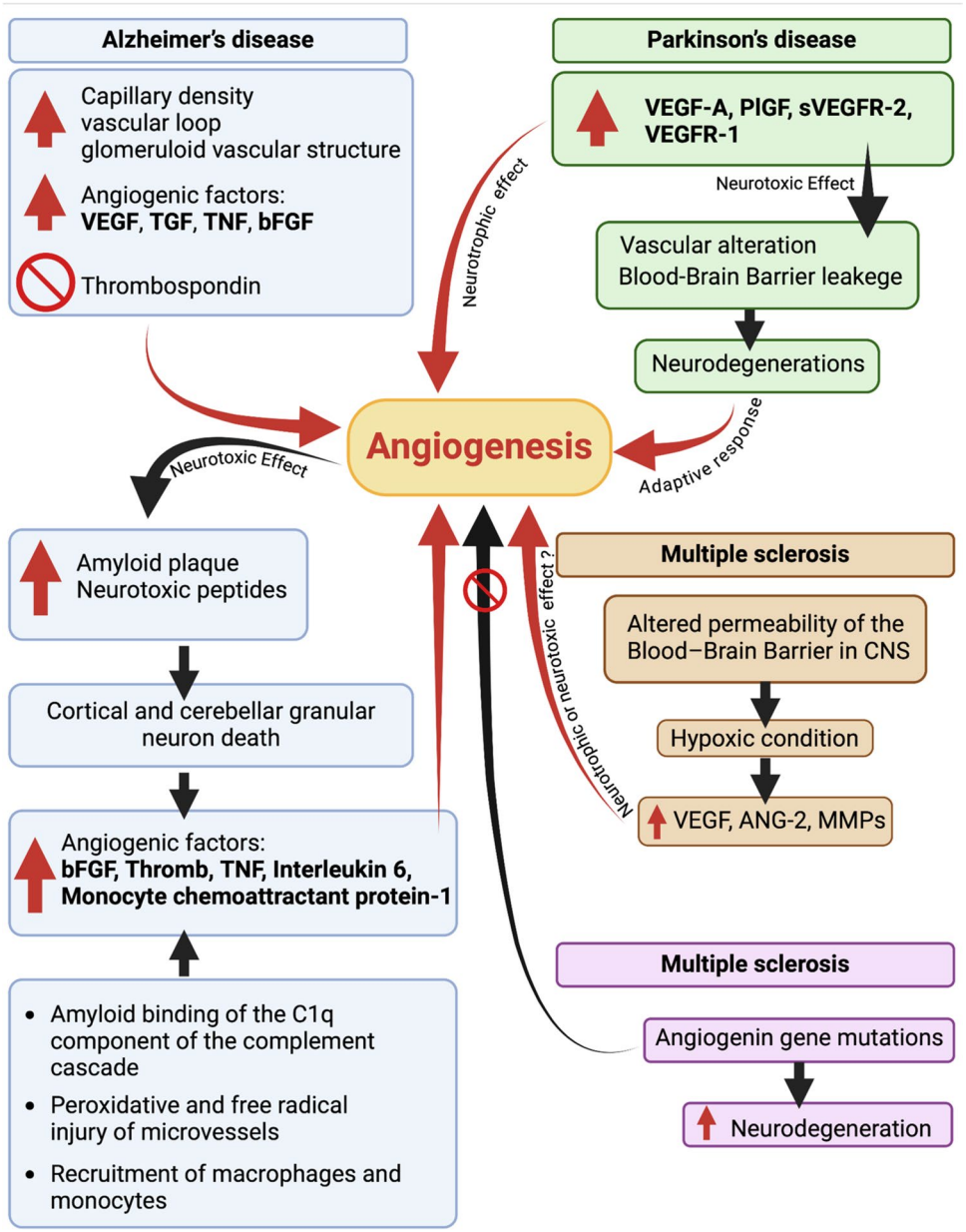

Fig. 3 Schematic representation of angiogenesis and its potential roles in neurodegenerative diseases. The flowchart illustrates angiogenic processes and their possible impact on Alzheimer's disease (blue panels), Parkinson's disease (green panels), multiple sclerosis (orange panels), and amyotrophic lateral sclerosis (pink panels). Red arrows indicate the promotion of angiogenesis, black arrows indicate neurotoxic effects, and blue arrows indicate effects that have not been fully defined (i.e., either neurotoxic or neuroprotective). The figure emphasizes the complex role of angiogenesis in the progression of neurodegenerative diseases, where it can play both adaptive and maladaptive roles

processes such as embryonic development, recovery from ischemic stroke-type incidents, and recovery from traumatic brain injury (Vallon and Chang 2014). Knowledge about cerebrovascular involvement in neurological disorders is rapidly expanding, and increasing evidence indicates that defects in angiogenesis, and the blood–brain boundary are causally related to the cognitive dysfunctions that may be found in the course of neurodegenerative disorders (Nicolakakis and Hamel 2011; Dyken and Lacoste 2018). More and more research reveals that neurovascular disorders play an important role in the pathophysiology of brain diseases throughout life, such as neurodevelopmental and neurodegenerative disorders (Ouellette et al. 2020; Nicolakakis and Hamel 2011; Dyken and Lacoste 2018; McConnell et al. 2019). Research shows that any disruption in blood flow, even from the smallest vascular networks, can have a profound impact on both neuronal homeostasis and functions (Sharma and Brown 2021). Therefore, attention is increasingly being devoted to the elucidation of the role that angiogenesis plays in the disruption of neuronal homeostasis and functions and in the subsequent development of brain diseases (Sharma and Brown 2021). Given the role of angiogenesis in the growth and/or maintenance of neurovascular units in the nervous system, a role for abnormal angiogenesis in neurodegenerative diseases has been hypothesized and aberrant angiogenesis has been proposed as a potential factor in the progression of neurodegenerative diseases (Parkes et al. 2018). Studies have shown that cerebral angiogenesis and neurogenesis are deeply interconnected from the earliest stages of development (Callahan et al. 2020). This condition lasts for the rest of life, which is why the interaction among the cerebral vascular system, and neuronal and non-neuronal cells in the brain is central to health and disease (Callahan et al. 2020). Increased angiogenesis has been revealed to provide a possible mechanism of action by which exercise may delay cognitive decline associated with aging (Callahan et al. 2020; Parkes et al. 2018). Moreover, pharmacological modulation of angiogenesis may serve new therapeutic purposes in the prevention of neurodegenerative diseases (Parkes et al. 2018). However, to date, there are no in vitro models that simulate long-term neurovascular dysfunction, therefore, new data in this aspect are provided by cross-sectional observation results (Parkes et al. 2018). The process of angiogenesis is now often correlated with clinical and neural imaging evidence of cognitive improvement, cerebral hypoperfusion, and neurodegeneration (Callahan et al. 2020). A retrospective cross-sectional study was conducted in a cohort of older adults who were clinically described as having normal cognitive functioning, mild cognitive impairment, or early AD (Cąkała and Strosznajder 2010). In addition to neuroimaging, peripheral blood testing including vascular endothelial growth factor, fibroblast growth factor, and β-amyloid peptide 40 was performed, and advanced polychromatic flow cytometry was used to phenotype circulating mononuclear cells to assess angiogenic activity (Callahan et al. 2020). Differences in cognitive functioning and increased VEGF levels have been observed in people with mild cognitive impairment. As is known, vascular endothelial levels are closely correlated with the concept of angiogenesis (Callahan et al. 2020).

The albumin quotient (Q_{alb}), a key marker of BBB permeability, has been found to be elevated in several studies involving individuals with preclinical AD, mild cognitive impairment (MCI), and established AD itself (Halliday et al. 2013; Skoog et al. 1998; Skillbäck et al. 2017; Janelidze et al. 2017). Yet, intriguingly, other studies have failed to detect a significant rise in Q_{alb} among AD patients unless certain vascular risk factors—such as mild hypertension, diabetes, coronary artery disease, or dyslipidemia—are also present (Bowman et al. 2012; Alkhalifa et al. 2023; Kciuk et al. 2024). This raises an intriguing question: is the breach of the blood–brain barrier in AD simply a byproduct of aging, or does it require the presence of these vascular risk factors? The complexity deepens when we consider that the majority of AD patients, especially in the elderly population, carry at least one of these vascular risk factors—approximately 65% of individuals aged 65 and 80% of those aged 85 (Lokovic et al. 2020; Montine et al. 2014).

The role of compensatory angiogenesis in neurodegeneration

Angiogenesis in the CNS is a complex process with both pathological and physiological implications. Pathological angiogenesis can exacerbate neurodegeneration by promoting BBB dysfunction, neuroinflammation, and vascular instability (Sweeney et al. 2018a). On the other hand, compensatory angiogenesis serves as an adaptive response to tissue hypoxia, a hallmark of the aging brain. Hypoxia contributes to vascular changes such as increased stiffness, tortuosity, and decreased vascular perfusion. Compensatory angiogenesis aims to restore oxygenation and nutrient delivery to neuronal tissues, supporting their survival and function. This adaptive mechanism is evident in the early stages of neurodegeneration, with increased expression of VEGF and other angiogenic mediators in response to hypoxic conditions (Zlokovic 2011). However, excessive or impaired angiogenesis, even if initially compensatory, can become pathological, exacerbating neurodegenerative processes by increasing vascular instability and inflammation (Sweeney et al. 2018a). Given this dual role, distinguishing between beneficial compensatory angiogenesis

and pathological angiogenesis is essential when considering therapeutic strategies. Antiangiogenic therapies, although promising in targeting pathological angiogenesis, may inadvertently suppress beneficial compensatory mechanisms if used indiscriminately. This highlights the importance of tailoring interventions to specific pathological contexts, ensuring preservation of beneficial angiogenic responses while mitigating harmful processes (Zlokovic 2011).

Alzheimer's disease (AD)

AD is characterized by a progressive, irreversible, degeneration of cells, predominantly occurring in the medial temporal lobe and neocortical regions of the brain. This degenerative process leads to a progressive decline in cognitive functions, notably dementia, accompanied by impairments in memory, decision-making, and speech, as well as disturbances in orientation (Cąkała and Strosznajder 2010). AD is a multifactorial disease; nevertheless, it may have a strong genetic component as demonstrated by the evidence that it occurs more often in certain families compared with the general population (Cąkała and Strosznajder 2010). Building upon these observations, AD has been classified into two forms: sporadic and familiar determined (FAD) (Cąkała and Strosznajder 2010). Early-onset familial AD (EOFAD) may develop, in which symptoms of dementia appear before the age of 65 and there is a positive family history of the disease (Wu et al. 2012). In EOFAD, there are mutations in the PS1, PS2, and APP genes, which leads to excessive production of β-amyloid (Wu et al. 2012). EOFAD is characterized by early onset, family history, a variety of neurological symptoms, and a more aggressive course compared to sporadic AD (Wu et al. 2012). Even if the strong genetic component of EOFAD is recognized, its pathophysiology and etiology are not fully known (Lepara et al. 2009).

Previous research has shown that excessive nitric oxide (NO) production, increased levels of oxidative stress, and cerebrovascular hypoperfusion are mayor pathomechanisms responsible for AD (Lepara et al. 2009). One of the main pathomechanisms of AD is oxidative stress, which is closely related to other neurodegenerative events such as impaired calcium homeostasis, metal dysregulation, mitochondrial dysfunction, protein misfolding, inflammation, and impaired autophagy (Nunomura and Perry 2020). Other factors exist that may increase the risk of developing AD (Skillbäck et al. 2017). These include hypertension, diabetes, smoking, obesity, and a history of dyslipidemia. (Mayeux and Stern 2012) Type II diabetes increases the risk of developing AD by approximately twofold (Mayeux and Stern 2012). The hyperinsulinemia associated with type 2 diabetes impairs brain clearance of β-amyloid by competing for the enzyme that breaks down insulin (Mayeux and Stern 2012). In the case of cigarette smoking, studies initially suggested that smoking reduced the risk of AD, but subsequent prospective studies have shown an increased risk or no association (Mayeux and Stern 2012). The most frequently reported risk factor for AD is cerebrovascular disease and its antecedents. Indeed, cerebrovascular disease often coexists with AD (Mayeux and Stern 2012).

Increased cholinergic metabolism may increase the risk of brain cells damage. The brains of AD patients invariably show cholinergic deficits, characterized by decreased levels of acetylcholine, choline acetyltransferase, and/or nicotinic acetylcholine receptors (Mayeux and Stern 2012). Accordingly, recent publications have noted that, to this day, AD is mistakenly considered to be a process entirely separate from aging, rather than one of its symptoms (Ambrose 2016). The angiogenesis hypothesis may provide new insights by suggesting a decline in angiogenic growth factors with age, which in turn leads to a reduction in microcirculation in the body (Ambrose 2016). Well-known modulators of adult neurogenesis include signal transducing pathways, the neurovascular system, the immune system, metabolic factors, and epigenetic adaptations (Vallon and Chang 2014). Many intrinsic and extrinsic factors, such as neurotrophic factors, transcription factors, cell cycle regulators, cell proliferation, neurogenic niche and differentiation into mature neurons, play an important role in the pathomechanism of AD. These factors operate in networks of signaling molecules that influence each other to build and maintain neural circuits, all of which contribute to both learning and memory (Vallon and Chang 2014; Ambrose 2016). Both the immune system and the vascular system are essential for generating neurons and determining neuron viability (Vallon and Chang 2014). Anti-inflammatory cytokines regulate mature neurogenesis in response to immune activation, while the neurovascular system controls the neural stem cell niche (Vallon and Chang 2014). In fact, the vasculature, immune cell populations, adhesion molecules, growth factors, and extracellular matrix also provide an environment for neural stem cells (Vallon and Chang 2014). Epigenetic changes during hippocampal neurogenesis also influence cognitive processes (Vallon and Chang 2014). Perfusion deficits can accelerate clinical deterioration and are associated and correlated with adverse treatment outcomes (Horgusluoglu et al. 2017). Therefore, cerebrovascular enhancement strategies should be an integral part of AD therapeutic efforts (Horgusluoglu et al. 2017). Such approaches have led to several innovative and experimental paradigms (Horgusluoglu et al. 2017). Some of them were capable of reproducing the features of AD, while others specifically mimicked the cerebrovascular pathology associated with AD, characterized by changes in the anatomical structures of cerebral vessels (Horgusluoglu

et al. 2017). It appears that angiogenesis is an extremely important component of the neurogenesis pathway, which itself undergoes dysregulation in AD (Greenberg and Jin 2013). Cellular factors play an essential role in angiogenesis along with humoral factors, the main representative of which is VEGF (Greenberg and Jin 2013). Research results clearly indicate that dysregulation of VEGF expression is associated with many neurodegenerative diseases (Storkebaum and Carmeliet 2004). These findings have led to increased interest in evaluating the therapeutic potential of VEGF as a neuroprotective agent in neurodegenerative diseases (Storkebaum and Carmeliet 2004). In AD, the brain endothelium releases a precursor substrate for β-amyloid plaque and a neurotoxic hormone peptide that kills cortical neurons (Vagnucci and Li 2003). As a result of cerebral hypoxia and inflammation, massive populations of mesothelial cells are activated in the process of angiogenesis (Vagnucci and Li 2003). Epidemiological studies have shown that long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs), statins, histamine H2 receptor blockers, or vascular calcium channel blockers appears to prevent AD (Vagnucci and Li 2003). It is believed that this proposed beneficial effect is based largely on the ability of these drugs to inhibit angiogenesis (Vagnucci and Li 2003). Accordingly, it has been proposed that AD is an angiogenesis-dependent disorder and that the development of anti-angiogenic drugs acting on abnormal intravascular brain endothelial cells may be able to prevent and treat AD (Vagnucci and Li 2003).

Parkinson's disease (PD)

PD is the second most common neurodegenerative disease following AD, and is associated with the loss of dopaminergic neurons in the Substantia Nigra compacta (SNc). PD is a multifactorial disease influenced by genetic predispositions, lifestyle choices, environmental influences, and various other factors (Kouli et al. 2018; Tanner and Goldman 1996). Globally, approximately 1% of people over the age of 60 suffer from PD, but in 10% of cases, the disease occurs at a younger age and is referred to as early-onset PD (Mächtel et al. 2022). As the global population ages, the incidence of PD is expected to rise, underscoring the crucial need for ongoing research to identify its risk factors (Kouli et al. 2018). In addition to age, emotional stress can also influence the severity of PD in people already affected by the disease (Tanner and Goldman 1996). Research suggests this is because stress triggers changes in the central dopamine system, which could theoretically contribute to the disease (Dugger and Dickson 2017; Sajib, et al. 2018; Tanner and Goldman 1996). There is currently no antemortem diagnostic test available for PD (Tanner and Goldman 1996), making its diagnosis challenging. The most dependable approach remains a specialized neurological examination (Tanner and Goldman 1996). Observations indicate that PD is more prevalent among individuals of Caucasian descent, potentially attributable to a shared genetic predisposition (Tanner and Goldman 1996). Specific mutations in PARK genes such as: DJ1, SNCA, PRKN, and PINK1 typically manifest as early-onset PD; whereas mutations in LRRK2 are associated with idiopathic PD, typically occurring later in life (Nichols et al. 2009) However, these mutations are responsible for less than 5% of PD cases (Nichols et al. 2009). The correlation between PD and altered vascular function has prompted research into factors potentially involved in BBB dysfunction (Al-Bachari et al. 2020). Studies in animal models of PD, have observed BBB disruption, providing support for the vascular neurodegeneration hypothesis (Al-Bachari et al. 2020). The same finding has not yet been confirmed in clinical trials, although there is evidence of striatal vascular formation within cerebral capillaries during the progression of PD (Yang et al. 2015). The study encompassed patients diagnosed with PD along with cerebrovascular conditions, as well as individuals without any known neurological disorders (Yang et al. 2015). These patients underwent contrast-enhanced dynamic magnetic resonance imaging (Yang et al. 2015), from which quantitative maps depicting the penetration rate of the contrast agent across the BBB and plasma volume were generated (Al-Bachari et al. 2020). Notably, significant findings were observed to be comparable between PD and cerebrovascular patients, indicating a similar burden of cerebrovascular disease despite lower cardiovascular risk factors (Al-Bachari et al. 2020; Yang et al. 2015). Furthermore, it is proposed that heightened angiogenesis is believed to be an adaptive response to pathological conditions and is regulated by basement membrane proteins with their integrin receptors (Bogale et al. 2021). Current research speculates that the presence of immature initial vasculature in PD may also contribute to increased BBB permeability (Bogale et al. 2021).

Multiple sclerosis (MS)

MS is an inflammatory disease of the brain and spinal cord, leading to focal lymphocytic infiltration and subsequent damage to myelin and axons (Compston and Coles 2008). In the early stages, the inflammation is transient and remyelination can occur, although it is not typically permanent (Compston and Coles 2008). The etiology of MS is thought to involve both genetic and environmental factors (Korn 2008). Research has revealed, new MS susceptibility forms linked to immune function, alongside the human leukocyte antigen (HLA) complex (Korn 2008). Although there is little evidence to support a purely environmental causative agent in the sense of an infectious agent, the autoimmune

hypothesis of MS is widely accepted (Korn 2008). Several etiological factors have been described in the pathogenesis of MS, such as altered immune function, genetics, and environmental factors (Anwar et al. 2023). MS is the most frequently observed demyelinating disease, with variable incidence (Korn 2008). Over the past three decades, there has been a documented increase in the incidence of MS among women. Between 70 to 88% of patients survive for 25 years following the onset of clinical symptoms, indicating a median time from symptom initiation to death ranging from 24 years to over 45 years. In the context of MS, there is a suggestion that heightened angiogenesis plays a role in both disease progression and remission following relapse (Korn 2008; Anwar et al. 2023; Leray et al. 2016). Genetic investigations have revealed a correlation between a cluster of angiogenesis pathway genes linked to vascular malformations and genes related to the HLA (Zakrzewska-Pniewska 2010). Additionally, studies have shown that gastric pentadecapeptide BPC 157 exerts a modulatory influence on angiogenesis during the healing processes of muscle and tendon (Brcic et al. 2009). Research has delved into elucidating the pro-angiogenic mechanism of BPC 157 through experimental models involving chickens and rats. Utilizing the chicken chorioallantoic membrane (CAM) assay and endothelial tubule formation assay, studies demonstrated that BPC 157 could augment vascular proliferation both in vivo and in vitro (Hsieh et al. 2017). Additionally, BPC 157 was found to expedite the restoration of blood circulation in ischemic rat hindlimb muscles, as evidenced by laser Doppler scanning, indicating its angiogenic promotion (Hsieh et al. 2017). Histological analyses of hindlimb muscles corroborated these findings, revealing an increased capillary count and heightened expression of VEGFR2 in rats receiving BPC 157. Further in vitro investigations using human vascular endothelial cells confirmed the increased expression of VEGFR2 mRNA and protein induced by BPC 157, though not VEGF-A (Hsieh et al. 2017). Furthermore, BPC 157 facilitated the internalization of VEGFR2 in vascular endothelial cells, an effect impeded the presence of Dynazor, an endocytosis inhibitor (Hsieh et al. 2017). BPC 157 activated the VEGFR2-Akt-eNOS signaling pathway in a time-dependent manner, which could also be suppressed by Dynazor (Hsieh et al. 2017).

Amyotrophic lateral sclerosis (ALS)

ALS is a neurodegenerative disease of motor neurons that manifests itself through the progressive loss of axons, dendrites, and neuromuscular connections (Ganne et al. 2023). The clinical picture is very variable, depending on the site of occurrence and the degree of involvement of the upper and lower motor neurons (Luna et al. 2022). Diagnosis is significantly difficult due to the variability of phenotypical manifestations and the lack of diagnostic biomarkers. The pathophysiology of ALS is still unknown, but altered protein homeostasis has been suggested to be a key player (Wijesekera and Leigh 2009). In ALS, there is an abnormal cytoplasmic aggregation of misfolded proteins, mainly DNA-binding protein 43 (TDP-43), and fused in sarcoma (FUS) (Wijesekera and Leigh 2009). The incidence of sporadic ALS (SALS) in the 1990s in Europe and North America ranged from 1.5 to 2.7 per 100000 inhabitants per year, with an equal incidence in these regions (Wijesekera and Leigh 2009). Research shows that men suffer from the disease up to four times more often than women, but with age this ratio decreases and after the age of 60. is 1:1 (Wijesekera and Leigh 2009). Explanations for this excess of men have been attributed to possible protective hormonal factors in women, the increased likelihood of men being exposed to putative risk factors, and the under recognition of older women in some population registries (Wijesekera and Leigh 2009). A recent study conducted by Greenway et al. has established a correlation between mutations in the angiogenin (ANG) gene and the susceptibility to developing ALS (Lambrechts et al. 2006). ANG was identified as a molecule involved in angiogenesis because itoccurred as a result of a hit here to VEGF, a prototypical course of VEGF that ultimately emerged as a molecule with a prior neuroprotective classification. Apart from VEGF, ANG is the second major angiogenic factor linked to ALS (Lambrechts et al. 2006). Another independent study uncovered a novel ANG signal peptide mutation, and careful analysis revealed an allelic association with the rs11701 nucleotide polymorphism (SNP) in familial ALS (FALS) (Conforti et al. 2008). The results of these research studies indicate the involvement of the ANG gene in ALS pathogenesis (Conforti et al. 2008). Furthermore, other studies have attempted to determine the relationship between angiogenesis and cell survival in the pathogenesis of ALS by collating the evidence presented in various research reports (Thakur et al. 2020). Phenotypes resembling human ALS have been successfully replicated in SOD1 mutant mice and through the targeted deletion of the hypoxia response element (HRE) from the promoter of the mouse VEGF gene (Thakur et al. 2020). Indirect evidence suggests that angiogenesis may play a role in mitigating oxidative stress and thus may increase cell survival. Key regulators of angiogenesis, namely VEGF and angiogenin are thought to primarily oversee this process. TDP-43 is usually found in the nucleus, but in many cases of ALS it accumulates in the cytoplasm (TDP-43 proteopathy) (Thakur et al. 2020). Interestingly, TDP-43 proteopathy is exacerbated in the presence of optineurin (OPTN) mutations, the genetic factor responsible for such accumulation (Thakur et al. 2020). The interaction of TDP-43 with progranulin may

further influence angiogenesis in ALS patients by regulating VEGF receptor activity (Thakur et al. 2020). Certain mutations in ubiquilins UBQLN2 and UBQLN4 indicate that ubiquitination plays a role in the pathobiology of ALS, but its relationship with angiogenesis has not been adequately studied to date (Thakur et al. 2020). Recent studies have shown that several mutations in RNA-binding proteins (RBPs) can also cause ALS. Ultimately, it has been argued that the role of angiogenesis in the increased survival rate of ALS is likely regulated by NF-κβ activation (Thakur et al. 2020). It has been hypothesized that the interaction between OPTN and TDP−43 may also influence the transcription of various angiogenic molecules (Thakur et al. 2020). Whether targeting angiogenic molecules or TDP-43 may provide clues to improving ALS survival rates when combined with current treatments, however, can only be verified with additional research (Thakur et al. 2020).

Inhibitors of angiogenesis

As a result of research that provided evidence of the connection between the angiogenesis process and the neurodegeneration process, research began on the possibility of using angiogenesis inhibitors in the prevention and/or treatment of neurodegenerative diseases (Fig. 4). The conducted studies have shown that these drugs may constitute potential therapeutic interventions for these diseases. This review provides an in-depth analysis of several agents, including VEGF, angiostatin, axitinib, everolimus, bevacizumab, semaxinib, and ranibizumab, shedding light on their usefulness in the treatment of neurodegenerative diseases. Each of these compounds exhibits unique therapeutic properties that render them compelling candidates for further investigation and potential utilization in slowing down disease progression but also ameliorating symptoms associated with neurodegeneration. The majority of these studies are limited in scope, preclinical in nature, and based largely on pharmacological tools that often lack specificity. Many of these compounds interact with immune pathways and peripheral systems, making it difficult to attribute observed effects solely to the modulation of angiogenesis within the CNS. Furthermore, the evidence for widespread or sustained angiogenesis in chronic neurodegenerative diseases remains inconclusive. In many cases, what is interpreted as angiogenic activity may instead reflect other forms of vascular remodeling—such as BBB disruption, pericyte loss, or basement membrane alterations—rather than true neovascularization.

Primarily, these substances showcase notable neuroprotective effects, crucial for preserving neuronal integrity and function amidst the pathological processes underlying neurodegeneration. Moreover, research indicates that these drugs possess the capacity to enhance cognition and memory by promoting synaptic plasticity and facilitating neurotransmission. Furthermore, these drugs demonstrate promising anti-inflammatory properties, crucial in mitigating neuroinflammation, a key driver of neurodegenerative

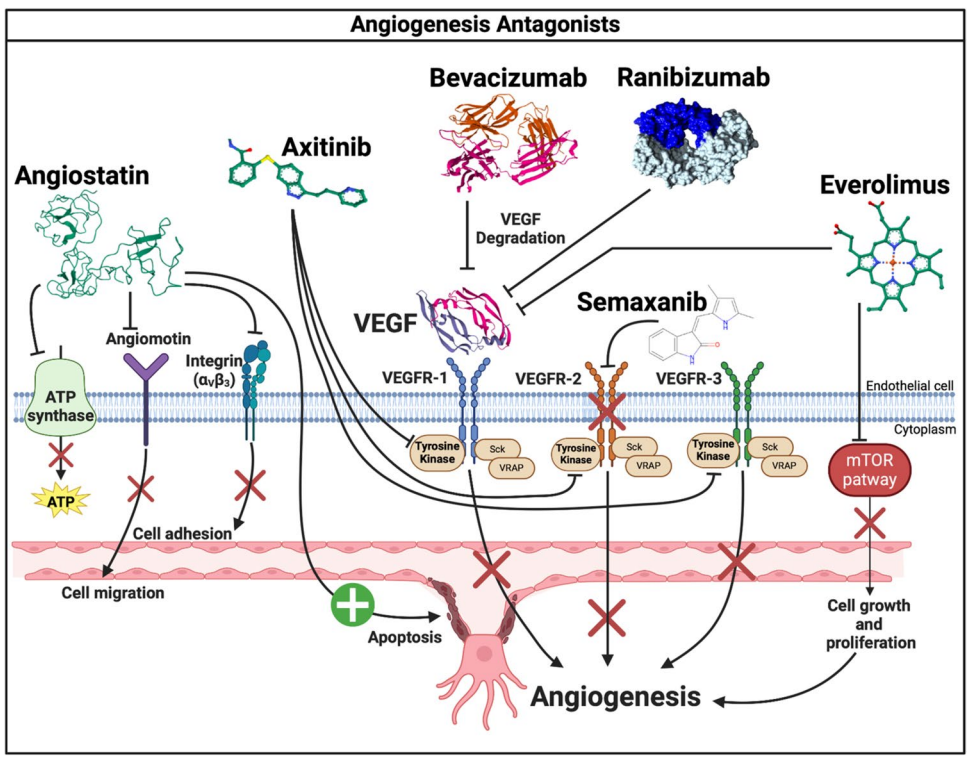

Fig. 4 Mechanism of angiogenesis inhibition: The figure illustrates the pathways targeted by angiogenesis antagonists, such as angiostatin, axitinib, bevacizumab, ranibizumab, semaxanib, and everolimus. Angiostatin blocks ATP synthase, angiomotin, and integrin (αvβ3), leading to inhibition of ATP production, cell migration, adhesion, and promotion of endothelial cell apoptosis. Axitinib inhibits vascular endothelial growth factor (VEGFR)−1, VEGFR-2, and VEGFR-3 tyrosine kinases, suppressing angiogenesis. Bevacizumab, ranibizumab, and everolimus degrade VEGF, blocking VEGF receptor activation, with everolimus additionally inhibiting the mammalian target of rapamycin (mTOR) pathway to suppress cell proliferation. Semaxanib specifically inhibits VEGFR-2, leading to suppression of angiogenesis. Created with Biorender

processes. By dampening inflammatory responses within the CNS, these compounds present a compelling strategy for attenuating disease-associated inflammation and preserving neuronal health. Additionally, these substances play a role in regulating vascular remodeling, essential for maintaining adequate blood flow to the brain and supporting neuronal function. By modulating angiogenesis and vascular integrity, these drugs may contribute to optimizing cerebral blood flow and nutrient delivery to neurons, thereby promoting overall brain health and potentially mitigating neurodegenerative processes. It should be noted, however, that these are few and preliminary studies that, on the one hand, provide valuable and promising data, but on the other hand, the results are limited and have not yet been sufficiently confirmed.

VEGF

While VEGF is renowned for its crucial role in angiogenesis and vascular regeneration, emerging evidence underscores its significance in neurological contexts as well. Recent studies have uncovered a fascinating aspect of the VEGF, shedding light on its multifaceted involvement in neurodegeneration, a domain previously less explored. Through mechanisms yet to be fully elucidated, VEGF orchestrates a cascade of events pivotal for vascular repair following ischemic insult, thereby fostering an environment conducive to neuronal survival and functional recovery (Yasuhara and Shingo 2004). Moreover, genetic inquiries have shed light on the intricate interplay between VEGF levels and neurodegenerative processes. Studies indicate that diminished VEGF expression precipitates neurodegeneration by compromising neural tissue perfusion, thus exacerbating neuronal vulnerability to ischemic insults and metabolic imbalances (Oosthuyse et al. 2001). It has been shown that reducing VEGF levels by 50% significantly impairs the angiogenesis process. This revelation not only underscores the criticality of VEGF in maintaining cerebral homeostasis but also implicates its dysregulation as a potential contributor to neurodegenerative pathologies. Additionally, studies have shown decreased regional cerebral blood flow in ALS patients (Waldemarv and Vorstrup 1992). It is known that motor neurons are particularly susceptible to free radicals generated during ischemia, and therefore chronic deficits in neural perfusion may contribute to the development of neuronal damage and disease progression (Kalaria 2002; Deckel and Duffy 2000). The mechanisms underlying how decreased VEGF levels impact neural perfusion have been postulated to involve impaired vascular regulation. Specifically, insufficient VEGF signaling may disrupt the intricate balance of vasodilation and vasoconstriction, crucial for maintaining optimal blood flow to the brain regions. This disruption in vascular regulation could lead to inadequate perfusion of neural tissues, exacerbating neuronal vulnerability to ischemic insults and oxidative stress (Lambrechts et al. 2006; Deckel and Duffy 2000). Importantly, perfusion disorders are not exclusive to ALS but have also been observed in other neurodegenerative conditions such as AD and HD (Lambrechts et al. 2006; Deckel and Duffy 2000). This suggests a common underlying mechanism involving impaired vascular dynamics, further emphasizing the intricate relationship between vascular health and neurodegenerative processes. Furthermore, it is noteworthy that perfusion deficits often manifest before the appearance of clinical symptoms in neurodegenerative diseases (Korn 2008). The early appearance of perfusion abnormalities emphasizes their potential role as prodromal indicators, accentuating the importance of proactive vascular surveillance in individuals at risk for neurodegenerative diseases. Insight into the preclinical phase of these diseases holds promise for identifying windows of opportunity for early intervention and implementing disease-modifying strategies aimed at arresting or slowing disease progression.The mechanisms of neurodegeneration discussed above indicate the clear therapeutic potential of VEGF in incurable neurodegenerative diseases (Korn 2008). *In vivo* studies have shown that VEGF enhances vascularization and reduces retrograde degeneration of corticospinal tract axons and thus stimulates axon regeneration in the injured brain area (Conforti et al. 2008) VEGF exerts this effect by restoring blood flow in the nerves as well as by directly affecting Schwann cells (Thakur et al. 2020). A study of the neuroprotective capacity of VEGF in an experimental model of PD showed that rats receiving continuous local infusion of VEGF into the striatum via encapsulated hamster kidney VEGF (hVEGF)-secreting cells showed a reduction in amphetamine-induced rotational behavior and neuronal protection (Hsieh et al. 2017; Yasuhara and Shingo 2004). VEGF can also induce neuronal regeneration by stimulating Schwann cell growth (Korn 2008). However, caution should be exercised because although the administration of VEGF has a beneficial effect by reducing the formation of edema, the infusion of VEGF may also cause vascular leakage, which may consequently result in hemorrhagic transformation of ischemic lesions (Korn 2008). VEGF has been shown to have a protective effect on neurons in several PD models (Korn 2008; Yasuhara and Shingo 2005). One such model is the rat model treated with 6-OHDA. Two sizes of capsules filled with cells secreting VEGF into the striatum were used (Yasuhara and Shingo 2005). Rats receiving the large capsule showed increased glial proliferation, brain swelling, and angiogenesis, while those receiving small doses showed preservation of a large number of tyrosine hydroxylase-positive fibers and a neuroprotective

effect on dopamine neurons, indicating that VEGF at low doses can potentially support PD treatment (Yasuhara and Shingo 2005). The above studies confirm the biological role of VEGF in neurodegenerative diseases. However, further, thorough research in this area is required, as caution should be exercised when considering the inclusion of VEGF in potential therapies for neurodegenerative diseases.

Angiostatin

Angiostatin, an endogenous inhibitor of angiogenesis, can block the growth of new blood vessels through a negative feedback homeostasis process (Cheng, et al. 2022). However, observations suggest that in the brains of AD patients, increased angiogenesis may disrupt this negative feedback loop, leading to an imbalance between angiogenesis and vascular inhibition. Studies have shown that plasma angiostatin levels were lower in patients with AD dementia and were negatively correlated with β-amyloid levels in plasma and cerebrospinal fluid (CSF) (Cheng, et al. 2022). In the study, promising results were observed following angiostatin treatment, such as reduced inflammation and regulation of vascular remodeling. Perhaps angiostatin could become a potential biomarker of brain angiogenesis in AD (Cheng, et al. 2022). Currently, however, there is no broader research in this area. There is a need to confirm the above-mentioned research results, as well as to thoroughly investigate the role of angiostatin in neurodegeneration, especially in preventing the development of these processes.

Axitinib

Axitinib is a small-molecule tyrosine kinase (TK) inhibitor targeting vascular endothelial growth factor receptors (VEGFRs). Originally developed as an anticancer medication, axitinib curbs angiogenesis, effectively limiting tumor growth and metastasis (Singh and Choi 2021). Its widespread approval for the treatment of renal cell carcinoma in numerous countries underscores its therapeutic significance in oncology. Axitinib emerges as a promising agent with beneficial effects on neurodegeneration within animal models of AD (Singh and Choi 2021). A study in a mouse model of AD assessed the effects of axitinib on cognitive abilities and memory (Yuan, et al. 2023). Mice treated with axitinib showed enhanced cognitive abilities, as well as greater exploration, and spatial memory (Singh and Choi 2021). The results of behavioral and molecular studies conducted on mice treated with axitinib showed significant improvement in cognitive functions, which correlated with increased expression of tight junction proteins ZO-1 and occludin. These observations suggest improved BBB function (Singh and Choi 2021). Axitinib reduced the destruction of tight junction proteins and reduced BBB permeability in mice, while increasing spatial awareness, exploration, associative memory, working memory, and lowering β-amyloid levels (Yuan, et al. 2023). This resulted in improved BBB integrity in mice. The neurodegenerative diseases AD, PD and ALS share many biochemical and neuropathological features (Yuan, et al. 2023). Currently, based on evidence from neuroimaging, postmortem studies, and cerebrospinal fluid testing, BBB dysfunction has been recognized as an early biomarker of neurodegenerative diseases (Yuan, et al. 2023). Dysfunction of barrier-type brain endothelial cells (BEC), i.e. the main part of the BBB, is considered one of the pathological changes induced by β-amyloid Aβ in AD (Sweeney et al. 2018a). A key feature of PD is the aggregation of the pathological α-synuclein protein in the form of intraneural Lewy bodies. BEC changes occur in the substantia nigra, locus coeruleus and caudate putamen, i.e. where abnormal α-synuclein aggregation is visible (Sweeney et al. 2018a). Structural damage to capillaries and BBB disruption have also been identified in postmortem studies of ALS patients (Sweeney et al. 2018a). Similarly, in the pathogenesis of MS, peripheral immune cells penetrate the BBB into the brain and destroy myelin membranes and neurons (Sweeney et al. 2018a). Activation of BECs by increasing the level of adhesion molecules has been shown to play a role in the recruitment of leukocytes to the CNS (Sweeney et al. 2018a). Therefore, drugs that affect BBB permeability represent potentially interesting strategies in neurodegenerative diseases. Further research, especially clinical trials, is also required in this area (Sweeney et al. 2018a).

Everolimus

Everolimus, which has been extensively profiled in clinical and preclinical studies, is an angiogenesis inhibitor that may be effective in the treatment of early stages of neurodegeneration through a short and cyclic regimen of administration (Cassano and Magini 2019). A study was conducted in a mouse model of AD in which short-term osmotic injection of everolimus was performed directly into the brain. After 4 weeks, behavioral, biochemical, and immunohistochemical tests were performed (Cassano and Magini 2019). Despite its limited penetration through the BBB, everolimus exhibited notable attributes that favored its efficacy within the CNS. Notably, it demonstrated slow metabolism within the brain and enhanced stability at physiological temperatures compared to rapamycin, another mTOR inhibitor (Cassano and Magini 2019). These pharmacokinetic properties position everolimus as a promising candidate for targeted neurodegenerative therapies. Additionally, inhibition of the mammalian target of rapamycin (mTOR) with everolimus reduced the levels of tau and amyloid precursor protein/amyloid β (APP/

Aβ) and improved cognitive function. Inhibition of mTOR extends lifespan and restores or delays many features of aging (Cassano and Magini 2019). Everolimus, as a rapamycin analog, is a selective inhibitor of mTOR in mammals and its associated signaling pathway (Fanoudi, et al. 2018). Excessive mTOR activity has been shown to be associated with the pathophysiology of cognitive deficits. Studies revealed that this drug improved behavioral, biochemical and histopathological parameters in a streptozotocin-induced rat model of AD (Fanoudi, et al. 2018). Additionally, everolimus reduces VEGF concentrations (Cassano and Magini 2019). Therefore, inhibition of hyperactivated mTOR may represent promising therapeutic targets for AD (Cassano and Magini 2019). Similarly, in the pathogenesis of MS, peripheral immune cells penetrate the BBB into the brain and destroy myelin membranes and neurons (Alavi and Fanoudi 2023). Activation of BECs by increasing the level of adhesion molecules has been shown to play a role in the recruitment of leukocytes to the CNS. Recent studies have demonstrated the immunomodulatory and neuroprotective properties of mTOR inhibitors (Alavi and Fanoudi 2023). The results of the study showed that everolimus can protect against glutamate-mediated cell death by inhibiting apoptosis.

Bevacizumab

Drugs with potential in the treatment of neurodegenerative diseases include bevacizumab (MacMillan and Furlong 2012). Bevacizumab is a drug approved for the treatment of several forms of cancer, such as lung, kidney, ovarian and mammary gland cancer. Bevacizumab is a monoclonal antibody that is directed against VEGF and can therefore inhibit angiogenesis (MacMillan and Furlong 2012). In a study conducted on a murine model of MS utilizing experimental autoimmune encephalomyelitis (EAE), the administration of bevacizumab demonstrated promising outcomes. Notably, it resulted in the inhibition of angiogenesis, a crucial process implicated in MS pathology, and concurrently led to a reduction in levels of angiopoietin 2, a protein associated with vascular remodeling and inflammation (MacMillan and Furlong 2012). Bevacizumab inhibited T-cell proliferation, attenuated vascular response, and reduced angiogenesis (MacMillan and Furlong 2012). The study revealed that early intervention with bevacizumab on VEGF function improved BBB integrity, cerebrovascular response, and long-term memory in mice (Zhang and Zhang 2024). Analysis of transcriptomic profiles identified bevacizumab-related genes associated with vascular integrity and function (Genovese and Impellizzeri 2022). These findings suggest that bevacizumab may represent a therapeutic option for early AD intervention. Furthermore, VEGF is believed to play a key role in traumatic brain injury (TBI), particularly in scenarios where Apolipoprotein E (ApoE) expression is absent (Genovese and Impellizzeri 2022). Studies have shown that bevacizumab, as a VEGF inhibitor, has demonstrated neuroprotective effects in several models of TBI (Genovese and Impellizzeri 2022). The specific binding of bevacizumab to VEGF-A protein reduces VEGF protein levels by limiting the formation of new blood vessels (Genovese and Impellizzeri 2022). Beyond its angiogenesis-inhibiting properties, bevacizumab exerts anti-inflammatory effects crucial for mitigating neuroinflammation and consequent neuronal damage. By reducing the activity of macrophages and impeding the infiltration of inflammatory elements into the brain parenchyma, bevacizumab contributes to a neuroprotective milieu (Genovese and Impellizzeri 2022). This multifaceted action underscores the potential of bevacizumab as a therapeutic agent not only in AD but also in various other neurodegenerative and neuroinflammatory conditions.

Semaxinib

In a comprehensive investigation utilizing a mouse model, researchers delved into the intricate involvement of VEGF in both acute and chronic EAE (Roscoe and Welsh 2009). EAE, induced by the peptide myelin oligodendrocyte glycoprotein (MOG), served as a clinically relevant model to study the dynamics of vascular lesions and the associated molecular alterations. Notably, mice that developed vascular lesions in the context of EAE exhibited heightened VEGF expression, indicative of its pivotal role in the pathogenesis of neuroinflammatory disorders (Roscoe and Welsh 2009). This upregulation of VEGF was accompanied by the formation of angiogenic factors, highlighting the intricate interplay between vascular remodeling and neuroinflammation in EAE pathology. Additionally, the deposition of laminin, a key component of the basement membrane crucial for vascular integrity, further underscored the vascular perturbations characteristic of EAE (Roscoe and Welsh 2009). To elucidate the therapeutic potential of targeting VEGF signaling in EAE, mice were treated with the selective VEGF receptor inhibitor semaxinib (Roscoe and Welsh 2009). This intervention aimed to mitigate the aberrant vascular responses and neuroinflammatory cascades associated with EAE pathology. By selectively inhibiting VEGF receptor activation, semaxinib offered a targeted approach to modulating vascular dynamics and potentially attenuating disease progression. In an acute study, semaxinib treatment led to significant clinical improvement, with less demyelination and cellular infiltration in the spinal cord. Treated animals also had fewer blood vessels per section than control animals and had significantly reduced laminin abnormalities. However, no improvement in clinical assessment, tissue pathology, differences in vessel number, or laminin expression in the lesion was observed with chronic drug administration.

Ranibizumab

Unfortunately, anti-VEGF drugs in some cases may increase the risk of neurodegeneration and the development of diseases such as atopic dermatitis (Sultana and Scondotto 2020). There have been reports of a potential signal for PD occurring after the administration of Ranibizumab to the vitreous humor of the eye during the treatment of retinal diseases such as macular degeneration related to age (AMD) (Sultana and Scondotto 2020). Parkinson-like symptoms were noticed approximately 2 years after taking the drug. Decreased synaptic plasticity and function, increased apoptosis, and impaired neuronal signaling were reported. Although the drug was administered topically, systemic suppression of VEGF occurred, suggesting potential off-target effects beyond the ocular compartment (Sultana and Scondotto 2020). A meta-analysis showed that intravitreal administration of ranibizumab was associated with systemic vascular adverse events, including embolic events—stroke and myocardial infarction (Sultana and Scondotto 2020). It's noteworthy that these Parkinson-like events following ranibizumab administration are distinguished by the absence of cortical and subcortical atrophy, suggesting a unique pathophysiological mechanism distinct from typical PD presentations (Sultana and Scondotto 2020). However, it is plausible that the heightened risk of neurodegeneration associated with ranibizumab may primarily affect individuals already predisposed to such side effects due to underlying factors like a family history of PD or AD, or the presence of uncompensated diabetes (Sultana and Scondotto 2020; Shim and Madsen 2018; Bogaert and Damme 2006).

Therapeutic implications: context-specific applications

The efficacy of antiangiogenic therapies is highly dependent on their application in the appropriate pathological contexts. Excessive angiogenesis, as seen in conditions such as cerebral ischemia or BBB disruption, may benefit from targeted antiangiogenic interventions. These therapies can reduce vascular permeability, stabilize the neurovascular unit, and attenuate inflammatory responses (Zlokovic 2011). Conversely, when angiogenesis serves primarily as a compensatory mechanism—as in the aging brain or during recovery from mild ischemic events—antiangiogenic interventions may disrupt brain adaptive processes. Therefore, careful patient stratification and the development of biomarkers to distinguish pathological from compensatory angiogenesis are crucial. Biomarkers such as VEGF levels, angiopoietin expression, and imaging data reflecting vascular remodeling can guide the use of antiangiogenic therapies in a context-specific manner (Ding and Zhang 2015). Future studies should prioritize the development of advanced experimental models to better replicate the chronic nature and complexity of neurodegenerative diseases. These models should integrate key features such as vascular remodeling, BBB integrity, and neuronal-vascular cell interactions to accurately simulate neurovascular dynamics. The importance of BBB integrity and vascular remodeling in neurodegeneration is supported by evidence highlighting their role in disease progression (Sweeney et al. 2018a; Pallone and Freedman 2021). Long-term clinical trials are crucial to assess the safety and efficacy of antiangiogenic therapies in different patient populations and disease stages. Such studies must consider the delicate balance between suppressing pathological angiogenesis and preserving compensatory mechanisms, as emphasized by studies evaluating the use of VEGF inhibitors in the treatment of glioblastoma multiforme (Vasudev and Reynolds 2021).

Identification of reliable biomarkers to distinguish pathological angiogenesis from compensatory responses is another critical area. Advanced molecular imaging and profiling methods are essential tools in this effort, and studies linking VEGF expression to BBB dysfunction and neurodegenerative pathology provide important insights (Dohgu and Banks 2013). Furthermore, exploration of combination therapies that combine antiangiogenic agents with neuroprotective or anti-inflammatory drugs presents a promising avenue. These clues underscore the need for multidisciplinary approaches to advance our understanding of angiogenesis in neurodegeneration and to develop therapeutic strategies that optimize efficacy while minimizing unintended consequences. Understanding the dual role of angiogenesis in neurodegeneration is crucial to developing effective therapeutic strategies. While antiangiogenic therapies hold promise, their use must be carefully tailored to specific pathological contexts to avoid disrupting compensatory mechanisms that support neuronal health. Future research, driven by advanced models, biomarker development, and clinical trials, will pave the way for innovative treatments that balance modulation of angiogenesis with preservation of neuronal homeostasis. By addressing these complexities, we can optimize therapeutic outcomes and improve the quality of life of patients suffering from neurodegenerative diseases.

Limitations of the review

While this review highlights the significant role of angiogenesis in neurodegenerative diseases and its potential therapeutic implications, several limitations require consideration. Despite the growing interest in the relationship between angiogenesis and neurodegeneration, there is a distinct lack of comprehensive studies in the scientific literature

that integrate and synthesize existing findings. This paucity of detailed data can limit the depth of analysis and may result in incomplete conclusions regarding the intricate interrelationships between these biological processes. Furthermore, much of the current knowledge is based on preclinical studies, making it difficult to extrapolate these findings to humans due to inherent differences in disease manifestation, progression, and individual biological responses. As such, this review highlights the urgent need for clinical trials targeting antiangiogenic therapies in neurodegenerative diseases, because without robust data from clinical studies, the efficacy and safety of such interventions remain speculative. Although this review also advocates for the exploration of personalized medicine approaches, the aforementioned limitations prevent comprehensive details on the effective implementation of these strategies.

Future directions

Further investigation of molecular mechanisms linking the processes of angiogenesis and neurodegeneration is essential. Clinical trials focusing on therapeutic interventions aimed at the use of angiogenesis inhibitors in the treatment of neurodegenerative diseases are necessary. Personalized medicine approaches should be explored, taking into account individual differences in the processes of development of the discussed diseases in response to the applied treatment.

Summary

Studies have shown a significant role of angiogenesis in the pathophysiology of neurodegenerative diseases. Angiogenesis and cerebral neurogenesis are closely linked, with angiogenesis being essential for proper brain function, ensuring proper metabolism and protecting against neurodegeneration. However, excessive or impaired induction of angiogenesis in the central nervous system can lead to pathological conditions. Increased expression of VEGF in the brain has been associated with cerebral ischemia, increased BBB permeability and pathological vascular remodeling, which may contribute to the progression of neurodegenerative diseases. Angiogenesis inhibitors can serve as therapeutic interventions for these diseases. Such inhibitors potentially have neuroprotective effects, improving cognition and memory by increasing synaptic plasticity and facilitating neurotransmission. In addition, their anti-inflammatory properties play a key role in regulating vascular remodeling, optimizing cerebral blood flow and ensuring nutrient delivery to support neuronal functions.

However, recent studies have highlighted the dual role of angiogenesis in neurodegeneration. While compensatory angiogenesis serves as an adaptive mechanism to counteract tissue hypoxia in the aging brain, pathological angiogenesis can exacerbate neurodegenerative processes by promoting BBB dysfunction, inflammation, and vascular instability. This duality highlights the need to carefully balance the suppression of pathological angiogenesis with the preservation of beneficial responses. Advanced experimental models integrating vascular remodeling, BBB integrity, and neurovascular interactions are essential to accurately simulate the dynamics of chronic disease. Identification of reliable biomarkers, together with imaging tools, is crucial to distinguish pathological angiogenesis from compensatory responses. Long-term clinical trials are needed to assess the safety and efficacy of these interventions in different patient populations and stages of neurodegenerative diseases.

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