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The VEGFs/VEGFRs system in Alzheimer's and Parkinson's diseases: Pathophysiological roles and therapeutic implications

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ABSTRACT

The vascular endothelial growth factors (VEGFs) and their cognate receptors (VEGFRs), besides their well-known involvement in physiological angiogenesis/lymphangiogenesis and in diseases associated to pathological vessel formation, play multifaceted functions in the central nervous system (CNS). In addition to shaping brain development, by controlling cerebral vasculogenesis and regulating neurogenesis as well as astrocyte differentiation, the VEGFs/VEGFRs axis exerts essential functions in the adult brain both in physiological and pathological contexts. In this article, after describing the physiological VEGFs/VEGFRs functions in the CNS, we focus on the VEGFs/VEGFRs involvement in neurodegenerative diseases by reviewing the current literature on the rather complex VEGFs/VEGFRs contribution to the pathogenic mechanisms of Alzheimer's (AD) and Parkinson's (PD) diseases. Thereafter, based on the outcome of VEGFs/VEGFRs targeting in animal models of AD and PD, we discuss the factual relevance of pharmacological VEGFs/VEGFRs modulation as a novel and potential disease-modifying approach for these neurodegenerative pathologies. Specific VEGFRs targeting, aimed at selective VEGFR-1 inhibition, while preserving VEGFR-2 signal transduction, appears as a promising strategy to hit the molecular mechanisms underlying AD pathology. Moreover, therapeutic VEGFs-based approaches can be proposed for PD treatment, with the aim of fine-tuning their brain levels to amplify neurotrophic/neuroprotective effects while limiting an excessive impact on vascular permeability.

Abbreviations: α-syn, α-synuclein; AAV, adeno-associated viral vectors; Aβ, amyloid-β; AChEIs, acetylcholinesterase inhibitors; AD, Alzheimer's disease; Ang-2, angiopoietin 2; APP, amyloid precursor protein; ARIA-E, amyloid related imaging abnormalities of edema; BBB, blood-brain barrier; CaSR, calcium-sensing receptor; CNS, central nervous system; CSF, cerebrospinal fluid; DA, dopamine; DAG, diacylglycerol; DBS-STN, deep brain stimulation of the subthalamic nucleus; ECM, extracellular matrix; ECs, endothelial cells; Fc, fragment crystallizable; GDNF, glial-derived neurotrophic factor; GnRH, gonadotropin-releasing hormone; HBMECs, human brain microvascular endothelial cells, HUMSCs, human umbilical cord mesenchymal stem cells; HUVECs, human umbilical vein endothelial cells; IP_3, inositol 1,4,5-trisphosphate; Kdr, kinase insert domain-containing receptor; L-DOPA, levodopa; LTP, long-term potentiation; MMP, matrix metalloproteinase; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydro-pyridine; mAb, monoclonal antibody; NMDA, N-methyl-D-aspartic acid; NRP-1, neuropilin-1; NRP-2, neuropilin-2; NRPs, neuropilins; 6-OHDA, 6-hydroxydopamine; PD, Parkinson's disease; PI3K, phosphoinositide 3-kinases; PLCγ, phospholipase Cγ; PlGF, placental growth factor; ROS, reactive oxygen species; scFv, single-chain variable fragment; SEMA3, class 3 semaphorin A; SNpc, substantia nigra pars compacta; sVEGFR-1, soluble vascular endothelial growth factor receptor-1; sVEGFR-2, soluble vascular endothelial growth factor receptor-2; sVEGFRs, soluble vascular endothelial growth factor receptors; TH+, tyrosine hydroxylase positive; VEGF-A, vascular endothelial growth factor A; VEGF-B, vascular endothelial growth factor B; VEGF-C, vascular endothelial growth factor C; VEGF-D, vascular endothelial growth factor D; VEGFs, vascular endothelial growth factors; VEGFR-1, vascular endothelial growth factor receptor-1; VEGFR-2, vascular endothelial growth factor receptor-2; VEGFR-3, vascular endothelial growth factor receptor-3; VEGFRs, vascular endothelial growth factor receptors.

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1. Introduction

1.1. The vascular endothelial growth factors (VEGFs)/vascular endothelial growth factor receptors (VEGFRs) system

The vascular endothelial growth factors (VEGFs) belong to a family of structurally related homodimeric proteins, including VEGF-A, -B, -C, -D, and placental growth factor (PlGF) in mammals [1,2]. Structurally, they are formed by antiparallel polypeptides covalently linked by two intermolecular disulfide bonds.

VEGFs transmit their signal by activating, with different binding specificity, tyrosine kinase receptors (VEGFRs), i.e., VEGFR-1 or fms-like tyrosine kinase-1 (Flt-1), VEGFR-2 or kinase insert domain-containing receptor (Kdr), and VEGFR-3 or Flt-4 [3–6]. For instance, VEGF-A binds to VEGFR-1 or VEGFR-2 homodimers as well as VEGFR-1/VEGFR-2 heterodimers, although the binding affinity for VEGFR-1 is higher than for VEGFR-2 [7]. VEGF-B and PlGF exclusively interact with VEGFR-1 homodimers; VEGF-C and VEGF-D activate VEGFR-2 and VEGFR-3 homodimers, in addition to VEGFR-2/VEGFR-3 heterodimers [2]. The semaphorin receptors neuropilin-1 (NRP-1) and neuropilin-2 (NRP-2) act as co-receptors for VEGFRs; in particular, NRP-1 forms complexes with VEGFR-1/-2, whereas NRP-2 preferentially interacts with VEGFR-3/VEGF-C, although it may also favor VEGFR-2 phosphorylation in response to VEGF-A or VEGF-C [8–12]. VEGFs can also directly bind to NRP-1 and NRP-2, thus activating a VEGFRs-independent signal transduction pathway [2,4,13,14].

All VEGFs exist as multiple and functionally distinct isoforms, produced by alternative exon splicing (VEGF-A, VEGF-B, and PlGF) or proteolytic cleavage (VEGF-C and VEGF-D) [15]. For VEGF-A, 16 isoforms have been described that derive from several transcripts ($VEGF_{110}$, $VEGF_{121}$, $VEGF_{145}$, $VEGF_{165}$, $VEGF_{183}$, $VEGF_{189}$, and $VEGF_{206}$) and differ for properties related to extracellular matrix (ECM) anchoring, and binding affinity for heparin and/or VEGFRs/NRPs [13,16]. For instance, $VEGF_{165}$, the most expressed and physiologically relevant isoform, has a single heparin-binding domain and can be both soluble and ECM-anchored; $VEGF_{145}$, $VEGF_{189}$ and $VEGF_{206}$ have two heparin-binding domains, show higher affinity for ECM- or cell surface-expressed heparin and are ECM-anchored, whereas $VEGF_{121}$ has very low affinity for heparin and is highly diffusible [17,18]; $VEGF_{183}$ is predominantly cell-anchored [19]. The ECM-bound VEGF-A isoforms can be also released as diffusible peptides after proteolytic cleavage mediated by proteases like plasmin and matrix metalloproteinase 3 (MMP3) [18]. All the various VEGF-A isoforms bind VEGFR-2 with nanomolar affinity, with $VEGF_{145}$ and $VEGF_{189}$ displaying the lowest affinities [16].

Alternative exon splicing produces two isoforms of VEGF-B, namely $VEGF\text{-}B_{167}$ and $VEGF\text{-}B_{186}$, forming 42 kDa and 60 kDa homodimers, respectively. Once secreted, $VEGF\text{-}B_{167}$ binds to cell-surface heparan sulfate proteoglycans through a heparin-binding domain that, instead, is missing in the more diffusible $VEGF\text{-}B_{186}$ [20,21].

VEGF-C and VEGF-D do not exist as alternative splicing-produced variants; rather, the post-translational proteolytic cleavage mediated by proteases (distinct for each VEGF) generates different VEGF-C and VEGF-D species [22]. VEGF-C, produced as a precursor protein, is activated by furin, PC5 and PC7 (intracellular secretory protein convertases), and is secreted as two 31/29 kDa subunits linked by disulfide bonds. Subsequent proteolysis in the extracellular space by plasmin and other proteases generates a 21 kDa non-disulfide-linked homodimeric VEGF-C that shows high affinity for VEGFR-2 and VEGFR-3 [23,24].

VEGF-D is secreted as a precursor that is then cleaved by different proteases producing various peptides, with distinctive receptor-binding properties and functions. Similarly to VEGF-C, a partially processed VEGF-D (still linked via disulfide bridges) can bind to VEGFR-3, while the mature VEGF-D binds to and activates both VEGFR-3 and VEGFR-2 [22,23,25].

PlGF exists as four isoforms (PlGF-1/4) produced by alternative splicing: PlGF-1 and -3 primarily bind to VEGFR-1, whereas PlGF-2 and -4 mainly signal through NRP-1. Moreover, although with lower affinity than for VEGFR-1, PlGF-1 also interacts with NRP-1, and PlGF-2 can bind to the soluble form of VEGFR-1 [26].

1.2. VEGFRs signaling pathways

VEGFRs comprise an extracellular region, with seven immunoglobulin (Ig) homology domains including the ligand-binding site, and an intracellular kinase domain that transduces the signal originating from the growth factor/receptor interaction. Indeed, VEGFRs homo- or heterodimerization resulting from the interaction with the cognate ligand induces a conformational change in the transmembrane domains that stimulates the kinase activity [27]. Autophosphorylation of specific tyrosine residues within the intracellular juxtamembrane domain produces docking sites for downstream effector proteins, like phospholipase Cγ (PLCγ) [28], which hydrolyzes phosphatidylinositol-4, 5-bisphosphate into diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP_3) [29]. The increased cytosolic concentrations of DAG and IP_3 activate the serine/threonine kinase ERK and Ca^{2+} signaling pathways, thus modulating the proliferation and migration of endothelial cells (ECs) [28]. VEGFR-1 has a weaker tyrosine kinase activity than VEGFR-2; nevertheless, it similarly activates ERK and phosphoinositide 3-kinases (PI3K)-Akt signaling pathways [30]. Likewise, VEGFR-3 stimulates Akt and ERK pathways and promotes the growth and migration of lymphatic ECs [31].

VEGFRs heterodimers can also induce biased signaling. For instance, VEGFR-1/VEGFR-2 activation favors VEGFR-1 signaling rather than the VEGFR-2 pathway [32]. Furthermore, ligand-independent VEGFRs homodimerization and activation have been reported; indeed, reactive oxygen species (ROS) can induce VEGFR-2 phosphorylation by the Src kinases, thus promoting PLCγ activation in the absence of VEGFs binding [33,34].

Besides the membrane-associated receptors, soluble isoforms of VEGFR-1 and VEGFR-2 have been described (sVEGFR-1 and sVEGFR-2), deriving from alternative mRNA splicing and only including extracellular immunoglobulin-like domains. These soluble isoforms are secreted in the ECM, where they act as decoy receptors for VEGFs signaling [35,36].

This review summarizes the current experimental evidence on the physiological and pathological roles of VEGFs/VEGFRs signaling in the central nervous system (CNS) and neurodegenerative disorders, such as Alzheimer's and Parkinson's diseases. Thereafter, we have evaluated the relevance of pharmacological VEGFs/VEGFRs modulation as novel and potential disease-modifying approach for these neurodegenerative pathologies.

2. Physiological and pathological functions of VEGFs/VEGFRs axis

The VEGFs/VEGFRs axis is essential in the processes of angiogenesis and lymphangiogenesis, i.e., in the formation of new blood and lymphatic vessels, respectively, from preexisting vasculature, in both physiological and pathological contexts. Angiogenesis involves dynamic events, like migration, growth, and differentiation of ECs, which are crucial events during embryogenesis and postnatal development (in the latter case, it is also referred to as vasculogenesis, representing the *de novo* formation of a primitive vascular network from EC precursors). Conversely, in adulthood, the endothelium is relatively quiescent and the formation of new vessels, from the preexisting ones, is limited to wound healing and repair of bone fractures, or specific stages of the female reproductive cycle [5,35]. Generation of blood vessels from the preexisting ones includes sprouting angiogenesis, during which specialized ECs (tip cells) with a highly motile phenotype respond to an angiogenic stimulus, and intussusceptive angiogenesis that is based on vessel splitting, a phenomenon also regulated by VEGF-A [37].

Dysregulation of VEGFs/VEGFRs pathways and consequent abnormal angiogenesis can be associated with different pathologies [37–40].

VEGF-A plays a pivotal role in both physiological and pathological angiogenesis, by responding to low oxygen levels. Actually, a hypoxic environment promotes the binding of hypoxia-inducible factor-1α (HIF-1α) to the hypoxia response element (HRE) within the *VEGF-A* promoter region, which results in the transcription of *VEGF-A* mRNA [5,40]. In ECs, VEGF-A mainly signals through VEGFR-2, which coordinates both developmental vasculogenesis in embryos and physiological angiogenesis in adults. Moreover, in different solid tumors, the VEGF-A/VEGFR-2 signaling pathway is involved in carcinogenesis, angiogenesis, and metastasis [41–44].

VEGFR-1 signaling is rather linked to pathological angiogenesis represented by neo-vessel formation in cancer and aberrant vascularization in other diseases, like diabetic retinopathy, exudative age-related macular degeneration, retinal vascular occlusions, retinopathy of prematurity [45–48]. VEGFR-1 stimulation by VEGF-A or PlGF leads to MMPs activation, cancer cell dissemination, and recruitment of protumoral myeloid cells into the tumor microenvironment, thus contributing to tumor progression [3]. Cancer cells may also form their own microcirculation by trans-differentiation into ECs (i.e., vasculogenic mimicry) [49] and VEGFs/VEGFR-1 pathways are involved in this process [49–51]. Moreover, PlGF/VEGFR-1 signaling is involved in inflammatory pathways associated with cardiovascular disorders [52,53] and autoimmune diseases, like rheumatoid arthritis [54].

VEGF-B is not physiologically relevant as pro-angiogenic factor [55], as it does not promote angiogenesis [56] nor stimulate vessel growth [57]. Accordingly, *VEGF-B* gene deletion in mice leads to a mild and life-compatible phenotype of atrial conduction defect [55]. On the other hand, VEGF-B has important roles in cell survival, apoptosis inhibition, and protection against oxidative stress in different cell types, including neuronal and vascular cells [58–67]. For instance, VEGF-B levels are reduced in heart failure and diabetic heart and *VEGF-B* gene therapy inhibits doxorubicin-induced cardiotoxicity in a murine model [60,61]. Moreover, VEGF-B contributes to the protective effect of resveratrol on different models of cardiac disease/injury [62–64]. Being oxidative stress also involved in neurological and metabolic disorders, stimulation of VEGF-B signaling might represent a potential therapeutic approach for such diseases.

VEGF-C and VEGF-D, although to a lower extent compared to VEGF-A, promote VEGFR-2-mediated angiogenesis [68,69] and, by activating VEGFR-3, regulate both physiological and pathological lymphangiogenesis [70].

PlGF has been identified as a pro-angiogenic factor having redundant roles in physiological vessel development and maintenance [71]. Furthermore, PlGF through VEGFR-1 contributes to the pathological angiogenesis occurring in cancer, heart-, limb-, and ocular-ischemia, delayed-type cutaneous hypersensitivity, atherosclerosis, rheumatoid arthritis, obesity, cartilage, and bone repair [71–75], as well as differentiation of tumor associated macrophages towards the protumoral M2 phenotype [76].

According to sVEGFRs decoy receptor function, sVEGFR-2 inhibits physiological and pathological lymphangiogenesis, by blocking VEGF-C-induced VEGFR-3 signaling [77], while sVEGFR-1 exerts an anti-angiogenic function, by either sequestering VEGF-A and PlGF released in the ECM or by directly preventing VEGFR-2 activation [36]. Dysregulation of sVEGFR-1 has been associated with different pathologies: reduced sVEGFR-1 expression is observed in age-related macular degeneration [78], whereas an excess of circulating sVEGFR-1 contributes to pre-eclampsia in pregnancy [79]. Also chronic kidney disease, cardiovascular dysfunction, and inflammatory states, like liver cirrhosis and acute pancreatitis, correlate with higher sVEGFR-1 plasma levels [80–83]. Finally, high sVEGFR-1 expression plays a role in melanoma progression, by promoting extracellular matrix invasion and metastasis through the interaction with α5β1 integrin expressed by tumor cells [84].

NRP-1, acting as VEGFR-1/-2 co-receptor, regulates VEGF-A mediated endothelial permeability, while NRP-2, as a VEGFR-3 co-receptor, is involved in the development of lymphatic vessels [11]. NRP-1 can also respond to different ligands in a VEGFR-independent manner, activating downstream signaling pathways and fostering angiogenesis as well as cell survival, proliferation, and motility in physiological and malignant conditions [85–87].

2.1. VEGFs/ VEGFRs functions in the central nervous system

2.1.1. VEGFs

The various VEGFs isoforms play essential roles in the development of the CNS and modulation of adult brain functions. VEGF-A is a master regulator of angiogenesis in embryonic and early postnatal brain, by mediating ECs proliferation, migration, and survival [13,88]; moreover, it promotes blood perfusion, regulates the functionality of the blood-brain barrier (BBB) by controlling microvascular density and permeability, and induces direct neurotrophic effects [89]. Furthermore, VEGF-A promotes neural stem cells proliferation in the neurovascular niches, such as the subgranular zone in the hippocampus and the subventricular zone, thus stimulating neurogenesis and astrocyte differentiation [13].

Under stress conditions, like hypoxia, VEGF-A preserves neuronal functions, by directly inducing axon extension and supporting synaptic plasticity or, indirectly, by either stimulating astrocyte proliferation and survival or prompting astrocytes and microglia to release trophic factors which are essential for the maintenance of neuronal connections [90,91]. VEGF-A-mediated neuroprotective effects have been reported in different neuronal cell types in the CNS, including cortical, hippocampal, midbrain dopaminergic, cerebellar, and retinal neurons [13,91–96].

In addition, VEGF-A can directly affect neuronal excitability, neurotransmission, and synaptic plasticity [97]. By regulating ion channels, such as voltage-gated Na^+ channels [98], outward delayed-rectifying K^+ channels [99], and high-voltage-activated Ca^{2+} channels [100,101], VEGF-A influences neuronal excitability and Ca^{2+} influx in hippocampal pyramidal neurons. In addition, VEGF-A, by VEGFR-2, regulates glutamate N-methyl-D-aspartic acid (NMDA) receptor function in cerebellar granule cells [102] and hippocampal CA1 pyramidal neurons [90], and enhances long-term potentiation (LTP) in the hippocampal dentate gyrus [103] and at CA3-CA1 glutamatergic synapses [104,105]. VEGF-A administration ameliorates synaptic deficits caused by cerebral ischemia, as reported for basal glutamate transmission, LTP, and neural oscillations in the hippocampus [106–108]. Importantly, VEGF-A-induced regulation of synaptic plasticity correlates with modifications in cognitive and memory performances [103,106,109]. Accordingly, hippocampal LTP impairment and spatial learning deficits associated to cerebral ischemia/reperfusion and vascular dementia are concurrently rescued by procedures like physical exercise [110] and transcranial repetitive magnetic stimulation [111] that increase VEGF-A levels.

VEGF-B, via VEGFR-1 activation, exerts neurotrophic and neuroprotective effects, by inhibiting apoptosis and blunting the oxidative stress that represents a key vulnerability factor for neurons, due to their great oxygen consumption and weak antioxidant system [58,65–67,112–114]. *In vitro,* VEGF-B-induced neurite outgrowth protects primary cerebellar granules, hippocampal and retinal neurons from glutamate-induced oxidative stress and death [67]. This effect is mirrored by the retinal degeneration and worsening of neurodegeneration following cerebral ischemic injury in mice with deletion of the *VEGF-B* gene [66,112,115]. Altogether, this evidence supports a key contribution of VEGF-B to neuronal metabolism and survival/regeneration [65–67,112,113].

VEGF-C acts as a trophic factor for the differentiation of oligodendrocyte precursor cells (OPCs) into mature oligodendrocytes, thereby controlling myelin production. OPCs proliferation is induced by VEGF-C in the optic nerve [116] and by VEGF-A in the medulla oblongata [117].

In addition, the VEGF-C/VEGFR-3 axis stimulates neurogenesis, by promoting proliferation of neural stem cells and their conversion into progenitor cells [116,118].

VEGF-D, via VEGFR-3, contributes to maintenance of dendritic arborization, as observed in primary cultures of hippocampal neurons and in adult murine hippocampus [119,120]. Moreover, it has neuroprotective effects against stroke-induced neuronal damage; indeed, intracerebral and nasal delivery of VEGF-D mimetic peptides reduces the degeneration of cortical layer II/III pyramidal neurons, and preserves dendritic architecture and synaptic connectivity [121]. Furthermore, VEGF-D promotes hippocampal neurogenesis and ameliorates learning and memory performance [122]. Differently, the absence of PlGF expression in the developing mouse brain precedes structural defects (formation of a relatively narrow cerebral blood vasculature) and blood flow alterations that increase susceptibility to stroke [123].

In contrast to the previously mentioned "positive" effects, an anomalous increase of VEGF-A release by astrocytes can lead to BBB disruption and enhanced microvascular permeability, the typical alterations found in inflammation-related neuropathies [124]. Moreover, VEGF-A and VEGF-D are overexpressed in glioblastoma, a highly aggressive brain tumor [125–127].

2.1.2. VEGFRs

Among the VEGFRs, VEGFR-2 is the main regulator of angiogenesis in embryonic and early postnatal brain [88], by mediating EC proliferation, migration, and survival [13]. Moreover, VEGFR-2 is essential for tip cell formation and vascular outgrowth in the retina [128]. Besides promoting angiogenesis, VEGFR-2 has additional neuroprotective roles, as it mediates VEGF-A-induced neuronal survival [91], neurogenesis [129], and astrocyte trans-differentiation into neurons in the ischemic brain [130].

VEGFR-1 has been associated with microglia activation/migration [131], astrocyte activation [132], adult olfactory neurogenesis [133], and neuroprotection likely mediated by VEGF-B [58,134]. Indeed, in the SOD1-G93A mouse model of amyotrophic lateral sclerosis, VEGFR-1 activation by VEGF-B at an early disease stage promotes the survival of motor neurons [113]. In contrast, VEGFR-1 activation by VEGF-A contributes to pathological processes underlying neuropathic pain, triggering hypersensitivity to noxious stimulation. In a model of neuropathic pain induced by the chemotherapeutic agent oxaliplatin, VEGFR-1 activation in the dorsal horn of spinal cord (consequent to increased astrocytic VEGF-A expression) has been reported [135]. Moreover, the neuropathic pain induced by oxaliplatin and by other neurotoxic drugs, like the anti-mitotic agents vincristine and paclitaxel, is prevented by *in vivo* administration of the anti-VEGFR-1 monoclonal antibody (mAb) D16F7 [135]. Of note, VEGFR-2 seems to play an opposite and protective role toward neuropathic pain, as inhibition of this receptor by a specific mAb (DC101), induces a pro-nociceptive effect. Furthermore, VEGFR-2 blockade exacerbates spinal cord neurodegeneration and hyperalgesia in a murine model of hyperglycemia-induced neuropathy [136]. This evidence supports a dichotomy between VEGF-A-activated VEGFR-2 and VEGFR-1, producing analgesic and proalgesic effects, respectively.

VEGFR-3 signaling in the brain is required to maintain dendritic arborization, neurogenesis, and neuroprotection [2,118–122].

Regarding NRPs roles in the CNS, NRP-1 was first described as an adhesion molecule [137] interacting with the class 3 semaphorin A (SEMA3) and regulating neuronal axon pathfinding [138]. It is known that both NRP-1 and NRP-2 are receptors of different SEMA3 family members and VEGF-A isoforms [139]. In addition to neuronal expression, NRP-1 is expressed in blood vasculature (both in endothelial and vascular smooth muscle cells), immune cells, and other cell types, like epithelial cells lining the surface of the respiratory and gastrointestinal tracts. Following activation by several ligands, including VEGF-A and SEMA3, NRP-1 modulates brain development and function, developmental angiogenesis in the hindbrain and retina [140], ocular neurovascular diseases [141], immune system function, and tumorigenesis [142,143]. NRPs signaling activated by SEMA3 is crucial for axon guidance, dendrite development, and neuronal migration, in both central and peripheral nervous system [14,97,144]. A specific VEGF-A isoform - $VEGF_{164}$ - signals exclusively through NRP-1 (without interacting with VEGFR-1 or VEGFR-2) and modulates processes such as: (*i*) the migration of facial branchiomotor neurons located in the hindbrain, (*ii*) the neuroprotection of gonadotropin-releasing hormone (GnRH) neurons during their migration from the nasal placode into the brain, and (*iii*) the axon guidance of retinal ganglion cells [145,146]. Among pure angiogenic cerebral events, NRP-1 relevance seems to be limited to the growth of ocular vessels. Accordingly, treating mice with mAbs that inhibit VEGF-A binding to NRP-1 hinders retinal angiogenesis [146,147].

Thus, current evidence supports the relevance of VEGFs in CNS development and shaping of neural connectivity in the adult brain. In fact, VEGFs/VEGFRs signaling can directly affect various neural cell types (neurons, astrocytes, and microglia) and deeply influence CNS functions in physiological conditions through several mechanisms (Fig. 1), suggesting that alteration of VEGFs/VEGFRs activity can play a role in pathological conditions.

2.2. The VEGFs/ VEGFRs system in Alzheimer's disease

Alzheimer's disease (AD) is the most frequent neurodegenerative disease, whose pathological hallmark is represented by abnormal protein aggregates, i.e., amyloid plaques, deriving from extracellular accumulation of beta-amyloid (Aβ) peptides, and neurofibrillary tangles, due to intraneuronal deposits of hyperphosphorylated tau protein [148,149]. Such protein aggregates, detected in hippocampus, cortex, and subcortical areas, trigger a slowly progressing deficit in interneuronal communication followed by neurodegeneration that cause severe memory deficit and cognitive impairment [150]. Additional factors, like neuroinflammation [151] and cerebrovascular defects, contribute to AD pathology. Indeed, both AD patients and murine disease models show a 10–20% reduction in cerebral blood flow that begins in the early stages and lasts throughout disease progression [152]. The reduced cerebral vascular system, unable to supply sufficient blood and to clear away the waste products of cellular metabolism, contributes to triggering a chronic inflammatory status involving astrocytes and microglia activation [153].

The role of the VEGFs/VEGFRs axis in AD has been actively investigated in the last two decades, with interesting albeit partially contradictory outcomes regarding the altered expression levels of VEGF-A in AD brain, its detrimental or protective functions and, consequently, uncertainty as to whether enhancement or inhibition of the downstream signaling might be useful for AD treatment. The following paragraphs summarize the available experimental evidence reported in the literature.

In animal models, an evident inflammatory reactivity (epitomized by an enhanced mobility of resident microglia), that correlates with increased expression of microglia-associated VEGF-A and neurodegeneration, has been observed after full-length Aβ intra-hippocampal injection [154,155]. VEGFR-1, which stimulates the chemotactic response of immune cells, is recognized as the VEGFR subtype involved in inflammatory/autoimmune conditions [3,156,157]. Thus, the increased mobility of microglia, consequent to Aβ peptide deposition, might be due the to the activation of VEGFR-1 by autocrine-released VEGF-A. The concomitant perturbation of the brain vasculature is ascribed to the paracrine activity of microglia-derived VEGF-A on ECs. Hence, microglia-expressed VEGFR-1 appears as a promising target for a neuroprotective strategy in AD. Treatment of mice with an anti-VEGFR-1 mAb (injected into the hippocampal CA1 layer) reduces VEGFR-1-dependent microglia mobilization and neurodegeneration induced by Aβ peptides. This effect is associated with enhanced neuronal viability and decreased Iba-1 expression (a microglia marker), compared

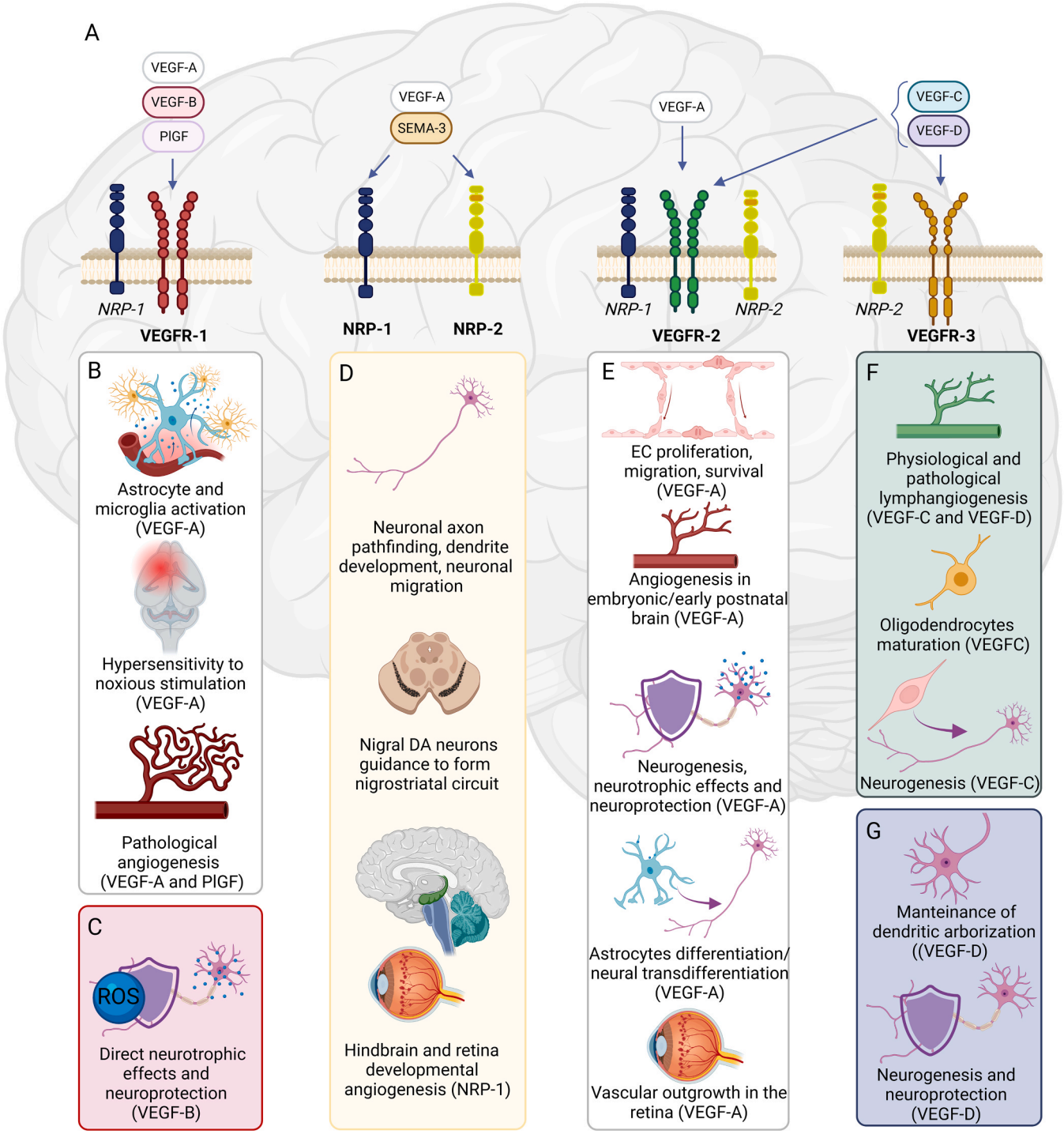

Fig. 1. VEGFs/VEGFRs canonical pathways and related functions in the central nervous system. A) The VEGFs family includes structurally related homodimeric proteins, i.e., VEGF-A, -B, -C, -D, and PlGF in mammals, with different binding specificity for their receptors, i.e., VEGFR-1, VEGFR-2 or VEGFR-3. Semaphorin receptors, i.e., NRP-1 and NRP-2, act as co-receptors (in italics) for VEGFR-1/-2 and VEGFR-2/-3, respectively, but they can also directly interact (in bold) with the ligands (e.g., VEGF-A and SEMA3), thus activating VEGFRs-independent signal transduction pathways. Other growth factors capable of directly activating NRP-1/NRP-2 have been omitted for simplicity. B) VEGF-A-induced VEGFR-1 activation contributes to astrocyte and microglia activation/migration, hypersensitivity to noxious stimulation, and pathological angiogenesis (also stimulated by PlGF/VEGFR-1 interaction). C) VEGF-B-induced VEGFR-1 signaling induces neurotrophic and neuroprotective effects by blunting oxidative stress. D) Activation of NRP-1 and NRP-2 by several ligands, including VEGF-A and SEMA3, is crucial for axon guidance, dendrite development, and neuronal migration. Of note, both NRP-1 and NRP-2 contribute to direct nigral DA neurons projection to form the nigrostriatal pathway. Moreover, VEGF-A/NRP-1 axis modulates developmental angiogenesis in the hindbrain and retina. E) VEGF-A-induced VEGFR-2 signaling is a key regulator of angiogenesis in embryonic and early postnatal brain, by mediating EC proliferation, migration, and survival; moreover, through VEGFR-2 stimulation, VEGF-A induces direct neurotrophic effects, regulates neurogenesis and neuroprotection, and promotes astrocyte differentiation/neural trans-differentiation in the ischemic brain. Finally, VEGFR-2 is essential for tip cells formation and vascular outgrowth in the retina. F) Both VEGF-C and VEGF-D, by binding to VEGFR-3, control physiological and pathological lymphangiogenesis. VEGF-C, via VEGFR-3, acts as trophic and differentiation factor for OPCs conversion into mature oligodendrocytes, thereby controlling myelin production, and stimulates neurogenesis. G) VEGFR-3 activation by VEGF-D contributes to the maintenance of dendritic arborization, provides neuroprotection following stroke, and promotes hippocampal neurogenesis.

to mice only receiving Aβ peptides [158]. By targeting VEGFR-1 signaling, also the naturally occurring compound paeoniflorin, isolated from the root of *Paeonia lactiflora Pallas*, reduces Aβ-induced microglia chemotaxis *in vitro* [159]. Interestingly, VEGFR-1 and VEGF-A show higher expression in AD brain samples, compared to samples from healthy individuals [159].

Notably, the buildup of Aβ and accumulation of pro-inflammatory cytokines (IFN-α, IFN-γ, IL-1) from activated microglia in AD brains stimulates VEGF-A release by astrocytes. Indeed, *in vitro* exposure of human astrocytes to $A\beta_{25-35}$ (an active fragment of the amyloidogenic $A\beta_{1-42}$ isoform) or to a cytokine mixture typically found in late onset AD brains, increases VEGF-A_{165} secretion [160] through a calcium-sensing receptor (CaSR)-mediated mechanism [161]. Based on this evidence, CaSR negative allosteric modulators (calcilytics) have been proposed as potential drugs against late onset AD [162]. Astrocyte-derived VEGF-A amplifies $A\beta_{1-42}$ effects on ECs, worsening endothelial barrier dysfunction and enhancing permeability [163]. In fact, TY-10 human brain microvascular ECs, co-cultured with immortalized human astrocytes in the presence of $A\beta_{1-42}$, show reduced expression of claudin-5, increased permeability to FITC-conjugated dextran, and enhanced MMP9 activity. Exposure to conditioned medium from an astrocyte culture previously exposed to Aβ is sufficient to enhance MMP9 activity in $A\beta_{1-42}$ treated TY-10 cells [163]. A similar endothelial perturbation is observed in a murine ECs monolayer (bEnd.3 cells) treated with conditioned medium from astrocytes exposed to $A\beta_{1-42}$ oligomers; this effect is attributed to an altered basal activity of VEGFR-2 and downstream ERK/Akt pathways [164].

Besides activation of inflammatory responses, likely linked to neurodegeneration, Aβ peptides can also directly lead to cerebrovascular alterations, as they accumulate around and within the cerebral vessel walls [165,166]. Significant abnormalities of the capillary endothelium are detected in AD brain samples, compared to non-AD controls, suggesting a compromised BBB. Accordingly, both *in vitro* and *in vivo* experiments show that soluble Aβ peptides have inhibitory effects on angiogenesis [167]. For instance, exposure to Aβ peptides dose-dependently inhibits capillaries formation by human brain ECs plated on matrigel [168], although this effect does not seem specific for brain ECs. Indeed, the outcome of intratumoral or intraperitoneal Aβ injection in nude mice xenografted with human glioblastoma (U87MG) and lung adenocarcinoma (A549) cells is an altered cerebrovascular architecture, capillary degeneration, and inhibition of tumor vascularization and growth [168].

Increased VEGF-A expression in human AD brain samples (both in neurons and astrocytes of entorhinal cortex and hippocampus) [169], or cerebrospinal fluid (CSF) [170] and peripheral blood [171] of AD patients, is suggested as an endogenous compensatory mechanism to counteract Aβ-induced vascularization damage. Bürger et al. report higher VEGF-A levels in the cerebral cortex of aged AD transgenic Tg2576 mice (21-month-old), compared to age-matched control animals, and demonstrate that VEGF-A affects β-amyloid precursor protein (*APP*) processing through sequential cleavages by the β- and γ-secretase complex [172]. Indeed, exposure of brain slices from Tg2576 mice to VEGF-A transiently decreases β-secretase activity and soluble $A\beta_{1-40}$ and $A\beta_{1-42}$ formation with a potential decrease of fibrillogenesis [172]. Other authors report a VEGF-A decrease in the brains of younger Tg2576 mice 6-month-old) and normalization of its levels by administration of the growth factor promotes non-amyloidogenic processing of APP [173]. In particular, *in vivo* treatment with intranasally injected VEGF-A increases the expression of α-secretase (also known as disintegrin and MMP domain-containing protein 10) and decreases the expression of β-secretase, leading to a reduced $A\beta_{1-42}$ production/accumulation and cognitive decline [173]. In fact, cleavage of APP by α-secretase leads to the release of the soluble non-amyloidogenic sAPPα peptide endowed with neuroprotective and memory-enhancing properties [174–176].

However, an excessive increase in VEGF-A plasma levels and signaling may have detrimental effects on blood vessels, as it may contribute to capillary obstructions in AD. In fact, in the APP/PS1 AD mouse model, peripheral VEGF-A inhibition, through a mAb directed against the murine VEGF-A_{165} isoform, increases occludin concentration in the cortex and hippocampus, improves the BBB integrity, decreases capillary stalling, and increases cerebral blood flow [177,178]. Differently from what is observed with lower VEGF-A levels, high VEGF-A levels (≥500 ng/mL), besides altering the vascular compartment, fail to counteract Aβ accumulation and neurodegeneration, thus suggesting a dose-dependent switch from a neuroprotective to a neurotoxic effect [179].

Contrasting evidence indicates a decreased VEGF-A expression in brain capillaries [180] and serum [181] from AD patients, compared to controls, that correlates with the severity of the cognitive impairment, and leads to postulate that exogenous VEGF-A supplement could restore its neuroprotective effects. Actually, intracerebral injection of VEGF-A-releasing nanoparticles in APP/PS1 mice reduces neuronal loss and improves behavioral deficits [182]. Similarly, APP/PS1 mice subjected to intracranial implantation of microcapsules containing VEGF-A-releasing cells (fibroblasts transfected to produce human VEGF-A and encapsulated within alginate microbeads) show higher brain vessel density, reduced Aβ deposits, and a lower number of apoptotic cells in the cerebral cortex, all changes associated with milder behavioral impairment [183]. The same experimental approach promotes *ex vivo* proliferation of neural precursors and VEGFR-2 overexpression in the cerebral cortex, while decreasing hippocampal acetylcholinesterase activity [184]. Recovery from memory and learning deficits, concomitant with neovascularization and reduced plaque accumulation in hippocampal layers, is also observed in the double transgenic AD mouse model 2xTg-AD transplanted with VEGF-A-overexpressing mesenchymal stem cells [185]. Similarly, intraperitoneal injection of VEGF-A in PDGF-$hAPP^{V717I}$ transgenic AD mice improves learning and memory performance, in parallel with a time-dependent increase in the number of hippocampal VEGFR-2/vWF (endothelial marker) and VEGFR-2/CD34 (endothelial progenitor marker) double positive cells, enhancement of choline acetyltransferase levels, and dampening of Aβ deposition [186]. The beneficial effects of adeno-associated virus (AAV)-VEGF-A, injected in the hippocampus of APP/PS1 mice, have also been ascribed to the preservation of mitochondrial function and biogenesis that are usually altered by Aβ [187]. Interestingly, an increase of hippocampal VEGF-A and VEGFR-2 mRNAs levels is associated with improvement of spatial learning and memory induced by physical activity (4-week treadmill aerobic exercise) in Aβ-injected Wistar rats, compared to resting Aβ-injected rats [188]. These data are in line with previous findings on VEGF-A involvement in running-promoted hippocampal neurogenesis [189].

Other experimental evidence indicates that treatment of APP/PS1 transgenic mice with VEGF-A-containing serum collected from wild-type mice has a protective effect consisting in reduced microglia reactivity [190]. The same treatment reduces neuroinflammation and neutrophil number, typically increased in the blood or brain of AD patients [191] and in preclinical AD models [192]. Recombinant or "native" VEGF-A (i.e., contained in the wild-type mouse serum) decreases neutrophil infiltration and enhances angiogenesis in APP/PS1 brains, by preventing the increase of CXCL1 secretion (a cytokine involved in AD brain infiltration by peripheral neutrophils) and the decrease of Cdk5 activity (a cyclin-dependent kinase that promotes EC proliferation and migration) induced by Aβ [190].

Restoring a proper VEGF-A/VEGFR-2 signaling also reduces AD-related synaptic dysfunction. Exogenous VEGF-A supplement to AD hippocampal neurons cultures, by normalizing VEGFR-2 signaling, partially rescues the Aβ-induced changes of dendritic spine morphology and density [193].

Another hypothesis suggests that, irrespective of changes in VEGF-A levels, the microvascular degeneration occurring in AD may derive from direct Aβ-VEGFR-2 interaction, antagonizing VEGF-A-induced receptor activation [194], or from VEGF-A sequestration in Aβ plaques [195], a

process that begins in early pathological stages and increases during AD progression [196]. Based on these findings, a peptide mimicking the VEGF-A amino acid sequence specifically recognized by Aβ oligomers has been recently designed and found to efficiently prevent Aβ-mediated VEGF-A sequestration, without disturbing VEGF-A-induced VEGFR-2 activation [197]. Furthermore, such blocking peptide induces the formation of large amorphous non-toxic Aβ aggregates (less prone to accumulate at synaptic sites), thus rescuing LTP in the APP/PS1 mouse AD model. However, the impact of *in vivo* treatment with the VEGF-A mimicking peptide on behavioral parameters is not evaluated in this study [197].

Human brain microvascular ECs (HBMECs) and human umbilical vein ECs (HUVECs) exposed to $A\beta_{1-42}$ oligomers acquire a senescence phenotype, showing an increased expression of the senescence-associated proteins β-galactosidase, p21, and p53. Moreover, $A\beta_{1-42}$ treatment correlates with a significant increase of VEGFR-1 and decrease of VEGFR-2 expression in the same ECs [198]. Accordingly, siRNA-mediated VEGFR-1 silencing prevents p21 up-regulation and reduces $A\beta_{1-42}$-induced senescence, while VEGFR-1 overexpression has the opposite effect [198]. These data support a role for VEGFR-1 in promoting AD pathological mechanisms, in contrast to the VEGFR-2 neuroprotective role.

To clarify the molecular mechanisms underlying AD-associated cerebrovascular alterations, a recent study investigated the soluble VEGFR-1 and VEGFR-2 isoforms (sVEGFR-1 and sVEGFR-2), by measuring their plasma levels in 120 healthy subjects, 75 individuals with mild cognitive impairment, and 76 patients with AD [199]. AD patients show increased VEGF-A plasma levels [171,199], but lower sVEGFR-1 and sVEGFR-2 in plasma and VEGFR-2 membrane expression in the brain [199], compared to healthy subjects. A decrease in VEGFR-2 mRNA levels occurs also in Aβ-exposed HUVECs and HBMECs, while reduced cerebral VEGFR-2 protein levels are found in the APPsw/PS1ΔE9 transgenic mouse AD model [199]. Therefore, in view of a VEGFR-2 downregulation, an unbalanced VEGF-A/sVEGFRs ratio can increase free VEGF-A levels and produce a preferential activation of membrane VEGFR-1 signaling. Such mechanism has been proposed to underlie Aβ-induced cerebral perfusion deficits (cerebral amyloid angiopathy, microvascular degeneration, and rupture of vessel wall) detected in AD brains [200,201].

More recent evidence suggests that PlGF, rather than VEGF-A, may play an early role in pathological cerebral angiogenesis observed in the J20 mice AD model through a cross-talk with angiopoietin 2 (Ang-2) [202]. Indeed, at an early stage of Aβ deposition (yet mainly intraneuronal, with few Aβ immunopositive vessels), VEGF-A does not seem to promote AD-related vessel abnormalities, since its levels are unaltered in the hippocampus and cortex of young AD mice, compared to wild-type animals [202]. Moreover, *in vitro* treatment of NMW7 neural stem cells with $A\beta_{1-42}$ directly increases PlGF and Ang-2 mRNAs expression, without affecting VEGF-A mRNA levels. The transcription factor NF-κB is suggested to be the upstream regulator of PlGF and Ang-2 induction in AD neurons, since Aβ deposition increases NADPH oxidase 2 activity and ROS production, both factors capable of inducing NF-κB activation [203,204].

VEGF-C has been also implicated in AD etiological mechanisms for its role in Aβ lymphatic clearance. Meningeal lymphatic vessels drain macromolecules from the CNS into cervical lymph nodes, thus their dysfunction can promote Aβ deposition. In APP/PS1 mice, exogenous administration of recombinant VEGF-C improves lymphangiogenesis and enhances Aβ oligomers clearance, leading to a reduction of spatial cognitive deficits [205,206]. Consistent with the impact of the impaired meningeal lymphatic drainage on microglia inflammatory response in AD, synergistic effects on Aβ plaque clearance, microgliosis reduction, and brain lymphatic vasculature development are observed by combining viral-mediated expression of VEGF-C and anti-Aβ mAbs in 5xFAD mice [207].

Of interest, in aged Tg2576 AD mice with a high Aβ-plaque load, upregulation of NRP-1, VEGF-A, and VEGFR-2 is observed in the entorhinal cortex starting from 20 months of age onwards, as compared to age-matched wild-type animals [208]. NRP-1 is also upregulated in the brain of 9-month-old 5xFAD AD mice (approximately 145%), compared to age-matched wild-type brains [209]. Moreover, patients with severe AD show a significant enhancement of *NRP-1* gene expression (179%) compared to healthy individuals, a finding not observed at initial or moderate AD stages [209].

Evidence on NRP-2 role in AD is limited to the observation that this receptor, in association with plexin, interacts with Aβ, and is involved in the Aβ-induced tau hyperphosphorylation and aggregation [210].

Although some of the previously mentioned results may not be easily reconciled at this time (i.e., differences in experimental settings and among animal models, meaning of VEGFs peripheral blood levels with respect of brain function), the current preclinical and clinical evidence points towards a scenario in which Aβ is able both to sequester VEGF-A and to stimulate VEGF-A release from glial cells. The microglia-derived VEGF-A, through an autocrine loop involving VEGFR-1 stimulation, may enhance microglia mobility and inflammatory reactivity, likely amplifying neurodegeneration (albeit microglia activation may have protective or deleterious role, according to AD severity, as reviewed in [211]). Astrocyte-derived VEGF-A may also worsen these processes and increase ECs sensitivity to $A\beta_{1-42}$ thus contributing to its negative effects on the cerebrovascular system. An opposite view suggests that astrocyte- and microglia-released VEGF-A may trigger a compensatory mechanism against the Aβ-induced cerebrovascular alterations, by affecting APP cleavage and reducing Aβ plaque formation. VEGFR-2 plays a neuroprotective function and reduced cerebral expression of this receptor can contribute to neurodegeneration. In addition, VEGFR-2 is required for preserving BBB integrity during Aβ plaque deposition. However, when VEGF-A plasma levels are extremely high, an excessive increase of BBB permeability may occur due to aberrant signaling through VEGFR-2 expressed on the endothelium of blood vessels [124]. The contribution of VEGFR-1 in AD pathology is further supported by the evidence that its specific ligand PlGF contributes to the pathological angiogenesis and cerebral perfusion deficits in AD brains. The different views on VEGFs/VEGFRs implications in AD are summarized in Fig. 2.

2.3. The VEGFs/VEGFRs system in Parkinson's disease

Parkinson's disease (PD) is a neurodegenerative disease characterized by severe motor deficits (postural instability, rigidity, resting tremor, and bradykinesia) and debilitating non-motor symptoms, including autonomic dysfunctions, sleep disturbances, cognitive impairment, and psychiatric symptoms, like depression and anxiety [212,213].

Although PD is now recognized as a multisystem disease with complex symptomatology reliant on overlapping dysfunctions in various neuronal populations, the degeneration of dopamine (DA) neurons in the substantia nigra pars compacta (SNpc) stands as the leading pathological hallmark primarily liable for motor dysfunctions in PD patients. Several pathological mechanisms contribute to initiate DA neurons degeneration, including an abnormal buildup of α-synuclein (α-syn) protein aggregates, oxidative stress, mitochondrial dysfunction, and impairment of the ubiquitine-proteasome system [214]. Besides such neuron-intrinsic processes, glial cells (astrocytes and microglia) can play multifaceted and even opposite roles in PD pathogenesis and progression, by either contributing to the propagation of neuroinflammatory mechanisms, that can worsen DA neurons degeneration, or releasing neurotrophic or protective factors, which can blunt nigral DA neurons loss [215–217]. Perturbations in the vascular system and blood supply are additional factors feasibly contributing to PD progression, as modifications of the vascular microenvironment surrounding DA neurons disrupt either nutrients delivery or drainage of toxic molecules, thus affecting DA neurons' survival [2].

Earlier evidence of an altered vascularization in PD refers to the

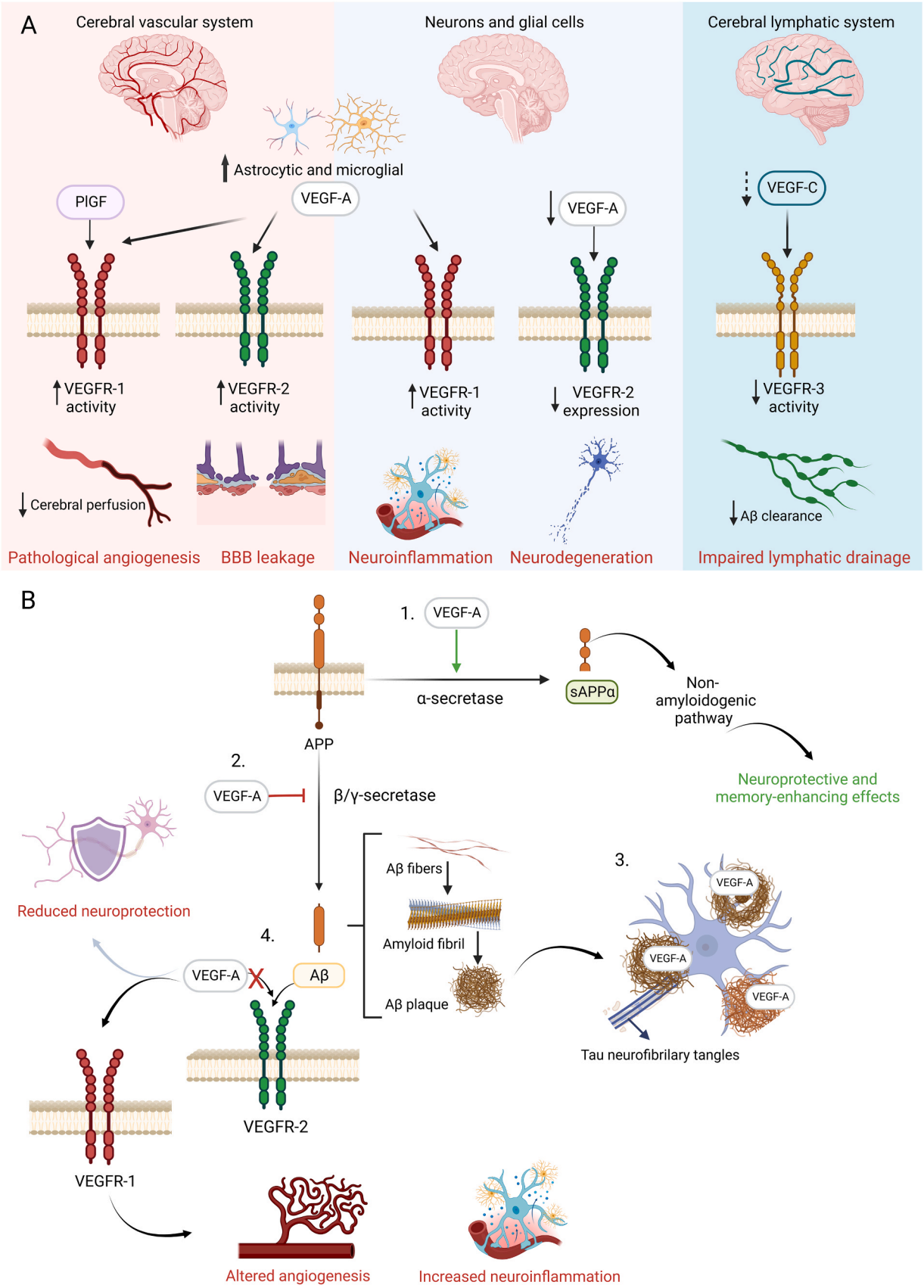

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Fig. 2. The VEGFs/ VEGFRs system in Alzheimer's disease. A) *Consequences of VEGFs/VEGFRs signaling alterations in the CNS*. The release of VEGF-A by astrocytes and microglia may be increased in AD brains. An excessive increase of VEGFR-1 stimulation on endothelial cells may contribute to the perturbation of brain vasculature. Moreover, PlGF, through VEGFR-1 activation, seems to play an earlier role, compared to VEGF-A, in the cerebral pathological angiogenesis and altered perfusion observed in AD brains. Excessively high VEGF-A levels may also overactivate VEGFR-2 in brain blood vessels with an aberrant increase of vascular permeability and consequent BBB leakage. Stimulation of the VEGF-A/VEGFR-1 signaling fosters neuroinflammation and neurodegeneration. Reduced VEGF-A levels and VEGFR-2 expression have been also reported in AD brain, thus hampering the protective effects mediated by the activation of this receptor in neurons. An impaired VEGF-C/VEGFR-3 signaling may reduce the Aβ lymphatic clearance (the dotted arrow refers to a hypothesized decrease in VEGF-C levels). B) *Interplay between Aβ and VEGF-A in AD*. (1) VEGF-A may promote Aβ precursor protein (APP) processing by α-secretase, that results in the release of sAPPα (a non-amyloidogenic peptide exerting neuroprotective and memory-enhancing properties) and (2) can reduce Aβ production from APP by inhibiting the sequential cleavages by β- and γ-secretases. (3) VEGF-A can be sequestered in Aβ plaques and (4) Aβ can directly interact with VEGFR-2 competing with VEGF-A for the binding to this receptor subtype. Such an effect, beyond blunting VEGFR-2 signaling, might favor VEGFR-1 stimulation by free VEGF-A, with consequent loss of VEGFR-2-mediated neuroprotection and increase of pathological angiogenesis and neuroinflammation.

reduction of close contacts between capillary walls and melanin-containing DA neurons in SNpc of PD patients [218]. Then, in the same brain region, angiogenesis (i.e., increased ECs number and microvascular density) along with irregularly shaped blood vessels and a leaky BBB [219–223] have been also documented.

Analyses of *VEGF-A* gene polymorphisms in PD patients identified the rs3025039 as a risk factor for sporadic PD [224,225]. Furthermore, VEGFs and VEGFRs protein expression is modified in PD patients and animal models. Precisely, VEGF-A, PlGF, and sVEGFR-2 levels are increased in the CSF of PD patients [226], while VEGF-A serum levels are similar to control subjects [227].

Moreover, post-mortem analyses of human brain tissues demonstrate higher levels of VEGF-A and VEGFR-1 in neuromelanin-containing DA neurons and astrocytes of SNpc, along with normal VEGFR-2 expression in DA neurons, as well as an increased number of ECs and vessels in PD patients, compared to healthy individuals [228]. High VEGF-A expression has been also reported in PD animal models, like 1-methyl-4--phenyl-1,2,3,6-tetrahydro-pyridine (MPTP)-lesioned monkeys [229] and transgenic mice expressing the mutated A53T form of α-synuclein (A53T-α-syn) [230], as well as in 6-hydroxydopamine (6-OHDA)-lesioned rats subjected to chronic levodopa (L-DOPA) treatments, a pharmacological regimen used to model L-DOPA-induced dyskinesia [221]. In these animal models, as in PD patients [228], VEGF-A overexpression appears prominently localized in astrocytes and associated with angiogenesis [221,229], in line with the key role of astrocyte-released VEGF-A in promoting ECs proliferation [231].

The factual impact of such VEGF-A and VEGFR-1 upregulation in PD progression is still unclear, as these modifications could be both protective and/or harmful. Abnormal VEGF-A upregulation could participate in PD pathogenic mechanisms and worsen BBB leakage. Vascular VEGF-A, in a sort of vicious circle, would activate astrocytes, and the consequential enhanced astrocytic VEGF-A release would contribute to vascular and BBB alteration [124,230,232]. Of note, crosstalk between α-synuclein, astrocytes, and astrocytic VEGF-A has been recently proposed as the leading mechanism of PD-associated BBB breakdown, based on the evidence that A53T α-syn overexpressing mice display a compromised BBB, due to reduced expression of tight junctions-related proteins (ZO-1, occludin, and claudin-5) and abnormal VEGF-A levels [230]. Treatment with the VEGFR-2 inhibitor SU5416 ameliorates BBB alterations of A53Tα-syn overexpressing mice, thereby supporting the involvement of this receptor subtype in VEGF-A-associated BBB impairment [230].

Yet, the VEGF-A upregulation observed in PD patients and preclinical models could also stand as part of a compensatory mechanism that limits the initial DA neurons distress through the interplay of various cell types, namely ECs, astrocytes, and neurons. Firstly, VEGF-A-induced ECs proliferation and angiogenesis, by enhancing blood perfusion of SNpc, might support DA neurons survival. Since nigral DA neurons need a constant energy supply to sustain their spontaneous pacemaker firing activity (considered the major vulnerability factor leading to their degeneration in PD) [233], VEGF-A-induced vascularization, by enhancing nutrient availability, could counteract their degeneration.

Furthermore, as mentioned above, VEGF-A has pleiotropic functions, including the induction of glial proliferation and neurogenesis, as well as direct neurotrophic/neuroprotective effects [234,235], all useful mechanisms to slowdown PD progression. In turn, activated astrocytes release several neurotrophic and neuromodulatory factors, feasibly affecting neuronal viability and function. VEGF-A has direct neurotrophic effects on nigral DA neurons, inducing axonal growth in ventral mesencephalon primary cultures [236,237]. Axonal growth and guidance of nigral DA neurons are also regulated by NRP-1 and NRP-2, through semaphorins SEMA3A, 3C, and 3F binding [238–242]. Such VEGFRs/NRPs-mediated neurotrophic functions, by preserving axonal integrity and dendritic branching of nigral DA neurons, could slowdown PD progression. Accordingly, exogenous VEGF-A, delivered by different methods, improves neuronal survival and motor deficits in various PD animal models. In 6-OHDA-lesioned rats, boosting striatal VEGF-A levels via encapsulated human VEGF-A releasing cells increases DA neurons' survival and improves motor behavior [243,244]. In rotenone-lesioned rats, intra-striatal injection of VEGF-expressing human umbilical cord mesenchymal stem cells (HUMSCs) reduces nigral DA neurons loss and motor alterations, i.e. apomorphine-evoked rotations [245]. In 6-OHDA-lesioned rats, intra-striatal injection of VEGF-A microencapsulated into biodegradable polymeric microspheres reduces PD-related motor impairment decreasing amphetamine-induced circling [246]. Moreover, in 6-OHDA-lesioned rats intra-striatal VEGF-A overexpression, obtained by infusion of adeno-associated viral vectors (AAV)-carrying the *VEGF* gene (AAV-VEGF), increases DA neurons survival and reduces motor behavior alterations [247]. Astrocytes appear as the major player in the mechanisms underlying such VEGF-A effects because neuroprotection associates with astrogliosis and higher glial-derived neurotrophic factor (GDNF) levels, without obvious vascular alterations (angiogenesis, or vessel and BBB alterations) [247]. *VEGF-A* gene delivery, through polylysine-modified polyethylenimine carriers, protects SNpc DA neurons in both 6-OHDA-exposed cell cultures and rats, which show also beneficial effects on motor alterations (like apomorphine-induced circling) [248].

Of note, intravenous injection of VEGF-A (encapsulated within poly-lactic-co-glycolic acid nanospheres) is similarly effective as intracerebral VEGF-A inoculation in protecting nigral DA neurons in 6-OHDA-lesioned rats [249]. Hence, by overcoming VEGF-A peripheral degradation and limited bioavailability, this approach broadens the potential applicability of VEGF-A-based therapeutics in human diseases.

Some evidence demonstrates that deep brain stimulation of the subthalamic nucleus (DBS-STN) - the surgical therapeutic approach used in advanced PD patients - induces VEGF-A upregulation and, consequently, microvasculature changes likely contributing to the DBS-STN therapeutic efficacy [250,251]. Precisely, it has been reported that DBS-STN application to 6-OHDA-lesioned rats induces VEGF-A upregulation in the striatum [250], while post-mortem analyses of human STN samples from PD patients demonstrate increased VEGF-A levels and angiogenesis in DBS-STN-subjected PD patients, in comparison with age-matched controls [251].

Furthermore, increased NRP-2 levels in the blood of PD patients are associated with DBS-STN [252], supporting the hypothesis that NRP-2 upregulation might contribute, in addition to VEGF-A, to mechanisms

underlying DBS-STN efficacy.

Physical exercise training - proposed as a non-pharmacological approach for PD treatment based on clinical evidence [253–257] and outcomes from PD models [258–260] - might produce beneficial effects in PD patients also by promoting angiogenesis and improving blood perfusion of the nigrostriatal DA circuit. Indeed, despite dedicated investigation of VEGF-A contribution to physical activity-associated benefits in PD patients is so far limited [261], treadmill running in aged rats increases microvessel density in the SNpc and VEGF-A mRNA in the midbrain, thus ameliorating aging-related alterations that can drive nigral DA neurons degeneration during PD progression [262,263]. Moreover, 4 weeks of treadmill exercise upregulates angiogenesis markers (VEGF-A or CD34) in the striatum of a rodent PD model [264], thus suggesting that VEGF-A may partake to physical exercise-induced benefits observed in PD patients.

Interestingly, additional evidence in preclinical PD models suggests that VEGF-A-induced neuroprotective effects are dose-dependent. Evaluation of low and high VEGF-A doses, intra-striatally injected in 6-OHDA-lesioned rats, demonstrates that low doses allow a better preservation of SNpc DA neurons and striatal tyrosine hydroxylase positive (TH^+) fibers together with a greater rescue of motor impairment. Conversely, high VEGF-A doses, besides being less neuroprotective, cause increased angiogenesis, glial proliferation, brain edema, and worsening of BBB leakage [265,266]. Accordingly, excessive VEGF-A expression is considered among the causal factors of PD-associated BBB breakdown [238,240], that with the ensuing vascular leakage and brain edema would compromise the neuroprotection achieved by a lower VEGF-A availability. Following this line of thinking, inhibition of VEGF-A signaling, rather than potentiation, would achieve a better outcome in patients with PD in advanced stages, in which severe BBB breakdown is present. Actually, VEGF-A blockade reduces BBB leakage in the A53T-α-syn PD mouse model [238].

Pain represents a common non-motor symptom of PD [267]. VEGF-A contribution to PD-associated pain has been recently evaluated and it has been reported that the cerebral inoculation of $VEGF_{189}$-expressing mesenchymal stem cells (hAMSC-VEGF) ameliorates the mechanical allodynia observed in 6-OHDA-lesioned mice. The underlying mechanism would involve a VEGF-A-induced downregulation of transient receptor potential vanilloid 1 (TRPV1), thereby supporting an analgesic VEGF-A role in PD-associated pain [268].

Beyond VEGF-A, other VEGFs are neuroprotective for SNpc DA neurons against neurotoxins-induced degeneration. In rotenone-exposed midbrain cultures, upregulation of *VEGF-B*, but not *VEGF-A*, is associated with increased DA neuron survival [114]. Likewise, in 6-OHDA-lesioned rats, VEGF-B ($VEGF\text{-}B_{167}$ and $VEGF\text{-}B_{186}$) preserves SNpc DA neurons and ameliorates motor alterations (i.e., reduces amphetamine-induced circling) [269]. Although the exact mechanism underlying VEGF-B-induced DA neuroprotection is currently unknown, the upregulation of antioxidant enzymes [65,66] could contribute to the VEGF-B-mediated neuroprotective effects observed in preclinical PD models.

Evidence regarding the VEGF-C effects in experimental PD models is limited to a single study, showing that VEGF-C intrastriatal injection ameliorates motor alterations in 6-OHDA-lesioned rats, but without significant neuroprotection of SNpc DA neurons [270].

Currently, the precise contribution of distinct VEGFRs to the pathogenic mechanisms underlying PD progression or to the VEGFs-induced neuroprotection is still mostly unknown. Nevertheless, VEGFR-2 inhibition by a VEGFR-2 and RET inhibitor (vandetanib) exacerbates SNpc DA neuron degeneration and motor deficits in 6-OHDA-lesioned rats [271], supporting a VEGFR-2 protective role on SNpc DA neurons. VEGFR-2 signaling pathways promoting DA neuron survival include VEGF-A-dependent PKC and ERK-1/2 activation, reported to lessen DA neuron degeneration in an *in vitro* 6-OHDA model [272]. Conversely, mechanisms underlying VEGF-B-induced neuroprotection of nigral DA neurons involve VEGFR-1 signaling, with activation of fatty acid transporter 1 (FATP1) and 4 (FATP4), as well as PI3K-Akt and ERK-1/2 pathways [273].

Hence, current evidence indicates that diverse VEGFs may impact on PD progression and SNpc DA neuron survival. VEGFs functions on DA neurons can be either indirect, i.e., through an action on ECs (with consequential modulation of angiogenesis and vascular permeability) or astrocytes (which release neurotrophic/neuroprotective factors and show VEGF-A-dependent activation), or direct, with stimulation of VEGFRs expressed on SNpc DA neurons. The overall outcome – in terms of effective neuroprotection and slowdown of PD progression – may depend on distinct VEGFs subtypes involved, extent of VEGFs signaling, and stage of pathology progression. As reported for VEGF-A, neuroprotection is evident at low doses, while higher levels produce vascular hyper-permeability and edema, with potentially detrimental effects on nigral DA neurons, especially in advanced stages of PD (Fig. 3).

Table 1 summarizes the current knowledge from preclinical studies evaluating how VEGFs/VEGFRs modulation contributes to the pathogenic mechanisms underlying AD and PD.

Literature search algorithm to identify appropriate, relevant, English-written articles in PubMed, and criteria adopted for the selection, from the retrieved results, of articles relevant to the topic to be included in the present review, is reported in Supplementary Fig. 1.

3. VEGFs/VEGFRs targeting for AD and PD treatment

3.1. VEGFs/VEGFRs-based therapeutics

The VEGFs/VEGFRs axis, by stimulating EC proliferation and migration, represents a clinically targetable pathway for the treatment of about 20 different types of solid tumors and retinal diseases associated with pathological angiogenesis [274–276]. To date, several drugs have been marketed and hundreds of clinical trials related to VEGFs/-VEGFRs inhibitors can be retrieved from the www.ClinicalTrials.gov website.

The clinically approved anti-VEGF-A drugs include full-length mAbs (bevacizumab and the bispecific mAb against VEGF-A and Ang-2 faricimab), antibody fragments [the Fab fragment ranibizumab and the single-chain variable fragment (scFv) brolucizumab], and VEGF-traps (aflibercept and conbercept, consisting of domains from VEGFR-1 and VEGFR-2, fused to the Fc portion of an IgG1, both able to bind not only VEGF-A but also PlGF and VEGF-B). The multi-targeted tyrosine kinase inhibitors (pazopanib, sunitinib, sorafenib, cabozantinib, lenvatinib, regorafenib, vandetanib, axitinib, ponatinib), hamper both VEGFR-2 and VEGFR-1 signaling [3,4,276,277]. Ramucirumab, a fully human mAb targeting VEGFR-2 extracellular domain, is another approved antiangiogenic agent that selectively prevents VEGF-A-mediated VEGFR-2 stimulation. However, inhibition of VEGF-A/VEGFR-2 signaling is associated with a variety of adverse effects, including hypertension, proteinuria, thromboembolic events, gastrointestinal perforation, bleeding, and impaired wound healing [278,279]. Conversely, selective targeting of VEGFR-1 might represent a safer approach, being this receptor exclusively involved in pathological angiogenesis in the adult. In this context, the only agent reaching phase 2 clinical trials is the fully human mAb IMC-18F1/icrucumab [280–282] that, like most of the experimental VEGFR-1 signaling inhibitors (e.g., KM1730 and KM1732), prevents receptor activation competing with its ligands for the binding to the extracellular domain. On the other hand, the murine anti-human VEGFR-1 D16F7 mAb represents an innovative agent, since it blocks VEGFR-1 activation and signal transduction without affecting ligand binding, as a non-competitive inhibitor [3]. Therefore, differently from other mAbs, D16F7 does not raise the levels of free VEGF-A, which could activate transmembrane VEGFR-2, and leaves unaltered the decoy function of sVEGFR-1. An alternative experimental strategy is based on specifically preventing PlGF-mediated activation of VEGFR-1 action with mAbs directed against the growth factor [e.g., TB-403 (RO5323441) and 16D3] [283–285].

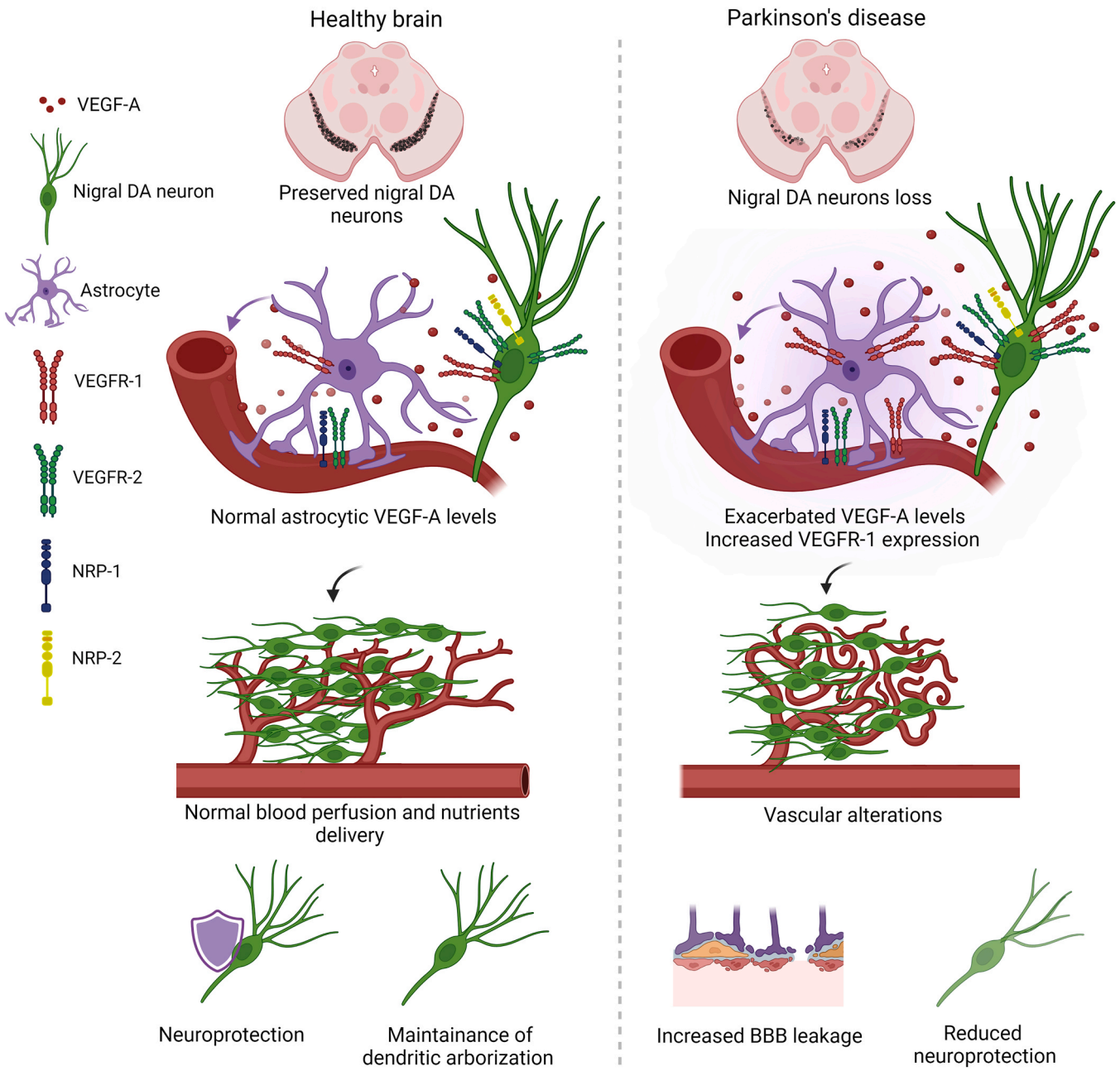

Fig. 3. VEGFs/VEGFRs roles in Parkinson's disease. Left) In the healthy brain, astrocyte-released VEGF-A, by acting on ECs, regulates blood vessel formation and permeability, ensuring adequate blood perfusion and nutrient delivery to nigral DA neurons, thereby sustaining neuronal survival. Moreover, VEGF-A directly induces neurotrophic effects on nigral DA neurons, by activation of VEGFR-1, VEGFR-2, NRP-1, and NRP-2, fostering axonal growth during development and preservation of dendritic arborization. Right) In PD, abnormal VEGF-A levels and increased VEGFR-1 expression in SNpc are associated with vascular abnormalities that can limit nutrient delivery to nigral DA neurons and dampen the drainage of toxic extracellular substances, thus promoting neurodegeneration. Exacerbated VEGF-A levels (overcoming the levels associated with neurotrophic/neuroprotective effects), by acting on VEGFR-1 and VEGFR-2, can also compromise BBB integrity, further amplifying neuroinflammation and nigral DA neuron degeneration.

Currently, modulation of VEGFs or VEGFRs is not recognized as a feasible approach to treat neurodegenerative diseases, including AD and PD, due to their multiple and complex effects in the CNS that critically influence brain homeostasis. In the next sections, we will consider the potential implications of targeting VEGFs/VEGFRs for these neurodegenerative diseases.

3.2. Treatment of AD and potential outcome of targeting VEGFs/VEGFRs signaling

The currently available oral drugs for AD include the acetylcholinesterase inhibitors (AChEIs) donepezil, galantamine, and rivastigmine, approved between 1996 and 2001, and the NMDA receptor antagonist memantine, approved in 2003 [286]. Although the small size of AChEIs (198–380 Da) and memantine (179 Da) allows their entry into the brain parenchyma, these agents induce rather limited symptomatic effects that mostly consist in the temporary slowing of disease progression [287]. More recently, the US Food and Drug Administration has approved two anti-Aβ mAbs: aducanumab (through the Accelerated Approval Pathway in 2021) and lecanemab (BAN2401, in 2023), to be administered intravenously every 4 or 2 weeks, respectively. Anti-Aβ mAbs have been proposed as innovative treatments for early AD, having

Table 1
VEGFs/VEGFRs effects in preclinical models of AD and PD.

Brain disease	Disease model	VEGF/ VEGFR subtype	Methodological information	VEGF/VEGFR effect	Ref.
Alzheimer's disease	Brain slices from Tg2576 mice	VEGF-A	Exposure to VEGF-A (1 ng/mL) for 6, 24, 72 h	– Reduction of soluble Aβ formation – Improvement of cognitive deficits	[172]
	APP/PS1 mice	VEGF-A	Intracranial implantation of alginate microbeads containing VEGF-A releasing fibroblasts	– Enhancement of brain vessel density – Reduction of cortical Aβ deposits and apoptotic cell death – Attenuation of behavioral impairment	[183]
	PDGF-hAPP^{V717I} mice	VEGF-A	Intraperitoneal injection of VEGF-A (8 μg/kg/d, for 3 days)	– Increase in hippocampal VEGFR-2/ vWF and VEGFR-2/CD34 double positive cells – Enhancement of choline acetyltransferase levels – Reduction of Aβ deposition – Improvement of learning and memory	[186]
	APP/PS1 mice	VEGF-A	Intracerebral injection of VEGF-A-releasing nanoparticles	– Decrease of cortical neurons loss – Improvement of behavioral deficits	[182]
	APP/PS1 mice	VEGF-A	Intracranial implantation of alginate microbeads containing VEGF-A releasing fibroblasts	– Increase of *ex vivo* proliferation of neural precursors – Increase of cortical VEGFR-2 expression – Decrease of hippocampal activity of acetylcholinesterase	[184]
	2xTg-AD mice	VEGF-A	Intracranial transplantation of VEGF-A overexpressing mesenchymal stem cells	– Recovery from memory deficits – Promotion of neovascularization – Reduction of hippocampal senile plaques accumulation	[185]
	Tg2576 mice	VEGF-A	Intranasal injection of VEGF-A (1 μg/20 μl/d, for 4 months)	– Increase of α-secretase expression – Promotion of non-amyloidogenic pathway – Improvement of cognitive decline	[173]
	APP/PS1 mice	VEGF-A	Inhibition of peripheral VEGF-A through an anti-VEGF-A_{165} mAb	– Increase of occludin levels in the cortex and hippocampus – Increase in cerebral blood flow – Improvement of BBB integrity – Decrease of capillary stalling	[177, 178]
	APP/PS1 mice	VEGF-A	AAV-induced VEGF-A production in the hippocampus	– Promotion of mitochondrial function and biogenesis	[187]
	Aβ exposed mouse hippocampal neurons	VEGF-A	Exposure to VEGF-A_{165} (50 ng/mL, for 30 min, 12 h, or 24 h)	– Normalization of VEGFR-2 activation – Prevention of synaptic dysfunction – Maintenance of dendritic spine density	[193]
	Primary hippocampal neurons from E17-18 C57Bl/6JRj mice and slices from APP/PS1 mice	VEGF-A	Exposure of neurons to Aβ oligomers derived from pre-incubation with a VEGF-A derived peptide (2 h at 37 °C) and slices to VEGF-A derived peptide (0.5 μM for 40 min before inducing LTP)	– Formation of large amorphous non-toxic Aβ aggregates – Rescue of LTP	[197]
	APP/PS1 mice	VEGF-A	Injection of wild-type mouse serum (intravenously) or recombinant mouse VEGF-A (intraperitoneally)	– Decrease of neutrophil infiltration – Enhancement of brain angiogenesis – Prevention of the increase of CXCL1 secretion and of the decrease of CdK5 activity	[190]
	Aβ exposed human astrocytes	Astrocytic VEGF-A	Co-culture with TY-10 human brain microvascular ECs	– Promotion of ECs sensitivity to Aβ – Enhancement of endothelial barrier permeability	[163]
	Aβ oligomers exposed murine astrocytes	Astrocytic VEGF-A	Co-culture with murine bEnd.3 ECs	– Perturbed endothelial barrier stabilization – Altered cell survival – Disrupted endothelial VEGFR-2 signaling	[164]
	hLEC human lymphatic ECs and APP/PS1 mice	VEGF-C	*In vitro* (100 ng/mL) and *in vivo* (5 μl from a stock 200 μg/ mL, intra-cerebroventricularly) administration of human recombinant VEGF-C	– Improvement of lymphangiogenesis – Enhancement of Aβ oligomers clearance – Reduction of spatial cognition deficits	[206]
	5xFAD mice	VEGF-C	Intra-cisterna magna injection of AAV carrying VEGF-C, plus intraperitoneal or intra-CSF injection of anti-Aβ mAbs	– Promotion of Aβ plaque clearance – Reduction of microgliosis – Expansion of CNS lymphatic vasculature	[207]
	Rat brains exposed to Aβ peptides	VEGFR-1	Injection of an anti-VEGFR-1 neutralizing mAb (10 μg) into the hippocampal CA1 layer	– Decrease of microglia activation and mobilization	[158]

(*continued on next page*)

Table 1 (*continued*)

Brain disease	Disease model	VEGF/ VEGFR subtype	Methodological information	VEGF/VEGFR effect	Ref.
				– Increase in the number of hippocampal neurons	
	HBMECs and HUVECs exposed to Aβ oligomers	VEGFR-1	siRNA-mediated VEGFR-1 silencing Viral vector-induced expression of a chimeric VEGFR-1/EGFR complex	– Reduction of senescence induction (normalization of p21 levels) – Induction of senescence (increase of p21 levels)	[198]
Parkinson's disease	6-OHDA-treated mouse midbrain cultures	VEGF-A	24 h pretreatment with $VEGF_{165}$ and $VEGF_{121}$ before exposure to 6-OHDA	– Increase of SNpc TH^+ DA neuron survival	[243]
	6-OHDA-treated mouse midbrain cultures	VEGF-A	Application of human VEGF-A (1-100 ng/mL) 2-4 h after 6-OHDA	– Increase of SNpc TH^+ DA neuron survival	[244]
	6-OHDA-lesioned rats	VEGF-A	Inoculation of human VEGF-A secreting cells in the striatum (1-2 weeks after 6-OHDA)	– Increase of SNpc TH^+ DA cell survival – Striatal astrocytes activation – Reduction of amphetamine-induced rotations	[244]
	6-OHDA-lesioned rats	VEGF-A	Inoculation of VEGF-A secreting cells in the striatum Two groups: 1) Low VEGF-A dose (11 ng/day); 2) High VEGF-A dose (38.8 ng/day)	Low VEGF-A dose: – Increase in DA neuron survival – Reduction of amphetamine-induced rotations High VEGF-A dose: – Less neuroprotective effects – Reduction of motor rescue – Angiogenesis – Glial proliferation – Brain edema	[265]
	6-OHDA-lesioned rats	VEGF-A	AAV-induced VEGF-A production in the striatum	– Increase of SNpc TH^+ DA cell survival – Reduction of amphetamine-induced rotations	[247]
	Rotenone-lesioned rats	VEGF-A	Transplantation of VEGF-A expressing human umbilical cord mesenchymal stem cells in the striatum	– Increase of SNpc TH^+ DA cell survival – Reduction of apomorphine-evoked rotations	[245]
	6-OHDA-lesioned rats	VEGF-A	Injection of VEGF-A encapsulating polymeric microspheres in the striatum	– Reduction of amphetamine-induced rotations	[246]
	6-OHDA-lesioned rats	VEGF-A	Polylysine-modified polyethylenimine mediated VEGF-A gene delivery in SNpc	– Increase of SNpc DA neurons survival – Preservation of striatal TH+ fibers – Reduction of microglia activation – Reduction of apomorphine-induced rotations	[248]
	6-OHDA-lesioned rats	VEGF-A	Intravenous injection of encapsulated VEGF-A (1 ng/mL)	– Increase of SNpc DA neurons survival	[249]
	6-OHDA-lesioned mice	VEGF-A	Inoculation of $VEGF\text{-}A_{189}$-expressing mesenchymal stem cell in cerebral ventricle	– Reduction of mechanical allodynia	[268]
	Rotenone-exposed midbrain rat neuronal cultures	VEGF-B	Application of $VEGF\text{-}B_{167}$ (0.5-50 ng/mL)	– Increase of TH+ DA neuron survival	[114]
	6-OHDA-lesioned rats	VEGF-B	Intrastriatal injection of $VEGF\text{-}B_{186}$ (3 μg), 6 h before 6-OHDA	– Reduction of amphetamine-induced rotations – Reduction of forepaw preference – Increase of SNpc TH+ DA neuron survival – Increase of striatal TH+ fiber density	[269]
	6-OHDA-lesioned rats	VEGF-C	Intrastriatal injection of VEGF-C	– Reduction of amphetamine-induced rotations	[270]
	6-OHDA-lesioned rats	VEGFR-2	Systemic treatment with a VEGFR-2 and RET inhibitor vandetanib (30 mg/kg/day, orally for 1 week)	– Exacerbation of SNpc DA neuron degeneration and motor deficits	[271]
	hA53T α-synuclein mice	VEGFR-2	Systemic treatment with the VEGFR-2 inhibitor SU5416 (25 mg/kg/day i.p. for 4 weeks)	– Preservation of BBB integrity	[230]

good brain penetration and beneficial effects in terms of Aβ plaque reduction; however, their use has been associated with rather modest symptomatic effects and, of outmost concern, with BBB disruption, cerebral microhemorrhages, and vascular edema [287]. Especially for aducanumab, the reduction of Aβ plaques and the evidence for brain penetration correlates with amyloid-related imaging abnormalities of edema (ARIA-E) [288], a form of vasogenic edema due to BBB disruption [289]. Furthermore, data from clinical trials on aducanumab [287] show plaque reduction associated with ARIA-E [290], suggesting that, due to their high molecular weight, therapeutic concentrations of anti-Aβ mAb can be reached in the brain only via a disrupted BBB. Other experimental anti-Aβ mAbs, that do not cause ARIA-E, fail to reduce Aβ

plaques accumulation. Regarding lecanemab, both preclinical and clinical investigations demonstrate less ARIA-E occurrence, when compared to aducanumab [291–293]; thus, alternative mechanisms other than BBB disruption may account for lecanemab brain penetration. Still, however, few deaths associated with brain hemorrhage call for caution regarding the issue of treatment safety and/or the choice of eligible patients [294].

Besides cholinergic neurotransmission and Aβ dysfunction, the search for new therapeutic targets for AD has been focused on tau accumulation, neuroinflammation, and cholesterol metabolism [295]. However, brain ECs, despite their crucial role in brain homeostasis [152] and potential contribution to AD (ECs from patients show the highest expression of AD risk genes [296]), have not been considered so far as therapeutic targets for this pathology.

The current knowledge on the therapeutic potential of targeting the VEGFs/VEGFRs axis in AD, deriving from preclinical studies, indicates that both activation and inhibition of VEGF-A signaling could produce valuable or detrimental outcomes, depending on whether VEGFR-1 or VEGFR-2 are considered. VEGF-A sequestration in Aβ deposits [195] and VEGF-A-induced behavioral rescue in AD mouse models [182–186] suggest exogenous VEGF-A administration as a strategy to counteract neurodegeneration and vascular abnormality occurring during AD progression. However, although the promotion of neo-angiogenesis for restoring blood flow to hypoperfused tissues has been extensively investigated in AD, the clinical use of VEGF-A does not offer valid therapeutic opportunities [297], likely due to an increased risk of excessive BBB breakdown and vascular leakage. In neurodegenerative diseases, including AD, dysfunction of the BBB functionality, in terms of increased permeability and transcytosis rate, on the one hand could enhance drug uptake, but, paradoxically, may also hamper drug retention in the brain [298–301]. Thus, a high dose of VEGF-A can contribute to worsening the latter condition [179]. On the other hand, inhibition of VEGF-A signaling may result in the loss of its neuroprotective activity.

Clarification of the mechanisms that regulate vessel permeability and neuroprotection could allow a differential and targeted therapeutic intervention [2] that preserves VEGF-A beneficial effects on neuron survival. Therefore, it is necessary to shed light on outcomes deriving from selective modulation of the various VEGF-A/VEGFRs pathways; based on the current scenario, limiting pathological VEGF-A/VEGFR-1 signaling, while preserving neuroprotective VEGF-A/VEGFR-2 activity may be suggested as a potentially valuable approach.

In particular, VEGFR-1 inhibition has been postulated as a strategy to treat AD [154,198], consistently with its pathological/proalgesic signaling. In this context, the unique mechanism of action of D16F7 mAb allows us to hypothesize that blockade of VEGFR-1 signaling might prevent microglia mobilization and neurodegeneration in AD brains, maintain VEGFR-2 functionality, and concomitantly avoid the supra-physiological cerebral accumulation of unbound VEGF-A, which could contribute to altered vessel permeability through excessive VEGFR-2 stimulation. This perspective, together with the demonstrated anti-cancer potential of D16F7 mAb against *in vitro* and *in vivo* tumor models, including glioma at the CNS site [302–305], stimulates further investigation on this topic. Despite the dysfunction of the BBB in neurodegenerative diseases and the consequent increased permeability, the maintenance of a certain level of BBB integrity still prevents the uptake by the brain of peripherally injected IgGs in different AD murine models [306]. In detail, it has been estimated that only 0.1–0.2% of systemically administered antibodies enter the CNS [307]. Expression of VEGFR-1 in endothelial cells, together with the ability of the anti-VEGFR-1 mAb D16F7 to bind endothelial cells, may favor receptor-mediated endocytosis and transcytosis at the lesion site contributing to overcoming the BBB. Despite the drawbacks in the use of full-length mAbs to target CNS expressed factors, a dual inhibitory approach with the bi-specific anti--VEGF-A and anti-Ang-2 mAb faricimab might hamper the PlGF/Ang-2 crosstalk involved in early AD pathological cerebral angiogenesis [202] and, later in the disease, the vascular alteration induced by VEGF-A accumulation.

Antibody fragments, including scFvs that contain only the variable heavy and light chains domains of the antigen binding site from the corresponding full-length mAb, linked by a flexible polypeptide linker, have been also proposed as a strategy to improve the therapeutic potential of mAbs, due to their smaller size, decreased immunogenicity and production costs [308,309]. Moreover, the absence of the fragment crystallizable (Fc) portion in a scFv, could allow to avoid the reverse transcytosis through which a full-length IgG undergoes efflux from the brain parenchyma via interaction between Fc and the neonatal Fc receptor [310].

Short synthetic VEGF-A binding peptides (heparin mimetics) may represent another possible alternative to the high molecular weight inhibitory agents (mAbs and VEGF-traps), allowing them to be easily incorporated into drug delivery systems at desired concentrations [275].

Activation of VEGF-C/VEGFR-3 signaling might also be foreseen as a feasible strategy in AD, based on preclinical evidence that VEGF-C administration reduces cognitive deficits in AD models [205,206] and by considering VEGF-C role in the regulation of lymphatic circulation that is dysfunctional in AD with a consequent impaired Aβ lymphatic clearance [205–207]. It has been hypothesized that a controlled spatial/temporal delivery and proteolytic VEGF-C activation may promote lymphatic filtration and improve the outflow of fluid, cells, and macromolecules from the CNS, thus offering potential benefits for AD, but also other brain diseases such as hydrocephalus, stroke, and multiple sclerosis [311]. The feasibility and safety of a VEGF-C–based therapy is demonstrated by the outcomes of a phase 1 study analyzing AAV-induced expression of human VEGF-C in damaged tissues for breast cancer-associated lymphedema to correct deficient lymphatic flow [312].

Non-pharmacological modulation of the VEGFs/VEGFRs system may also be achieved through physical exercise. In experimental AD models, physical exercise increases hippocampal VEGF-A and VEGFR-2 mRNAs levels, improving spatial learning and memory [188]. The mechanisms through which exercise may exert beneficial effects in AD comprise a modulation of hippocampal volume, synaptic transmission, mitochondrial function, neuroinflammation, growth factors expression, and brain metabolism [313]. Moreover, by affecting VEGF-A levels, physical exercise can improve the age-induced microvascular alterations and reduced cerebral perfusion [313,314]. The optimal training protocol to obtain therapeutic benefits in AD combines aerobic-, strength-, balance-, and coordination exercises, along with cognitive and social activities [313]. However, a clinical trial including AD patients performing moderate aerobic training on the treadmill shows negligible cognitive improvement and unchanged amount of circulating neurotrophins, among which $VEGF_{165}$, compared to control patients [315]. Therefore, the factual implication of VEGF-A in physical exercise-induced benefits in AD patients requires further investigation.

3.3. Treatment of PD and potential outcome of targeting VEGFs/VEGFRs signaling

Current pharmacotherapy of PD includes mere symptomatic drugs that provide temporary relief of motor symptoms without stopping disease progression. Approved PD therapeutics are effective on motor deficits in early disease stages, while beneficial effects wear off with long-term use, and unfortunately are poorly effective on non-motor symptoms. Replacement of adequate DA levels and signaling is the main strategy exploited by approved PD therapeutics, like the DA precursor L-DOPA, DA agonists, or DA catabolism inhibitors (i.e., monoamine oxidase type B inhibitors and catechol-O-methyl-transferase inhibitors) [316]. Beyond pharmacological agents, surgical procedures to implant electrical stimulators for DBS-STN are used in advanced stages of refractory PD [317].

Since PD therapeutics are not disease-modifying drugs, the identification of neuroprotective agents to slowdown the disease progression

remains an unmet necessity. Neurotrophic factors have been extensively evaluated as candidate neuroprotective agents for nigral DA neurons in PD [318,319]. Nonetheless, despite encouraging outcomes in preclinical studies, human clinical trials with neurotrophic factors [so far mainly focused on glial cell-derived neurotrophic factors (GDNF) family] produced contradictory and inconclusive results [320]. Thus, this therapeutic approach for PD remains theoretical, but ongoing investigations are attempting to understand the limiting factors that might hamper its efficacy in clinical trials.

Preclinical evidence in different PD models, showing VEGF-A-induced neuroprotection of SNpc DA neurons [243–249,265,268], strongly supports the therapeutic potential of exogenous VEGF-A administration for PD treatment. However, as previously discussed, VEGF-A can produce opposite (protective or detrimental) and dose-dependent effects on nigral DA neurons. Unwanted side-effects, like abnormal angiogenesis and increased vascular permeability, due to high VEGF-A levels, would exacerbate brain edema and neuroinflammation, boosting PD progression and abrogating neuroprotection achieved with lower VEGF-A levels. Therefore, potential therapeutic strategies aimed at VEGF-A delivery into the brain should take into great consideration the dosage regimen concerning the pathological progression. At advanced stages of PD progression, paradoxically, inhibition of VEGF-A/VEGFR-2 signaling would produce an amelioration of the already compromised BBB functionality, eventually counteracting the associated brain edema and neuroinflammation [230].

Preclinical evidence showing neuroprotection of nigral DA neurons by exogenous VEGF-B administration in different PD models indicates VEGF-B as a potential disease-modifying factor, that could be exploited in innovative PD therapeutics. Of note, differently from VEGF-A-based protocols, the exogenous application of VEGF-B, which displays low angiogenic properties, would avoid worsening the BBB leakage typically observed in advanced PD stages.

Regarding VEGF-C, although so far limited evidence supports its beneficial effects on motor function in a PD murine model [270], improvement of motor performances has been recently reported in an ischemic stroke murine model upon intrathecal injection of an AAV-expressing VEGF-C [321]. Thus, while it can be speculated that exogenous VEGF-C administration may produce some benefits for PD treatment, still additional investigation is required to factually demonstrate its therapeutic potential for PD treatment. Likewise, future studies in PD models are needed to investigate whether VEGF-D - that displays neurotrophic and neuroprotective effects - might represent an additional factor to be considered in the search of novel pharmacological strategies to slow-down PD progression.

4. Conclusions and open issues

Existing evidence indicates that the VEGFs/VEGFRs axis plays multifaceted roles in the regulation of essential brain functions. Moreover, the results of preclinical studies suggest that VEGFs/VEGFRs targeting is worth evaluation as a potential disease-modifying approach for AD and PD treatment. Nevertheless, additional investigations are required to clarify the clinical implication of differential modulation of VEGFR-1 and VEGFR-2 signaling, in terms of risk-benefit ratio as well as optimal drug formulation required to improve the stability of VEGFs-mimicking agents and brain penetration of high molecular weight biologics.

CRediT authorship contribution statement

Mercuri Nicola Biagio: Writing – review & editing. **Barbaccia Maria Luisa:** Writing – review & editing. **Lacal Pedro Miguel:** Writing – review & editing. **Ceci Claudia:** Writing – review & editing, Writing – original draft, Conceptualization. **Graziani Grazia:** Writing – review & editing, Writing – original draft, Conceptualization. **Ledonne Ada:** Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of Competing Interest

The authors declare no conflicts of interest. The funding sources did not have any role in the preparation of this paper.

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The Graphical abstract and Figs. 1, 2, and 3 were created with BioRender.com.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.phrs.2024.107101.

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