Neuroprotective effects of direct activation and transactivation of PDGFβ receptors

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Abstract
Platelet-derived growth factor (PDGF) receptors are expressed throughout the body, including the central nervous system (CNS). Although the physiological role of PDGF receptors in the developed CNS is not fully characterized, PDGF signaling appears to provide neuroprotective effects against several neuronal insults. One of the best-characterized neuroprotective effects of PDGF type-β receptors is against human immunodeficiency virus (HIV) protein-induced neurotoxicity, with potential physiological relevance to HAD. PDGFβ receptors are also neuroprotective against glutamate excitotoxicity, which is associated with both stroke and neurodegenerative diseases, including Alzheimer’s disease. The neuroprotective effects of PDGFβ receptors occur both via direct activation by ligand (PDGF-BB), as well as by PDGFβ receptors activated downstream of G protein-coupled receptor signaling. In addition to the involvement of PDGF signaling in various pathologies and potential therapies, there is also an emerging body of evidence that PDGF may serve as a biomarker for neurological or psychiatric diseases.

Keywords: Platelet-derived growth factor receptor, serotonin, glutamate, transactivation

PDGF SIGNALING
There are two major platelet-derived growth factor (PDGF) receptor isoforms (α and β) and four ligand isoforms (A-D) that form homo- or hetero-dimers. PDGF ligands exist as dimers of four polypeptides:
PDGF-A, -B, -C, and -D that can either homo- or hetero-dimerize into PDGF-AB, -AA, -BB, -CC, and -DD\(^2\). The PDGF ligands act through PDGF \(\alpha\) and \(\beta\) receptors\(^1\) and both are necessary for normal physiological development\(^3\). Upon binding PDGF, receptors dimerize and the tyrosine kinase domains transautophosphorylate one another on multiple tyrosine residues. Effectors such as phospholipase C (PLC) \(\gamma\), phosphatidylinositol 3-kinase (PI3-kinase), Src family tyrosine kinases, tyrosine phosphatases such as SHP-2, and a GTPase-activating protein for Ras are activated after phosphorylation of the PDGF receptor\(^4\). Thus, by direct activation of effector proteins or via cytoplasmic adaptor proteins, PDGF receptors initiate a wide variety of downstream signaling pathways.

PDGF and its receptors are widely expressed throughout the central nervous system (CNS)\(^4\) and are involved in neuronal growth and differentiation\(^8\) although their physiological role in mature neurons is not yet fully characterized. PDGF\(\beta\) receptors are found in pyramidal neurons in the hippocampus\(^6,7\) whereas the PDGF\(\alpha\) receptor and its primary ligand, PDGF-AA, are found in both neuronal\(^8\) and non-neuronal\(^9\) cells. Herein, we will briefly review the direct and indirect [i.e., GPRC - receptor tyrosine kinase (RTK) transactivation] neuroprotective effects of PDGF receptor signaling, with a focus on the PDGF\(\beta\) receptors. Sil and colleagues have recently reviewed the PDGF system in the central nervous system and provided a comprehensive and detailed description of PDGF expression and signaling in CNS cell types including neurons, astrocytes, microglia, oligodendrocytes, signaling in the spinal cord, and the role of the PDGF system in the blood-brain-barrier\(^4\).

**THERAPEUTIC APPROACHES TO MODULATING PDGF SIGNALING**

Several approaches to target PDGF signaling have been proposed or evaluated, and many hold promise despite technical, logistical, and therapeutic challenges. As large growth factors, PDGF ligands are classified as biologics and would require parenteral administration. Even so, they are too large to cross the blood-brain barrier and enter the CNS, thus would require intrathecal administration directly into the cerebrospinal fluid, or direct injection into the brain, such as intracerebroventricular injection\(^16\). An alternative approach, discussed below, could be to indirectly transactivate PDGF receptors after the activation of G protein-coupled receptors (GPCRs). On the other hand, approaches to inhibit PDGF receptor signaling include antibodies that target PDGF ligands or receptors, small molecule inhibitors of PDGF receptor kinase activity, genetic manipulations, or targeting specific downstream signaling pathways at the receptor level\(^2\). Papadopolous and Lennartsson recently reviewed the approaches to inhibit PDGF signaling in cancer therapies and provided a detailed description of current and future therapies that target the PDGF system\(^11\). Indeed, beyond the neuroprotective roles discussed here, the PDGF system holds the potential to better understand and perhaps treat several non-neuronal disease states including cancer, fibrosis/connective tissue disorders, and vascular disease\(^12\).

**HUMAN IMMUNODEFICIENCY VIRUS - ASSOCIATED NEUROCOGNITIVE DISORDER**

Although specific dementias have distinct pathologies, disease courses, and outcomes, all include neuronal dysfunction, and many include disruptions in neurotransmitter homeostasis and signaling. Alterations in glutamate homeostasis in particular, including excitotoxicity, contributes to the pathology of ischemia and several neurodegenerative diseases\(^13\). As dementias progress, accumulation of toxic proteins or aggregates, coupled with neuronal dysfunction and inflammation, reduce neuronal cell viability. Thus, there is a significant interest in the role of neuroprotective signaling pathways to treat these conditions.

Human immunodeficiency virus (HIV)-associated neurocognitive disorders (HAND) are neurocognitive complications resulting from HIV infection and are classified as: asymptomatic neurocognitive impairment, mild cognitive motor disorder and HIV-associated dementia (HAD), in order of severity\(^14\). As the efficacy of antiretroviral therapies has improved, the transformation of HIV-infection from a fatal disease to a
chronic one has resulted in an increase in the prevalence of HAND\(^{15}\). Despite their effectiveness in the periphery, limited penetration of antiretroviral therapies into the CNS also contributes to adverse neuronal consequences\(^{16}\). Although the virus does not infect neurons directly, the viral proteins released from infected perivascular macrophages and microglia in the CNS can interact with neurons and cause neuronal damage and loss\(^{17}\). Several growth factors, such as brain-derived growth factor (BDNF) and fibroblast growth factor (FGF), as well as PDGF-BB, have demonstrated neuroprotective effects against HIV protein toxicity\(^{18-20}\).

Down-regulation of the PDGF-B chain at both the mRNA and protein level is observed in neuroblastoma SH-SY5Y cell cultures treated with gp120, an HIV envelope glycoprotein, and this protein exerts neurotoxic effects on SH-SY5Y cells, including increased cell death and loss of neurites\(^{21,22}\). These toxic effects are attenuated by pretreating the cells with PDGF-BB prior to incubation with gp120 in both SH-SY5Y cells and rat cortical neurons\(^{21,22}\). The neuroprotective effects appear to be associated with a reduction in apoptosis, as measured by reduced gp120-mediated activation of caspase-3 and increased Bcl-xl/Bax ratio\(^{23}\). Peng and colleagues identified several effectors downstream of PI3K/Akt required for neuroprotective effects\(^{22}\). GSK-3β inactivation leads to nuclear translocation of β-catenin and NF-κB, transcription factors that are involved in cell proliferation and differentiation\(^{22}\). Additional potential neuroprotective mechanisms include phosphorylation of Bad, downregulation of the pro-apoptotic protein, Bax, and the inhibition of gp120-induced release of mitochondrial cytochrome C\(^{22}\).

PDGF is also neuroprotective against toxicity induced by another HIV-1 protein, Tat\(^{20,23}\). PDGF-BB activation of the PDGFβ receptor increases dendrite length and cell viability (via an anti-apoptotic effect) in rat primary midbrain neurons exposed to Tat\(^{22}\). PDGF-BB also reduces reactive oxygen species (ROS) production and caspase-3 activation and these effects involve the regulation of ion channels, specifically, TRPC subtypes TRPC 5 and TRPC 6, and calcium influx\(^{24}\). The PDGF-mediated neuroprotection against Tat via TRPC is also confirmed in vivo: PDGF is able to protect dopaminergic neurons in adult mice injected with HIV-1 Tat and TRPC activity contributes to the protection\(^{25}\). Zhu et al.\(^{25}\) examined the PDGF-mediated neuroprotection against Tat in differentiated SH-SY5Y cells and observed the same neuroprotective effect observed by Yao in rat primary neurons and the neuroprotective effect also involves elevation of intracellular Ca\(^{2+}\) and requires Ca\(^{2+}\) influx. N-methyl-D-aspartate (NMDA) receptors may also be involved, as the NMDA receptor antagonist MK-801 is able to abolish Tat-induced toxicity in differentiated SH-SY5Y cells\(^{25}\).

In addition to direct neuronal toxicity, HIV proteins can impair neurogenesis in the hippocampus\(^{26}\). The PDGF system is important for neurogenesis, both in the developing and mature CNS\(^{27}\). PDGF-BB can increase the number of neural progenitor cells (NPC) in the rat hippocampus in the presence of Tat\(^{26,28}\) as well as after cocaine administration\(^{28,29}\). Similar to the previous findings by the Buch group, a role for p38, JNK, MAPK, and GSK3β and for the TRPC channel and calcium signaling are involved in this neuroprotective pathway\(^{24}\). Knocking-down PDGFβ receptor expression reduces neurogenesis after middle cerebral artery occlusion in mice, further suggesting a crucial role for PDGF-associated neurogenesis after neuronal injury\(^{30}\).

While many of the neuroprotective effects exerted by the PDGF system appear to be due to PDGF-BB, other ligands also exert protective effects. For example, PDGF-CC is also protective against Tat via similar downstream signaling pathways (PI3K/Akt/TRPC) as PDGF-BB\(^{31}\) and PDGF-CC was recently shown to reverse synaptic changes caused by Tat\(^{31}\).

**STROKE AND ISCHEMIA**

One of the major areas of PDGF neuroprotection studies has been focused on the direct inhibitory effect of PDGF on NMDA receptors and the associated neuroprotection against NMDA receptor-induced toxicity.
Valenzuela et al.\textsuperscript{[32]} electrophysiological studies were the first to reveal the inhibitory effect of PDGF on NMDA receptors. Brief activation of PDGF receptors by PDGF-BB can trigger long-lasting inhibition on NMDA receptors in rat hippocampal slices, cultured hippocampal neurons, and \textit{Xenopus} oocytes\textsuperscript{[32,33]}. The mechanism of this inhibition involves PLC\textgreek{\gamma}-induced elevation of intracellular Ca\textsuperscript{2+} and protein phosphatase activity downstream of Ca\textsuperscript{2+} signaling to modulate the NMDA receptor function\textsuperscript{[33]}. Follow-up studies determined that PDGF\textbeta\ receptor signaling selectively inhibits NR2B-containing NMDA receptors and decreases surface localization of NR2B subunits\textsuperscript{[9]}. Abelson tyrosine kinase activated downstream of PDGF\textbeta\ receptors or added directly (intracellularly) to hippocampal neurons similarly inhibits NMDA receptor signaling\textsuperscript{[34]}. In addition to the inhibition of NMDA receptor signaling, PDGF-BB also reduces oxidative stress and calpain activation induced by hydrogen peroxide via reduction in intracellular calcium and via the PI3 kinase signaling pathway\textsuperscript{[35,36]}.

Excess glutamatergic signaling, and subsequent over-activation of NMDA receptors, is one of the signaling events associated with neurotoxicity after stroke. Tseng and colleagues directly examined the neuroprotective effect of PDGF-BB against glutamate- or NMDA-induced excitotoxicity in cultured hippocampal neurons and found that PDGF-BB pretreatment can protect neurons from these insults in both dose- and time-dependent manners\textsuperscript{[27]}. Pretreatment with 10 ng/ml of PDGF-BB for 24 h is required for maximal effect\textsuperscript{[27]}, although as little as 10 min of PDGF-BB pretreatment is sufficient to protect neurons from NMDA receptor-induced toxicity, if applied immediately prior to the insult\textsuperscript{[7]}. Besides the direct inhibition of the NMDA receptor, PDGF-associated neuroprotective effects against excitotoxicity are also attributed to its ability to increase glutamate reuptake by modulating the activity of the glutamate transporter, EAAC1. Sims and colleagues found that PDGF can increase the activity and surface expression of EAAC1 and these effects depend on the activation of PI3 kinase\textsuperscript{[38]} and the activation of Akt\textsuperscript{[39]}.

\textit{In vivo}, pretreatment with PDGF-BB, but not AA, two days before forebrain ischemia in rats protects CA1 pyramidal neurons from delayed neuronal death on day 7 after ischemia in a dose-dependent manner\textsuperscript{[40]}. Continuous infusion of PDGF-BB for 7 days into the cerebral ventricles of gerbils with transient forebrain ischemia improves their performance on a passive avoidance task and subsequent histological examinations revealed that PDGF-BB increases neuronal survival and the number of remaining synapses\textsuperscript{[41]}. Administration of PDGF-BB into the left neocortex of Sprague-Dawley rats for 7 or 14 days before ischemia decreases the neocortical infarction with the size of infarction the smallest in the 14-day group\textsuperscript{[42]}. Egawa-Tsuzuki and colleagues found that PDGF-B infusion before and after NMDA injection reduces the size of lesions in young rats when their endogenous expression of PDGF-B in neurons is low\textsuperscript{[43]}.

Clearly, the application of PDGF ligands preceding a controlled insult is neuroprotective, but likely not a feasible therapeutic approach in humans where the insult is not typically predictable. Interestingly, PDGF signaling may be used as an endogenous neuroprotective response by the CNS after the damage has already occurred. For example, focal ischemia in rat brains causes a rapid increase in PDGF-B chain isoform mRNA transcripts that peaks at 24 h\textsuperscript{[44]} (a similar upregulation of PDGF-B occurs in myocardial tissue after ischemia\textsuperscript{[45]}). PDGF-BB expression is also increased after ischemic preconditioning in the gerbil hippocampus\textsuperscript{[46]}. PDGF\textbeta\ receptor expression rises rapidly after ischemia in the rat brain\textsuperscript{[47]}. Furthermore, the expression of PDGF-A and PDGF-B mRNA and PDGF-BB and PDGF-AB dimer protein expression rises in neurons and supports cells surrounding areas damaged by ischemic events in humans\textsuperscript{[48]}. In addition, mice without the PDGF\textbeta\ receptor gene are vulnerable to NMDA receptor-induced excitotoxicity in terms of increased cell death and lesion size\textsuperscript{[49]}. There is a considerable amount of evidence that activation of the PDGF system prior to these neuronal insults is neuroprotective and that these insults also upregulate PDGF system components.
A NOTE ON THE BLOOD-BRAIN BARRIER

Although not a direct neuronal or neuroprotective effect, PDGF signaling has a significant, perhaps much more significant, indirect impact on neuronal health due to its effects on pericytes, angiogenesis, and the blood-brain barrier. As our focus is on the neuroprotective effects of PDGF signaling, we will not review PDGF’s vascular effects in detail as these have been reviewed elsewhere\cite{24,30,31}. While the role of PDGF signaling in the blood-brain barrier is not yet fully understood, several lines of evidence demonstrate that PDGF signaling increases blood-brain barrier permeability, resulting in neuronal damage, while others have demonstrated positive effects of PDGF signaling on blood-brain barrier function and recovery after neuronal insults. Examples of the impact, both positive and negative, of PDGF signaling have been reported for stroke\cite{52-54}, HAND\cite{24,55,56}, Alzheimer’s disease (AD)\cite{57}, Parkinson’s disease (PD)\cite{58}, epilepsy\cite{59}, and neuroinflammation\cite{60,61}.

ALZHEIMER’S DISEASE

AD is a progressive neurodegenerative disease characterized by cognitive decline\cite{62}. One of the hallmarks of AD is amyloid-β accumulation which begins decades before clinical diagnosis of the disease\cite{62}. There is emerging evidence that the PDGF system is involved in AD pathology. For example, PDGF-BB is one of the cytokines that differs between post-mortem patients with high amyloid-β accumulation loads that did not have cognitive symptoms vs. those that did experience cognitive decline\cite{63}. Amyloid-β is produced by the proteolytic cleavage of the amyloid precursor protein (APP)\cite{64} and the PDGF system appears to play a role in APP homeostasis. In astrocytes, PDGF treatment increases sAPPα activity two-fold and this effect is blocked by the broad-spectrum tyrosine kinase inhibitor, genistein\cite{65}. Using a recombinant protein expressing system in Hela cells, Gianni and Zambrano, along with other colleagues, demonstrated that PDGF-BB can induce γ-secretase mediated APP proteolysis by activating PDGF receptors and found Src and Rac1 but not ERKs, PI3K or Abl tyrosine kinase were involved in that signaling pathway\cite{66,67}. Further studies have identified that the cytodomain of APP (containing YENPTY motif) is required for PDGF-induced APP proteolysis\cite{66,67}.

The mechanism(s) of amyloid-β toxicity in neurons involve both non-specific and receptor-dependent pathways\cite{68-70}, including interactions with receptor tyrosine kinases\cite{69}. In SH-SY5Y cells, application of PDGF-BB increases cell number and this effect is inhibited in the presence of amyloid-β\cite{71}. PDGF-BB-induced phosphorylation of the PDGFβ receptor is also blocked by amyloid-β, however, no physical association between amyloid-β–PDGF-BB was detected\cite{71}. Indirect activation (i.e., transactivation - see the section below) was not affected by amyloid-β\cite{71}. We have previously demonstrated that direct or indirect (GPCR-mediated) activation of the PDGFβ receptor can protect neurons against NMDA receptor-dependent toxicity\cite{72}. However in the presence of amyloid-β, PDGF-BB application was no longer able to prevent NMDA-induced toxicity, suggesting that amyloid-β may promote neurodegeneration by blocking a key neuroprotective pathway in the brain.

PARKINSON’S DISEASE

Similar to AD, there is evidence that PDGF and other neurotrophic factors may also be involved in the pathogenesis and treatment of PD due to both its neuroprotective and trophic effects (see two recent reviews\cite{71,74}). The levels of PDGF-BB and PDGF-AA are correlated with the level of plasma α-synuclein in PD patients, suggesting PDGF may be a potential biomarker for PD\cite{75}. PDGF-BB provides protective effects against a toxicant associated with PD, rotenone, by countering its effects on mitochondria and ROS production in both cell lines and in astrocytes\cite{76,77}. With the latter finding among those sparking interest in targeting PDGF signaling in astrocytes in neurologic disease as a therapeutic approach\cite{74,78}. These and other studies led to human trials with PDGF-BB in phase I clinical trial for PD (a dose-escalation study of intracerebroventricular PDGF-BB delivered via an infusion pump, from 0.2 to 5 μg/day)\cite{10}. PDGF-BB
showed good tolerability and resulted in a dose-dependent increase in dopamine transporter expression measure via positron emission tomography (PET) scan, but little to no symptomatic improvement\(^{(10)}\). Analogous to our own findings demonstrating amyloid-\(\beta\) could impair PDGF receptor signaling\(^{(71)}\), one of the pathogenic processes in PD, a-synuclein, impairs some PDGF-induced processes (chemotaxis) but not others (intracellular signaling to ERK)\(^{(46)}\). In addition to PDGF-BB, PDGF-CC has demonstrated neuroprotective effects in several neuronal toxicity studies, including 6-OH-dopamine-induced neuronal cell death, in signaling pathways associated with GSK3\(\beta\)\(^{(91)}\).

**NEUROPROTECTIVE EFFECTS OF PDGF RECEPTOR TRANSACTIVATION**

Growth factor receptors such as the PDGF\(\beta\) receptor can be activated directly by their endogenous ligand or be transactivated by signals initiated through other receptors in the absence of PDGF ligand\(^{(82,83)}\). Classic transactivation of growth factor receptors occurs within minutes after activation of GPCRs. For example, the activation of D2-family dopamine receptors initiates an intracellular signaling cascade that increases PDGF\(\beta\) receptor phosphorylation and activity, including an increase in ERK1/2 phosphorylation\(^{(84)}\). The transactivation of RTK receptors by GPCR initiation may regulate a signaling cascade that differs from those activated by direct ligand binding\(^{(85)}\).

5-HT7 receptors are \(G_{\alpha}S\)-coupled receptors; their activation leads to an increase both in adenylyl cyclase activity and in the intracellular level of cyclic AMP\(^{(86)}\). 5-HT7 receptors are expressed in the prefrontal cortex, hippocampus, thalamus, hypothalamus, and the amygdala in both neurons and support cells\(^{(87)}\). 5-HT7 receptors increase the number of dendrites and promote synapse formation in neurons\(^{(88)}\). 5-HT receptors including the 5-HT7 receptor are also able to transactivate PDGF\(\beta\) receptors (and TrkB receptors)\(^{(89,90)}\).

PDGF\(\beta\) receptors can inhibit NR2B-containing NMDA receptors and this can result in neuroprotective effects. Similarly, transactivating PDGF\(\beta\) receptors, downstream of dopamine receptors, also results in neuroprotection against NMDA-induced toxicity\(^{(91)}\). 5-HT7 receptor agonists also lead to an increase in the expression of PDGF\(\beta\) receptors and its phosphorylation at tyrosine 1021, the PLC\(\gamma\) binding site associated with PDGF-induced inhibition of NMDA-evoked currents\(^{(89)}\). After the application of 5-HT7 receptor agonists to cultured cells or primary hippocampal or cortical cultures, the cells are resistant to NMDA-induced toxicity due to the upregulation and activation of PDGF\(\beta\) receptors\(^{(75)}\). In addition, activation of the 5-HT7 receptor also selectively changes the expression and phosphorylation state of the NR2B subunit of the NMDA receptor, similar to what was observed with dopamine and PDGF-BB-induced changes in NMDA receptor expression\(^{(72)}\). Interestingly, although long-term agonist treatment with 5-HT7 ligands inhibits NMDA receptor activity via PDGF\(\beta\) receptors, acute, direct activation of 5-HT7 receptors increases NMDA-evoked currents\(^{(72)}\).

PDGF\(\beta\) receptor transactivation may also play a role in BBB function. PDGF\(\beta\) receptor signaling protects endothelial cell function and BBB integrity after \(\beta\)-arrestin activation subsequent to protease-activated receptor 1\(^{(93)}\). Thus, in addition to GPCR-PDGF\(\beta\) receptor transactivating and directly impacting neuronal health, transactivation or indirect activation of PDGF signaling may also impact BBB integrity in the context of stroke or other neurological diseases.

**PDGF AS A BIOMARKER**

As noted above, the impact of the PDGF system on the vasculature may be more important clinically than the direct effects of this signaling pathway on neurons. Similarly, although there are intriguing possibilities for the development of novel treatments targeting the PDGF system in neuronal health, using PDGF ligands as biomarkers for disease may be more impactful, at least in the short term. For example, the presence of PDGF-AA in cerebrospinal fluid (CSF) of HIV-infected individuals was negatively associated
with HAND[94]. Stroke patients have higher levels of circulating PDGFβ receptor-positive cells[95]. PDGF-BB is consistently among the growing number of proteins and molecules identified as biomarkers in the CSF of AD patients[96-98] and is potentially a serum biomarker for PD[99]. PDGF-BB levels are also elevated in patients with amyotrophic lateral sclerosis[100]. PDGF-BB may be a biomarker for schizophrenia[101] as well as having links to the disease via genetic differences in both PDGF-B and PDGFβ receptor genes[102]. Last, mutations in PDGF-B and PDGFβ receptor genes are both biomarkers for, and causative agents of, familial brain calcification[103,104].

CONCLUSION

PDGF signaling is crucial for healthy CNS development. In recent years, its role in the developed CNS, and even in the aging CNS, has been linked to various neuropathologies and neuroprotective pathways. Understanding, and possibly targeting, the PDGF system will be crucial to our understanding and treatment of stroke and neuronal damage, dementias including HAND and Alzheimer's disease, and in Parkinson's disease. In addition to understanding ligand-activated PDGF receptor signaling, indirect, GPCR-mediated transactivation of the PDGFβ receptor, provides a link between GPCR-targeted therapies and PDGF system changes.

DECLARATIONS

Authors’ contributions
Made substantial contributions to conception and design of the study: Vasefi M, Beazely MA
Participated in drafting the article and revising the content: Vasefi M
Contributed in revising the article and approved the revised version: Beazely MA

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Not applicable

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Both authors declared that there are no conflicts of interest.

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Not applicable.

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