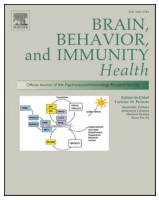
Brain, Behavior, & Immunity - Health 38 (2024) 100796

Contents lists available at ScienceDirect

Brain, Behavior, & Immunity - Health

journal homepage: www.editorialmanager.com/bbih/default.aspx



The potential role of the p75 receptor in schizophrenia: neuroimmunomodulation and making life or death decisions

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ARTICLE INFO

Keywords:
p75
Schizophrenia
Trophic signalling

ABSTRACT

The nerve growth factor receptor, also referred to as tumour necrosis factor II and the p75 neurotrophin receptor (p75), serves pleiotropic functions in both the peripheral and central nervous system, involving modulation of immune responses, cell survival and cell death signalling in response to multiple ligands including cytokines such as TNFα, as well as proneurotrophins and mature neurotrophins. Whilst *in vitro* and *in vivo* studies have characterised various responses of the p75 receptor in isolated conditions, it remains unclear whether the p75 receptor serves to provide neuroprotection or contributes to neurotoxicity in neuroinflammatory and neurotrophin-deficit conditions, such as those presenting in schizophrenia. The purpose of this mini-review is to characterise the potential signalling mechanisms of the p75 receptor respective to neuropathological changes prevailing in schizophrenia to ultimately propose how specific functions of the receptor may underlie altered levels of p75 in specific cell types. On the basis of this evaluation, this mini-review aims to promote avenues for future research in utilising the therapeutic potential of ligands for the p75 receptor in psychiatric disorders, whereby heightened inflammation and reductions in trophic signalling mechanisms coalesce in the brain, potentially resulting in tissue damage.

1. Introduction

The nerve growth factor (NGF) receptor, also referred to as tumour necrosis factor (TNF) receptor II, CD120b and the p75 neurotrophin receptor (p75), is one of two tumour necrosis factor receptors (p55 and p75), which exhibit limited structural similarity to neurotrophic Tropomyosin kinase (Trk) receptors, lack the intracellular tyrosine kinase domain that elicits pro-survival signalling with Trk receptors and additionally encompass an intracellular death domain (Chao and Hempstead, 1995). Compared to p55, p75 is strongly inducible, implicating a more adaptive role of p75 in responding to neurotrophins (Vandenabeele et al., 1995). P75 is critical for neurodevelopment and neurogenesis as p75-deficient mice display significant reductions in neuroblasts and newborn neurons, alongside behavioural abnormalities indexing altered neurocircuitry (Catts et al., 2008; Young et al., 2007; Meier et al., 2019).

The p75 receptor was initially classified as a low-affinity receptor for the neurotrophin NGF, yet p75 binding affinity directly to other mature neurotrophins including brain-derived neurotrophic factor (BDNF), Neurotrophin-3 and Neurotrophin-4/5 has also been identified and implicated in pro-survival signalling (Rodriguez-Tébar et al., 1990). P75 also modulates Trk receptor signalling by forming heteromeric complexes with Trk receptors, including the dominant receptor for BDNF, $TrkB^{TK+}$, which enhances BDNF binding affinity to $TrkB^{TK+}$ and promotes pro-survival signalling in neurons (Saadipour et al., 2017). Conversely, p75 receptor binding to precursor proneurotrophin isoforms, proBDNF and proNGF, activates cell-cycle arrest and apoptotic signalling (Jansen et al., 2007). The intracellular receptor-interacting protein 2 (RIP2) serves as a bifunctional switch for the death domain of the p75 receptor to activate apoptotic pathways by proneurotrophin binding (Khursigara et al., 2001). The cytokine TNFα is also a ligand for p75 receptors (Peschon et al., 1998). Under normal physiological conditions, activation of p75 by TNFα is neuroprotective and assists in maintaining cellular homeostasis and regulating synaptic plasticity (Barger et al., 1995).

Widespread reductions in BDNF and the $TrkB^{TK+}$ receptor at the transcriptional and protein level are reported in the cortex and hippocampus of people with schizophrenia (Weickert et al., 2003, 2005; Ray et al., 2011), alongside elevated pro-inflammatory cytokines, including TNFα, across multiple brain regions in ~45% of people with schizophrenia (Fillman et al., 2013; Purves-Tyson et al., 2021; North et al., 2021; Zhu et al., 2022a), highlighting that trophic deficits may be

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https://doi.org/10.1016/j.bbih.2024.100796
Received 30 November 2023; Received in revised form 6 March 2024; Accepted 12 May 2024
Available online 14 May 2024

unable to meet higher demands required to maintain neuronal health and vitality in neurotoxic conditions. As such, the p75 receptor may be upregulated to either promote BDNF binding to neuronal TrkB receptor, or conversely may be responding to the ensuing neurotoxicity by activating cell death pathways. Given the pleiotropic function of the p75 receptor in mediating cell survival, cell death and responding directly to the pro-inflammatory cytokine, TNFα, in multiple cell types, p75 receptor expression may be altered in the brain in schizophrenia, where neuronal health may be compromised in the context of neuroinflammation, and reflected in peripheral p75 measures. As such, this mini-review aims to explore how the functions of the p75 receptor in neurons, immune cells, oligodendrocytes and endothelial cells may contribute to neuroinflammation, trophic deficits, brain volume loss and white matter dysfunction evident in schizophrenia.

2. Alterations in p75 receptor expression in schizophrenia

Increased plasma levels of p75 receptor protein are reported in first-episode psychosis patients compared to clinical high-risk individuals and controls (He et al., 2019), with higher ratios of p75/TrkB protein found in serum of first-episode psychosis patients compared to unaffected siblings and controls (Yesilkaya et al., 2022), reflecting a trophic imbalance preceding diagnosis and treatment that may favour apoptotic functions of the receptor. Whilst plasma p75 protein levels were found to positively correlate with positive and negative symptom scores in schizophrenia (Zakowicz et al., 2023), other studies report no changes in p75 protein in the plasma of schizophrenia patients compared to controls (Haack et al., 1999; Yesilkaya et al., 2022), with some reporting lower serum levels of p75 receptor protein (Zakharyan et al., 2014; Chen et al., 2017; Turhan et al., 2016). A potential contributor to the heterogeneous results of studies assessing peripheral p75 receptor expression in schizophrenia is the prevalence of single nucleotide polymorphisms (SNPs) of the p75 receptor evident in patients. The rs11466155 and rs2072446 SNPs are more commonly reported and are associated with higher p75 levels in plasma, whereas, the rs734194 and rs11466162 SNPs, which lead to lower p75 receptor expression, are less commonly reported in schizophrenia patients compared to controls (Zakharyan et al., 2014; Zhao et al., 2022). Moreover, as these studies utilised antibodies targeting the extracellular domain of the p75 receptor, it remains unclear whether these reported alterations in peripheral p75 receptor expression specifically affect the functions elicited by the death domain of the p75 receptor or modulate capacity for neurotrophin binding either directly to p75 or indirectly through facilitation of neurotrophin binding to Trk receptors.

Nonetheless, alterations in p75 receptor expression in the brain in schizophrenia may play a more pertinent role in schizophrenia pathology, particularly considering the widespread reductions in brain volume of people with schizophrenia (van Erp et al., 2016; van Haren et al., 2008), which may support a prominent role of the apoptotic function of the p75 receptor in the schizophrenia brain. However, studies assessing p75 receptor expression and function in the schizophrenia brain are limited. Dunham et al. (2009) assessed gene and protein expression of the p75 receptor in post-mortem human hippocampal tissue obtained from schizophrenia (n = 15) and control (n = 13) cases and did not find hippocampal p75 mRNA and protein expression to be altered in schizophrenia cases compared to controls. Additionally, individuals with schizophrenia who carried the minor allele of rs11466117 had higher p75 protein expression in the molecular layer, granule cell layer and hilus of the hippocampus, compared to homozygous carriers (Dunham et al., 2009). Based on this preliminary analysis, alterations in p75 receptor expression in other brain regions cannot be ruled out. Although the hippocampus is a key brain region of interest implicated in schizophrenia neuropathology, p75 receptor dysregulation may be more prominent in other brain regions such as the midbrain, whereby excessive dopamine production, underlying psychotic symptoms of schizophrenia, may further exacerbate neurotoxicity through increased reactive oxygen species generation (Howes et al., 2013; Grima et al., 2003).

3. Contextualising cell-specific signalling mechanisms of the p75 receptor in schizophrenia

3.1. Neurons

Grey matter volume deficits precede first-episode of psychosis in schizophrenia, with diagnosis peaking in young adulthood (21–25 years) (Nenadic et al., 2015; Takayanagi et al., 2011). Therefore, neurodevelopmental dysregulation may set the stage for abnormal neural connectively and brain volume loss in schizophrenia. As the p75 receptor plays a pertinent role in maintaining normal physiology in the central nervous system (Kordower and Mufson, 1992), and is critical in neurodevelopment and adult neurogenesis, p75 receptor dysfunction may preface risk for schizophrenia onset and progression (Meier et al., 2019; Catts et al., 2008; Young et al., 2007). Colantuoni et al. (2008) assessed age-related changes in expression of genes implicated in susceptibility for schizophrenia in the human prefrontal cortex of healthy controls and found increases in p75 receptor expression across the ages of 18 to 30 to pose the greatest risk for the development of schizophrenia.

Studies aiming to identify which specific cell types are lost to underlie these volumetric deficits in schizophrenia report reductions in genes and proteins reflecting loss of cortical and subcortical parvalbumin-containing γ-aminobutyric acid (GABA) neurons in post-mortem human brain tissue obtained from people with schizophrenia compared to controls (Purves-Tyson et al., 2021; Beasley et al., 2002). As the p75 receptor dynamically regulates parvalbumin-expressing GABA neuron maturation and connectivity, these deficits in parvalbumin-containing neurons in schizophrenia may result from p75 receptor dysfunction in these neurons, particularly during a critical neurodevelopmental window (Baho et al., 2019). Moreover, p75 can regulate the balance of excitatory and inhibitory neurotransmission by modulating cell surface expression of GABA and glutamatergic receptors - $GABA_A$ and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic (AMPA) respectively, thereby potentially contributing to disinhibition of glutamatergic input to the basal ganglia and resulting subcortical hyperdopaminergia (Stellwagen et al., 2005).

The p75 receptor may also serve trophic functions in neurons to promote survival. Mechanisms of neuronal survival mediated directly by p75 receptor activation rely on persistent nuclear factor-kappa B (NfkB) activation (Marchetti et al., 2004). However, NfkB transcription in cortical regions of people with schizophrenia with elevated pro-inflammatory cytokines is weak compared to controls presenting with neuroinflammation (Murphy et al., 2020), perhaps reflecting reduced capacity for pro-survival functioning of the p75 receptor in neuroinflammatory conditions presenting in schizophrenia.

3.2. Immune cells

In neuroinflammatory conditions, the p75 receptor may preferentially bind to TNFα with a high affinity and be upregulated in glial cells – astrocytes and microglia - to positively or negatively regulate inflammatory responses or initiate apoptosis (Abd-El-Basset et al., 2021; Dopp et al., 2002). TNFα mRNA is increased in the midbrain and cortex of schizophrenia cases with a high inflammatory biotype, compared to controls, with no changes at the protein level (Zhu et al., 2022a,b; Purves-Tyson et al., 2021; Fillman et al., 2013), possibly suggesting a higher turnover of TNFα mediated by binding to the p75 receptor. Accompanying these elevations in pro-inflammatory cytokine levels are increases in gene and protein expression of markers of astrocytes reported across multiple brain regions in schizophrenia (Catts et al., 2014; Purves-Tyson et al., 2021; Feresten et al., 2013), alongside ultrastructural abnormalities in hippocampal astrocytes observed in post-mortem

human brain tissue of people with schizophrenia compared to controls (Kolomeets and Uranova, 2010). Astrocytic upregulation of the p75 receptor is demonstrated *in vivo* in response to nerve injury (Zhou et al., 1996) and is associated with blood-brain barrier disruption (Qin et al., 2022).

Astrogliosis in schizophrenia is postulated to stem from hypofunctional regulatory T cells in the face of chronic low-grade inflammation, leading to disinhibition of microglial activation by astrocytes and resulting in excessive synaptic pruning by microglia, which may contribute to widespread brain volume loss in schizophrenia (Corsi-Zuelli and Deakin, 2021). Reduced numbers of regulatory T cells (Steiner et al., 2010), yet with a greater proportion exhibiting active morphology, are evident in cerebrospinal fluid (Nikkilä et al., 2001) and isolated peripheral blood mononuclear cells obtained from schizophrenia patients compared to controls (Sahbaz et al., 2020). Altered levels of the p75 receptor may be implicated in regulatory T cell dysfunction in schizophrenia as p75 plays a pertinent role in T cell secretion of cytokines, by acting as a costimulatory receptor for T cell activation and regulating the balance between effector and regulatory T cells (Kim et al., 2006). Depletion of regulatory T cells is demonstrated to attenuate infiltration of T cells to the brain, contributing to astrogliosis in a model of traumatic brain injury (Krämer et al., 2019), supporting this as a mechanism of immune dysfunction in schizophrenia that may be mediated by the p75 receptor.

However, microglial activation in schizophrenia is not consistently described in schizophrenia (Doorduin et al., 2009; Di Biase et al., 2017; Plavén-Sigray et al., 2018). These inconsistencies across studies may reflect a higher turnover of microglia in neuroinflammatory conditions in schizophrenia. Excessive phagocytic activity of microglia is implicated in schizophrenia (Jenkins et al., 2023; Purves-Tyson et al., 2020), and may reciprocally lead to the lethal demise of microglia mediated by p75 apoptotic signalling. On the other hand, TNFα binding to p75 receptors directly on microglia neutralises oxidative stress and can preserve microglial integrity (Dopp et al., 2002). Additionally, p75 receptor activation by neuron-derived NGF diminishes the antigen-presenting capacity of microglia in hippocampal slices by reducing inducibility of major histocompatibility complex class II (MHC II) molecules (Neumann et al., 1998). However, this diminution of the adaptive immune response may impede on the competency of microglia to respond effectively to inflammatory stimuli and potentially contribute to quiescent microglial phenotypes observed in neuroinflammatory conditions in schizophrenia (Zhu et al., 2022b).

3.3. Oligodendrocytes

P75 receptor expression in oligodendrocytes has both regenerative potential and can also promote cell death (Casaccia-Bonnefil et al., 1996; Ladiwala et al., 1998). Hence, in the case of schizophrenia, regenerative properties of the p75 receptor may prevail in the absence of neuroinflammation, whereas in neuroinflammatory conditions, oligodendrocytes may be vulnerable to cell death in response to increased levels of TNFα in high inflammation schizophrenia cases. Indeed, myelin dysfunction as well as reductions in subcortical and cortical oligodendrocytes and associated genes are observed in schizophrenia in association with neuroinflammation (Uranova et al., 2007; Hof et al., 2003; Flynn et al., 2003; Hakak et al., 2001; Tkachev et al., 2003). Post-mortem analysis of the prefrontal cortex of people with schizophrenia shows reductions in the number of cells immunoreactive for oligodendrocyte transcription factor, which is expressed in maturing oligodendrocytes, without any paralleled changes in the number of oligodendrocyte precursor cells (Mauney et al., 2015). Additionally, oligodendrocyte degeneration in schizophrenia is observed in electron microscopy analysis of post-mortem human prefrontal cortex tissue obtained from people with schizophrenia through apoptotic and necrotic profiles of oligodendrocytes, as well as atrophy of myelinated fibres, which are most pronounced in layer 5 (Uranova et al., 2007, 2011; Kolomeets and Uranova, 2019).

3.4. Endothelial cells

The p75 receptor is also found to be expressed in endothelial cells (Slowik et al., 1993). Activation of the p75 receptor has been shown to perpetuate blood-brain barrier disruption in models of stroke and nerve injury (Gschwendtner et al., 2003; Shanab et al., 2015). As such, the p75 receptor may play a role in the restructuring of vasculature in the schizophrenia brain, particularly in neuroinflammatory conditions, whereby peripheral immune cells may infiltrate to sites of brain tissue damage. Impediments to blood-brain-barrier integrity and vasculature alterations are reported in the prefrontal cortex, hippocampus and midbrain in schizophrenia (Cai et al., 2020; Najjar et al., 2017; Zhu et al., 2023). Post-mortem analysis has also demonstrated peripheral macrophage infiltration in the brain of people with schizophrenia (Purves-Tyson et al., 2020; Zhu et al., 2022b; North et al., 2021; Weissleder et al., 2021).

3.5. Potential for p75 receptor-targeted therapies in schizophrenia

One possibility is that small molecule ligands such as LMA11A-type compounds, which block proneurotrophin binding to p75, may have utility in minimising potential neuronal damage during the neuroinflammatory state in schizophrenia (Xiong et al., 2022). In support of this, small molecule ligands targeting the p75 receptor have high central nervous system bioavailability and show neuroprotective and anti-inflammatory effects in animal models of infection, neurodegeneration and injury, by specifically activating pro-survival pathways of p75 signalling (Xie et al., 2021; Nasoohi et al., 2023). However, further investigation of p75 receptor function in inflammatory conditions associated with neuropsychiatric illnesses is required (Ibáñez and Simi, 2012).

4. Conclusions

The pleiotropic functions of the p75 receptor in multiple cell types provides a wide scope for p75 receptor dysregulation to contribute to inflammation, neurotrophic deficits, and neurodegeneration in schizophrenia. The regulatory potential of the p75 receptor on immune responses elicited by multiple cell types in the peripheral and central nervous system spans multiple mechanisms that may contribute to the enduring widespread inflammation presenting in schizophrenia, which relates to symptom severity. Whilst brain volume loss progresses with duration of illness, p75 receptor expression and function is not well characterised throughout the human brain, particularly in individuals with schizophrenia. Future studies aiming to characterise the cellular distribution of p75 in the schizophrenia brain will pave the way forward toward understanding functional consequences of potential alterations in p75 receptor expression and guide how to effectively target its role in schizophrenia neuropathology and associated neuroinflammation. Furthermore, to ascertain whether p75 receptor signalling supports trophism in the absence of neuroinflammation or conversely cell death in neuroinflammatory conditions, quantification of other receptor-interacting proteins would be advantageous to decipher the switch between p75-mediated survival and apoptotic signalling pathways in blood and post-mortem human brain samples of people with schizophrenia. Altogether, the p75 receptor may be a disease-modifying factor in schizophrenia, which may contribute to other neuropathologies underlying the illness and warrants further investigation in schizophrenia and other psychiatric illnesses.

CRediT authorship contribution statement

Jessica Chandra: Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of competing interest

There are no conflict of interest among all authors.

Data availability

No data was used for the research described in the article.

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