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PHYSIOPATHOLOGY OF TYROSINE KINASE RECEPTORS IN THE BRAIN

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ABSTRACT

Tyrosine kinase receptors (TKRs) are a subclass of cell surface proteins with phosphorylating enzymatic activity, selective for tyrosine residues. At the level of brain neurons, these receptors play an important role in axonal growth, synapse formation, neuroprotection and plasticity. The TKR family includes receptors TkrA, TkrB, and TkrC, that can bind several specific ligands such as the neurotrophin-3 (NT-3). TKRs also include epidermal growth factor receptors (EGFR), fibroblast growth factor receptors (FGFR), and insulin-like growth factor receptors (IGFR). In healthy neurons, TKRs play physiological roles such as survival and differentiation. Ligand-induced TKR activation participates in axonal guidance and branching. NT-3 is an important protein in the nervous system, is involved in neuronal pathophysiology, and during early brain development, NT-3 influences synapse formation and stabilization. Epidermal Growth Factor (EGF) is a protein ligand that stimulates cell growth, proliferation, and differentiation by binding to its receptor EGFR. EGFR is a member of the TKR family of receptors and when it is activated it dimerizes its receptor and its tyrosine kinase domain becomes active, leading to autophosphorylation. Microglia express TKRs as colony-stimulating factor 1 receptor (CSF1R), which is important for microglial survival and activation. This reaction can trigger inflammation that contributes to neurodegenerative diseases. Inflammation may be due to dysregulation of TKRs in astrocytes and blood-brain barrier (BBB) disruption. TKRs play an important role in brain inflammation and targeting these molecules could provide therapeutic effects.

KEYWORDS: *Tyrosine, kinase, receptor, CNS, neuron*

INTRODUCTION

Tyrosine kinase receptors (TKR) are a subclass of cell surface receptors that are necessary for phosphorylating enzymatic activity and are selective for tyrosine residues (1). They play a key role in neuronal signaling, development, and plasticity, and have intrinsic tyrosine kinase activity, which is essential for their function in signal transduction (2). At the neuronal level, these receptors are involved in processes such as axonal growth, synapse formation, and neuroprotection (3). TKRs have a transmembrane protein structure consisting of an extracellular domain that binds specific ligands such as growth factors. The transmembrane domain attaches the receptor to the neuronal membrane; while the intracellular domain contains the tyrosine kinase domain that auto-phosphorylates upon activation. In neurons, TKRs include TkrA, TkrB, and TkrC receptors that bind neurotrophin-3 (NT-3), nerve growth factor (NGF), and brain-

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derived neurotrophic factor (BDNF) (4). In addition, TKRs also include epidermal growth factor receptors (EGFR), fibroblast growth factor receptors (FGFR), and insulin-like growth factor receptors (IGFR) (5).

DISCUSSION

TKRs play a physiological role in healthy neurons by mediating some important processes related to neurotrophic signaling (6). TkrA promotes the survival and differentiation of sympathetic and sensory neurons by binding to NGF, while TrkB supports synaptic plasticity and survival via BDNF, and TkrC aids development via NT-3 (7). Moreover, ligand-induced TKR activation participates in axonal guidance and branching.

TKRs support oligodendrocyte precursor cells, which are responsible for producing myelin (8). Ligand-induced TKR activation participates in axonal guidance and branching. TkrB plays a key role in synaptic plasticity, long-term potentializing and memory formation (9). TKRs are involved in neuroprotection, and during stress, they improve neuronal survival (10).

NT-3 is an important protein in the nervous system which is involved in neuronal physiopathology (11). It is part of the neurotrophin family, which includes NGF, BDNF, and neurotrophin-4/5 (NT4/5) (12). These molecules participate in neuronal survival, differentiation, and maintenance (13). During early brain development, NT-3 influences the formation and stabilization of synapses, ensuring that neuronal circuits are properly connected (14). NT-3 is involved in learning and memory maintenance, modulates the growth of dendrites and axons, promotes the myelination of neurons, and improves signal transmission in the central nervous system (CNS) (15).

TKRs are membrane proteins involved in cell survival, proliferation, differentiation, metabolism, and migration (16). They play an important role in brain function, including immunology, bridging neurobiology and neuroimmunology (17). They are high-affinity cell surface receptors and can bind various growth factors, hormones, and cytokines (18). After TKRs bind to their ligand, they undergo dimerization and autophosphorylation on specific tyrosine residues, which activates downstream signaling cascades (19). TKRs are crucial for neuronal development, survival, and synaptic plasticity. The main TKRs in the brain are neurotrophins NGF, BDNF, and NT-3. These are crucial for neuronal physiology and cellular homeostasis. EGFR is involved in the proliferation and repair of glial cells, while the vascular endothelial growth factor receptor (VEGFR) is important in the formation of new vessels (angiogenesis) of the cerebral system and also in neurovascular processes (20). EGF is a protein that stimulates cell growth, proliferation and differentiation by binding to its receptor, the EGFR, a member of the TKRs receptor family. By binding to its receptor EGFR, EGF dimerizes it and its tyrosine kinase domain becomes active, leading to autophosphorylation. This reaction triggers the cascade of the MAPK/ERK and PI3K/AKT biochemical pathways, promoting cell survival and proliferation (21).

The platelet-derived growth factor receptor (PDGFR) regulates the development of oligodendrocytes and astrocytes, which are important for myelination and neuroinflammation, while FGFR is implicated in neurogenesis and repair mechanisms following injury (22). Microglia are immune cells with macrophagic activity that express TKRs such as colony-stimulating factor 1 receptor (CSF1R), which is crucial for microglia survival and activation (23). This activation triggers inflammation, contributing to neurodegenerative diseases such as Alzheimer's and Parkinson's. In the brain, EGFR and FGFR are expressed by astrocytes and modulate the response to injury and inflammation (24). Dysregulation of TKRs in astrocytes can disrupt the BBB and cause inflammation (16).

CONCLUSIONS

In conclusion, TKRs are involved in both physiological and pathological mechanisms of the CNS, depending on the specific receptors and ligands. TKRs are proteins that also play an important role in neuroinflammation. This suggests that targeting TKRs as therapeutic factors could be useful for treating neurodegenerative and neuroinflammatory diseases.

Conflict of interest

The authors declare that they have no conflict of interest.

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