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Review

GDNF–Ret signaling in midbrain dopaminergic neurons and its implication for Parkinson disease

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ABSTRACT

Glial cell line-derived neurotrophic factor (GDNF) and its canonical receptor Ret can signal together or independently to fulfill many important functions in the midbrain dopaminergic (DA) system. While Ret signaling clearly impacts on the development, maintenance and regeneration of the mesostriatal DA system, the physiological functions of GDNF for the DA system are still unclear. Nevertheless, GDNF is still considered to be an excellent candidate to protect and/or regenerate

Abbreviations: 6-OHDA, 6-hydroxy-dopamine; Akt, PKB, protein kinase B, serine/threonine-specific protein kinase; BDNF, brain derived neurotrophic factor; CaMKIIβ, calcium-calmodulin-dependent protein kinase II β isoform; cAMP, 3′,5′-cyclic adenosine monophosphate; catecholamine, monoamine, neurotransmitter type including dopamine, epinephrine (adrenaline) and norepinephrine (noradrenaline); CCCP, carbonyl cyanide m-chlorophenyl hydrazone; Cdc42, cell division control protein 42 homolog, a plasma membrane-associated small GTPase of the Rho family; COMT, catechol-O-methyltransferase; CoREST, co-repressor for element-1-silencing transcription factor, a chromatin-modifying corepressor complex that acts with REST (repressor for element-1 silencing transcription factor) complex; GABA, γ-aminobutyric acid, inhibitory neurotransmitter in mammalian central nervous system; GTPase, cycles between an active GTP-bound and an inactive GDP-bound state; DA, dopaminergic; DAT, dopamine transporter; DJ-1, deglycase, oxidative stress sensor and redox-sensitive chaperone and protease; DOK1/4/5/6, docking proteins, have a PH and SH3 domain; EGFP, enhanced green fluorescent protein; EGR1, early growth response protein 1, Zif268 (zinc finger protein 225), NGFI-A (nerve growth factor-induced protein A), is a zinc finger transcription factor; Enigma, adaptor protein of the PDZ-LIM family; ER, endoplasmatic reticulum; ERK, extracellular-signal-regulated kinases, classical MAPKs; FosB/ΔFosB, FBJ murine osteosarcoma viral oncogene homolog B, a transcription factor with a truncated Δ form; FRS2, fibroblast growth factor receptor substrate 2, adaptor protein; GAP1/2, GTPase-activating proteins 1 and 2; GDNF, glia cell line-derived neurotrophic factor; GFLs, GDNF family of ligands; GFRα, GDNF family receptor α; GPI, glycosylphosphatidylinositol; GRB2/7/10, growth factor receptor-bound protein 2, 7 and 10, adaptor proteins; gsk3β, glycogen synthase kinase 3β; HIF-1a, hypoxia-inducible factor-1alpha; IRS1/2, insulin receptor substrate 1, adaptor protein, contains a PTB and PH domain; JNK, c-Jun N-terminal kinases, members of the MAPK family of proteins; Kv4.3 and KChip3, subunits of the Ca^{2+}-sensitive, voltage gated A-type K+ channel; LIM, (acronym combining the first letters of three proteins – Lin11, Isl-1 and Mec-3 – that have this common domain) protein interaction domain of two contiguous zinc finger domains, separated by a two-amino acid residue hydrophobic linker; MEN2B, multiple endocrine neoplasia 2 type B, mutation in the kinase domain of the Ret leading to constitutive active receptor; MAOA/MAOB, monoamine oxidases A and B; MAPK, mitogen-activated protein kinase, can phosphorylate serine, threonine, and tyrosine, e.g. p38MAPK; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NCAM, neuronal cell adhesion molecule; NF-κB, nuclear factor 'kappa-light-chain-enhancer' of activated B-cells, transcription factor family with Rel homology domain (RHD); NGF, nerve growth factor; Nurr1, orphan nuclear receptor and transcription factor; PACE4, PCSK6, proprotein convertase subtilisin/*k*exin type 6; PC5A, PC5B, and PC7, proprotein convertases; PD, Parkinson disease; PDZ, (acronym combining the first letters of three proteins – post synaptic density protein (PSD95), Drosophila disc large tumor suppressor (Dlg1), and zonula occludens-1 protein (zo-1) that have this common domain) protein interaction domain; PH, pleckstrin homology domain; PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase; PINK1, PTEN-induced putative kinase 1; PKA, protein kinase A, a family of cAMP-dependent protein kinase; PLCγ, phospholipase γ cleaves the phospholipid phosphatidylinositol 4,5-bisphosphate (PIP2) into diacyl glycerol (DAG) and inositol 1,4,5-trisphosphate (IP3) ppp3R1/ppp3CB, calcineurin subunits; PTB, phosphotyrosine-binding domains; PI, phosphotyrosine-interaction domain; PTEN, phosphatase and tensin homolog; Rac1, Ras-related C3 botulinum toxin substrate 1 (Rho family), a small GTPase, like CDC42; Raf, (rapidly accelerated fibrosarcoma/rat fibrosarcoma) family of serine/threonine-protein kinase; Ras, (Rat sarcoma) family of small membrane-associated GTPase; Rho, (Ras homolog) family of small GTPases including Cdc42, Rac1, and RhoA; Ret, (rearranged during transfection) canonical GDNF receptor, a receptor tyrosine kinase; RRF, retro-rubal field; Ser/Thr, serine and threonine, which can be phosphorylated; Shank3, SH3 and multiple ankyrin repeat domains 3, proline-rich synapse-associated protein 2 (ProSAP2); SHC, SH2 domain containing transforming protein 1; SHP-2, cytoplasmic SH2 domain containing protein tyrosine phosphatase; SN, substantia nigra; SNP, single-nucleotide polymorphism analysis; SorLA, sorting protein-related receptor with A-type repeats, a member of the mammal Vps10p domain receptor; SOS, son of sevenless, family of guanine nucleotide exchange factors that act on Ras; Src, (sarcoma protein) membrane-associated tyrosine kinase with different Src homology (SH) domains characteristic for all 9 members of the Src family kinases; Tyr, tyrosines, which can be phosphorylated; TGF-β, transforming growth factor β is a secreted protein that controls proliferation and cellular differentiation; TIEG, TGF-β-inducible early-response gene, a zinc finger transcription factor Vav2, adaptor protein and guanine nucleotide exchange factor for the Rho family of Ras-related GTPases; VPS10P, vacuolar protein sorting 10 protein-domain receptors are type 1 transmembrane proteins; VTA, ventral tegmental area

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the mesostriatal DA system in Parkinson disease (PD). Clinical trials with GDNF on PD patients are, however, so far inconclusive. Here, we review the current knowledge of GDNF and Ret signaling and function in the midbrain DA system, and their crosstalk with proteins and signaling pathways associated with PD.

1. Introduction

The neurotransmitter dopamine is produced by dopaminergic (DA) neurons and modulates diverse functions in the brain and throughout the body, including movement, memory, motivation and emotions [1,2]. The cell bodies of DA neurons are grouped in the ventral midbrain in the substantia nigra (SN), the ventral tegmental area (VTA) and the retro-rubal field (RRF). Axonal projections of midbrain DA neurons are split into the mesostriatal and the mesocorticolimbic pathways [1]. The complex projections, functions and interactions of distinct types of midbrain DA neurons have recently been further dissected [3–10]. To briefly summarize, the mesostriatal pathway connects the SN and some VTA DA neurons with the dorsal striatum and is important for the control of voluntary movement. The mesocorticolimbic pathway projects from the VTA, the dorsal tier of the SN and the RRF to the ventral striatum (caudate nucleus and putamen), nucleus accumbens, olfactory tubercle, septum, amygdala, habenula, hippocampus and cortex and is involved in cognitive, rewarding/aversive and emotion-based behavior. According to its diverse projections and functions, alterations of the midbrain DA system can lead to a variety of neurological diseases. For example, the progressive loss of SN DA neurons in particular and the related dopamine deficit within the dorsal striatum cause the classical motor-function related symptoms in Parkinson disease (PD) [11,12]. Characterizing the rare familial cases of PD with mutations in specific genes has shaded light onto the etiology of PD and facilitated the discovery of common pathological alterations, such as mitochondrial dysfunction, metabolic and oxidative stress, axonal transport defects, and abnormal protein degradation and aggregation [13,14]. The heterogeneity of midbrain DA neurons suggests that a multitude of signaling events are required during development and maintenance to ensure proper functioning including different neurotrophic support [9,15–17]. The midbrain DA system is largely conserved between humans and rodents and studies in transgenic mice have identified the basic requirements for generation and maintenance of the DA system [1,18,19] (Fig. 1). Here we review the emerging roles of neurotrophic factors for the midbrain DA system during physiological and pathophysiological conditions such as PD, with a focus on GDNF (glial cell line-derived neurotrophic factor) and Ret (rearranged during transfection) signaling.

2. Role of neurotrophic factors in the midbrain DA system

Neurotrophic factors are a diverse group of polypeptides that function as growth and survival factors during development, adulthood and aging [20,21]. According to the neurotrophic factor hypothesis originally postulated by Rita Levi-Montalcini and Victor Hamburger, more neurons are born during embryogenesis than later survive, and target-derived neurotrophic factors are one limiting factor determining which neurons survive or die during pre- and postnatal development [22]. They can also stimulate axon outgrowth and guidance [23–25]. Neurotrophic factors also prevent degeneration associated with neurodegenerative diseases, stimulate differentiation and synaptogenesis, and are essential for maintaining normal physiological functions in the nervous system, including adult synaptic plasticity and behavior [21,26–30]. In general, neurotrophic factors may be secreted into the extracellular space from both neurons and glia. They can diffuse and are actively transported over long distances in antero- and retrograde directions [31,32]. Neurotrophic autocrine loops have been suggested to support midbrain DA neuron survival in culture [33]. DA neurons require specific neurotrophic factors and their cell surface receptors for proper in vivo differentiation and maintenance, which have not yet been fully characterized [17,34]. Neurotrophic factors of the DA system include the neurotrophins such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), as well as the four GDNF family ligands (GFLs) GDNF, neurturin, artemin and persephin, which are distantly related members of the transforming growth factor-β superfamily and the focus of this review [17,35,36].

3. Function of neurotrophic factor GDNF in the midbrain DA system

In general, GFLs mediate their actions by utilizing a complex signaling network consisting of several different binding and signaling partners [37]. As summarized in Fig. 2, each GFL binds with high affinity to one of the glycosylphosphatidylinositol (GPI)-linked GDNF family receptor α (GFRα) members 1–4 [17]. GDNF binds with high affinity to GFRα1, which is the only GFRα receptor expressed at high mRNA and protein levels in midbrain DA neurons [38,39]. GFRα1 is alternatively spliced and both isoforms are highly expressed in the SN [40–42]. The long a form including the exon 5 encoded sequence was found to bind GDNF less efficiently than the short b form lacking the exon 5 encoded sequence; the long a form also promotes axon outgrowth through MAPK, Rac1 and Cdc42 signaling, in contrast to the short b form [41,42]. GFRα2 is also expressed in the ventral midbrain, but in non-DA neurons [43–45]. GFRα3 and GFRα4 seem not to be expressed in the ventral midbrain [46,47]. The GDNF/GFRα1 signaling complex can recruit transmembrane receptors such as the canonical GDNF receptor Ret, a receptor tyrosine kinase [17,48–50], or the neuronal cell adhesion molecule (NCAM) [51–53], to trigger downstream signaling events in midbrain DA neurons (Fig. 2).

GDNF seems to be the most prominent neurotrophic factor within the midbrain DA system and a promising therapeutic candidate for neuroprotective and regenerative interventions in PD patients [21,54,55]. GDNF was described more than 20 years ago as a survival factor for rat embryonic DA neurons of the midbrain in culture [23]. Later, this positive in vitro survival effect of GDNF was extended to other neuronal cell types such as motor neurons, adrenergic neurons, parasympathetic neurons, enteric neurons, and somatic sensory neurons [17,56–59].

Mature GDNF is a homo-dimeric glycoprotein [23]. GDNF is expressed as a pre-pro-domain containing precursor protein with

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