The Role of Glial Cell Line-Derived Neurotrophic Factor in the Functioning of the Nervous System (Review)

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Glial cell line-derived neurotrophic factor (GDNF) is one of the most important factors participating in the neuronal survival as well as promoting the differentiation and maintenance of various cellular populations in the central and peripheral nervous systems. In contrast to other neurotrophic factors, GDNF does not directly bind to its receptor. For the implementation of GDNF biological functions, the presence of co-receptor, acting as a mediator in the interaction with the receptor, is necessary required. Receptor with tyrosine kinase activity (Ret) regarded as the main receptor to GDNF, able to subsequent launch an intracellular molecular cascade.

Particular attention to GDNF investigation caused by the fact that, among other neurotrophic factors GDNF has potent neuroprotective effect. Therefore, GDNF is considered as a possible factor for the correction of various nervous system disorders, including neurodegenerative diseases.

In this review basic information concerning the molecular structure of GDNF and its receptors as well as the mechanisms for implementation the main functions of GDNF from the beginning of active receptor complex formation to the subsequent launching of intracellular signaling cascades until appropriate cellular response achieving, is collected. Furthermore, the review contains the data, indicating the possible GDNF effect on synaptogenesis.

Key words: glial cell line-derived neurotrophic factor; GDNF; co-receptors; GFRα; receptor with tyrosine kinase activity Ret.

Neurotrophic factors are polypeptides which regulate the development, maintenance, functioning and plasticity of vertebrate central nervous system. Although they were initially identified as factors involved in the neuronal survival, they also control many other processes, from cell proliferation, the differentiation of axons, the growth of dendrites and synaptic transmission modulation to the functional neural networks activity [1, 2].

The effects of neurotrophic factors lie in their modulation of biological processes at different levels. Generally, this influence is concerned with the regulation of gene expression, controlling the production of functionally significant proteins, receptors and neurotransmitters, and with respective switching on and/or off the alternative regulatory systems [3–5].

One of the endogenic neurotrophic factors regarded as a powerful therapeutic agent is glial cell line-derived neurotrophic factor (GDNF). Its main action is connected with the influence on the central nervous system, however its additional functions and effects on other tissues, are also described [6–8].

GDNF is a necessary factor for normal brain development in the embryogenesis as it contributes to the survival and differentiation of different populations of neurons. GDNF plays a significant neuroprotective role in neurodegenerative diseases and in other pathologies of the central nervous system. Many studies have shown its therapeutic action in Parkinson's disease and during ischemic processes. However, a question concerning the mechanisms of GDNF effects implementation remains unclear and further investigation of these issues is required [9–12].

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The structure of glial cell line-derived neurotrophic factor

Glial cell line-derived neurotrophic factor was first purified from glial cells in 1993 and was identified as a survival factor for the embryonic dopaminergic neurons *in vitro*. Afterwards it became clear that GDNF also acts as a powerful neurotrophic factor for other types of neurons in the central and peripheral nervous systems *in vivo* [13, 14].

GDNF is a protein molecule which contains a cysteine "knot" and characterizing by two long signal sequences formed by pairs of anti-parallel β-strands [15]. To form a dimer, monomers are bound in a "head-tail" arrangement. Due to the anti-parallel orientation, GDNF has a left-right symmetry indicating that the structure of this neurotrophin contains a symmetrical binding site for a dimerized receptor. A structural and functional analysis has shown the first 39 amino acids at the N-terminal of GDNF are not required for its biological activity. Moreover, 3D structures at the N-terminal are not detected. The C-terminal is crucial for GDNF stability and for its biological activity: at the C-terminal there is a β-spiral signal sequence that takes part in GDNF binding with GFRα1-receptor [16–18].

An immature GDNF molecule contains 211 amino acids, and includes signal sequence cleavage sites and a pro-domain. Mature molecules have a molecular mass of 35 kDa and exist in 134 amino acids. During maturation, the protein is glycosylated and a homodimer is formed through covalent disulfide bonds [13]. Only in the form of the glycosylated homodimer, GDNF is able to implement its different biological functions. GDNF is initially synthesized in the form of pro-neurotrophin — pro-GDNF.

Two forms of the immature peptide obtained by alternative splicing of mRNA were detected: (a)pro-GDNF, and (b)pro-GDNF. (b)pro-GDNF can induce the Ca^{2+}-dependent depolarization in neurons [19]. It was discovered that the isoform (a)pro-GDNF is localized in the Golgi apparatus, while the (b)pro-GDNF is associated with the secretory fraction. The roles of different GDNF isoforms are not currently identified. The human brain has additional protein isoforms, one of them being typical of patients with Alzheimer's disease [20].

The GDNF gene is located on 5p12-P13.1 chromosome. It consists of two exons, one of them encodes the mature GDNF protein as well as the cleavage site used for pro-GDNF formation [21, 22].

The GDNF family contains four members: glial cell line-derived neurotrophic factor, neurturin, artemin and persephin. They all play important role in the maintaining of viability, proliferation, differentiation and migration of neuron populations [23].

Neurturin (NRTN) is approximately 42% homologous to the sequence of mature GDNF. It was demonstrated that NRTN influences on the dopaminergic neurons survival *in vitro* and *in vivo* [24–26]. Despite the homology and the ability for binding with the same group of receptors, the biological NRTN effects are different from the GDNF-mediated effects.

Persephin (PSPN) is approximately 40% identical to GDNF and NRTN. Like all other members of GDNF family it helps to maintain the vital activity of many neuron types, including the brain dopaminergic neurons, motor neurons and the forebrain basal cholinergic neurons [27–31].

Artemin (ARTN) is the most distant member of GDNF family, being only 36% homologous to GDNF. It was shown artemin contributes to the survival and maintenance of sensory and sympathetic neurons *in vitro*. It able to prevent neuropathic pain and morphological and neurochemical changes in animals' brains. However, the expression of this GDNF family member is limited to the embryonic period [32–37].

GDNF receptors

GDNF signaling cascades is mediated by binding with a membrane-bound receptor consisting of 2 units. One of them, GFRα, is a ligand-binding component, specific for the GDNF family ligand co-receptor, the other is a receptor with tyrosine kinase activity Ret. Together they form a functional unit of the receptors for binding with GDNF [38–40].

The GFRα co-receptors family includes four representatives (GFRα 1–4), which determine the specificity of the ligand and act as supplementary co-receptors for GDNF [41]. GFRα structure has no intracellular domain, therefore this receptor performs the role of a signal transmitter to other proteins, in particular to Ret — a receptor with tyrosine kinase activity, which in turn activates several intracellular signaling cascades [23, 42, 43].

GDNF acts not only at the site of its synthesis, but also remotely. It was found that neurons are capable of GDNF endocytosis. Absorbed by the cells bodies and the proximal dendrites using the retrograde transport system, GDNF is transferred to the cell body and to the afferent synapses [44–47].

Each ligand of the GDNF family has preferred co-receptors GFRα: GFRα1 — for GDNF [38, 39], GFRα2 — for neurturin [48–51], GFRα3 — for artemin [32, 52, 53] and GFRα4 — for persephin [54, 55].

The structure of the GFRα1 receptor includes three domains (D1, D2 and D3) that are common to all mammals. GFRα1 (molecular weight about 47 kDa) consists of 468 amino acids, and has three potential N-binding sites for glycosylation. It was shown that this protein is bound to the cellular surface by the GPI-anchor (glycosylphosphatidylinositol anchor). GFRα1 can also be an alternative receptor for neurturin for Ret activation. However, NRTN-GFRα1 binding is much weaker than with GFRα2 [38, 56–58].

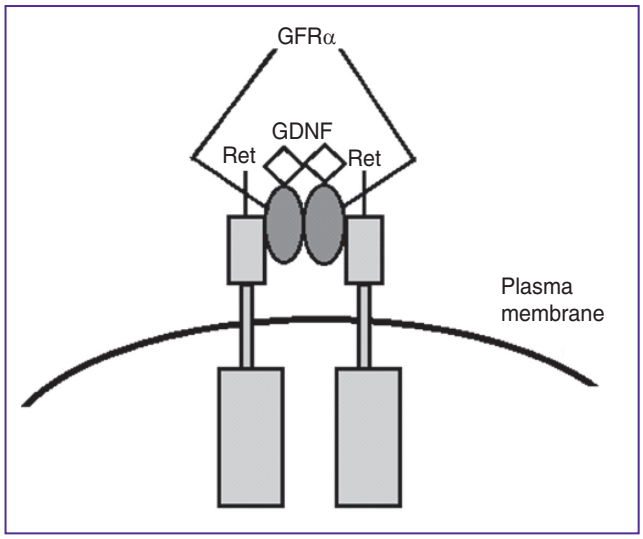

Figure 1. GDNF signaling activation via Ret. GDNF: glial cell line-derived neurotrophic factor; GFRα: specific co-receptor for GDNF; Ret: receptor with tyrosine kinase activity

In 1997 the alternative GFRα1 isoforms — GFRα1a and GFRα1b, resulting in alternative splicing, were determined [51, 59, 60]. GFRα1a is expressed in all parts of the nervous system, while GFRα1b was found in the peripheral tissues [53, 59–61].

For further signal transmission the GDNF/GFRα complex binds with Ret, acting as a common signal receptor for ligands of glial cell line-derived neurotrophic factors family (GFLs) (Figure 1) [42, 56, 62, 63].

The gene, encoding the receptor with tyrosine kinase activity, is a proto-oncogene which was discovered in 1985. It has been noted its participation in the activation of DNA reconstruction [64].

Ret is a transmembrane protein; in its extracellular part there are four repeated cadherin-like calcium-binding sites and a cysteine-enriched domain. The difference between Ret extracellular region and the other tyrosine kinase receptors is the lack of leucine repeats, the immunoglobulin and the fibronectin-like domains which are common to many other similar receptors [65–67]. The intracellular part is a typical tyrosine kinase domain, consisting of two parts. The tyrosine kinase domain mediates autophosphorylation after the receptor activation. Based on its homology with cadherin, the cadherin-like domains can mediate cellular adhesion, though their functions are not currently well-defined [68]. The calcium-binding site, located between the second and third cadherin-like domains, is required for folding, secretion and signal transmission [69–72]. The cysteine-enriched domain exists in 16 cysteine residues and plays a binding role with the co-receptor GFRα [73].

The key Ret functions are performed by the intracellular kinase domain. Ligand-induced Ret-dimerization of two closely located catalytic domains causes mutual transphosphorylation and the further signal transmission to intracellular proteins [74–76].

Ret-mediated GDNF signaling includes two main signal cascades which are contributed to cell survival in a variety of neuronal and non-neuronal populations: the Ras/ERK (MAPK), and PI3K/Akt pathways (Figure 2).

An evolutionarily earlier signaling cascade — mitogen-activated protein kinase (MAPK) — plays a fundamental role in the regulation of different cellular processes, including embryogenesis, proliferation, the cellular growth, differentiation and survival, based on the signals obtained from the cellular surface as well as those reflecting the cellular metabolic state [77–79].

Launching of MAPK cascade by GDNF/GFRα/RET complex leads to the activation of several transcription factors (including c-fos and c-myc, p53, SMAD1–4, Sap1a, SP1 and Elk-1), which are participated in the control of cellular mobility, proliferation, differentiation and survival [77, 80, 81]. The known effect of increasing the survival is carry out due to phosphorylation and RSK (p90 ribosomal S6 kinase) activation, in turn phosphorylating the transcription factor CREB, causing the "survival" genes activation [82, 83].

Phosphoinositol-3-kinase (PI3K) is the main viability regulator of variety cellular populations [84]. There are two main routes to PI3K activation: 1) PI3K can be directly activated by GTP-bound Ras, or 2) activation with the Grb2/GAB1/2-complex formation. The PI3K/Akt signal pathway can suppress the caspase-3 and -9 action, the apoptotic protein, BAD, and can activate the "survival" genes (Bcl-2 and IAPS), as well as causing the transcription factors phosphorylation, suppressing their ability to activate the apoptotic genes [85, 86].

GFRα expression in lacking Ret regions, and the capacity of GDNF for activating signal mechanisms in constant cell lines and primary neural cultures with low Ret expression, indicates the presence of Ret-independent pathway for GDNF/GFRα1 signal transmission. The neural cell adhesion molecule (NCAM) was identified as a new GDNF-receptor in neurons [87]. Subsequently it was found that NCAM is also a supplementary receptor for at least two members of GDNF family ligands — NRTN and ARTN [88].

NCAM — molecules of non-cadherin adhesion system, are transmembrane proteins once crossing the plasma membrane. The intracellular domains take part in the cellular signal transmission. The major intracellular part of NCAM polypeptide chain is folded into five immunoglobulin-like domains and also includes one or two domains that are similar to repeats occurring in fibronectin molecules [89, 90].

GFRα1 — NCAM binding leads to the formation a high-affinity receptor to GDNF, with further activation of the cytoplasmic Src-like kinase, Fyn, and the focal adhesion kinase, FAK. The presence of GDNF contributes to cell adhesion via Fyn and FAK, while the GDNF lacking causes GFRα1 inhibition of NCAM-mediated cellular

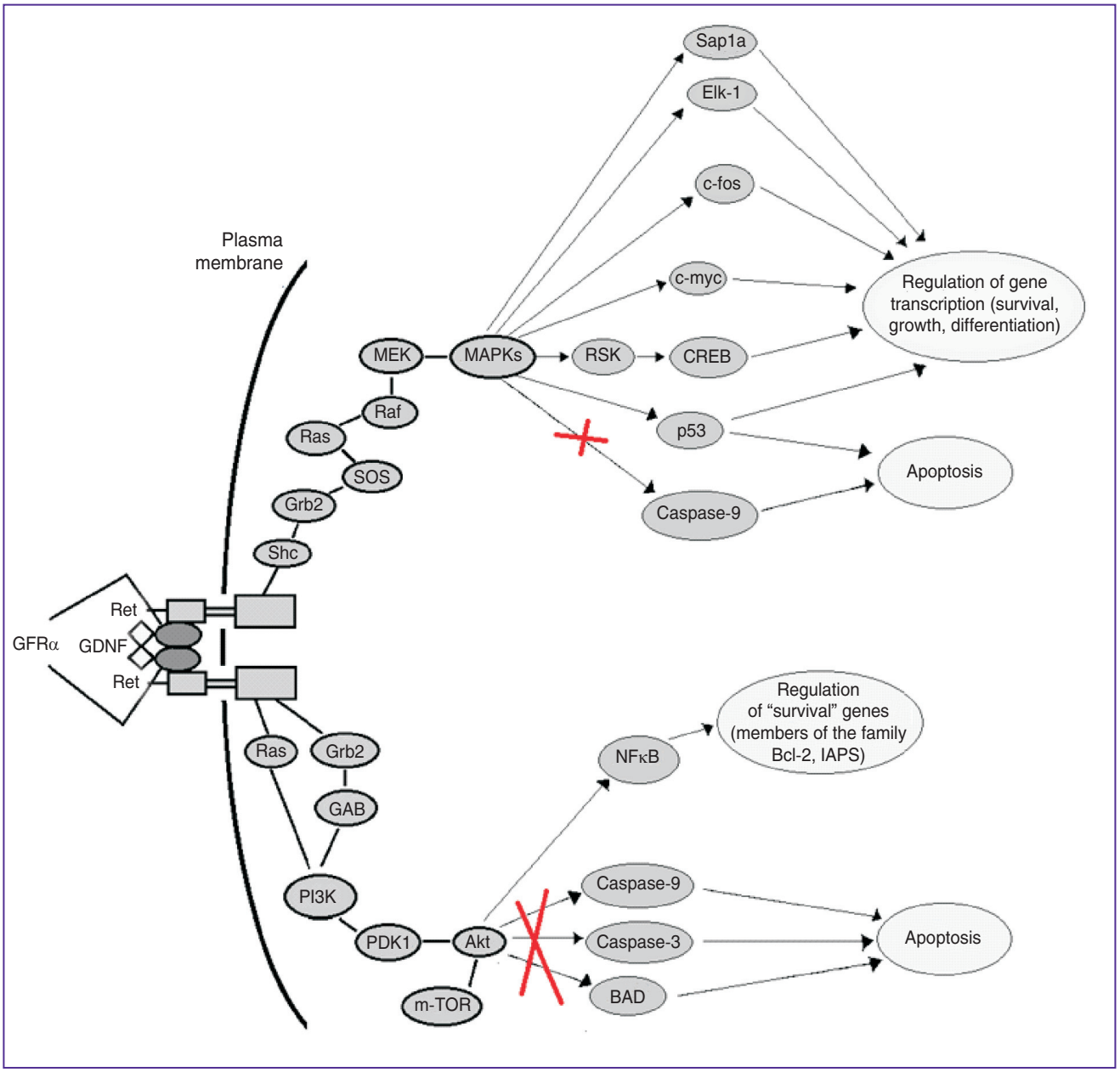

Figure 2. Schematic representation of GDNF signaling pathways through the GFRα/Ret-receptor complex. Akt: protein kinase B; BAD: pro-apoptotic protein; c-fos: protein-regulator of transcription of a number of inducible genes; c-myc: gene, encoding protein — transcription factor; CREB: cAMP-dependent transcription factor; Elk-1: ETS-domain-containing protein, activator of transcription; GAB: adaptor protein, activator of PI3K; GDNF: glial cell line-derived neurotrophic factor; GFRα: specific co-receptor for GDNF; Grb2: adaptor protein; m-TOR: protein kinase with serine-threonine specificity; MAPK: mitogen-activated protein kinase; MEK: kinase of MAPK; NFκB: transcription nuclear factor kappa B; p53: transcription factor regulating the cellular cycle; PDK1: phosphoinositide-dependent protein kinase; PI3K: phosphoinositol-3-kinase; Raf: serine-threonine protein kinase; Ras: small GTF-binding protein; Ret: receptor with tyrosine kinase activity; RSK: p90 kinase of ribosomal protein S6; Sap1a: transcription factor; Shc: adaptor protein; SOS: guanine nucleotides exchange factor

adhesion [87, 91]. GDNF binding with NCAM stimulates the Schwann cells migration, the growth of axons in the hippocampus and cortical neurons without depending on the presence of a receptor with tyrosine kinase activity [92, 93].

GDNF influence on synaptogenesis

According to modern views, the minimal functional unit of the nervous system is a neural network. Thus the processes of memory consolidation, transmission

and storage of information take place at the level of neuron networks [94–96]. Each neuron that is a part of a network is continuously participating in the transmission of information. The overall signal obtained from the neurons, causes a change in their membrane potential and the generation of an action potential which in turn is transmitted to other neurons involved in this functional ensemble. The data concerning the role of certain signal molecules (especially GDNF) in the functioning of the whole network is of special interest.

Some representatives of GFLs family take part not only in the development of synapses, but also in synaptic plasticity. It was shown that GDNF able to stimulate the release of neurotransmitter in midbrain dopaminergic neurons and in neuromuscular synapses, and thus, regulates the formation and functional properties of the synaptic endings. An increase in the number of clusters of presynaptic vesicles observed in midbrain dopaminergic neurons reveals the role of GDNF in presynaptic differentiation [97, 98]. Interestingly, GDNF modulates the A-type of K^+ channels and, thus, neuronal excitability *in vitro* [99]. It was also revealed that chronic GFLs application induces a considerable increase in the number and size of presynaptic vesicles and the clusters of acetylcholine receptor (AchR), indicating that GFLs family members are able to coordinate the development of neuromuscular synapses via pre- and post-synaptic mechanisms [100]. Moreover, in dopaminergic neurons cultures GDNF causes rapid and reversible excitability of neurons. This effect supposed to be caused by K^+ channels suppression, involving in the mechanisms that switch on MAPK activation. GDNF also leads to an increase in the permeability of Ca^+ channels. Changes in excitability of neurons and ion channels result in functional modulation of synaptic transmission. Thus, GDNF able to consider as a substance that actively affects on the pattern of neural networks functional activity [101, 102].

Investigation the role of GDNF and its main receptor in the stabilization of synaptic contacts at the early stages of synaptogenesis is of special interest. According to the expression time studies, and the localization of GDNF and its receptor in the developing hippocampus, GDNF and GFRα1 are ligand-induced molecules for cellular adhesion [103]. An immobilized source of exogenic GFRα1, by imitating postsynaptic localization, can induce differentiation of the hippocampal neurons. Similar effects were obtained for excitatory and inhibitory hippocampal neurons [103]. However, the issue of whether this mechanism is typical to all neuronal populations remains open. It was shown that GDNF-induced the development of presynaptic terminals does not depend on Ret-mediated intracellular mechanisms, but is partially depends on NCAM. Therefore, additional effector molecule reactions are likely to take part in the development [104, 105]. The capacity of GDNF to cause transhomophylic interactions between GFRα1 molecules regarded as one of the mechanisms of synaptogenesis. This mechanism is connected with soluble and membrane-bound molecules actions [106].

The studies revealed that the neurotrophic factors GDNF and BDNF can stimulate promotor activity of GluR2 subunits of AMPA receptors, playing a significant role in synaptogenesis and the formation of neural networks, as well as in synaptic plasticity, including long-term potentiation (LTP) and long-term depression (LTD) [107, 108, 109], through neuron suppressing element (NRSE) [110].

Conclusion

GDNF plays a key role in neurogenesis and also is a necessary factor for maintaining the viability and functioning of neurons. The GDNF protective action connected with ability to inhibit apoptosis, triggering the signal cascades that affect on gene expression. GDNF implements the neurotrophic activity through the formation of an active complex with its receptors — GDNF/GFRα/Ret. This complex activates the MAPK and PI3K signaling pathways which leads to the transcription factors activation and to the suppression of pro-apoptotic proteins and caspases.

Despite this, the physiological mechanisms of GDNF action and the whole spectrum of its neuroprotective potential have not been fully discovered. Study of all aspects of GDNF influence on neural brain networks adaptation to stress-conditions, as well as on the solution to the problem of protein penetration through the hematoencephalic barrier could stimulate the development of new therapeutic strategies and the creation of medicines based on this neurotrophic factor application.

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Conflicts of Interest. The authors have no conflicts of interest.

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