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GDNF — A potential target to treat addiction ☆

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ABSTRACT

The glial cell line-derived neurotrophic factor (GDNF) is a secreted protein, best known for its role in the development of the central and peripheral nervous systems and the survival of adult dopaminergic neurons. More recently, accumulating evidence suggests that GDNF plays a unique role in negatively regulating the actions of drugs of abuse. In this article, we review these data and highlight the possibility that the GDNF pathway may be a promising target for the treatment of addiction.

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1. Introduction

GDNF is a distant member of the transforming growth factor β superfamily that was originally isolated from the rat B49 glial cell line (Lin et al., 1993). GDNF is expressed throughout the central nervous system during development (Schaar et al., 1993; Stromberg et al., 1993; Choi-Lundberg & Bohn, 1995; Nosrat et al., 1996), and is also expressed in the adult brain, albeit in more restricted areas. High levels of the growth factor are found in the striatum (dorsal striatum and nucleus accumbens), thalamus, cortex and hippocampus (Springer et al., 1994; Choi-Lundberg & Bohn, 1995; Nosrat et al., 1996; Pochon et al., 1997; Trupp et al., 1997; Golden et al., 1998; Golden et al., 1999; Barroso-Chinea et al., 2005). Although GDNF is expressed in astrocytes, in the adult brain GDNF is mainly expressed and detected in neurons (Pochon et al., 1997; Barroso-Chinea et al., 2005). As described below, a major site of action of GDNF is the midbrain in which the growth factor is expressed at low levels under basal conditions (Golden et al., 1998; Semba et al., 2004; He et al., 2005). The major source of GDNF to the midbrain is the striatum where GDNF is retrogradely transported by dopaminergic neurons of the substantia nigra pars compacta (SNc) and the ventral tegmental area (VTA) (Tomac et al., 1995b; Lapchak et al., 1997; Kordower et al., 2000; Ai et al., 2003; Barroso-Chinea et al., 2005).

2. GDNF-mediated signaling

The main pathway by which GDNF transduces its signal is via the activation of the Rearranged during transfection receptor (Ret) (Jing

Abbreviations: ERK1/2, extracellular signal-regulated kinase 1/2; GDNF, glial cell line-derived neurotrophic factor; GFRα1, GDNF family receptor α1; HET, heterozygote; HSP90, heat shock protein 90; MAPK, mitogen-activated protein kinase; Nac, Nucleus accumbens; 18-MC, 18-methoxycoronaridine; MEK, MAPK/ERK kinase; PI3K, phoshatidylinositol 3 kinase; PLCγ, phospholipase Cγ; Ret, Rearranged during transfection receptor; SN, substantia nigra; SNc, substantia nigra pars compacta; TH, tyrosine hydroxylase; VTA, ventral tegmental area; WT, wild-type.

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et al., 1996; Treanor et al., 1996; Trupp et al., 1996; Eketjall et al., 1999). Ret is the product of the c-*ret* proto-oncogene and is a receptor tyrosine kinase (Tsui-Pierchala et al., 2002a). Activation of the GDNF pathway is initiated via the ligation of GDNF to its co-receptor, GDNF family receptor α1 (GFRα1), which is a glycosylphosphatidylinositol (GPI)-linked membrane-associated protein (Jing et al., 1996; Treanor et al., 1996; Eketjall et al., 1999), and the recruitment of Ret to the GFRα1-GDNF complex (Jing et al., 1996) (Fig. 1). GFRα1-Ret association can occur when both are expressed on the same cell (*cis* signaling), or when GFRα1 is presented in a soluble form (*trans* signaling) (Paratcha et al., 2001) (Fig. 1). Upon complex formation, Ret is activated by autophosphorylation (Durbec et al., 1996; Coulpier et al., 2002), leading to the activation of the mitogen-activated protein kinase (MAPK) extracellular signal-regulated kinase 1/2 (ERK1/2), as well as the phosphatidylinositol 3 kinase (PI3K) and phospholipase Cγ (PLCγ) cascades (Airaksinen & Saarma, 2002) (Fig. 1).

GFRα1 and Ret are expressed in several brain regions in the developing and adult brain, including the cerebellum, hypothalamic nuclei, the amygdala and the hippocampus (Trupp et al., 1997; Glazner et al., 1998; Golden et al., 1998; Burazin & Gundlach, 1999; Golden et al., 1999; Matsuo et al., 2000). Very low or negligible levels of GFRα1 and Ret are detected in the striatum, however the receptors are particularly abundant in the SNc and the VTA (Trupp et al., 1997; Glazner et al., 1998; Golden et al., 1998; Burazin & Gundlach, 1999; Golden et al., 1999; Matsuo et al., 2000; Sarabi et al., 2001; Jain et al., 2006). Interestingly, the distribution of GFRα1 and Ret expression does not necessarily overlap. For example, GFRα1, but not Ret, is expressed in the cortex and adult hippocampus (Trupp et al., 1997; Glazner et al., 1998; Golden et al., 1998; Burazin & Gundlach, 1999; Golden et al., 1999). The absence of Ret in these brain regions suggests the existence of GDNF signaling pathways that are independent of Ret. To this effect, Paratcha et al. (2003) reported that GDNF also signals via a direct interaction of GDNF with the neural cell adhesion protein, NCAM. This mode of activation results from the association of GFRα1 with NCAM, which promotes high-affinity binding of GDNF to NCAM (Paratcha et al., 2003). The association of GDNF to the adhesion receptor leads to the activation of the Src family of tyrosine kinases including Fyn, and the subsequent stimulation of Schwann cell migration and axonal outgrowth in hippocampal and cortical neurons (Paratcha et al., 2003). Interestingly, Chao et al. reported that the functional blockade of NCAM with anti-NACM inhibitory antibodies antagonizes the effects of GDNF on midbrain dopaminergic neurons in vitro and in vivo (Chao et al., 2003), suggesting a role for this pathway even in brain regions that express Ret.

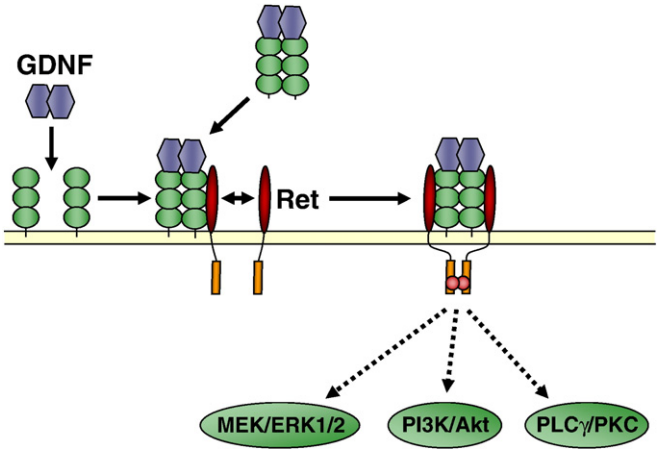

Fig. 1. GFRα1 and Ret-mediated GDNF signaling pathways. Ligation of GDNF to GPI-anchored GFRα1 (*cis* signaling) or soluble GFRα1 (*trans* signaling) increases the affinity of GFRα1 for Ret, inducing its recruitment and dimerization. Ret is activated by autophosphorylation of tyrosine residues shown in red, leading to the activation (in green) of several signaling pathways, such as the MAPK (ERK1/2), PI3K and PLCγ pathways. MEK: MAPK/ERK kinase. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

An important factor in the regulation of the GDNF pathway is the compartmentalization of its receptors within or outside of lipid rafts. Lipid rafts are membranal microdomains that contain high levels of cholesterol, sphingolipids and GPI-anchored membranal proteins, and are thought to function as platforms for signaling cascades (Harding & Hancock, 2008; Kinoshita et al., 2008). In neurons, lipid rafts play an important role in growth factor signaling, cell adhesion, axon guidance and synaptic transmission (Tsui-Pierchala et al., 2002b). The GPI-linked GFRα1 is localized, at least in part, to lipid rafts, and upon GDNF binding to GFRα1, the complex recruits Ret into the rafts, leading to the activation of the receptor and to the association of Ret with the downstream kinase, Src (Tansey et al., 2000; Encinas et al., 2001). Soluble GFRα1 (*trans* activation) can also recruit Ret into the lipid rafts, however at a much slower rate (Paratcha et al., 2001), and interestingly, Pierchala et al. (2006), recently showed that lipid rafts play an important role in protecting the Ret receptor from proteosome-dependent degradation.

The most well-documented consequence of the activation of GDNF-mediated signaling cascades is an increase in gene transcription (Trupp et al., 1999; Hayashi et al., 2000; Jongen et al., 2005). For example, GDNF was found to increase the expression of the calcium binding protein frequenin (Wang et al., 2001), and the expression of the bone marrow zinc finger 3 (BMZF3) was increased in neuroblastoma cells upon incubation with GDNF (Suzuki et al., 2008). Activation of the PI3K signaling pathway in substantia nigra neurons by GDNF leads to increased expression of yet another calcium binding protein, Calbindin (Wang et al., 2008). We showed that the activation of the MAPK pathway by GDNF leads to the initiation of a positive autoregulatory loop in which the growth factor upregulates its own expression resulting in a sustained activation of Ret (He & Ron, 2006). Interestingly, a recent study identified a transmembrane protein, Lrig1, that acts to negatively regulate the GDNF-mediated pathway by interacting with Ret, resulting in the inhibition of GDNF binding and the activation of the MAPK (Ledda et al., 2008). It would be of great interest to determine possible interaction between the positive and negative mechanisms of activation of the GDNF signaling pathways.

3. GDNF's functions

GDNF promotes survival of mesencephalic dopamine neurons in culture (Lin et al., 1993) and plays an essential role in the development and survival of motor neurons, the development of sympathetic and sensory neurons, and kidneys (Moore et al., 1996; Pichel et al., 1996; Sanchez et al., 1996), as well as in hippocampal synaptogenesis (Ledda et al., 2007). GDNF was also shown to promote survival and re-growth of dopaminergic neurons in the adult brain following injury (Beck et al., 1995; Tomac et al., 1995a; Hou et al., 1996), and is an essential factor for the maintenance and survival of adult dopamine neurons (Pascual et al., 2008). For example, repeated injections of GDNF adjacent to the SN prevented axotomy-induced loss of tyrosine hydroxylase (TH)-expressing neurons in that brain region (Beck et al., 1995), and adenoviral delivery of GDNF into the SN protected against degeneration of dopamine neurons following injection of 6-hydroxydopamine in the striatum (Choi-Lundberg et al., 1997). Injection (Tomac et al., 1995a) or lentiviral delivery (Kordower et al., 2000) of GDNF into the SN and striatum protected against nigrostriatal degeneration induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which is toxic to dopaminergic neurons. GDNF has also been shown to selectively protect dopaminergic neurons, as compared to serotonergic neurons, against the neurotoxic effects of methamphetamine (Cass, 1996). As such, its potential as a therapeutic agent for the treatment of pathologies such as Parkinson's disease has been widely explored (Georgievska et al., 2002; Eslamboli et al., 2003; Azzouz et al., 2004; Kirik et al., 2004; Eslamboli et al., 2005).