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# Biology of GDNF and its receptors — Relevance for disorders of the central nervous system

Carlos F. Ibáñez [a,b,c,d,*], Jaan-Olle Andressoo [e]

[a] Department of Physiology, National University of Singapore, Singapore 117597, Singapore
[b] Life Sciences Institute, National University of Singapore, Singapore 117456, Singapore
[c] Department of Neuroscience, Karolinska Institute, Stockholm S-17177, Sweden
[d] Stellenbosch Institute for Advanced Study, Wallenberg Research Centre at Stellenbosch University, Stellenbosch 7600, South Africa
[e] Institute of Biotechnology, University of Helsinki, Helsinki 00014, , Finland

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ABSTRACT

A targeted effort to identify novel neurotrophic factors for midbrain dopaminergic neurons resulted in the isolation of GDNF (glial cell line-derived neurotrophic factor) from the supernatant of a rat glial cell line in 1993. Over two decades and 1200 papers later, the GDNF ligand family and their different receptor systems are now recognized as one of the major neurotrophic networks in the nervous system, important for the development, maintenance and function of a variety of neurons and glial cells. The many ways in which the four members of the GDNF ligand family can signal and function allow these factors to take part in the control of multiple types of processes, from neuronal survival to axon guidance and synapse formation in the developing nervous system, to synaptic function and regenerative responses in the adult. In this review, we will briefly summarize basic aspects of GDNF signaling mechanisms and receptor systems and then review our current knowledge of the physiology of GDNF activities in the central nervous system, with an eye to its relevance for neurodegenerative and neuropsychiatric diseases.



## 1. Basic signaling mechanisms and receptor systems for the GDNF ligand family

Following the isolation of GDNF (Lin et al., 1993), additional ligands structurally similar to GDNF were identified and characterized. Work by different laboratories showed that the GDNF ligand family consists of four proteins: GDNF, Neurturin, Artemin and Persephin, all isolated within 5 years of the GDNF discovery (for a review, see (Airaksinen and Saarma, 2002)). The characterization of GDNF receptors would follow soon thereafter. Biochemical studies of GDNF signaling (Trupp et al., 1996) as well as analyses of *Gdnf* knock-out mice (Pichel et al., 1996) led to the realization that the, previously orphan, receptor tyrosine kinase RET was a signaling receptor for GDNF (for a review, see (Ibanez, 2013). Later work showed that GDNF binding to RET was of low affinity and required an auxiliary ligand-binding subunit that was to be called GDNF Family Receptor alpha 1, or GFRα1 (for a review, see (Airaksinen and Saarma, 2002)). In total, four GFRα-like receptors were identified (i.e. GFRα1 to 4), each with selectivity (although not exclusive specificity) for each of the four members of the GDNF ligand family. These receptors bind GDNF ligands with high affinity but they do not themselves signal, as they lack an intracellular domain and are anchored to the plasma membrane through a lipid linkage (GPI-anchor) (reviewed in (Airaksinen and Saarma, 2002)). In complex with a cognate GFRα receptor, GDNF ligands acquire high affinity for RET. The downstream signaling elicited by the GDNF/GFRα1/RET complex has many of the characteristic features of receptor tyrosine kinases, including activation of the Ras/MAP kinase and PI3K/AKT pathways (reviewed in (Ibanez, 2013)). The intensity and duration of RET signaling can be modified by the ability of the GPI-anchor of GFRα co-receptors to partition into sub compartments of the plasma membrane, such as lipid rafts (reviewed in (Paratcha and Ibanez, 2002)), as well as cleavage by membrane phospholipases, which allows GFRα receptors to function in soluble form (Paratcha et al., 2001). This latter phenomenon, also called "trans" signaling, explains why GFRα co-receptors are expressed by many cells and tissues in the absence of RET and can thereby display non-cell autonomous functions (reviewed in (Paratcha and Ledda, 2008; Ibanez, 2010)). Trans signaling may also have therapeutic applications, as infusion of soluble GFRα1 has recently been shown to potentiate dopaminergic neuron function during normal aging (Pruett and Salvatore, 2013). The physiological significance of lipid raft signaling by the GFRα1/RET complex has recently been demonstrated in vivo (Tsui et al., 2015).

In addition to RET, some members of the GDNF family can signal by interaction with the Neural Cell Adhesion Molecule (NCAM) (Paratcha et al., 2003). Although GDNF can interact directly with NCAM, high

* Corresponding author at: Department of Physiology, National University of Singapore, Singapore 117597, Singapore.
*E-mail address:* phscfi@nus.edu.sg (C.F. Ibáñez).
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affinity binding and downstream signaling are dependent on the presence of cognate GFRα co-receptors (reviewed in (Paratcha and Ledda, 2008; Ibanez, 2010). The specificity and physiological relevance of NCAM as a GDNF signaling receptor has been documented in multiple studies by several different laboratories (see for example (Charoy et al., 2012; Duveau and Fritschy, 2010; Euteneuer et al., 2013; Nielsen et al., 2009; Sjöstrand and Ibanez, 2008; Sjöstrand et al., 2007; Wan and Too, 2010)). GDNF signaling through NCAM can result in the activation of Src-like kinases and MAP kinases and contributes to the regulation of several different processes, including neurite outgrowth and synapse formation (reviewed in (Paratcha and Ledda, 2008)). In addition to intracellular signaling, GDNF and GFRα1 have also been shown to affect cell behavior through specific effects on cell adhesion (reviewed in (Ibanez, 2010)). GFRα1 has been shown to antagonize NCAM-mediated cell adhesion (Paratcha et al., 2003), a phenomenon that depends upon direct interaction of GFRα1 with the fourth Ig domain in NCAM (Sjöstrand and Ibanez, 2008). In this context, GFRα1 would have the capacity to exert biological effects in the absence of either GDNF or RET. Ongoing analysis of different brain areas in *Gfra1* mutant mice is beginning to shed light on the physiological relevance of this activity. Independently of NCAM, GFRα1 has been shown to function as a cell adhesion molecule in its own right, albeit one regulated by its ligand GDNF, a concept that has been termed ligand-mediated cell adhesion (Ledda, 2007; Ledda et al., 2007). Different lines of evidence suggest that this activity can contribute to synapse formation in the hippocampus, as reviewed in greater detail below. It should also be mentioned that other work has hinted at the presence of additional GDNF receptors besides GFRα1, RET and NCAM. Syndecan-3 has been shown to interact with GDNF through its heparin sulfate chains (Bespalov et al., 2011). Finally, the activities of GDNF on GABAergic interneurons of the medial ganglionic eminence (MGE), reviewed in greater detail below, have been shown to require GFRα1 but to be independent of either RET or NCAM (Pozas and Ibanez, 2005). More recent work has shown that GDNF may signal through a transmembrane protein that is distinct from other receptors known to be present in MGE cells, including MET or ErbB4 (Perrinjaquet et al., 2011).

As the main focus of this review is on GDNF activities in brain, peripheral actions of GDNF and related ligands will only be briefly mentioned here. Following its discovery as a neurotrophic factor for brain dopaminergic neurons, it was soon realized that GDNF has also powerful activities in peripheral neurons, including retinal ganglion cells, sympathetic, parasympathetic and sensory neurons (see for example (Baudet et al., 2000; Fundin et al., 1999; Jing et al., 1996; Ohnaka et al., 2012; Rossi et al., 1999; Trupp et al., 1995)). More recent work has shown that GDNF ligands can regulate pain responses by modulating sensitization of sensory neurons to different stimuli (Alvarez et al., 2012; Lippoldt et al., 2013; Sakai et al., 2008a). The link between GDNF and RET would further establish GDNF as one of the primary branching factors for the ureteric buds of the developing kidney (Sainio et al., 1997; Shakya et al., 2005) and a key regulator of the development and maintenance of neurons in the enteric nervous system (Enomoto et al., 1998; Wang et al., 2010; Young, 2001). GDNF has also been found to be a potent regulator of spermatogonial self-renewal and differentiation (Meng et al., 2000) and is required in adult stages for the maintenance of the spermatogonial stem cell pool (Savitt et al., 2012). In addition, early investigations pointed to the importance of GDNF signaling for motoneuron survival (Henderson et al., 1994; Oppenheim et al., 2000), and more recently differentiation (Haase et al., 2002), axon guidance (Bonanomi et al., 2012; Kramer et al., 2006) and neuromuscular connectivity (Baudet et al., 2008). In particular, fusimotor motoneurons appear to be most sensitive to GDNF (Gould et al., 2008). Interestingly, GDNF was recently shown to elicit different effects on motoneuron axons versus cell bodies (Zahavi et al., 2015). Delivery of GDNF in a cell therapy paradigm has been shown to prolong lifespan and ameliorate disease progression in a rat model of familial amyotrophic lateral sclerosis (ALS) (Krakora et al., 2013).

## 2. GDNF function and therapeutic potential in the brain dopamine system

The main motor symptoms in Parkinson's disease (PD) are caused by gradual loss of midbrain dopamine neurons residing in the substantia nigra pars compacta (SNpc) and projecting mainly into the dorsal striatum (Björklund and Dunnett, 2007a; Meissner et al., 2011). Since halting or reversing treatments for PD are not available, the initial discovery of GDNF as a survival factor for midbrain dopaminergic neurons in culture generated great excitement in the field and was quickly followed by in vivo studies and subsequently clinical trials. The successes and draw-backs of GDNF based therapies in PD (discussed in greater detail below) highlight a need for a greater understanding of the physiology of endogenous GDNF in vivo.

### 2.1. GDNF expression in the nigrostriatal dopamine system

In mice, the SNpc contains about 10,000 to 15,000 dopaminergic neurons which express GDNF receptors RET and GFRα1 (Golden et al., 1999; Hunot et al., 1996; Trupp et al., 1997). These mainly project via the medial forebrain bundle to the dorsal striatum, which expresses GDNF (Björklund and Dunnett, 2007b). The axonal tree of an individual dopaminergic neuron branches extensively, covering on average 1.5% of the total striatal volume, thus with an estimated capacity to influence approximately 75,000 striatal neurons (Matsuda et al., 2009). In the striatum, GDNF is predominantly expressed by parvalbumin positive interneurons which make up 0.7% of all striatal neurons (Hidalgo-Figueroa et al., 2012). Thus, on average, about 525 GDNF-expressing neurons reside within the area covered by an individual dopaminergic axonal tree. As a consequence, the axonal trees of dopaminergic neurons are highly overlapping, covering the mouse striatum about 225 times. This redundant innervation is likely to be important, and it may explain the remarkable compensatory capacity of the nigrostriatal dopaminergic system: PD becomes symptomatic only after more than 50% of striatal dopamine levels and 30–40% of SNpc neurons are lost (Burke and O'Malley, 2013). In rodent models of PD, it was shown that the axonal trees of the remaining axons can re-innervate the striatal areas left vacant by the degenerating dopaminergic neurons (Burke and O'Malley, 2013; Parish et al., 2001), opening an opportunity to halt or reverse the progression of PD via GDNF delivery.

### 2.2. Ectopic GDNF application for PD therapy

Intracranial delivery of GDNF potentiates striatal dopamine system function and midbrain dopaminergic neuronal survival in several models of chemically-induced PD in rodents (Beck et al., 1995; Hoffer et al., 1994; Tomac et al., 1995; Winkler et al., 1996) as well as non-human primates (Gash et al., 1996). Interestingly, GDNF delivery into the striatum, but not to the SNpc, results in functional recovery in rodent PD models (Kirik et al., 2000, 2004), underlying the importance of GDNF delivery to its physiological site of expression for the treatment of PD. Upon intracranial delivery, GDNF induces re-growth of degenerating dopaminergic axons in PD animal models (Meissner et al., 2011) and in aging human brain (Love et al., 2005). In clinical trials, however, the effects of intracranial GDNF delivery varied from positive clinical benefits (Gill et al., 2003; Love et al., 2005; Patel et al., 2005) to no effect (Lang et al., 2006). Variability in GDNF delivery systems, statistical considerations and issues with patient grading and inclusion criteria have left several clinical trials inconclusive (Lang et al., 2006; Sherer et al., 2006). At the time of this writing, two clinical trials are ongoing, one using an improved preparation of GDNF protein, the other based on adeno-associated virus (AAV) delivery. While hopes are still high that GDNF based therapies may be able to alleviate or halt the degenerative process in PD patients, several still unresolved concerns will need to be addressed before concrete progress is made in this area. Because GDNF is a strong chemo-attractant for axons of dopaminergic

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neurons, ectopic GDNF application results in growth of the re-innervating axons towards the GDNF injection site, instead of the original innervation targets, resulting in aberrant sprouting (Georgievska et al., 2002, 2004; Hudson et al., 1995). Another concern relates with GDNF dosing, which usually exceeds endogenous GDNF levels by at least one or two orders of the magnitude and has been linked to undesired side-effects. Virally delivered GDNF was shown to result in down-regulation of the levels of tyrosine hydroxylase (TH), the key enzyme in dopamine synthesis (Georgievska et al., 2004; Rosenblad et al., 2003). Ectopic GDNF administration has also been reported to cause hyperactivity (Emerich et al., 1996; Hebert and Gerhardt, 1997; Hebert et al., 1996; Hudson et al., 1995) as well as reduced food intake and bodyweight (Hudson et al., 1995; Manfredsson et al., 2009).

### 2.3. Endogenous GDNF function in the brain dopamine system

The brain dopamine system largely matures during the first postnatal weeks. Two waves of programmed cell death are known to take place during the first two postnatal weeks, paralleled by maturation of striatal innervation as striatal GDNF levels peak towards the end of the second week (Airaksinen and Saarma, 2002; Burke, 2003; Hidalgo-Figueroa et al., 2012; Oo et al., 2005; Trupp et al., 1996). In this regard, it is intriguing that both RET as well as GFRα1 are expressed in midbrain dopaminergic neurons from very early stages of their development in the mouse embryo (Golden et al., 1999). Mice that develop without GDNF die at birth due to agenesis of kidney and enteric nerves, while the brain dopamine system is still intact at this age in these mutants (Moore et al., 1996; Pichel et al., 1996; Sánchez et al., 1996). On the other hand, heterozygous *GDNF* mutants, with about half GDNF levels in the striatum, display rather mild changes in the brain dopaminergic system at postnatal and adult stages (Boger et al., 2006; Granholm et al., 2011). Similar results have been obtained in null mutants of the *GFRA1* gene (Cacalano et al., 1998; Enomoto et al., 1998).

Conditional ablation of RET expression in dopaminergic neurons has no detectable effect on striatal dopamine levels or cell integrity in the SNPc until about 9 months of age (Jain et al., 2006). After this age, however, up to 30% dopaminergic neuron loss was observed in conditional mutant mice that were between 1 and 2 years old (Kramer et al., 2007), suggesting that endogenous GDNF signaling through RET is only required for long term maintenance of the dopaminergic nigrostriatal system. In vitro experiments have suggested that RET is the main GDNF receptor in midbrain dopaminergic neurons (Taraviras et al., 1999). Whether other GDNF receptors, such as NCAM or Syndecan-3, play any significant roles in the development or maintenance of the brain dopamine system has not yet been established. Besides development and maintenance, RET signaling may exert potent neuroprotective functions in the face of a neural challenge or insult. A recent study has shown that mice lacking both *Parkin* (a gene linked to PD pathogenesis (Exner et al., 2012)) and *RET* in SNPc dopaminergic neurons exhibited accelerated dopaminergic neuron and axonal loss compared with either Parkin-deficient or RET-deficient mice, due to impaired mitochondrial morphology and function (Meka et al., 2015). The results of this study highlight a cross-talk between the PD protein network and GDNF signaling which may have implications for development of therapeutic strategies in PD.

Conditional ablation of GDNF expression has been investigated in a number of ways. In the first study, whole-body inactivation of the *GDNF* gene was induced in mice at one month of age using a tamoxifen-inducible Cre-mediated strategy (Pascual et al., 2008). These researchers reported 60–70% loss of dopaminergic neurons in the midbrain 7 months after tamoxifen treatment. Strikingly, overall GDNF levels in striatum were reduced by only 50% in these animals. These results suggested the possibility that GDNF may utilize receptors distinct from RET in adult midbrain dopaminergic neurons or, alternatively, that lack of GDNF/RET signaling from early stages of development triggers compensatory mechanisms that rescue dopaminergic neuron survival (Ibanez, 2008). A more recent study repeated these experiments using a similar set up but with an independently generated line of conditional *GDNF* mutant mice. In addition, this new study also induced deletion of the *GDNF* gene via intrastriatal delivery of a virus expressing Cre recombinase as well as using pan-neuronal Cre expression from the *Nestin* gene (Kopra et al., 2015). In contrast to the first study, these researchers found that neither of the three approaches affected dopaminergic neuron survival in the SNPc nor dopamine levels in the striatum up to an age of 19 months. The stark discrepancy between these two studies has been attributed to several factors, including differences in genetic background and extent of reduction of GDNF levels. Ongoing studies by other laboratories may help to resolve the disparity of these results. Even if it is finally demonstrated that dopaminergic neuron survival is not dependent on GDNF in vivo, it is still possible that endogenous GDNF regulates the function of dopaminergic neurons or modulate their survival under stress situations, such as PD. Several recent gain-of-function studies have brought some light on these possibilities.

Transgenic overexpression of either GDNF or GFRα1 in the forebrain of mice using a CAMKII promoter was reported to increase dopaminergic neuron numbers in the SNPc and protection of striatal dopaminergic fibers, but not cell bodies, to an excitotoxic lesion that mimics PD in rodents (Kholodilov et al., 2004, 2011). In line with these results, infusion of recombinant GFRα1 in the SNPc was also reported to increase TH and dopamine content in the SNPc of aged rats (Pruett and Salvatore, 2013). As GFRα1 is thought to require GDNF to function, these results were interpreted as evidence for a role of endogenous GDNF in midbrain dopaminergic neuron development or maintenance. On the other hand, as discussed above, ectopic administration of GDNF or GFRα1 does not necessarily reflect the functions of the endogenously expressed proteins and can even lead to confounding effects. A few studies have attempted to overcome these limitations by enhancing GDNF function through manipulation of endogenous genes in the pathway. Mice carrying a mutation found in patients suffering of multiple endocrine neoplasia type B (MEN2B) that constitutively activates the RET receptor showed a global enhancement of the nigrostriatal system, including increased number of dopaminergic neurons in the SNPc, increased levels of TH and dopamine transporter (DAT), as well as elevated striatal dopamine levels (Mijatovic et al., 2007, 2008, 2011). A more recent study has reported results obtained from GDNF hypermorphic mice which displayed two-fold elevated GDNF expression following introduction of a transcription stop signal in the 3′ untranslated region (UTR) of the endogenous *Gdnf* gene (Kumar et al., 2015). Further work revealed that a site in the *Gdnf* 3′ UTR sequence interacted with micro RNAs (miRNAs) that negatively regulate GDNF expression by destabilizing *Gdnf* mRNA and possibly its translation. Increased GDNF protein expression was detected in striatum of these mice leading to increased number of dopaminergic neurons in the SNPc and elevated dopamine levels in striatum. In contrast to previous studies using ectopic GDNF expression or administration, no aberrant sprouting of dopaminergic axons, down-regulation of TH levels or hyperactivity were observed. Importantly, striatal dopaminergic axons, although not SNPc cell bodies, were protected in a PD model induced by supranigral lactacystin application. The effects of increased levels of endogenous GDNF showed similarities, but also differences, from constitutive RET activation after MEN2B mutation. Interestingly, enhanced TH expression and reduced spontaneous locomotion was only observed in MEN2B RET mice (Mijatovic et al., 2007). GDNF hypermorphic mice also showed enhanced striatal dopamine release and re-uptake as a result of elevated DAT activity (Kumar et al., 2015). Although this result is what would be expected from a dopaminotrophic factor such as GDNF, a recent study using *Ret* knock-out heterozygous mice reported somewhat contradicting observations (Zhu et al., 2015). These researchers found enhanced dopamine uptake as well as increased surface localization and DAT activity in dopaminergic axons specifically in the ventral striatum of these mice, suggesting that RET signaling negatively regulates DAT activity. Clearly, more work needs

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to be done to resolve how GDNF/RET signaling regulates DAT activity and expression, an activity that may have important implications for the role of these molecules in a range of conditions, including addictive behaviors, as discussed below.

## 3. Other GDNF activities in the CNS: relevance for neuropsychiatric disorders

Although most research on the function of GDNF and its receptors has concentrated on midbrain dopaminergic neurons, the realization that GDNF receptors are present in many other brain regions set the stage for investigations of GDNF activities in other classes of neurons and their implications for neurological conditions other than Parkinson's disease.

### *3.1. Hippocampal synaptogenesis*

GDNF and two of its receptors, GFRα1 and NCAM, but not RET, are expressed by hippocampal neurons during embryonic and early postnatal stages (Ledda et al., 2007). While NCAM was exclusively localized presynaptically, GFRα1 was present at both pre- and post-synaptic sites (Ledda et al., 2007). A series of studies established that GFRα1 can function as a Ligand-Induced Cell Adhesion Molecule (LICAM) at synaptic sites (reviewed in (Ledda, 2007)). Thus, GFRα1 promoted adhesion between cells only in the presence of GDNF, providing a novel mechanism of cell–cell contact regulated by external factors. In hippocampal neuron cultures, GDNF was found to increase the number of synapses. Moreover, ectopic presynaptic sites could be induced by the contact of beads coated with GFRα1 in the presence of soluble GDNF (Ledda et al., 2007), indicating an instructive role of GDNF/GFRα1 in synapse formation. This effect was in part dependent on presynaptic expression of NCAM. Mutant mice with reduced levels of GDNF showed decreased presynaptic maturation and reduced number of presynaptic sites formed during hippocampal synaptogenesis (Ledda et al., 2007), supporting a role for GDNF signaling in hippocampal presynaptic assembly in vivo. Whether postsynaptic GFRα1 molecules may also contribute cell-autonomously to differentiation of post-synaptic sites remains to be explored.

### *3.2. GABAergic neurons*

In the forebrain, inhibitory (GABAergic) interneurons are generated in the ventral telencephalon and migrate tangentially to the developing cortex, hippocampus and olfactory bulb (recently reviewed in (Bartolini et al., 2013)). The main region of GABAergic neurogenesis in the forebrain is localized to the ganglionic eminences, transient neurogenic sites in the embryonic mammalian brain. The medial and caudal ganglionic eminences (MGE and CGE, respectively) are the main contributors of cortical GABAergic neurons, while the lateral ganglionic eminence (LGE) mainly contributes inhibitory interneurons to the olfactory bulb. Both GDNF and GFRα1 have been found to be expressed in the MGE and along the tangential migratory pathway of GABAergic cells in the developing cerebral cortex (Pozas and Ibanez, 2005). In vitro studies demonstrated that GDNF can promote the functional and morphological differentiation of MGE-derived GABAergic neurons and function as a chemoattractant for GABAergic cells in explants from the MGE and the subventricular zone (SVZ) (Paratcha et al., 2006; Pozas and Ibanez, 2005). Using neurons extracted from different strains of knock-out mice, these effects were shown to require GFRα1, but neither NCAM nor RET. In fact, soluble GFRα1 supplied exogenously to MGE cultures promoted GABAergic differentiation and migration even in cells lacking endogenous GFRα1 (Perrinjaquet et al., 2011), arguing for the existence of a new transmembrane receptor partner. An independent set of studies implicated the heparan sulfate proteoglycan syndecan-3 as a novel receptor for GDNF in MGE-derived GABAergic neurons, although its functions do not appear to depend on GFRα1 (Bespalov et al., 2011). Importantly, mutant mice lacking GFRα1 showed reduced numbers of tangentially migrating GABAergic neurons and fewer inhibitory neurons in cortex and hippocampus at birth (Pozas and Ibanez, 2005). Using a mouse model with deficits in GFRα1 signaling that by-passes the postnatal lethality of global GFRα1 knock-outs, it could be later demonstrated that GFRα1 contributes to the development and allocation of parvalbumin expressing GABAergic neurons in the cerebral cortex (Canty et al., 2009). Intriguingly, these mice showed decreased inhibitory activity in the cortex and displayed increased social behavior compared to control mice (Canty et al., 2009), suggesting a positive relationship between cortical excitability and social behavior, a finding that is in agreement with some models of human autism (Tabuchi et al., 2007).

GFRα1 signaling has also been shown to play an important role in the development of the olfactory system. Mice lacking GFRα1 showed deficits in all major classes of GABAergic interneurons in the olfactory bulb (OB), including those expressing tyrosine hydroxylase, calbindin and calretinin (Marks et al., 2012). As GFRα1 itself was not expressed by matured GABAergic neurons in the OB, these deficits may be due to non-cell-autonomous functions of GFRα1 in other elements of the olfactory system. In fact, mutant mice displayed impaired neurogenesis in the olfactory epithelium, reduced migration of olfactory ensheathing cells and stunted growth of sensory neuron axons. As a consequence, the OB nerve layer was thin and glomeruli were disorganized in the mutants (Marks et al., 2012). Similar deficits were observed in mice lacking GDNF (Marks et al., 2012). It is also possible that GFRα1 could function transiently and cell-autonomously in subpopulations of OB interneuron precursors to regulate their differentiation, migration, or survival before their final allocation in the OB. Addressing these possibilities will require the generation and analysis of conditional mutant mice lacking GFRα1 specifically in GABAergic OB interneurons.

Intriguingly, several other types of GABAergic neurons also express GFRα1, raising the possibility of a more general role of GDNF signaling in GABAergic neuron development and function. GABAergic neurons of the septum express GFRα1 from early stages of development. Some of these cells may contribute precursors to the OB. Others are resident in basal and medial septum and may have intrinsic functions within these nuclei. GABAergic neurons of the cerebellum, including Purkinje cells (a projection neuron) and basket cells (a type of cerebellar interneuron) express GFRα1 transiently during their development (M. Sergaki and C.F. Ibanez, unpublished observations). Specific targeting of GFRα1 in these cell populations will be necessary to establish its precise cellular functions. Taken together, these studies suggest an emerging role of GDNF/GFRα1 signaling in the development and function of multiple classes of GABAergic neurons in the mammalian brain.

### *3.3. Exercise, blood–brain barrier and microglial activation*

An intriguing aspect of adult GDNF expression and function is the possibility of it being regulated by physical activity. Studies in rodents have shown upregulated GDNF expression in several CNS structures following short-term as well as chronic exercise. In one study, striatal GDNF levels were found to be dramatically increased after forced limb use in rats (Cohen et al., 2003). Increased GDNF expression correlated with enhanced neuroprotective effects in the 6-OH dopamine model of Parkinson's disease, although it is unclear whether the neuroprotection observed can be attributed to enhanced GDNF signaling or to other effects of exercise. In another study, both voluntary as well as involuntary exercise led to pronounced increase in GDNF protein in the spinal cord of young rats (McCullough et al., 2013). Also in older animals, low-intensity running led to GDNF increased levels. Interestingly, both young and old exercised animals showed a doubling in cholineacetyltransferase (ChAT) positive motor neuron cell body areas (McCullough et al., 2013). These studies suggest that GDNF expression can be regulated by experience, in particular physical activity, leading to intrinsic neuroprotective and neuroregenerative outcomes.

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Alterations in the blood–brain barrier (BBB) and blood–nerve barrier (BNB) have been implicated in several neurological conditions, including stroke and dementia. A few recent studies have highlighted the role of GDNF in the maintenance of functional properties of cellular elements of the BBB and BNB, including pericytes and endothelial cells. GDNF was found to increase the expression of claudin-5 and the trans-endothelial electrical resistance in microvascular endothelial cells derived from either brain or peripheral nerves (Shimizu et al., 2012). Claudin-5 has been recognized as one of the most important components in the maintenance of BBB integrity and function. In this case, the source of GDNF was localized to brain and peripheral nerve pericytes, respectively, indicating a paracrine role of GDNF in BBB and BNB maintenance. Another study found that GDNF very efficiently induced trans-endothelial electrical resistance recovery following serum withdrawal in cultures of human endothelial cells (Yosef and Ubogu, 2012). This effect involved signaling via the RET receptor tyrosine kinase as well as upregulation of Claudin-5 expression and cytoskeletal reorganization. These studies suggest important functions of the GDNF/RET signaling system in the maintenance of BBB and BNB integrity and function.

Microglial activation has been recognized as a major factor in the pathogenesis of several neurodegenerative diseases and has been implicated as a main source of inflammation contributing to the neuronal dysfunction and degeneration. Factors secreted by astrocytes have been shown to reduce the phagocytic activity and the production of reactive oxygen species by activated microglia. Further experiments established GDNF as one of the major astrocyte-derived components responsible for these effects (Rocha et al., 2012). These results indicate that GDNF may be an important regulator of microglial activation and suggest that GDNF may be able protect from neurodegeneration through the inhibition of neuroinflammation.

### 3.4. Stroke, epilepsy and Alzheimer's disease

A multitude of studies have investigated the effects of brain ischemia on the mRNA and protein expression of GDNF and its receptors. The consensus from a large body of literature supports the idea that both focal and global ischemia results in upregulation of GDNF protein levels by a transcriptional mechanism (reviewed in (Duarte et al., 2012)). Also the levels of GFRα1, but not RET, have been reported to increase after different ischemia paradigms (Duarte et al., 2012). The fact that GFRα1, but not RET, was found to be upregulated suggests trans-acting functions for the GFRα1 receptor, as previously documented in peripheral neurons (Ledda et al., 2002; Paratcha et al., 2001). Although many of those studies have interpreted the induction of GDNF and GFRα1 expression after ischemia as a sort of self-defense neuroregenerative reaction, the actual functional consequence of this endogenous response is unclear, given the current lack of loss-of-function studies in this area. On the other hand, many gain-of-function studies, using either local administration of purified protein, viral vectors or transplantation of GDNF-expressing cells, have documented neuroprotective effects of exogenous GDNF in different experimental models of focal and global brain ischemia (reviewed in (Duarte et al., 2012)). These treatments induced a number of neuroprotective effects, including reduction in infarct size and brain edema, as well as decrease in neuronal apoptosis in the penumbra region surrounding the core of the stroke. These effects may be a combination of direct anti-apoptotic actions, namely by promoting the survival of compromised neurons, and indirect effects, such as enhanced proliferation, migration or survival of neuronal precursors generated as a result of the insult (Kobayashi et al., 2006). Although the majority of studies have explored neuroprotective activities by administration of GDNF in advance of the ischemic insult, some studies were also able to show significant, albeit more modest, neuroprotection when GDNF was administered after the ischemic injury, typically within a relatively narrow window of up to 4–6 h post insult (Duarte et al., 2012). Thus, although the available evidence does support neuroprotective effects of GDNF in cerebral ischemia, the role of endogenous GDNF, the cellular mechanisms involved and the possible utility of GDNF or GDNF mimetics in the treatment of stroke remain relatively unexplored. Conditional alleles of the *Gdnf* gene may be useful in addressing possible endogenous neuroprotective functions of GDNF in stroke and ischemia. Such approach may also help elucidating the actual cellular targets of GDNF action in ischemia. Given that GDNF has been shown to exert effects in pericytes, endothelial cells and microglia, and may also affect BBB integrity and neuroinflammation (see previous section), it would seem important to investigate further these activities in the context of ischemia.

The involvement of the GDNF signaling system in epilepsy has been mainly studied from two different angles. The first one, more traditional, has focused on regulation of GDNF expression after epileptic seizures and possible neuroprotection from seizure-induced neuronal loss using gain-of-function approaches. Here, as in the case of stroke, several examples of GDNF upregulation after neuronal hyperactivation have been described (see for example (Reeben et al., 1998; Trupp et al., 1997)). However, administration of GDNF was shown to afford neuroprotection only in a subset of studies (e.g. (Martin et al., 1995)) but not others (e.g. (Kanter-Schlifke et al., 2009)), despite the fact that, in both cases, exogenous GDNF ameliorated seizure development. Differences in neuroprotection could have been due to the different experimental paradigms used to induce epilepsy and to alternative routes of GDNF administration. A second class of studies have focused on endogenous functions of GDNF and its receptors in network activity and seizure development using loss-of-function approaches. Due to its effects on GABAergic neuron development, defects in GFRα1 signaling lead to cortical hyperactivity and increased sensitivity to sub-threshold doses of epileptogenic agents (Canty et al., 2009). Although this result would be in agreement with gain-of-function studies that demonstrated anti-epileptic effects of exogenous GDNF administration, it stands in contrast to defects in signaling by the related receptor GFRα2, which have been shown to impair the development and persistence of kindling epilepsy (Nanobashvili et al., 2000). Although GDNF can also bind to GFRα2 (Trupp et al., 1998), this receptor displays higher affinity for the GDNF-related molecule neurturin (reviewed in (Airaksinen and Saarma, 2002)). This raises the intriguing possibility that two different, but structurally and functionally related, receptors in the GDNF family, namely GFRα1 and GFRα2, play opposed roles in neuronal activation and seizure development. More studies are needed to establish this, as well as its possible mechanistic basis. Although blockade of NCAM has also been shown to limit epileptogenesis and seizure-induced neurodegeneration (Duveau and Fritschy, 2010), it is not clear whether this effect is due to reduced GDNF signaling via NCAM.

Alzheimer's disease (AD) leads to progressive loss of cognitive function and dementia, and affects over 10% of people after 65 years of age. AD diagnosis can be difficult and may come too late for a majority of patients. Great efforts are being made on the identification of molecular biomarkers that could identify pre-symptomatic individuals with mild cognitive impairment who may eventually convert to AD. Intriguingly, a study of over 250 AD patients identified 18 signaling proteins in blood plasma, one of which was GDNF, that could be used to classify blinded samples from AD and control subjects with great accuracy (Ray et al., 2007). In this study, GDNF levels were found to be decreased in plasma of AD patients compared to controls. Whether GDNF is only a biomarker or also a factor with an active role in pathogenesis or disease progression is the key question here. It is not difficult to envision how a signaling molecule such as GDNF, with potent effects on neuronal maturation, cell survival, synapse formation and more, can affect cognitive functions and, if aberrantly or insufficiently expressed or secreted, contribute to cognitive decline. Given the complexities of AD pathogenesis, however, the difficulty at present is to narrow down potential processes for GDNF involvement. The ability of GDNF to prevent degeneration of noradrenergic neurons of the locus coeruleus (Arenas et al., 1995), a nucleus in the brain stem that declines during AD progression (Bondareff

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et al., 1982; Tomlinson et al., 1981), may have relevance in this context and could represent a potential entry point for further studies. A more recent report has offered a potentially more direct link by showing effects of GDNF on the release of the β-amyloid peptide, a major component of amyloid plaques in the AD brain, from human neuron-like cells, without increased expression of amyloid protein precursor (APP) or secretases (Scholz et al., 2013). RET knock-down in those cells diminished β-amyloid release, suggesting effects mediated by a tyrosine kinase signaling cascade. There are several mouse models of AD which could be crossed with mice deficient in GDNF or RET signaling. However, at present, no genetic studies have addressed the importance of endogenous GDNF, GFRα1 or RET in the development of AD phenotypes in such models.

### 3.5. Neuropsychiatric disorders

In this last section, we summarize results from a subset of studies that have investigated possible roles of GDNF and its receptors in a range of neuropsychiatric conditions, including addiction, anxiety, depression, obsessive-compulsory and bipolar disorders, autism and schizophrenia.

The prominent role of midbrain dopaminergic neurons in the circuits involved in addictive behaviors spurred interest in the possible involvement of GDNF and its receptors in addiction. Dopaminergic transmission regulates self-administration of drugs of abuse, and they in turn increase dopamine levels in striatum of rodents and humans. The first study linking GDNF signaling with addiction reported that GDNF infusion into the ventral segmental area (VTA) of the midbrain suppressed the effects of prolonged cocaine administration, including several biochemical and behavioral adaptations to drug intake (Messer et al., 2000). Both cocaine and amphetamines have also been reported to modulate GDNF expression and downstream signaling, although the results of different studies vary depending on whether acute or chronic effects of drug intake are being examined (reviewed in (Carnicella and Ron, 2009)). A role for endogenous GDNF in the regulation of addictive behavior is suggested by studies with anti-GDNF blocking antibodies and mutant mice heterozygous for a null allele of the *Gdnf* gene which displayed increased sensitivity to the rewarding effect of cocaine and methamphetamine (Carnicella and Ron, 2009). Several studies have now established GDNF as an endogenous negative regulator of a range of biochemical and behavioral adaptations to psychostimulants. Although it was initially reported that GDNF does not contribute to the mechanisms that enhance locomotor activity in response to ethanol (Carnicella et al., 2009), a recent study showed that GDNF hypermorphic mice run more than wild type controls after amphetamine injection (Kumar et al., 2015). GDNF has also been found to suppress the action of other drugs, including opioids and ethanol. Exogenous GDNF administration has been shown to rapidly repress excessive consumption of ethanol, but endogenously produced GDNF would appear to be relevant for controlling ethanol drinking behaviors only after a period of abstinence (Carnicella et al., 2008). Further studies using conditional mouse mutants, lacking GDNF in selective areas of the brain thus by-passing the early lethality of null global mutants, will be required to establish the precise role of endogenous GDNF in addictive behaviors. Unfortunately, the mechanisms by which GDNF counters the rewarding value and neuroadaptations induced by psychostimulants are unknown. Clearly, given the known range of GDNF bioactivities, synaptic remodeling and changes in synaptic responses could result in alterations in midbrain dopaminergic circuits which ultimately influence addictive behaviors. Specifically, the effects of GDNF signaling on the regulation of DAT activity, as discussed earlier, are worth investigating further in the context of addiction.

Interest in a possible role of GDNF in anxiety and depression stemmed from the discovery of associations between a subset of polymorphisms in the *Gdnf* gene and these conditions. Association of two *Gdnf* gene variants with anxiety, but not with depression, in humans was reported in one recent study (Kotyuk et al., 2013), while another study of Chinese individuals did find an association between a different *Gdnf* gene variant and depression risk (Ma et al., 2013). A separate line of enquiry has examined possible correlations between plasma or serum GDNF levels and depression scores in different groups of patients of varied ethnical origins. Despite some variable results, the majority of these studies performed so far agree that circulating GDNF levels are significantly decreased in patients with depression (e.g. (Diniz et al., 2012; Tseng et al., 2013)), including one recent meta-analysis of over 500 patients (Lin and Tseng, 2015). It should be noted that at least one earlier study reported increased plasma GDNF levels in late-onset depression (Wang et al., 2011). One more recent study found no difference in plasma GDNF between patients with major depressive disorders and controls at baseline, but reported significantly lower levels patients showing recurrent depression episodes than in first-episode patients independently of treatment (Lee et al., 2015). Although GDNF has been suggested as a possible anti-depressant agent, intra-cerebroventricular administration of GDNF failed to produce an antidepressant effect in a mouse strain genetically predisposed to depressive-like behavior, despite alterations in several components of serotonin synthesis and signaling (Naumenko et al., 2013). Moreover, the role of endogenous GDNF in anxiety and depression behaviors, if any, is not understood. Treatment of mice with the anti-depressant fluoxetine was shown to elevate endogenous GDNF protein and mRNA levels in total brain extracts and hippocampus (Ubhi et al., 2012), although the relevance of these observations is unclear. Together, studies so far appear to indicate a possible diagnostic value of plasma GDNF levels in depression, but whether GDNF may play a role in the development, progression or treatment of this and related mood disorders is unclear at the moment.

A recent study found significantly elevated serum GDNF levels during the manic phase of patients with bipolar disorder (BD) (Tunca et al., 2015), a result that would be in agreement with data from patients with depression syndrome (see above). The same study found a positive correlation between GDNF levels and usage of antidepressants in patients with obsessive compulsive disorder (OCD), which is also in agreement with an earlier OCD study (Fontenelle et al., 2012). However, as indicated earlier, not all BD studies agree, and one from 2011 found in fact lower levels of circulating GDNF in BD patients in mania compared to euthymia, the relatively stable mood state in BD (Barbosa et al., 2011).

An earlier study examining associations between polymorphisms in several genes encoding neurotrophic factors, including *GDNF*, and incidence of attention deficit hyperactivity disorder (ADHD) found no strong correlation with *GDNF* gene variants (Syed et al., 2007). A later study, however, found increased levels of plasma GDNF in a cohort of 86 ADHD children compared to healthy controls (Shim et al., 2015). Also recently, a *GDNF* polymorphism was found to be significantly associated with Tourette syndrome (Huertas-Fernández et al., 2015), a disorder frequently accompanied by ADHD and OCD as comorbidities. An early study reported an association between a polymorphism in the gene encoding GFRα1 and the incidence of schizophrenia (Moises et al., 2002). Moreover, the *GDNF* gene is located within a region in chromosome 5 which has been indicated as a potential schizophrenia susceptibility locus by genome scans (Suarez et al., 2006). However, a more recent analysis of polymorphisms in the *GDNF* gene failed to find any association with this syndrome (Williams et al., 2007). More recently, serum GDNF levels were studied in several affected patients and found to be significantly increased in schizophrenics compared to controls (Tunca et al., 2015). Given the known roles of GDNF in the maturation and allocation of cortical GABAergic interneurons, as reviewed above, a possible role of GDNF in such disorders could be due to alterations in one or several of these types neurons, including parvalbumin interneurons (Canty et al., 2009). Alterations in this class of interneurons have been linked to a number of cognitive disorders, including TS, ADHD and autism (e.g. (Gant et al., 2009; Kalanithi et al., 2005; Wöhr et al., 2015)) as well as schizophrenia (e.g. (Gant et al., 2009; Lodge et al., 2009; Sakai et al., 2008b)).

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## 4. Conclusions and future directions

Although GDNF was initially discovered as a neurotrophic factor for midbrain dopaminergic neurons, and most of the research effort has so far concentrated in understanding its functions in the nigrostriatal system, there are still many important questions that need to be resolved in this "classical" area of GDNF research before we have a level of understanding that can be safely and efficiently translated into clinical practices. With regards to the development and adult function of the brain dopaminergic system, we now understand that elevation of GDNF signaling at its normal sites of expression is sufficient to enhance neuron survival and function. Whether endogenous GDNF is required for these functions is still unclear. Although it would appear, from the majority of studies performed to date, that endogenous GDNF/RET signaling is not necessary for the development and initial maintenance of midbrain dopaminergic neurons, it can indeed exert important regulatory effects on the function and injury responses of these neurons, as demonstrated by its effects on DAT activity, cocaine sensitivity and neuroprotection upon loss of Parkin in adult animals. If it turns out that GDNF mainly affects adult dopaminergic neuron function and injury responses, the question then arises as to why RET and GFRα1 are already expressed at embryonic stages of development in these neurons. From a therapeutic perspective, the recent demonstration of neuroprotective effects in a PD model after increased expression of GDNF from endogenous sites, without many of the side effects observed following ectopic GDNF administration, is encouraging. The future challenge here will be to devise strategies to elevate endogenous GDNF expression by means other than genetic manipulation. In this regard, evidence demonstrating beneficial effects of physical activity in PD (Borrione, 2014) as well as upregulation of GDNF expression after exercise (Cohen et al., 2003) is intriguing and deserves further attention.

In view of the neuroprotective effects of GDNF in cerebral ischemia, the function of GDNF on the cellular components of the BBB needs to be characterized more thoroughly. Such understanding may open more effective avenues for GDNF based therapies in stroke and ischemic damage. The observation that GDNF levels in serum or plasma are decreased in AD patients, if confirmed by further studies, is interesting, not only from a more immediate diagnostic perspective, but also for development of novel therapeutic strategies in the longer term. As noted earlier, however, this will require considerably more work. Based on initial observations, further characterization of the role of GDNF and RET signaling in β-amyloid release in primary neurons would seem like a good point of entry in this research. The current availability of improved lines of mice with mutations in the *Gdnf*, *Gfra1* and *Ret* genes, together with the many AD mouse models already developed, could also offer a good opportunity to test a possible role for GDNF signaling in AD pathophysiology. Finally, the emerging role of GDNF and GFRα1 in the development and allocation of forebrain GABAergic neurons provides a good conceptual basis from which to explore possible roles for these proteins in several neuropsychiatric conditions, such as depression, autism and schizophrenia, for which an indirect link with GDNF has been established through genetic linkage or protein levels in plasma. More direct investigations using loss- and gain-of-function approaches will be constrained by the limitations of the available animal models for these rather complex syndromes. For studies of depression, investigating in greater detail the responses to anti-depressants, such as fluoxetine, in hypo and hypermorphic mutants of GDNF signaling components may offer some insights into their possible functions. A genetic mouse model of Tourette syndrome (Godar et al., 2014) could also represent a valuable tool to approach the role of the GDNF system in ADHD and OCD.

In this article, we have attempted to summarize our current knowledge of the physiological activities of GDNF and its receptors in the central nervous system, with special attention to neurodegenerative and neuropsychiatric diseases. Overall, the field has matured considerably since the initial characterization of molecular components and basic functions. Progress has been particularly substantial in the elucidation of GDNF actions in the brain dopaminergic system. However, despite much effort, we still have an incomplete understanding of why endogenous GDNF is there and for what purpose. The last decade has been marked by a considerable expansion of the field and the realization that GDNF has many other functions outside the nigrostriatal system. The future challenge here lies in increasing our mechanistic understanding of the many so far correlative observations. A common challenge for the future of all GDNF research will be to harness this basic knowledge for the design of better therapies.

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