Therapeutic potential of glial cell line-derived neurotrophic factor and cell reprogramming for hippocampal-related neurological disorders

Overview

Functional neurological disorders such as Alzheimer’s disease (AD), epilepsy, and depression are related to hippocampal dysfunction. In this context, research and development of novel therapeutic tools like gene therapy and cell reprogramming strategies may open new avenues for the treatment of these devastating pathologies. Since glial cell line-derived neurotrophic factor (GDNF) remains a valuable therapeutic gene in the hippocampus, we summarized the role of this molecule in the pathophysiology of these diseases. We highlighted the most salient reports focusing on GDNF gene therapy as a neuroprotective strategy for hippocampal dysfunction. In order to potentiate GDNF gene therapy and cell reprogramming for neurological diseases by combining them in the future, we have revised and updated the studies reporting the regenerative effects of cell reprogramming in the brain, which is a novel and promising approach.

Search Strategy and Selection Criteria

Studies cited in this review published from 1962 to 2020 were searched on the https://pubmed.ncbi.nlm.nih.gov database using the following keywords: GDNF, aging, Alzheimer’s disease, epilepsy, depression, gene therapy, cell reprogramming, Yamanaka genes.

Role of Glial Cell Line-Derived Neurotrophic Factor in Aging and Hippocampal-Related Neurological Disorders

GDNF biology

GDNF was identified and purified from the B49 glioma cell line based on its ability to promote survival, neurite outgrowth, cell size, and dopamine uptake of dopaminergic neurons in dissociated rat mesencephalic cultures (Lin et al., 1993). GDNF is the founding member of the GDNF family of neurotrophic factors, which additionally includes three other structurally related members: neurturin, persephin, and artemin (Kotzbauer et al., 1996; Baloh et al., 1998; Milbrandt et al., 1998). The members of the GDNF family belong to the transforming growth factor beta superfamily. GDNF is active as a glycosylated disulfide-bonded homodimer, which triggers a signal through a multicomponent receptor complex containing the transmembrane RET tyrosine kinase and the GDNF family receptor α (GFRα) (Durbec et al., 1996; Trupp et al., 1999). Four GFRα-like receptors have been identified (i.e., GFRα1 to 4), each with different selectivity and specificity for each of the four members of the GDNF neurotrophic family. The GDNF/GFRα1/RET triggers both the Ras/MAP kinase and phosphoinositide 3-kinase/AKT tyrosine kinase pathways (Ibáñez, 2013). The anchoring to the plasma membrane of these receptors depends on lipid linkage, GPI-anchor partition...
into lipid rafts, which modulates the intensity and duration of RET signaling (Paratcha and Ibanez, 2002). In addition, GFRα receptors can become independent of RET and act in a soluble form (trans-signaling) when cleaved from the plasma membrane by phospholipases (Paratcha et al., 2001). The third member of this multi-component receptor is the neural cell adhesion molecule which signals the activation of Src-like and MAP kinases (Paratcha et al., 2003). Moreover, Syndecan-3 has been described as an alternative signaling receptor of GDNF in the brain without the involvement of the conventional ones mentioned above. The Syndecan-3 chains binding to heparan sulfate activate Src family kinases (Bespalov et al., 2011).

The GDNF family of neurotrophic factors and its receptors constitute one of the main neurotrophic networks of the CNS. Although the GDNF family has been focus mostly on the midbrain of Parkinson's disease animal models, new research has been diverting towards other brain regions such as the hippocampus and its neurological disorders summarized as follows.

**Impact of aging on GDNF expression in the hippocampus**

Aging is the main risk factor for neurodegenerative disorders. In the rat hippocampus, it may result in decreased neurogenesis, increased astrogliosis and reactive microglia (Morel et al., 2015; Pardo et al., 2017).

In murine models, it has been reported that GDNF is reduced in the cerebral cortex of aged mice (Lee et al., 2000) as well as in the hippocampus of the senescence-accelerated mouse brain (Miyazaki et al., 2003). However, in 6–13-month-old Fischer 344 rats, GDNF expression level significantly increased in the frontal cortex, but no significant change was observed in the hippocampus (Matsunaga et al., 2006). In humans, it has been reported a decrease in the expression levels of GDNF in plasma from patients with mild cognitive impairment (Siegel et al., 2000).

**GDNF role in cognition**

GDNF and its receptors are expressed within the temporal lobe, particularly in the pyramidal and granule cells of the hippocampus. However, in the normal mature brain GDNF is mainly produced in neurons (Marco et al., 2002). GDNF and GFRα-1 are expressed in both neurons and astrocytes (Nicole et al., 2001). The GFRα1 synaptic localization was determined in neuronal cell cultures, indicating the role of GDNF/GFRα1 in synapse formation (Ledda et al., 2007).

The suggestion that endogenous GDNF may be critical for cognitive abilities derives from a study in mice subjected to a deletion of the GDNF gene. These animals showed a reduction in GDNF mRNA and selective impairment of their performance in the spatial memory in the Morris water maze (Gerlai et al., 2001).

A recent study performed in conditional mutant mice lacking GFRα1 in the newborn granular cell population demonstrated significant pattern separation impairment compared to the control group. This mnemonic impairment could be explained by the deficit observed in dendrite outgrowth and the lack of mature spines, which would lead to an altered integration of newborn hippocampal cells (Bonafina et al., 2019).

A first genetic study demonstrated that the lack of function of GFRα2 in mice resulted in significant impairment in the performance of the animals in three different tests of learning and memory. The mutant mice exhibited reduced contextual memory and context discrimination in contextual fear conditioning and showed impaired behavioral flexibility in spatial learning, and decreased retention of conditioned taste aversion memory tests (Volikar et al., 2004). These findings demonstrated that GDNF and GFRα family receptors play a crucial role in cognition and compromise the hippocampal integrity on neurodegenerative diseases associated with cognitive decline (Scheff et al., 2006; McKinnon et al., 2009). We summarized the most relevant findings of GDNF role in AD, epilepsy, and major depressive disorders.

**Alzheimer’s disease**

AD, a neurodegenerative pathology with high prevalence and morbidity is accompanied by progressive memory deficit, cognitive impairment, and dementia (Querfurth and LaFerla, 2010). At the molecular level, AD is characterized by extracellular deposition of amyloid beta (Aβ), the formation of neurofibrillary tangles, and tau hyperphosphorylation. Neurodegeneration involves selective neuronal death into vulnerable brain regions, in particular the hippocampus and cerebral cortex, where apoptosis may play a role in the process (Honig and Rosenberg, 2000).

At present, there are no effective therapies to reverse its progression. Thus, efforts center on searching molecules as clinical markers for early detection or therapeutic strategies. In line with this, clinical studies reveal that GDNF level increased in cerebrospinal fluid and its serum concentration decreased in the early stages of AD (Straten et al., 2011). Another study found increased GDNF levels in plasma of AD patients (Markstainer et al., 2011). Nevertheless, in the postmortem middle temporal gyrus of AD patients, it was found that the expression pattern of novel human GDNF isoforms was down-regulated (Airavaara et al., 2011). In the same line, a study found the serum GDNF levels significantly reduced in mild cognitive impairment and AD patients (Forlenza et al., 2015).

**Temporal lobe epilepsy**

The most common epilepsies in adults originate focally in structures such as hippocampus, EC, or amygdala and are named temporal lobe epilepsies (TLE) (Yilmazer-Hanke et al., 2000; Lévesque et al., 2013). The hippocampal Cornus Ammonis (CA) region and the dentate gyrus (DG) are involved in seizure generation and hippocampal sclerosis (Reyes-Garcia et al., 2018). Induction of an epileptic status with kainic acid (KA) or pilocarpine produces spontaneous seizures that continue for the rest of the animal's life. Epileptic rodents show permanent neuronal loss and synaptic reorganization in the hippocampus, similar to those of patients with TLE. One of the plastic changes is related to an increase in neurogenesis in DG, but these new neurons present aberrant network reorganization (Benzon et al., 1997; Parent et al., 1997).

On the other hand, kindling also induces structural changes in the brain that can be permanent, such as the sprouting of the DG Mossy fiber pathway and astrocyte hypertrophy with an accompanying increase in hilar volume in the DG (Cavazos et al., 1990, 1991, 1994; Adams et al., 1997, 1998).

Brain damage in animal models of epilepsy generates a rapid cellular response traduced in both immediate early genes and neurotrophic factors genes expression (Sperk et al., 1994).

An association between GDNF expression in the hippocampus and epilepsy is suggested by the observation that seizures increase the levels of GDNF mRNA and protein (Humpel et al., 1994; Kokaia et al., 1999) and by the fact that seizures can be suppressed by local overexpression of GDNF into the hippocampus (Yoo et al., 2006; Kaner-Schliffe et al., 2007, 2009). A recent finding on the contribution of miRNAs to the pathophysiology of epilepsy demonstrated that GDNF is silenced by miR-451 in a KA model causing neuronal damage. Moreover, GDNF overexpression contrasts miR-451 effect (Weng et al., 2020).

**Mood disorders**

Mood disorders are a group of psychiatric illnesses that can...
Gene therapy has undergone a remarkable advance in the improvement of gene delivery and expression as well as in safety, cell-type specificity, and regulability by small molecules (Zhang et al., 2012; Simonato et al., 2013). Gene transfer to the CNS has significant challenges due to the relative inaccessibility of both the brain and spinal cord. A relevant obstacle is the blood-brain barrier (BBB), which prevents gene vectors from reaching their therapeutic targets within the CNS. There are some approaches to overcome this problem; one of them is the use of osmotic solutions to disrupt of the BBB. Currently, Mannitol solutions disrupt the BBB transiently and reversibly (Zhang et al., 2012; Simonato et al., 2013). Gene transfer to the brain due to the presence of a tetracycline analog, doxycycline (DOX) (Coll et al., 2020). In vivo gene therapy (e.g., injection in the coordinates of CA1 dorsal hippocampus; Figure 1), gene expression silencing is achieved by means of a non-invasive procedure, addition to or removal of DOX from the drinking water. Indeed, a safer and more sophisticated approach would be to construct a helper-dependent adeno viral vector harboring GDNF and GFP genes. Viral vectors commonly used are: helper-dependent adenoviral, adeno-associated, retroviral and herpes-derived vectors, which have specific advantages such as the large size of the gene insert they can accommodate, a wide variety of cells they can transduce, and an extended duration of transgene expression (Simonato et al., 2013).

In line with this, we engineered a regulatable Tet-off system which consists in two adenovectors: the first adenovector harbors the cDNA for rat GDNF and the Aequorea victoria Green Fluorescent Protein (GFP) controlled by murine Cytomegalovirus promoter. The second adenovector harbors the tetracycline transactivator protein gene controlled by the murine Cytomegalovirus promoter, which represses gene expression conditioned by the presence of a tetracycline analog, doxycycline (DOX) (Coll et al., 2020). Regulating in vivo gene therapy (e.g., injection in the coordinates of CA1 dorsal hippocampus; Figure 1), gene expression silencing is achieved by means of a non-invasive procedure, addition to or removal of DOX from the drinking water. Indeed, a safer and more sophisticated approach would be to construct a helper-dependent adeno viral vector harboring GDNF and GFP genes under the tetracycline regulatory system (Lehmann et al., 2019).

Gene Therapy with Glial Cell-Line-Derived Neurotrophic Factor for Neurological Disorders

Gene therapy concepts and upgrade

Gene therapy has undergone a remarkable advance in the improvement of gene delivery and expression as well as in safety, cell-type specificity, and regulability by small molecules (Zhang et al., 2012; Simonato et al., 2013). Gene transfer to the CNS has significant challenges due to the relative inaccessibility of both the brain and spinal cord. A relevant obstacle is the blood-brain barrier (BBB), which prevents gene vectors from reaching their therapeutic targets within the CNS. There are some approaches to overcome this problem; one of them is the use of osmotic solutions to disrupt of the BBB. Currently, Mannitol solutions disrupt the BBB transiently and reversibly by shrinking endothelial cells and opening the tight junctions (Cosolo et al., 1989). Another approach consists of intranasal delivery, which provides direct absorption of the molecules through the trigeminal and olfactory pathways from the nasal cavity. This possesses the advantage of the direct entrance, low doses, and rapid action in the brain (Erd et al., 2018).

On the other hand, gene therapy offers unique advantages for the long-term delivery of neurotrophic factors to specific CNS regions affected by neurodegenerative processes. Non-viral gene delivery vehicles, such as naked DNA, RNA, liposomes, and nanoparticles, can harbor large cargo and possess lower costs than viral systems. Approaching ex-vivo encapsulated cell biodelivery (ECB) of a therapeutic agent has so far achieved only low levels of therapeutic gene expression during short periods (Fjord-Larsen et al., 2012; Tornøe et al., 2012; Emerich et al., 2014). ECB consists of therapeutic cells encapsulated in a polymer membrane, which has the advantage that the pores in the membrane are large enough to allow the therapeutic agent to diffuse into the surrounding tissue but small enough to protect the cells against immune response. ECB is safe to perform in vivo gene therapy in the brain due to the advantage of retrievability. A large number of genetically modified viruses have proven to efficiently transduce host cells with the therapeutic gene they harbor. Viral vectors commonly used are: helper-dependent adeno viral, adeno-associated, retroviral and herpes-derived vectors, which have specific advantages such as the large size of the gene insert they can accommodate, a wide variety of cells they can transduce, and an extended duration of transgene expression (Simonato et al., 2013).

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Figure 1 | In vivo silencing of regulatable two-vector system in the rat hippocampus.

(A) Microphotography of a single pyramidal neuron in the CA1 pyramidal layer transduced with the recombinant adeno viral vector harboring green fluorescent protein. (B) Hippocampal coronal section from a rat injected with the regulatable two-vector system. Notice that absence of transduced cells in the CA1 pyramidal layer. The addition of DOX in the drinking water represses GFP expression. Unpublished data.

GDNF against age-related cognitive deficit

The first therapeutic report was performed in aged-impared Fisher 344 rats, and it comes from the intracerebroventricular administration of the GDNF peptide that significantly improved spatial learning in the cue version of Morris water maze (Pelleymonter et al., 1999).

Afterthought, GDNF was infused in the striatum of 2-month-old Sprague-Dawley rats for 28 days. In this work, new cells were identified by light and electron microscopic immuno staining. GDNF significantly increased cell proliferation in the hippocampus by 78%, showing evidence that this molecule increased neurogenesis in the hippocampus of adult rats (Chen et al., 2005).
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The first gene therapy approach derives from an injection of a lentiviral vector harboring GDNF gene in the CA1 dorsal hippocampus of aged-impaired Fisher 344 rats. The over-expression of GDNF in hippocampal astrocytes improved spatial cognitive performance demonstrated by an enhancement of memory retention of the platform location in the test probe trials (Pertusa et al., 2008).

GDNF treatment in animal models of Alzheimer’s disease
One of the first studies, performed in a rabbit model of AD induced by aluminum complexes, showed that the GDNF administration can protect against AD-like chances (Ghirbi et al., 2001). A recent report in a 7-month-old transgenic mouse model of AD (3xTgAD) has shown that GDNF was down-regulated and this condition was reverted after 6 months of voluntary exercise (Revilla et al., 2014a). Additionally, it has been reported that GDNF gene therapy using a lentiviral vector in 10-month-old 3xTg-AD mice for 6 months showed an improvement in learning and memory (Revilla et al., 2014b).

Another gene therapy approach, Kanter-Schlifke and collaborators used a recombinant adenovirus-associated viral (rAAV) vector-based GDNF. Researchers showed that GDNF suppresses seizures in two models of TLE. First, when rAAV-GDNF was injected prior to hippocampal kindling, the number of generalized seizures decreased, and the prolongation of behavioral convulsions in fully kindled animals was prevented. Second, injection of rAAV-GDNF after kindling increased the seizure-induction threshold. Finally, rAAV-GDNF decreased the frequency of generalized seizures during the self-sustained phase of status epilepticus (Kanter-Schlifke et al., 2007). In a subsequent study in rats, ex-ovo gene therapy employing ECB devices containing genetically modified cells that can release GDNF showed seizure suppression in the hippocampus of kindled rats. However, the optimization of the amount of GDNF released by ECB devices seems to be essential to obtain an antiepileptic effect, with a moderate increase in delivered GDNF levels appearing to be more beneficial (Kanter-Schlifke et al., 2009).

Another approach using ECB-GDNF implanted unilaterally into the seizure focus in the hippocampus of KA epileptic rats effectively decreased the number of spontaneous and recurrent seizures in epileptic rats (Nanobashvili et al., 2018).

Finally, long-term gene therapy with ECB-GDNF implanted directly into the hippocampus of pilocarpine-induced epileptic rats revealed that GDNF reduced seizure frequency by 75% within 2 weeks after treatment and by 93% after 3 months of treatment (Paolone et al., 2019).

Cell Reprogramming for Neurological Disorders

Epigenetics and cell reprogramming
Epigenetic marks refer to changes in gene expression due to reversible covalent modifications without altering the DNA sequence. They can be transmitted to the next generation but are susceptible to environmental modifications, explaining the clinical heterogeneity which confronts traditional genetics (Wu et al., 2001; Urdinguio et al., 2009). These epigenetic marks regulate DNA replication, gene expression, and DNA damage responses in not only physiological but also pathological conditions (Portela et al., 2010).

Cell reprogramming is the conversion of cells from one identity to another. For a long time, cell fate was considered irreversibly determined. It used to be explained by Waddington’s epigenetic landscape, in which pluripotent cells were found on top of a hill and descended irreversibly into a valley, which represented their differentiation, an energetically stable state from which they were not able to escape.

In 1960, the first finding challenging this dogma emerged, when John Gurdon achieved the development of a complete organism by inserting the nucleus of a tadpole gut cell into UV-enucleated eggs (Gurdon, 1962). This study and others indicated that cell fate was reversible, and that the cellular nucleus in more late stages of development retained the information necessary to directly develop the different cell types of an individual (Davis et al., 1987; Campbell et al., 1996).

In 2006, Yamanaka and Takahashi overexpressed the Oct-4, cMyc, Klf-4, and Sox2 transcription factors, now also known as Yamanaka factors, in mouse fibroblasts (Takahashi and Yamanaka, 2006; Lehmann et al., 2019). These cells acquired the phenotype of blastocyst-like cells and were named induced pluripotent stem cells (iPSC). From an iPSC, they could be differentiated into any type of cell of any tissue belonging to the three germ layers of a natural embryo. Since then, iPSCs have established cell reprogramming as a strategy with considerable potential for the diagnosis and therapy of different diseases, including those in the field of neurodegeneration.

Cell reprogramming for the treatment of Alzheimer’s disease
In 2009, transplantation of neural precursors into a rat model of AD had been shown to promote improvements in the animal’s behavior. With the advent of iPSC technology, the possibility of using neural stem cells derived from iPSCs as cell therapy in brain-related diseases arose (Moghadam et al., 2009; Tincer et al., 2016). Since then, various approaches have been developed to obtain induced neural stem cells, which are promising cells since they give rise to different neuronal and glial cell types, in addition to being expandable in vitro by several passages.

One strategy used to obtain neural precursors was the pluripotency factor-mediated direct reprogramming, in which pluripotency genes are expressed transiently, by manipulating the epigenetically unstable state of cells and leading it towards the phenotype, in this case, of neural precursors (Kim et al., 2011; Winiecka-Klimek et al., 2015; Capetian et al., 2016; Connor et al., 2018). Other emerged strategies can be encompassed in transdifferentiation, in which neural precursors were obtained by direct differentiation of fibroblasts through specific transcription factors or miRNAs (Lujan et al., 2012; Yang et al., 2017).

Cell reprogramming to patient-specific cells of interest allows the study of the cellular phenotype of diseases that otherwise would be inaccessible. Through in vitro modeling, it is hoped to achieve the development of specific drugs for their treatment (Mertens et al., 2016).

In 2011, induced neuronal cells were obtained from the transdifferentiation of human fibroblasts with the transcription factors Bnn2, Ascl1, and Myt1 in combination with the factor NEUROD1. These cells possessed the morphology of mature neuronal cells (Pang et al., 2011).

More specifically in Alzheimer’s modeling, skin fibroblasts from patients with familial AD have been converted to induced neuronal cell through a cocktail of seven chemicals, obtaining the same morphology, electrophysiology, and gene expression
Potential of cell reprogramming for the treatment of epilepsy and major depression disorder

It is reasonable to believe that dysregulation of the epigenome would have a significant role in neurological disorders such as TLE and MDD. The reversibility of these changes opens a range of therapeutic possibilities. Over the past two decades, artificial transcription factors have been developed by fusing a DNA-binding domain to one or more effector domains to allow gene activation and repression (Falahi et al., 2015). The first effector domain was generated by the binding of zinc finger modules (ZF), potentially targeting unique genes by incorporating six ZF that can bind to the 18 base-pair (bp) genomic location (Pavletich et al., 1991).

Researchers have been focused primarily on those transcription factors that can control the genes that drive circuit excitability, seizures, and epilepsy. In line with this, a transcription factor, repressor element silencing transcription factor 1 (REST), has been characterized. REST is strongly induced in the hippocampus in both kainate and pilocarpine models of TLE (Palm et al., 1998). This factor orchestrates many genes known to be involved in neuronal excitability (Roopra et al., 2001).

Regarding MDD, a recent study has implemented selective chromatin remodeling in a region involved in controlling the molecular and behavioral effects of exposure to drugs and stress. The FosB locus was targeted for its role in the pathophysiology of drug addiction and depression in the nucleus accumbens in both rodents and humans. ZF has been engineered to recognize DNA-binding domain to a given catalytic site, which allows gene-targeted transcriptional regulation at a locus of interest. Based on this result, it selectively activated the FosB gene in mouse nucleus accumbens with a Herpes Simplex viral vector, thus mimicking this unique pathological modification of histone in depressed humans. Animals were studied under the paradigm of chronic social defeat stress. The results showed that Herpes Simplex viral vector-injected mice showed a depressive-like behavior (Heller et al., 2014). In the same way, Sun et al. (2015) demonstrated that the ATP-dependent chromatin remodeling can be a novel therapeutic target in depressed patients to mediate depressive-like behavior. These results represent a promising area of research in the treatment of patients with MDD.

Conclusion

The described studies indicate that neurological disorders, including AD, epilepsy, and MDD, are complex multifactorial processes that include chronic alterations in the structure and function of neural circuitry. GDNF and its GFRα family receptors play a crucial role in cognition including spatial memory retention and pattern separation, two behavioral traits associated with hippocampal dysfunction during aging and AD. On the other hand, the strategy of locally increasing GDNF levels in the hippocampus could represent a possible way of suppressing status epilepticus in TLE and diminish symptoms in MDD.

GDNF gene therapy in the hippocampus has the potential to benefit these disorders by increasing GDNF levels and promoting a healthy neuron environment and neural plasticity. In line with this, the ability to regulate transgene expression to the newly engineered vectors as the adeno viral-based one or ECB could constitute a significant advantage for long-term treatments, or for those approaches circumscribed to a temporary window of expression.

Cell reprogramming emerges as a potentially effective strategy to attenuate age-related dysfunctions in the central nervous system, including neurodegenerative diseases.
Moreover, epigenome remodeling shows enormous potential as an innovative therapeutic approach to treat many human diseases, including TLE and MDD.

It is expected that in the coming years, cell reprogramming makes it possible to implement personalized regenerative medicine for neurological disorders.

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