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Review

Glial Cell Line-derived Neurotrophic Factor (GDNF) Therapy for Parkinson's Disease

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Many studies using animals clarify that glial cell line-derived neurotrophic factor (GDNF) has strong neuroprotective and neurorestorative effects on dopaminergic neurons. Several pilot studies clarified the validity of continuous intraputaminal GDNF infusion to patients with Parkinson's disease (PD), although a randomized controlled trial of GDNF therapy published in 2006 resulted in negative outcomes, and controversy remains about the efficacy and safety of the treatment. For a decade, our laboratory has investigated the efficacy and the most appropriate method of GDNF administration using animals, and consequently we have obtained some solid data that correspond to the results of clinical trials. In this review, we present an outline of our studies and other key studies related to GDNF, the current state of the research, problems to be overcome, and predictions regarding the use of GDNF therapy for PD in the future.

Key words: cell transplantation, clinical trial, encapsulation, gene therapy, neurodegenerative disease

Parkinson's disease (PD) is characterized by the degeneration of dopaminergic neurons in the nigrostriatal system [1, 2]. The established treatment for PD is oral L-DOPA [3, 4] and stereotaxic surgeries such as deep brain stimulation [5]. In Europe and the United States, fetal nigral cell transplantation has also been performed in PD patients. However, after 2 randomized clinical trials revealed insufficient functional recovery in older patients and delayed dyskinesia in some patients [6, 7], the momentum for exploring a new therapy for PD using stem cells or neurotrophic/growth factor increased. Stem cell therapy might be the most useful therapeutic option for PD, because recent molecular/cell biological development enables us to make dopaminergic neurons from embryonic stem cells [8] or mesenchymal stem cells [9]. However, there are many problems in terms of safety and efficiency as well as ethical issues to be resolved; these problems should be overcome before this therapy is clinically applied. Neurotrophic/growth factor might also be useful for PD. Since Dr. Lin and her colleagues isolated glial cell line-derived neurotrophic factor (GDNF) and demonstrated that GDNF enhances the survival and morphological differentiation of dopaminergic neurons [10], many laboratory studies have examined GDNF therapy as a treatment for various diseases of the central nervous system (CNS), including stroke [11], spinal cord injury [12], traumatic brain injury [13] and neurodegenerative diseases, such as PD [14, 15] and amyotrophic lateral sclerosis (ALS) [16].

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GDNF is considered to be one of the strongest neuroprotectants for dopaminergic neurons. Based on the successful results of animal experiments, clinical trials were performed for PD patients using GDNF. In this review, recent findings with regard to GDNF therapy are described, as is the current status of GDNF therapy for PD patients.

Therapeutic Effects of GDNF on PD Model of Animals

Mechanisms of GDNF therapy. GDNF, a member of the transforming growth factor β [10], is known to demonstrate neuroprotective and neurorestorative effects on dopaminergic neurons [17–20] through a heterodimetric receptor complex consisting of a transmembrane receptor tyrosine kinase, Ret, and the ligand binding component GDNF-family receptor α1 (GFRα1) [21, 22]. Cell survival/death decisions are determined in part through the activation of a specific intracellular signaling cascade, such as the phosphatidylinositide 3 kinase pathway and the mitogen-activated protein kinase pathway [21, 23].

Key experiments using GDNF for PD model of animals. Dr. Hebb and his colleagues demonstrated that GDNF enhanced the survival of fetal rat dopaminergic neurons for the purpose of transplantation [18]. GDNF therapy by ventricular infusion using an osmotic minipump suppressed the neuronal degeneration induced by 6-OHDA [19, 24]. *In vivo* gene delivery of GDNF was also a feasible neuroprotective strategy for PD [20]. Recently the importance of transplanted cells as neurotrophic/growth factor suppliers has been re-evaluated [25]. Similarly, GDNF secreted by transplanted cells is considered to be one of the reasons that therapeutic effects are achieved by cell transplantation [26, 27]. Our group demonstrated that the implantation of encapsulated GDNF-secreting cells into 6-OHDA-lesioned striatum resulted in protective effects on dopaminergic neurons [28–30]. Rats receiving an implantation of GDNF-secreting cells at 2 weeks after 6-OHDA lesions were induced showed more neurorestorative effects compared to those receiving the implantation 4 weeks after 6-OHDA lesions were induced [29]. After this study was completed, we performed a new experiment using earlier timing for the implantation; that is, the implantation was performed simultaneously with and at 1, 2, and 4 weeks after the 6-OHDA lesions were induced, with GFRα1 expression in the striatum and substantia nigra being evaluated at 1 and 2 weeks after the 6-OHDA lesions were induced [30]. In the study, the earlier implantation of GDNF resulted in a more improved behavioral score and better preserved dopaminergic neurons with a higher expression level of GFRα1 [30], thus revealing that GDNF-responsive fibers and neurons are necessary for GDNF therapy.

Advantages of GDNF therapy using encapsulated cell transplantation. Encapsulated cell transplantation has been clinically used for the treatment of diseases arising from hormone-producing organs like the pancreas and parathyroid [31, 32]. For the CNS diseases, encapsulated ciliary neurotrophic factor (CNTF)-producing cells and chromaffin cells were transplanted into ALS patients and patients with severe chronic pain, respectively [33, 34]. As described in the previous section, encapsulated cell transplantation was used to administer GDNF to a PD model of rats in our laboratory. Encapsulated cell transplantation has many advantages [35] (Fig. 1). 1) Various neurotransmitters or neurotrophic factors can be produced continuously from encapsulated cells with tailored properties. Cells inside the capsule survive with a sufficient supply of nutrients and oxygen through the semipermeable membrane and are capable of secreting factors outwards. 2) Few immune reactions and no immunological rejection arise because the cells inside are protected by a stiff envelope. The molecular sieve prevents immunocompetent cells from invading the capsule and attacking the donor cells. 3) Tumorigenesis does not occur because the donor cells stay inside the capsule. 4) The capsule can be removed from the transplanted brain when problems arise after transplantation. 5) Various cells including immortalized cell lines can be transplanted safely as surviving donors with almost no ethical problems. Compared to the infusion using a pump system, the delivery of freshly made factor with no degradation and the absence of a need for pump implantation are the advantages of encapsulated cell transplantation. A single administration of GDNF was useful for the PD model of rats [36], and delayed short-term GDNF administration close to the substantia nigra

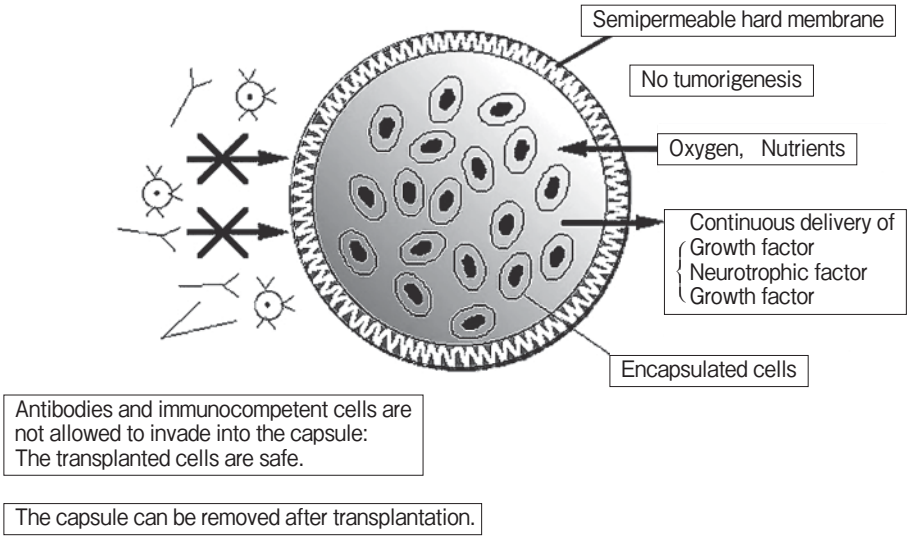

Fig. 1 Scheme of encapsulated cells. Capsules are made with semipermeable membrane. Oxygen and nutrition can freely move into the capsule, although antibodies and immunocompetent cells cannot pass through the membrane. In addition, the trophic factor or neurotransmitter secreted from cells inside the capsule can be expanded around the capsule.

protected against neuronal degeneration [37]. However, the study revealed that short-term GDNF administration could not achieve a long-term rescue of the nigral cells. Indeed, PD is slowly progressive, so a long-lasting effect is desirable. In our recent study, we used encapsulated cells secreting fresh GDNF at about 20 ng per day for 2 months *in vivo* [30]. Although the dose was relatively low compared to some studies, intraparenchymal continuous infusion appeared to be more effective than intraventricular infusion [38].

Current State of GDNF Therapy for PD Patients

Success of intraputaminal GDNF infusion in PD patients. Based on the successful results of the animal experiments described above, a clinical trial using GDNF was begun for PD patients. However, the initial several studies demonstrated that the intraventricular injection of GDNF did not improve the motor scores of PD patients and caused many side effects such as nausea, anorexia, vomiting, weight loss, hyponatremia, paresthesias including Lehrmitte signs and psychotic manifestations [39, 40]. The researchers considered that the unexpected poor results might be due to inappropriate GDNF delivery, because intraputaminal GDNF infusion to aged non-human primates ameliorated the behavioral score and the metabolism of dopamine with no problematic side effects [41]. Dr. Gill and his colleagues then reported successful results using intraputaminal GDNF infusion in 2003 [42]. The direct administration of GDNF into the putamen of five PD patients improved the patients' Unified Parkinson's Disease Rating Scale (UPDRS) score in the off-medication state after 1 year with no serious side effects. Moreover, medication-induced dyskinesia was reduced by 64% and was not observed in the off-medication state during chronic GDNF delivery [42]. After this report, several groups demonstrated the therapeutic effect of GDNF on PD patients [43–45]. Dr. Gill's group in England continued GDNF infusion for 2 years and reported good outcomes with no side effects [44]. The same group demonstrated neuropathological evidence that GDNF infusion for 43 months caused sprouting of dopaminergic fibers in accordance with functional recovery [43]. In Kentucky, Dr. Slevin and his colleagues demonstrated that even unilateral GDNF infusion achieved bilateral improvement of motor functions with transient paresthesia in 20% of patients [45].

Recent controversy and hope surrounding GDNF therapy for PD patients. However in

2005, Amgen, the company holding the patents on GDNF therapy for PD, brought the clinical trial using GDNF to a halt, but not the pre-clinical and basic research [46, 47]. The main reasons for this decision were the negative results of the recent randomized controlled trial and the neutralizing anti-GDNF antibody found in 3 of 34 patients [48]. The latter was a factor even though these three patients were asymptomatic and the bioactivity and toxicity of the neurtralizing antibody remains to be explored. In addition, cerebellar lesions were found in monkeys receiving a high dose of GDNF [46, 48]. These results and the decision of Amgen disappointed the patients and researchers involved in this study, and there has been fierce controversy over the decision [49–52]. However, it is too early to conclude that GDNF therapy is not feasible for PD patients, as such a conclusion would be based on just one study including several problems (an atypically younger patient population, and the GDNF dose and delivery system used in this study) as described in Dr. Baker's letter [53]. As many new experimental treatments are unlikely to be unqualified successes at first, we should re-consider the potential problems in the studies of GDNF therapy. If the administration of GDNF for a long time causes problems, we should investigate the long-term outcomes for patients receiving the GDNF infusion for just a few months. Alternatively, the effectiveness of intermittent administration of GDNF could be investigated. There are many questions to be answered before this research direction is abandoned. Recently, MRI analyses of nine PD patients with GDNF therapy revealed no cerebellar lesions in accord with a lack of cerebellar dysfunctions [54]. Continuous and steady efforts like the study from Kentucky are required, although the future of GDNF therapy is still unknown.

GDNF secreted from transplanted cells in PD patients. Recently the importance of transplanted cells as suppliers of trophic factors has come to light. In clinical application, autologous cells are relatively safe for patients and present almost no ethical issues; they are considered to be strong potential candidates for therapies for PD [55–57]. Dr. Arjona reported that 6 patients with advanced PD underwent bilateral transplantation of autologous carotid body cell aggregates into the striatum [55]. Bilateral intrastriatal transplantation was performed in six PD patients with both pre- and post-transplant (18 months) evaluations. No patients demonstrated side effects, including dyskinesia. In addition, 5 of 6 patients showed ameliorated UPDRSⅢ in their off-state. Carotid body-grafted Parkinsonian animals showed a nigrostriatal dopaminergic neurorestoration, at least partially resulting from GDNF secretion from the grafted cells [58]. In our laboratory, the therapeutic effects of genetically engineered GDNF-secreting neural stem cells are also being explored using a PD model of animals to enhance the therapeutic effects of the neural stem cell itself.

Conclusions

Key animal experiments, including our recent findings related to GDNF and clinical trials of GDNF therapy for PD patients, are described in this review. The future of GDNF therapy is uncertain, although GDNF has strong neuroprotective and neurorestorative effects. Steady and continuous efforts are required to elucidate the potencies of GDNF and its potential contribution to PD patients.

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