Peer reviewed article

Restorative neuroscience: concepts and perspectives

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Summary

There is increasing interest in the search for therapeutic options for diseases and injuries of the central nervous system (CNS), for which currently no effective treatment strategies are available. Replacement of damaged cells and restoration of function can be accomplished by transplantation of cells derived from different sources, such as human foetal tissue, genetically modified cell lines, embryonic or somatic stem cells. Preclinical and clinical trials have shown promising results in neurodegenerative disorders, like Parkinson's and Huntington's disease, but also ischaemic stroke, intracerebral haemorrhage, demyelinating disorders, epilepsy and traumatic lesions of the brain and spinal cord. Other studies have focused on finding new ways to activate and direct endogenous repair mechanisms in the CNS, eg, by exposure to specific neuronal growth factors or by inactivating inhibitory molecules. Neuroprotective drugs may offer an additional tool for improving neuronal survival in acute or chronic CNS diseases. Importantly however, a number of scientific issues need to be addressed in order to permit the introduction of these experimental techniques in the wider clinical setting.

Key words: neural transplantation; stem cells; neurotrophic factors; neuroprotection; regenerative medicine

List of Abbreviations

AAV	adeno-associated virus
AD	Alzheimer's disease
ALS	amyotrophic lateral sclerosis
APP	amyloid precursor protein
ARTN	artemin
beta-Gal	beta-galactosidase
BDNF	brain-derived neurotrophic factor
BFGF	basic fibroblast growth factor
BMP	bone morphogenetic protein
CDNF	conserved dopamine neurotrophic factor
CNTF	Ciliary neurotrophic factor
CK	creatine kinase
CNS	central nervous system
EGF	epidermal growth factor
ES	embryonic stem cell
FDG	fluorodopa deoxyglucose
FGF	fibroblast growth factor
GABA	gamma-aminobutyric acid
GDNF	glial cell line-derived neurotrophic factor
GFL	GDNF family ligand
GFP	green fluorescent protein
HD	Huntington's disease
ICH	intracerebral haemorrhage
IGF	insulin-like growth factor
IL	interleukin
MS	multiple sclerosis
NGF	nerve growth factor
NT	neurotrophin
NTN	neurturin
OEC	olfactory ensheathing cell
PCr	phosphocreatine
PERV	porcine endogenous retrovirus
PET	positron emission tomography
PD	Parkinson's disease
PSP	persephin
SOD1	superoxid dismutase 1
SVZ	subventricular zone
SV40	simian virus 40
TGF	transforming growth factor
TH	tyrosine hydroxylase
VM	vental mesencephalon

No financial support declared.

Introduction

The diseased or damaged brain has limited regenerative capacity, which is mainly of a functional and not of a structural nature. There are a number of neurodegenerative processes, neurovascular pathologies and traumatic lesions of the central nervous system (CNS) for which there are currently no effective treatment options available. These are usually devastating diseases with a major impact on quality of life, showing a chronic course and are associated with high socioeconomic costs. Due to increasing life expectancy and a higher prevalence of neurodegenerative and neurovascular pathologies in the elderly population, these disorders will become even more important for our society in the future and there is need for the development of new, adequate treatment options.

To develop strategies for repair of the impaired brain and spinal cord, extensive research efforts have been implemented particularly during the last two decades. Effective *in vitro* and *in vivo* models have been developed in order to replicate the core pathology of the underlying disorders. The concept of neural transplantation has evolved as an instrument for replacing the neurons lost in degenerative processes, trauma, and vascular lesions, as well as for replacing glial cells in the context of demyelinating lesions. Major advances in basic research have enabled first clinical trials, which have proved that this approach is feasible and effective. In addition, strategies have been developed to influence endogenous stem cell proliferation, migration and differentiation in the brain.

Nevertheless, there are still a number of major limitations to overcome, such as lack of sufficient and well-characterised donor tissue, suboptimal survival and functional integration of transplanted cells, the presence of side effects, and the missing knowledge on factors influencing migration, growth and differentiation of transplanted stem and progenitor cells. In addition, and importantly also a number of ethical issues needs to be addressed. In this article we discuss the possibilities and limitations in cell replacement strategies and also address current research in restorative neuroscience. Notably, the current review deals with a rather specific part of current plasticity research and does not cover the entire field of neuronal plasticity, like for example, mechanisms of synaptic plasticity [1, 2], activity dependent modulation of axonal motility [3], effects of dietary restriction [4], potential of environmental enrichment [5], the impact of adaptive learning for rehabilitation [6], assessment of structural plasticity by transcranial magnetic stimulation [7], multimodal imaging of brain reorganisation [8], and the importance of nuclear medicine imaging in rehabilitative treatment evaluation [9].

Neural transplantation for Parkinson's and Huntington's disease

Allogenic neuronal tissue harvested within certain developmental windows has been reported to survive, extend axons and make connections with the surrounding host brain after transplantation. Parkinson's disease (PD) and Huntington's disease (HD), common neurodegenerative disorders with relatively selective loss of certain subpopulations of neurons, have received the most attention with respect to therapies designed to replace the missing neurons [10, 11]. While there are effective symptomatic treatments for PD, the applied drugs become less effective with the progression of the disease and produce significant side effects. In HD, there are at present only few symptomatic treatments available, which are most effective in controlling the psychiatric abnormalities associated with this disease. Both PD and HD can be mimicked in experimental *in vitro* and *in vivo* models to replicate the underlying pathological processes permitting study of cell replacement strategies under laboratory conditions.

Transplantation of foetal neuronal tissue

Parkinson's Disease

Idiopathic PD is the second most common neurodegenerative disorder and affects more than 1% of all individuals over the age of fifty years [12]. In Switzerland, about 10 000 to 12 000 persons suffer from this disease. As the incidence of PD rises with age, it is expected that this number will increase significantly because of the aging character of our society [13]. Clinical symptoms are resting tremor, bradykinesia, rigidity and postural imbalance [14, 15]. PD is characterised by a predominant and progressive loss of dopaminergic neurons in the substantia nigra pars compacta in the upper brain stem, which leads to a profound loss of dopaminergic input into the striatum. It has been shown that complex I activity is defective

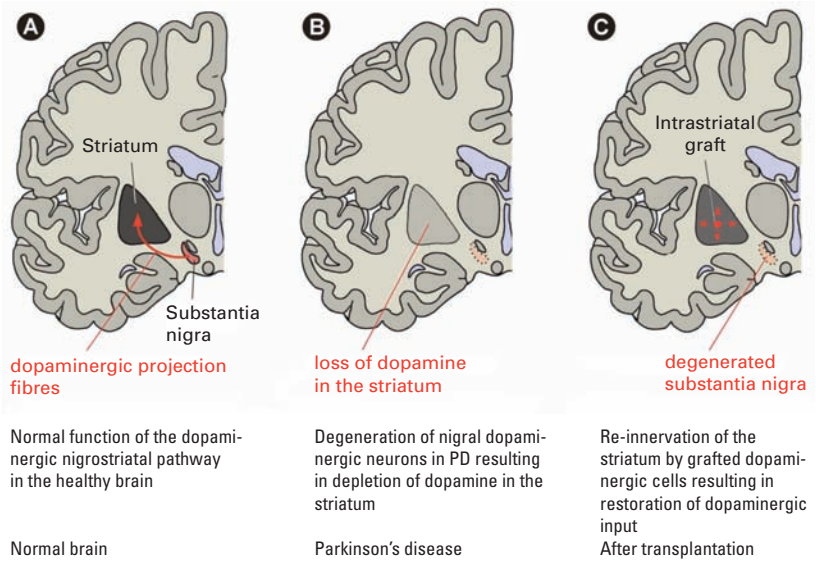

Figure 1

Schematic drawing of transplantation of dopaminergic cells in a patient suffering from Parkinson's disease (PD). In the healthy brain, dopaminergic input to the striatum is provided by the nigrostriatal projection system (A). In PD, degeneration of the dopaminergic neurons in the substantia nigra leads to dopamine depletion in the striatum and thus dysfunction of the extrapyramidal system (B). After intrastriatal transplantation of dopaminergic neuronal precursor cells, these differentiate into neurons, establish functional connections to the surrounding striatal cells and restore the dopaminergic input to the striatum (C).

in multiple tissues from PD patients [16], and that there is a maternal association in the hereditary form of PD [17], suggesting a mitochondrial basis for this disease.

Due to the fact that PD represents a rather selective degenerative process of mainly dopaminergic neurons of the nigrostriatal pathway, this pathology has been considered as particularly suitable for the application of cell replacement therapies (fig. 1). Extensive *in vivo* studies have shown that foetal ventral mesencephalic (VM) allografts display long-term survival in the host brain, making and receiving connections from host neurons [18, 19] (fig. 2). The transplanted tissue releases dopamine in a regulated fashion and reverses many of the behavioural deficits seen in animal models of PD [20, 21]. Based on the experimental data, first clinical trials with neuronal transplantation in patients were started in the late 1980s. Foetal nigral tissue can be transplanted safely into the caudate and putamen bilaterally in patients with PD and with little post-operative complications [22, 23]. The function of the grafted cells can be assessed by fluorodopa deoxyglucose positron emission tomography (FDG-PET). Neuropathological evidence has been provided that human foetal VM grafts survived and reinnervated the host striatum of a PD patient who had shown significant clinical improvement as well as enhanced fluorodopa uptake on PET scans [23–26]. Long-term graft survival was confirmed in two patients with persisting high FDG uptake when investigated 6 and 12 years after surgery [27, 28]. Significant clinical improvement associated with graft survival has been reported by several groups, mainly characterised by reduced rigidity and bradykinesia, with the ability to completely withdraw L-DOPA treatment after surgery in the most successful cases.

Notably, less than 20% of the transplanted dopaminergic cells survive the transplantation procedure [24, 29]. Studies in rats indicate that most of these cells die within one week posttransplantation [30], predominantly by apoptosis [31]. Hence it has become evident from the clinical trials performed so far that significant clinical improvement is only achieved after grafting of a sufficient amount of VM tissue (cells from 3 to 4 human embryos per side) [32, 22] followed by favourable integration of the grafted dopaminergic neurons into the host brain. In addition, the position of the graft has been shown to play a major role in the pathogenesis of novel dyskinetic behaviour after transplantation in PD rats, and widespread grafting could be an option to overcome this problem [33].

The recently reported double-blind studies by Freed and coworkers and Olanow and colleagues both failed to meet their primary end points [34, 35]. Moreover, several patients developed severe side effects including dystonia and dyskinesias [34, 36,37]. This might have been due to insufficient dopamine release by the transplants [35, 38]. Both studies, however, included subjects who had failed drug therapy and it has been suggested that patient selection may explain the negative results reported by Olanow and colleagues [39]. It is likely that better results can be expected with improved transplant protocols [35, 40, 41]. The complexity of these problems should not be underestimated and clinical applications should be planned with great care [37, 42]. These notions ask for improved understanding of the transplantation approaches and require extended experimental studies. Winkler and co-authors concluded that with further improvement and refinement of the grafting procedure there is every

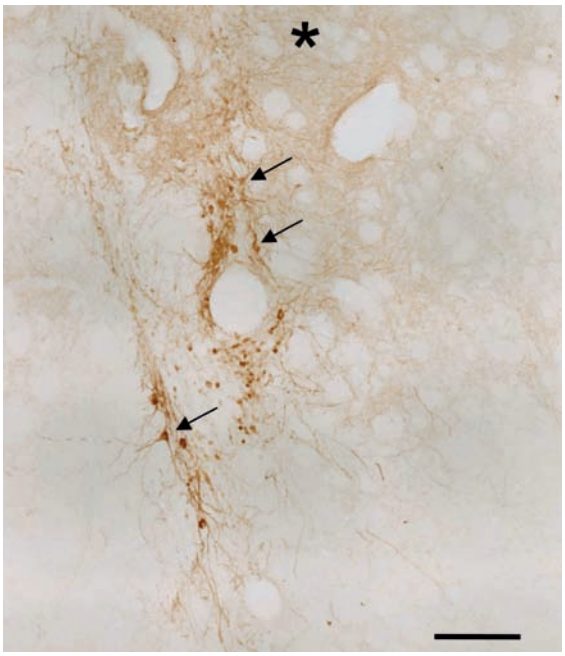

Figure 2

Photomicrograph of rat embryonic dopaminergic precursor cells transplanted in a rat model of Parkinson's disease and immunohistochemically stained for tyrosine hydroxylase (TH). TH-immunoreactive grafted cells (arrows) survive in the host brain and extend TH-immunoreactive axons into the denervated striatum (asterisk). Scale bar: 200 µm.

reason to believe that cell transplantation can be developed into a safe and efficacious restorative therapy for advanced not too seriously affected PD patients [41].

Taken together, neural transplantation therapy in PD using tissue from aborted foetuses is likely to remain experimental due to questions regarding standardisation and purity of cell material [37, 42]. Due to the above mentioned limitations, transplantation of human foetal tissue has therefore been largely abandoned at present and the basic research focuses on alternatives to human foetal tissue as a graft source, eg, transplantation of immortalised neuronal cell lines, embryonic and neural stem cells, porcine tissue and genetically modified cells [43].

Huntington's disease

HD is a chronic autosomal dominant inherited neurodegenerative disorder with full penetrance by mid-adult life and clinically presents with progressive choreoathetotic movements in combination with severe cognitive and emotional dysfunction [44, 45]. The symptoms typically appear between the age of 30 and 40 years and deteriorate over a 10–20 year period, finally leading to death [46]. HD has an overall prevalence rate in Europe of approximately 10 per 100 000 people [47]. The main pathological finding is a selective loss of the GABA-ergic medium sized spiny projection neurons in the striatum. The gene (IT15) located on the short arm of chromosome 4 [48] responsible for the expression of HD and its associated protein, huntingtin [49], have been identified through genetic research. The gene has been shown to contain a multiplication of CAG trinucleotide repeats responsible for different grades of severity in the course of the disorder, while the function of huntingtin has still to be elucidated. A defect in energy metabolism has been proposed as one of the potential pathogenetic mechanisms [50]. Nevertheless, a wide gap still remains between the knowledge about the neuronal substrates of HD and the ability to prevent or alleviate the progression of the disorder.

Transplantation of embryonic striatal precursor cells has been shown to restore deficits in experimental animal models of HD [51–53]. Similarly to the situation in PD, clinical trials for cell replacement strategies in HD using human foetal tissue as cell source revealed survival of grafts in the host brain. Most of the trials on cell transplantation in HD published so far were dealing with feasibility and safety issues. On the basis of theses results, one can assume that cell replacement for HD using foetal tissue is safe for the patients [54, 55]. Particularly interesting is the fact that in the study of Hauser et al. surviving graft tissue did not contain mutant huntingtin, indicating that the transplanted tissue was not affected by the pathology of the host brain [56, 57]. In a recent study, Keene and co-workers reported on long-term survival and neuronal differentiation of transplanted foetal tissue, however, the host brain was found to be poorly innervated. In line with this observation, the clinical benefit was found to be rather poor in transplanted patients [58]. Based on the outcome of this study, it was highlighted that it is mandatory to perform clinical trials in HD with great care and by means of blinded, well-designed and controlled studies [59]. Nevertheless, the outcome of the French HD trial showed minor but significant clinical improvement in some of the transplanted patients [60, 61]. A multi-centre trial was recently initiated to evaluate the best protocols for cell replacement in HD in order to make this technique available for a broader range of non-specialist centres and to verify these initial promising results (for review see: [62]). As stated for cell transplantation approaches in PD, foetal tissue will not provide a sufficient and standardised cell source for grafting a large number of HD patients. Importantly to note, cell transplantation is considered at present to be the only choice for restorative treatment of HD patients, hence research in this area as well as searching for alternative cell sources should be pursued [62].

Xenotransplantation

Xenotransplantation means that tissue is transplanted across the species barrier. Using organs from other species has long been considered for overcoming a shortage of human donor organs, such as heart, kidney and liver [63].

As a non-endangered species, pigs are considered a suitable source of donor tissue allowing sterile dissection of large quantities of pathogen-free tissue of the optimal embryonic age. A relatively large brain size combined with a protracted gestational period may provide the basis for long-distance axonal growth after grafting, facilitating efficient innervation of the host striatum. To what extent grafted dopaminergic neurons are affected by the on-going disease is still not known, but natural species differences, including genetic resistance in response to the disease process, could provide an important advantage promoting long-term survival and function of grafted porcine cells.

The transplantation of embryonic porcine xenografts has been established after extensive studies in Sweden and in the USA, both in PD and HD [64]. A clinical safety trial with porcine tissue including 12 Parkinson patients has been published [65, 66]. Moderate clinical improvements in some of the patients were reported. In the brain of a patient who died for unrelated causes a very limited survival rate of the dopaminergic neurons, not accompanied by major rejection processes, was observed [65]. This finding may point to lack of trophic support of grafted tissue after transplantations similar to the suggestions made in respect to allografts.

The risk of spread of infection across the species barrier (xenozoonosis), particularly by

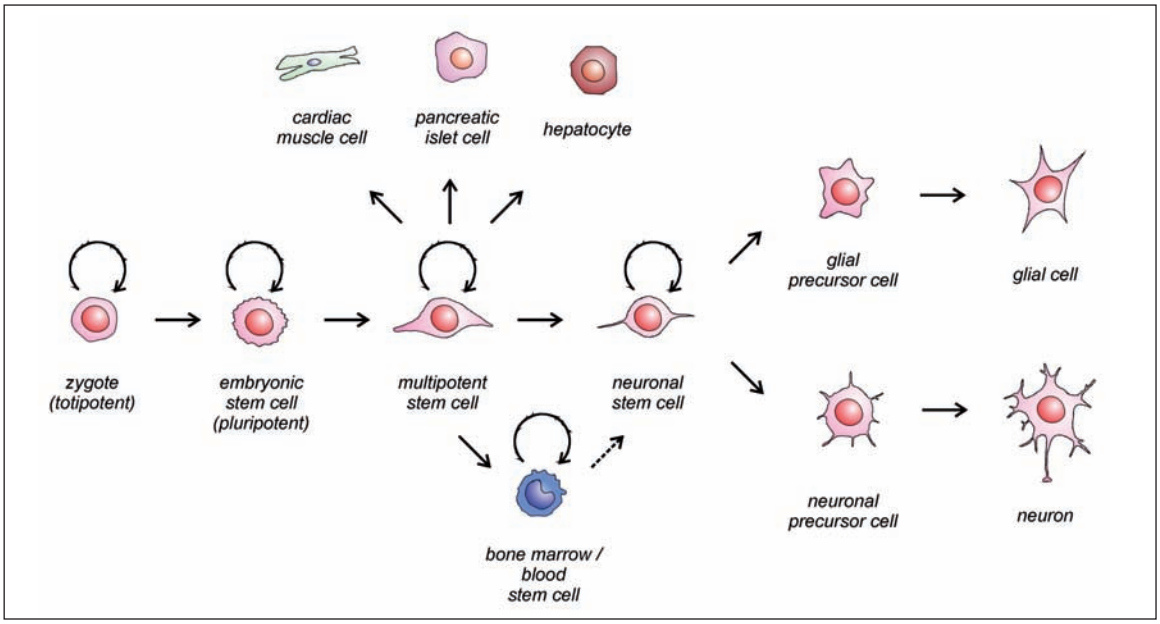

Figure 3

Diagram illustrating the potential for differentiation of stem cells. Embryonic stem cells can differentiate into almost all cells of our body. With ongoing maturation, their ability to differentiate into different types of cells becomes more and more restricted. The differentiation capability of neural stem cells is restricted to the neuronal and glial lineage. Bone marrow stem cells have the capability to transdifferentiate into neural stem cells (dashed arrow). Stem cells can proliferate indefinitely (self-renewal; circular arrows).

porcine endogenous retroviruses (PERVs), remains a major obstacle that hampers further clinical studies. However, in several studies investigating the possibility of cross-species infectivity, including a retrospective analysis of 160 human transplant recipients exposed to porcine tissue, no evidence for such transmission has been found [67, 68]. Cross-species rejection issues requiring immunosuppression of the host constitute another unsolved problem. The ability to genetically modify species such as the pig to express human genes and silence those provoking immune response has enabled interesting perspectives for genetically engineered cells in this context. The production of a gal-α-1,3-galtransferase transgenic pig [69] represents a significant advance towards eliminating hyperacute and acute vascular rejection.

Stem cells

Stem cells are undifferentiated cells without mature, tissue-specific characteristics that in response to proper stimuli are able to proliferate, to reproduce themselves and to produce generations of progenitor cells, which can differentiate into one or more cell types.

Several strategies are currently being investigated aiming at transplanting cells derived from a variety of different stem cells, including embryonic stem (ES) cells, neural stem cells, bone marrow or mesenchymal stem cells as well as umbilical cord blood stem cells (fig. 3).

Human ES are derived from preimplantation embryos generated for *in vitro* fertilisation. Within a few days after fertilisation, they can be removed from the inner cell mass of the blastocyst, dissociated and propagated in specialised cell culture media, where they can proliferate indefinitely [70]. Differentiation of these cells can be induced by changing culture conditions and exposure to specific growth factors. Due to their pluripotency, ES cells can potentially become any cell in the body, which offers a huge potential for cell replacement therapies [71].

Neural stem cells are found in already developed tissues of the foetus or the newborn, juvenile

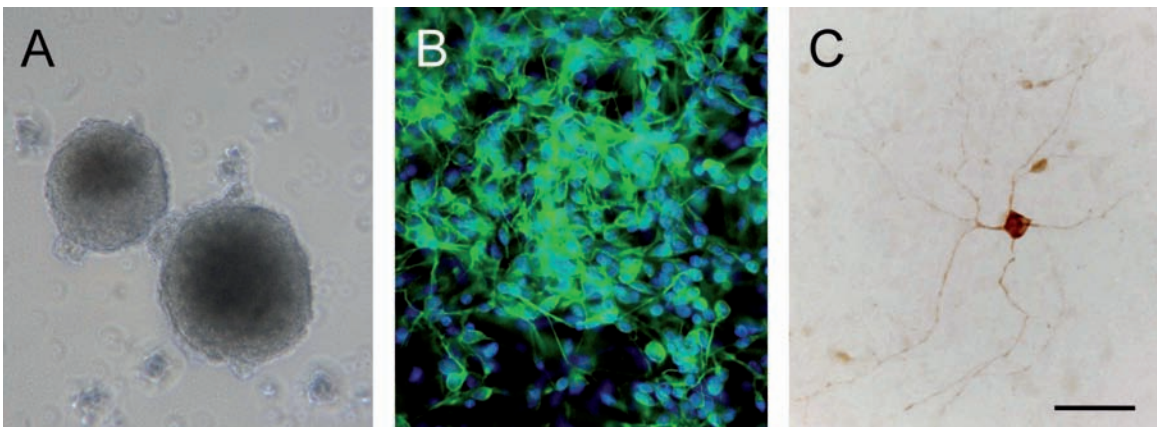

Figure 4

Photomicrographs of rat embryonic subventricular zone stem cells cultured as neurospheres (A). Differentiation of the cultured cells (Hoechst staining, blue) towards the neuronal phenotype is demonstrated by microtubule associated protein 2 immunostaining (green) and neurite outgrowth (B). Further differentiation towards specific neuronal subpopulations, eg, dopaminergic cells, is demonstrated using immunohistochemistry for the catecholaminergic marker tyrosine hydroxylase (C). Scale bar: 200 μm (A), 50 μm (B/C).

and adult organism. They represent a source of immature cells with the potential to renew themselves (immortality), and give rise to cells restricted to the neuronal and glial lineage. These cells are found in specific brain regions such as the subventricular zone (SVZ), hippocampus, cortex and spinal cord [72–74], in the developing and in the adult brain [75–77]. Isolated neuronal stem cells are able to proliferate in response to different growth factors, such as basic fibroblast growth factor (bFGF) or epidermal growth factor (EGF), and to differentiate towards specific neuronal and glial phenotypes when culture conditions are altered [78] (fig. 4). Hence drugs that influence the differentiation of stem cells and neuronal precursors into a specific neurochemical phenotype therefore hold a potential for improving cell replacement techniques [79]. These cells furthermore have the ability to migrate and form functional synapses with the surrounding neurons. In both HD and PD, transplantation of stem cell and progenitors have been reported to resulted in improvement of these disease states in animal models [42, 79, 80, 81]. Recent studies have suggested that bone marrow stem cells transplanted into mice are able to migrate into specific regions of the brain, including the olfactory bulb, cortex, hippocampus and cerebellum, and differentiate into cells that appear to be neurons [82, 83]. The studies suggest that bone marrow may be an easily available source of neural cells with potential for treating neurological disorders. Another study was able to show development of neuronal phenotypes after intravenous administration of previously harvested umbilical cord blood cells [84]. First experimental studies using umbilical cord stem cells have reported promising results after ischaemic insults [85], traumatic brain injury [86], amyotrophic lateral sclerosis [87] and intracerebral haemorrhage [88]. Both the usage of autologous bone marrow and umbilical cord blood stem cells offer the advantage of tolerance by the host immune system. Moreover, they can be administered by injection into a peripheral blood vessel, therefore not requiring brain surgery.

In each of these paradigms, the main problem to be solved is the missing knowledge how transplanted cells differentiate. This includes the risk of uncontrolled growth and tumour formation in the host brain. In addition, the usage of ES cells has raised severe ethical concerns, particularly in the USA, which may hamper basic research and clinical application in the future [89]. In addition, many cell lines have recently been reported to be contaminated by murine pathogens [90]. Human stem cells cultured in the presence of animal cells or sera have also been shown to incorporate foreign sugars into their surface proteins, which may provoke immune response [91]. According to these findings, most stem cell lines have to be re-established using environments free of animal cells and sera in respect to enable a safe application in humans.

Neuronal cell lines

Immortalised neuronal precursor cell lines kept in culture might offer an additional, theoretically unlimited source of specific cells of the neuronal or glial lineage for transplantation [92]. As an example, the clonal cell line RN33b was generated from embryonic rat raphe nucleus and transduced with the temperature sensitive mutant of the Simian Virus 40 (SV40) large T-antigen [93]. The transplanted cells can be detected by reporter genes for beta-galactosidase (beta-Gal) and green fluorescent protein (GFP). Several studies have shown that transplanted RN33b cells are able to survive in the brain and spinal cord, differentiate into specific neuronal phenotypes in a region-specific fashion [94, 95], and establish electrophysiologically active axonal projections [96] (for review see: [80]). Notably, transplantation of cells derived from cell lines contains the same obstacles as transplantation of non-transformed neural stem cells.

Neural transplantation for other neurodegenerative diseases

Amyotrophic lateral sclerosis

ALS is a rare neurodegenerative disorder characterised by the loss of the large cholinergic motor neurons in the spinal cord and degeneration of the neurons in the motor cortex, resulting in progressive paralysis and ultimately death. The underlying pathological process remains enigmatic, however, mutations in the superoxid dismutase 1 gene (SOD1) have been identified, resulting in protein misfolding and toxicity on the vulnerable cholinergic cells [97]. So far, no effective treatment options are available for patients suffering from this disease.

Basic research has proven that transplanted human ES cells can be differentiated into cholinergic motor neurons [98]. They survive in a rodent model of ALS and show functional benefits [99]. However, it has been argued that these effects are related on the differentiation of stem cells into glial cells producing trophic support for dying motor neurons rather than by direct motor neuron replacement [100]. Preliminary stem cell transplantations in patients using autologous blood- and bone marrow-derived cells have shown the absence of major side effects, but no or only slight clinical efficacy [101, 102]. It has to be concluded that the biological issues have to be clarified before further applications on patients should be performed.

Alzheimer's disease

Alzheimer´s disease (AD) is the most common neurodegenerative disorder. About 5% of the population over 65 is suffering from the disease. As the overall life expectancy is prolonged with the advancement in medical science, the incidence of AD related to aging has dramatically risen [103]. The underlying pathological mechanisms are not yet understood, although aging and genetic predisposition have been identified as major risk factors. AD starts in the mesiotemporal region which in the course of the disease shows strong alterations [104, 105]. AD also severely affects neurons in the frontal and parietal association neocortex, leading to progressive dementia. The pathological hallmarks of AD are extracellular plaques and intracellular tangles constituted of amyloid , a peptide derived from amyloid precursor protein (APP). It is not clear, however, whether these pathological accumulations are the markers or the causes of AD.

Notably, Hock and co-workers reported that immunisation of patients with aggregated amyloid β-42 resulting in the production of antibodies against amyloid β slowed cognitive decline in AD [106]. The outcome of a large randomised, placebo-controlled, double-blind trial, however, did not reveal the anticipated results and was interrupted following reports of meningoencephalitis [107]. Nevertheless, there is proof of concept of this therapy for AD [108,109]. In line with this statement, a monoclonal antibody (Bapineuzumab) designed to reduce the amount of amyloid β in the brain co-developed by the companies Elan and Wyeth is currently in phase II clinical trial and foreseen charging towards phase III trial in 2008.

Importantly, many different neurotransmitter systems, in particular the cholinergic, noradrenergic and serotonergic system, are involved in the degeneration processes in AD [110]. Current drug therapies, usually based on cholinesterase inhibitors, only relieve some of the associated symptoms of the disease, if at all [111]. Due to the extensive degeneration of multiple neuronal phenotypes in widespread brain areas, establishing a cell replacement strategy in AD is considered one of the most demanding challenges in restorative neuroscience. So far, experimental studies using embryonic cholinergic transplants in animals suffering cholinergic depletion in different brain regions such as hippocampus, septal area, basal forebrain and neocortex have shown functional benefits [112, 113]. Due to the above-mentioned problems and the nascent stage of basic research, no clinical studies of cell replacement in AD patients have been carried out so far.

Demyelinating diseases

Multiple sclerosis (MS) is the most prominent pathology in the group of demyelinating diseases, with a prevalence of 110 cases per 100 000 inhabitants in Switzerland [114]. Nowadays, potent immunosuppressive and immunomodulating treatment regimens are available and allow the prevention of severe irreversible neurological deficits in most cases. However, there are still patients with MS resistant to conventional therapy, resulting in disabling neurological sequelae. In order to offer these patients strategies for myelin repair, numerous attempts to develop cell-based therapies have been made during the past decade. In MS, the disease process is primarily directed against oligodendrocytes and/or myelin, with neuronal structures such as axons relatively spared until late disease [115]. Therefore, reparative therapy has primarily to be focused on restoring the oligodendrocytes supplying the axons with myelin, without the need to re-establish a disrupted neuronal circuitry. Interestingly, Schwann cells, which usually provide myelin and glial support in the peripheral nerve, have shown good results in myelin repair, both in the brain [116] and particularly in the spinal cord [117]. Comparable effects have been found using olfactory ensheathing cells (OECs) in spinal cord demyelination [118]. Finally, stem cells have been shown to possess a considerable remyelinating potential [119]. A recent study using transplantation of pluripotent ES cells in an antibody/complement-induced demyelination model in the rat spinal cord demonstrated survival of the cells, differentiation both in oligodendrocytes and astrocytes and formation of new glial sheets [120].

So far, first clinical studies including implantation of dissociated rat Schwann cells [121, 122], transplantation of oligodendrocyte lineage precursor cells [123, 124], transplantation of oligodendrocyte precursors derived from cell lines [125, 126], and OECs [127] have been carried out with limited success. Critical parameters that require further investigations include the developmental stage of the oligodendrocyte precursors to be transplanted, the insufficient survival of transplanted cells, particularly in the context of a systemic immunoresponse against these cells and significant differences between human and rodent oligodendrocyte progenitor cells.

Neural transplantation for specific neurological disorders

Ischaemic stroke

Cerebral ischaemic stroke is one of the leading cause of death and disability among the elderly people worldwide and has an incidence of 150 per 100'000 people per year [128]. Due to the recent advances in the diagnosis, treatment and

rehabilitation in stroke, the percentage of patients suffering severe neurological deficits has constantly dropped in the last decade, and the severity of the sequelae has been reduced. However, there are still many patients suffering from irreversible brain parenchyma defects due to stroke, with about 60% of them requiring care two weeks after the insult [128]. Hence, stroke places a heavy burden on national health care systems and demands for the development of novel effective treatment options.

Importantly, multiple different neuronal phenotypes and glial cells in different brain areas, eg, cortex, basal ganglia and thalamus, are affected in cerebral stroke. Therefore this pathology poses special conditions that impact the potential success of cell replacement therapies. Because the disease affects both gray and white matter, immature cells that have the potential to differentiate into appropriate neuronal and glial phenotypes are considered as best suitable for transplantation. So far, restorative strategies have focused on the striatum, due to clear anatomical definition, good stereotactical accessibility and less degree of white matter involvement than in cortical stroke, therefore allowing a less complex approach [129]. First clinical trials of neural transplantation in stroke have been launched in the late 1990s. One study investigated the transplantation of cells from the immortalised cell line NT2, which is derived from a human testicular germ cell tumour [130]. In preclinical studies, grafted NT2 cells, which terminally differentiate into mature neuronal phenotypes after intracerebral transplantation [131], showed significant improvements in behavioural tests after focal cerebral ischaemia [132]. A first clinical study to investigate the safety of transplantation of NT2 cells after basal ganglia infarction was started in 12 patients [133]. Up to date, no adverse effects of the procedure have been reported. Subsequently, a randomised trial with observer-blinded neurological evaluation was started in 14 patients with substantial motor deficits after basal ganglia infarction. Again, no adverse effects of the transplantation were present. However, patients with NT2 grafts showed only a trend towards a better functional outcome [134]. Another group investigated xenotransplantation of porcine foetal striatal precursor cells derived from the lateral ganglionic eminence, which previously have been reported to improve deficits in animal models of HD [64]. After focal ischaemia, intrastriatal transplantation of these cells leads to graft survival and differentiation of transplanted cells into glia and neurons with a striatal phenotype. There was evidence for synaptogenesis both with the host brain and within the graft. Four weeks after transplantation, animals showed significant behavioural improvements as compared with controls. However, no effects were found at later time points [67]. In a first clinical trial transplanting foetal porcine tissue, it was reported that two out of the five treated patients showed functional improvement after four years of clinical follow-up [135].

Basic and clinical research in neuronal transplantation for stroke is still in an early stage. Particularly, using cell replacement approaches for stroke, it remains unclear if the transplanted neurons themselves promote functional recovery or if the transplants modulate the response of the brain to ischaemic neurogenesis, synaptogenesis, angiogenesis and inflammation. Actually, there are a number of new preclinical studies of neuronal transplantation in stroke carried out (for review see: [136]). At present, transplantation of bone marrow stromal cells, which can be transdifferentiated to neuronal progenitors by exposure to specific growth factors, human umbilical blood cord stem cells, human adipose stromal cells and human neural stem cells have been investigated with varying success [137]. Interestingly, recent studies have demonstrated that intravenous infusions of umbilical cord blood can ameliorate neurological deficits associated with ischaemic brain injury in rodents, but it again remains unclear whether growth factors secreted from these cells are responsible for the induced regeneration processes rather than integration of the transplanted cells in the brain [138]. It can be assumed that inducing *de novo* neurogenesis may provide a more effective therapeutic strategy to promote recovery from stroke rather than transplanting exogenous cells [138].

Intracerebral haemorrhage

Spontaneous intracerebral haemorrhage (ICH) represents at least 10% of strokes in the Western population [139] and constitutes one of the most devastating forms of cerebrovascular disease. No direct treatment of the brain damage caused by ICH is currently available. Like in ischaemic stroke, progress in experimental neurobiology gives hope that new brain repair strategies using stem cell transplantation could be also advantageously employed against this disease state. So far, only two preclinical studies of neuronal tissue grafting in ICH have been reported. One study did not report any functional improvement after transplantation of foetal brain tissue [140]. Another report showed integration of intravenously administrated human neuronal stem cells in the damaged brain and functional recovery in rats undergoing ICH [141]. Intense research efforts are currently being undertaken to establish a more reproducible animal model of ICH and to improve neuronal transplantation in this context [142, 143].

Trauma to the brain and spinal cord

Traumatic injury to the brain and spinal cord usually results in irreversible neurological deficits that can only partially be compensated by activation of other neural networks, which functionally replace the damaged neurons. During the last two decades, advances in both basic and clinical re-

search have markedly improved our understanding of the cellular and molecular mechanisms in brain and spinal cord trauma [144–146]. In addition, sophisticated cerebral and spinal lesion models have been developed that allow the study of traumatic events and adequate treatment strategies *in vivo* [147].

In this context, it is important to note that neutralising the inhibitory effects of NOGO-A, which is a potent inhibitor of neurite outgrowth in the adult CNS, resulted in enhanced fibre growth and functional recovery in rodent and primate models of spinal cord injury [148]. The first clinical trial assessing the therapeutic potential of antibodies to NOGO-A is currently in progress [149].

Neural transplantation has turned out to be an important therapeutic option at least in experimental studies [145, 150, 151]. Various cell types have been investigated because of their considerable potential for promoting axonal regeneration. Schwann cells and OECs are glial elements that have both the capacity to stimulate fibre outgrowth as well as to remyelinate the tissue. Studies have shown a potential benefit of the transplantation of Schwann cells [152] and OECs [153] in models of complete and incomplete transection as well as contusion of the spinal cord. While there are no published studies of Schwann cells transplantation in humans so far, first clinical trials have shown that transplantation of autologous OECs is feasible, however there were no significant effects on neurological outcome [154]. Bone marrow stromal cells, which show stem cell-like attributes and pluripotency [155] and can both differentiate in neurons and glia [82, 83], have been found to promote functional recovery in spinal cord injury models. In addition, first studies have proven that human stem cells can differentiate into neurons and glia and promote locomotor recovery in spinal cord-injured mice [156].

Epilepsy

Medically intractable epilepsy, which means that the seizures are resistant to treatment with a combination of different anticonvulsive drugs, is usually treated surgically with ablative procedures to remove epileptogenic foci, eg, by performing selective amygdala-hippocampectomy or temporomesial lobectomy [157]. The precise underlying pathology of idiopathic epileptic seizures remains enigmatic in most cases, however, a imbalance between inhibitory and excitatory neurotransmitters in favour of the latter is usually considered to be present [158]. Cell-based therapies, such as the transplantation of inhibitory neurons like GABA-ergic cells, might therefore be useful for correcting the imbalance and thus preventing or alleviating seizures without the need for irreversible ablative surgery. First preclinical trials with transplantation of genetically engineered, GABA-releasing precursors [159] or human neural stem cells [160] in rats suffering from seizures have shown to decrease neuronal excitability and to raise the seizure threshold. With the advance of research, transplantation of inhibitory neurons therefore might become a novel, less aggressive treatment option for patients suffering from intractable epileptic seizures.

Strategies to improve cell replacement approaches

Neurotrophic Factors

Nerve growth factors or neurotrophic factors are proteins produced by glial cells and neurons during the development of the CNS that play important roles in controlling and coordinating neuronal growth, survival and differentiation. Many of them have been identified promoting survival and/or differentiation of specific neuronal subpopulations *in vitro* and *in vivo* (table 1). Among the most effective are the neurotrophin family members nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-4/5 (NT-4/5) and the glial cell line-derived neurotrophic factor (GDNF) family ligands (GFLs) [161, 162]. The GFLs belong to a distant branch of the transforming growth factor-β superfamily [163, 164], which comprises GDNF [165], neurturin (NTN) [166], Persephin (PSP) [167] and artemin (ARTN) [168] and have been described as being potent survival factors for midbrain dopamine neurons, motoneurons, noradrenergic neurons, and sympathetic, parasympathetic and sensory neurons [164, 169–173]. Neuroprotective effects of GDNF have been reported in experimental models of PD [174]. In addition, GDNF has been found to induce the expression of the dopaminergic marker tyrosine hydroxylase (TH) in late developmental stages of cultured neural progenitor cells and may therefore provide a robust tool to interfere with final cell fate specification of neural precursor cells [175]. A very recent study by Lindholm and co-workers described a novel neurotrophic factor for dopamine neurons: conserved dopamine neurotrophic factor (CDNF), which was at least as efficient as GDNF in their experimental settings, suggesting that CDNF might be beneficial for the treatment of PD [176].

Preliminary clinical trials with neurotrophic factors have been carried out in PD, HD, ALS and AD (table 2). Notably, the first attempts to apply factors failed to demonstrate any significant clinical benefits, despite positive preclinical data [177]. It is assumed that this was due primarily because

Table 1
Growth factors with neurotrophic activity*.

Growth factor	References
Artemin (ARTN)	Baloh et al., 1998 [168]
Bone morphogenetic protein (BMP) family	Chen et al., 2004 [215] Harvey et al., 2005 [216]
Brain-derived neurotrophic factor (BDNF)	Barde et al., 1987 [217] Leibrock et al., 1989 [218]
Ciliary neurotrophic factor (CNTF)	Lin et al., 1989 [219] Stockli et al., 1989 [220]
Conserved dopamine neurotrophic factor (CDNF)	Lindholm et al., 2007 [176]
Epidermal growth factor (EGF)	Morrison et al., 1988 [221]
Fibroblast growth factors (FGFs)	Gospodarowicz et al., 1986 [222] Grothe and Timmer, 2007 [223]
Glial cell line-derived neurotrophic factor (GDNF)	Lin et al., 1993 [164] Beck et al., 1995 [169]
Insulin-like growth factors (IGF), insulin	Aizenman et al., 1986 [224] Baskin et al., 1987 [225]
Interleukins (IL)	Spranger et al., 1990 [226] Kamegai et al., 1990 [227] Hama et al., 1990 [228]
Nerve growth factor (NGF)	Whittemore and Seiger, 1987 [229] Thoenen et al., 1987 [230] Hefti, 1986 [231]
Neurturin (NTN)	Widenfalk et al., 1997 [232] Horger et al., 1998 [233] Akerud et al., 1999 [234]
Neurotrophin-3 (NT-3)	Hohn et al., 1990 [235] Maisonpierre et al., 1990 [236] Rosenthal et al., 1990 [237]
Neurotrophin-4/5 (NT-4/5)	Hynes et al., 1994 [238] Widmer and Hefti, 1994 [239]
Persephin (PSP)	Milbrandt et al., 1998 [167] Zihlmann et al., 2005 [240]
Transforming growth factor α (TGF-α)	Derynck, 1988 [241] Code et al., 1987 [242]
Transforming growth factor β (TGF-β)	Ren and Flanders, 1996 [243]

* This table lists only a selection of growth factors and correspondingly only a selection of references.

Table 2
Neurotrophic factors in clinical trials.

Neurotrophic factor	Disease	References
BDNF	ALS	Bensimon et al., 1999 [244]
		Kalra et al., 2003 [245]
CNTF	ALS / HD	Bloch et al., 2004 [186]
IGF-1	ALS	Borasio et al., 1998 [246]
		Lai et al., 1997 [247]
GDNF	PD	Nutt et al., 2003 [248]
		Lang et al., 2006 [249]
NGF	AD	Tuszynski et al., 2005 [187] CERE-110: Adeno-associated virus (AAV)-based delivery of β-NGF in subjects with mild to moderate Alzheimer's disease. Available at http://clinicaltrials.gov/ct/show/NCT00087789?order=1.
NTN	PD	Safety of CERE-120 (AAV2-NTN) in subjects with idiopathic Parkinson's disease. Available at http://clinicaltrials.gov/ct/show/NCT00252850?order=1.

of the poor blood-brain barrier permeability of these proteins [178]. Recent developments of new delivery methods, eg, adeno-associated virus (AAV) mediated transfer [179], have revived the interest in these potential nervous system protein therapeutics [177]. A first small open-label clinical trial provided evidence that direct infusion of GDNF into the putamen of PD patients resulted in improvement of motor scores [180]. The benefits of intracerebral delivery of GDNF, however, could not be substantiated in a recent double-blinded placebo-controlled study. Moreover,

safety concerns emerged [181]. One elegant method for delivering neurotrophic factors to the brain is the use of encapsulated cell lines engineered to produce neurotrophic factors [182–184]. Its major advantage is a continuous, almost unlimited supply of these molecules. Encapsulation in a porous polymer membrane also provides a high safety level in regard to tumour formation while allowing exchange of metabolites. In addition, it separates the xenogenic cells from the host immune system [182]. So we have previously shown that implantation of encapsulated genetically engineered fibroblasts producing GDNF resulted in better survival and host integration of transplanted dopaminergic cells in the rat [185]. A phase I study that evaluated intracerebral administration of CNTF in subjects with HD, using a device formed by a semipermeable membrane encapsulating a cell line engineered to synthesise CNTF, demonstrated the safety, feasibility, and tolerability of this gene therapy approach [186].

A new promising window of neurotrophic factor delivery to the brain has been opened by the study of Tuszynski and colleagues [187]. In a phase I human clinical trial, autologous genetically modified fibroblasts releasing NGF were transplanted in eight patients with early stage AD. The preliminary results indicate that *ex vivo* NGF gene delivery is safe and seems to provide trophic support to degenerating cholinergic neurons [188]. Neurotrophic factor delivery to the brain may also be achieved by means of transplanting native or modified stem cells. So it has been described that transplantation of mesenchymal stem cells results in improved functional outcome in animal models of neurological disorders. These cells have, however, generally only a limited ability to differentiate into neurons. A recent study now showed that transplanted human adult mesenchymal stem cells released neurotrophins, which offers the possibility that co-transplantation of such cells with tissue grafts results in improved functional outcome [189].

Neuroprotective drugs

Survival of neuronal cells exposed to oxidative and metabolic stress can be improved by antioxidants, which act as free radical scavengers. One of these substances is the lazaroid tirilazad mesylate, which inhibits lipid peroxidation and can be used for pretreatment of grafts and/or can be postoperatively administrated to the transplanted patients. So Brundin and colleagues were able to show improved survival of rat and human dopaminergic cells *in vitro* and *in vivo* [190], however, only discrete effects could be demonstrated in patients [191].

Compounds that inhibit neuronal apoptosis [192] have been thoroughly investigated as potential drugs for improving neuronal cell survival. Such different substances as minocycline, a tetracyclin antibiotic [193], cytokines like erythropoietin [194] and granulocyte-colony stimulating factor [195], specific inhibitors of enzymes involved in apoptosis like the caspase inhibitor zVAD [196] and many others have been identified to possess anti-apoptotic properties on neuronal cells. However, caution must be exercised in view of possible side effects to successfully transfer therapeutic compounds to the clinic. Due to their long-established safety, minocycline and erythropoietin are the most appealing candidates for clinical trials in patients.

Creatine

The specific functional properties of neuronal tissue make high demands on cellular energy resources. Rapid changes in ATP demands are occurring during physiological function of neurons, while cellular energy reserves are very small [197]. Widely distributed cellular processes and sites of very high energy consumption localised at remote locations from the cell body, such as synapses, require mechanisms to facilitate energy transfer within the cell. The phosphocreatine/creatine kinase (PCr/CK) system has been described as playing a key role for maintaining the cellular energy homeostasis in neurons [198, 199]. Due to its function as a temporal ATP buffer and a carrier for high energy phosphates from sites of ATP production to sites of ATP consumption, it prevents marked changes in the concentrations of ADP and ATP, which has been postulated to be crucial in neuronal cells [200].

Despite intense research activities, the aetiology of neuronal death in neurodegenerative diseases still remains widely unclear. However, there are a number of similarities in the fundamental biochemical processes involved in the pathogenesis and progression of these otherwise different pathological states. The concepts of energy depletion, oxidative stress, excitotoxicity, and mitochondrial dysfunction have been implicated in HD, PD, ALS, and several hereditary mitochondrial neuromuscular disorders [201, 202, 203]. Although these processes may be directly or indirectly involved in the pathogenesis of a given disease, they converge in final common pathways of either necrosis or apoptosis. Substantial evidence indicates that energy dysfunction plays either a primary or secondary role in cell death in neurodegenerative and neuromuscular disorders, and even in normal aging. Agents that counteract these defects may therefore be useful as novel therapeutic strategies. Therapeutic supplementation of creatine has been reported to improve cellular ATP resources, inhibit apoptosis and therefore exert neuroprotective properties [204, 205]. In respect to neurorestorative paradigms, we have shown that creatine exposure protected dopaminergic (Fig. 5) and GABA-ergic neurons in experimental *in vitro* models of PD [206] and HD and induced differentiation of neuronal precursors towards the GABA-ergic phenotype [207]. Furthermore, creatine provided neuroprotection on dopaminergic cells during storage in an organ-

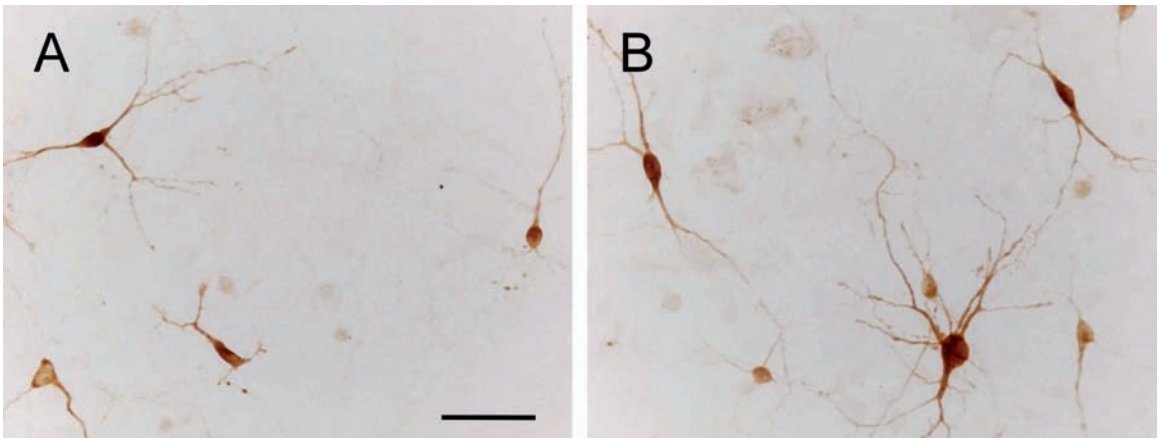

Figure 5

Neuroprotective effects of creatine exposure on densities of dopaminergic neuronal precursors immunostained for the catecholaminergic marker tyrosine hydroxylase in mesencephalic cultures. Cells were grown for 7 days in vitro in absence (A) or presence (B) of creatine [5 mM] in the culture medium. Note the promotion of morphological differentiation of the neurons after exposure to creatine. Scale bar: 50 μm.

otypic tissue culture system [208]. Creatine seems therefore to be one of the most promising neuroprotective substances. In line with this notion, a number of clinical trials were launched or are planned for PD, HD, and ALS.

Endogenous regeneration

The presence of endogenous stem cells and persistent neuronal production in specific regions of the adult human brain [209] suggests a previously unrecognised capacity for regeneration in the CNS. In particular two brain regions, namely the subgranular zone of the hippocampal dentate gyrus, and the forebrain subventricular zones of the lateral ventricles, have been identified as containing stem cells giving rise to neurons and glia [210]. Using 5-bromo-2'-deoxyuridine 5'-monophosphate labeling, it has been shown that experimental stroke [211] and also intermittent hypoxia [212] resulted in stimulation of neurogenesis in the adult brain. It may be speculated that activation or recruitment of these endogenous stem cells, eg, by administration of appropriate drugs and growth factors, might offer fascinating new treatment options for various neurological disease states and also means to prevent brain atrophy during normal aging [213, 214].

Future directions

The findings reported from preclinical and clinical studies demonstrate that cell replacement strategies have the potential to become novel and effective therapeutic approaches for repair of the brain and spinal cord after a variety of degenerative, vascular and traumatic lesions. However, due to the limitations described above, these techniques still remain experimental and can only be applied to small groups of patients in the context of clinical studies, if at all. There are mainly three limitations that have to be overcome in the next years if these strategies should achieve clinical significance. First, a better understanding of the treated disorders is required to further develop and improve regenerative strategies and to achieve a better survival and functional integration of the grafted cells under pathological conditions. Second, the shortage of donor tissue and ethical issues demand an improvement in transplantation efficacy and forced research for alternative tissue sources, like autologous stem cells and neuronal cell lines. Third, possible side effects, eg, dyskinesias after cell transplantation in PD, have to be elucidated and prevented by adequate means.

In our opinion, given the complexity of the field, only a multimodal approach that includes the development of reliable tissue sources, advanced techniques for tissue storage and neural transplantation, effective drugs such as growth factors to induce differentiation towards the required specific neuronal phenotype, and neuroprotective agents to improve sustained graft survival will ensure a successful clinical application of cell replacement strategies. Another potential goal of restorative neuroscience might consist of harvesting a patient's own neural stem cells, *in vitro* expansion and induction of differentiation to the required neuronal phenotypes and reimplantation into the damaged structures of the CNS. If we manage to gain further knowledge how stem cells are activated, differentiate, migrate and establish structural and function interaction with the surrounding cells of the host brain and the extracellular matrix, it may be possible to achieve neuronal repair by activating the endogenous stem cells without the need for any transplantation [138]. This could be accomplished by application of appropriate growth factors and other molecules that interfere with neuronal proliferation and differentiation, for example. Furthermore it may be speculated that activation of endogenous stem cells might prevent atrophy and functional loss in the aging brain, an issue that will become more and more important in the context of our increasing life expectancy.

Conclusions

The field of restorative neuroscience and regeneration in the CNS represents a research area where increasing efforts hope to provide therapeutic options for pathologies for which currently no effective treatment strategies are available. However, much more research is needed to characterise and understand the biology of different types of cells intended for cell replacement therapies both *in vitro* and *in vivo*. Existing clinical data suggest that transplantation is technically feasible and can be carried out safely, but the data on functional outcome and long-term efficiency is still rather preliminary. Taken together, we propose that cell replacement strategies in combination with appropriate growth factors and / or neuroprotective drugs hold the potential to be effective treatment options for a variety of neuropathological conditions.

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