We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

5,300
Open access books available

131,000
International authors and editors

160M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

2

Regenerative Medicine for Cerebral Infarction

Masahiro Kameda and Isao Date
Department of Neurological Surgery, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences
Japan

1. Introduction

Tissue plasminogen activator (t-PA) is the gold standard drug for cerebral infarction in the acute phase (Adams et al., 2007), but it cannot be administered to all cerebral infarction patients. Some patients who survive the acute phase of cerebral infarction suffer from permanent hemiparesis in the chronic phase, which highlights the need for regenerative medicine to play a more important role in treating such individuals. There are two primary approaches to the use of regenerative medicine for patients with cerebral infarction: exogenous stem cell therapies, and enhancement of endogenous stem cells.

Stem cell transplantation is one of the most widely employed strategies using exogenous stem cells. Many studies with experimental animals have shown that stem cell transplantation enhances functional recovery after cerebral infarction (Kameda et al., 2007; Takahashi et al., 2008). Based on the results of animal experiments, several clinical trials for patients with cerebral infarction are currently ongoing, using stem cell transplantation techniques, typically with mesenchymal stem cells (Detante et al.). However, these clinical trials have been started despite a lack of results showing that transplanted stem cells can reliably replace infarct areas. The principal purpose of cell transplantation in these cases is cell replacement, or replacement and restoration of infarct areas. Nevertheless, only a few percent of the transplanted cells typically survive during the chronic phase of cerebral infarction (Lindvall & Kokaia, 2006). Even more problematic is the fact that few of these transplanted stem cells differentiate into neurons with immunohistological and electrophysiological properties (Anderova et al., 2006). Based on these reports, some scientists maintain that functional improvements can be achieved without cell-replacement, that the effects of trophic factors secreted by the transplanted cells are sufficient (Cabrer et al., 2010; Shimada & Spees, 2011).

Another approach that regenerative medicine can take is enhancement of endogenous stem cells, based on methods that are less invasive than the use of exogenous stem cells. Deep brain stimulation (DBS) for Parkinson's disease patients is an example of a standard therapy now used in clinical situations. A previous report using animal subjects has shown that DBS can enhance the neurogenesis of endogenous stem cells (Toda et al., 2008). Based on this report, we evaluated the effectiveness of electrical stimulation on animals with cerebral infarction. Recently, we showed that electrical stimulation of the cerebral cortex during the acute phase of cerebral infarction exerted anti-apoptotic, angiogenic and anti-inflammatory effects through the PI3K-Akt signaling pathway (Baba et al., 2009). Moreover, we showed

that striatal electrical stimulation during the chronic phase of cerebral infarction was effective due to enhancement of endogenous stem cells in response to glial cell-line derived neurotrophic factor (GDNF) and vascular endothelial growth factor (VEGF) upregulation (Morimoto et al., 2010). Electrical stimulation had therapeutic benefit in cerebral infarction cases not only during the acute phase, but also during the chronic phase, which suggests that electrical stimulation has considerable therapeutic potential.

This review summarizes the current consensus concerning regenerative medicine for cerebral infarction, focusing on stem cell transplantation and electrical stimulation techniques, and briefly describes strategies for applying these methods in a clinical setting.

2. Approaches to regenerative medicine for cerebral infarction

2.1 Stem cell transplantation using exogenous stem cells

2.1.1 Donor cell sources

Stem cell transplantation is one of the most established strategies based on the use of exogenous stem cells. Currently, many different types of stem cell can be cultured and transplanted, including induced pluripotent stem cells (iPS cells) (Takahashi & Yamanaka, 2006), embryonic stem cells (ES cells) (Wang et al., 2011), neural stem cells (NSCs) (Kameda et al., 2007; Muraoka et al., 2006) , mesenchymal stem cells (MSCs) (Kurozumi et al., 2004; Wang et al., 2010) , and hematopoietic stem cells (Shyu et al., 2006), and some of these have already been used in clinical trials. Every type of stem cell has unique advantages and disadvantages. Deciding what type of stem cell to transplant requires careful consideration of availability, immune system response, ethical concerns, and the possibility of tumor genesis.

Concerning the availability of stem cells for transplantation, iPS and ES cells are the most promising candidates, but the possibility of tumor formation must be addressed. Many researchers have searched for methods that prevent tumor formation. Regarding iPS cells, for example, Maekawa et al. showed that using maternal transcription factor Glis1 instead of oncogenic c-Myc enhanced the generation of iPS cells when expressed together with key transcription factors Oct3/4, Sox2, and Klf4 (Maekawa et al., 2011).

The majority of animal experiments have demonstrated the neuroprotective effect of transplantation using allografts of adult NSCs or MSCs in the acute phase of ischemia (Kameda et al., 2007; Takahashi et al., 2008), but the effectiveness of stem cell transplantation during the subacute or chronic phase of ischemia was not seen (de Vasconcelos Dos Santos., 2011). To avoid the problem of rejection by the immune system, and ethical issues, autologous stem cell transplantation using adult NSCs and MSCs is attractive, but considerable time is needed to expand these cells so that sufficient quantities are available. Muraoka et al. established an autologous NSC transplantation model using adult rats, in which NSCs were removed from the subventricular zone of adult Fischer 344 rats using stereotactic methods (Muraoka et al., 2008). The NSCs were expanded, which required approximately three weeks, and microinjected into normal hippocampus in the autologous brain. At the present time, MSCs are considered to be a more useful donor cell source in clinical settings than adult NSCs. In Japan, the first clinical trial of autologous MSC transplantation was performed for a patient in the chronic phase of cerebral infarction (Honmou et al., 2011). Detante et al. have started a clinical Phase II trial using autologous MSC transplantation for patients with cerebral infarction, with inclusion criteria that patients must have ischemic stroke confirmed by MRI within the previous 14 days. Based on

the previous results from animal experiments as well as the current clinical situation, autologous stem cell transplantation is considered to be of significant benefit to patients who were not administered rt-PA, provided it is performed in the acute phase three hours after onset.

2.1.2 Delivery methods

There are several stem cell delivery methods, such as intraparenchymal transplantation, intravenous administration and intraarterial administration. With any of these methods, the number of surviving transplanted donor cells is thought to affect the extent of recovery from cerebral infarction. Intraparenchymal transplantation can be performed so that stem cells are delivered in the ischemic penumbra, and it is thus the best method for placing the largest number of stem cells in the desired area of the brain, but this is the most invasive method. Intravenous administration, on the other hand, is the least invasive, but most stem cells end up in the liver and lung (Wang et al., 2010), leaving a much smaller number of stem cells surviving in the area of the ischemic penumbra compared with the intraparenchymal transplantation method. This is why the quantity of stem cells administrated intravenously in animal experiments is roughly an order of magnitude larger than that used in other delivery methods (Li et al., 2008; Lundberg et al., 2011). Lappalainen et al. detected an accumulation of graft cells which were intraarterially administrated in the ischemic brain, using SPECT/CT, but such cells were not observed when administrated intravenously (Lappalainen et al., 2008). At the present time, relatively few papers have explored intraarterial methods of administering stem cells for cerebral infarction in animal models. However, an endovascular technique, superselective intraarterial administration to the penumbra via a micro-catheter, can be performed in a clinical situation, and this method is expected to be less invasive than intraparenchymal transplantation.

2.1.3 Graft survival

Although the therapeutic effect of stem cell transplantation depends upon the rate of stem cell survival, research to date has reported that only approximately 5% survives after transplantation (Lindvall et al., 2004). Cytoprotection can enhance the percentage of graft survival. In particular, GDNF has been shown to be an effective neurotropic factor against ischemic injury. Its neuroprotective effect mainly derives from activation of the phosphatidylinositide-3-kinase/Akt (PI3K/Akt) and mitogen-activated protein kinase/ERK (MAPK/ERK) pathways (Nicole et al., 2001; Treanor et al., 1996). During transplantation, stem cells are subject to hypoxic-ischemic injury. Wang et al. showed that graft survival was enhanced by pretreatment with GDNF for three days before NSC transplantation (Wang et al., 2011). Because brain tissue architecture is disrupted in the ischemic brain, the use of biodegradable scaffolds may help transplanted stem cells regenerate and/or restore damaged brain structures and functions, by affecting cell differentiation, morphology, adhesion, or gene expression (Kleinman & Martin, 2005; Steindler, 2002). Jin et al. showed that transplantation of human neural precursor cells (NPCs) in Matrigel scaffolding at the time of transplantation partially improved therapeutic outcome compared to that of NPCs without Matrigel scaffolding, and that the use of NPC/Matrigel cultures dramatically improved the therapeutic effect (Jin et al., 2010). These reports indicate that, when using transplantation methods employing pre-treatment with GDNF, or Matrigel scaffolding, cytoprotective effects that enhance the survival rate of stem cells require time to develop *in*

vitro before transplantation and that such development might be related to the enhanced cytoprotective effects observed after transplantation.

2.1.4 Functional recovery mechanisms: cell-replacement versus paracrine effects

In experiments with animals, many researchers have confirmed that stem cell transplantation provides neuroprotective effects immediately after transplantation, based on behavioral analyses and histological analyses that show reductions in infarct volume (Kameda et al., 2007; Kurozumi et al., 2004; Takahashi et al., 2008). Histological analyses also showed that the neuroprotective effects were due to enhanced angiogenesis (Onda et al., 2008), anti-apoptotic effects (Kameda et al., 2007; Kurozumi et al., 2004), and so on. A recent paper showed that mononuclear bone marrow cells played a role in a rapidly developed neuroprotective effect by increasing cerebral blood flow six hours after transplantation, followed by evidence of angiogenesis (Fujita et al., 2010). Yilmaz et al. described remarkable induction of genes for nerve guidance survival (e.g., cytokine receptor-like factor 1, glypican 1, Dickkopf homolog2, osteopontin), as well as increased expression of neurogenerative, nerve guidance, and angiogenic factors (bFGF, bone morphogenetic protein, angiopoietins, neural growth factor), after transplantation with bone marrow stromal cells (Yilmaz et al., 2010). Angiogenesis and anti-apoptotic effects are preferable for neuroprotection, and if the goal were limited to functional recovery, these neuroprotective mechanisms might be sufficient. However, in a strict sense, stem cell transplantation is expected to provide for cell replacement, since stem cells have two outstanding capacities, namely, self-renewal and pluripotency, which means that they can produce neurons, astrocytes and oligodendrocytes (Gage, 2000; Okano, 2002; Temple, 2001).

Cell-replacement therapy requires that transplanted stem cells survive in the damaged brain, differentiate into mature cells, then replace neurons of several phenotypes, and reconstruct new networks with host cells. Several approaches have been studied to enhance neuronal differentiation, and one approach is to transplant site-specific cells. If the site-specific characteristics of NSCs can be maintained during *in vitro* expansion, such cells may differentiate into site-specific neurons after transplantation. Another approach is to modify the cellular characteristics of the stem cells differentiation by transfecting a trophic factor gene (Kameda et al., 2007; Kurozumi et al., 2004). We have showed that, compared with unmodified stem cells, neuronal differentiation is enhanced by transplanting into the ischemic brain adult neural stem/progenitor cells that were modified to secrete GDNF. This enhancement of the differentiation is usually difficult to detect in the ischemic core, and is typically found only in the small ischemic boundary zone. Also, we are still not able to effect a complete replacement of the damaged infarct area using transplanted stem cells.

Liu et al. have shown that DCX-expressing immature neurons in the subventricular zone (SVZ) do not exhibit a Na+ current, and their resting membrane potential is approximately -25mV in the absence of ischemic insult, however, after ischemic insult, such neurons do exhibit a Na+ current, and the membrane potential is hyperpolarized to about -54mV, a voltage similar to that of mature neurons. They also showed that gene analysis indicates that immature DCX cells express immature markers for Sox 2 and nestin in the absence of ischemic insult, but tyrosine hydroxylase (TH) is expressed as a mature marker after ischemic insult (Liu et al., 2009). After ischemic insult, immature stem cells become able to express the same phenotypes as mature neurons.

Research published during the last three years, however, indicates that cell replacement via stem cells transplantation is not essential to functional recovery (Ramos-Cabrer et al., 2010; Shimada & Spees, 2011). Previously, there was a research trend that aimed specifically at developing cell replacement therapies, as many researchers sought better methods to improve graft survival rates and enhance neuronal differentiation. Nevertheless, the present survival rate for transplanted cells during the chronic phase of cerebral infarction remains in the single digits (Lindvall et al., 2004), and few transplanted stem cells differentiate into neurons with immunohistological and electrophysiological properties (Anderova et al., 2006). This has been interpreted by some researchers as indicating that functional improvements can be achieved without cell replacement, and that the effects of trophic factors secreted by the transplanted cells are sufficient. Ramos-Cabrer et al. recently have shown that post-stroke functional recovery after stem cell transplantation is due to paracrine mechanisms, not cell replacement. They found no evidence of surviving grafted stem cells six months after stem cell transplantation, and, compared with control animals, functional recovery was confirmed even during the chronic phase of cerebral infarction (Ramos-Cabrer et al., 2010). This report supports a new interpretation concerning the importance of paracrine mechanisms to functional recovery from cerebral infarction. Based on this new interpretation, clinical trials using stem cells to treat cerebral infarction are presently ongoing (Detante et al.).

2.1.5 Future directions

An increasing number of research papers on stem cell transplantation are focused on the neuroprotective effects provided by paracrine mechanisms (Shimada & Spees, 2011; Sun et al., 2010). Although cell replacement therapy is likely to remain an important target of stem cell transplantation, the focus on paracrine mechanisms will spur the development of clinical trials, for which long-term efficacy and safety are crucial evaluative factors. Thus, standardization of techniques will be more important compared with the procedures used in animal experiments. Furthermore, it has been reported that the quality of transplanted stem cells profoundly affects the functional outcome. Assmus et al. reported the results of the REPAIR-AMI (Reinfusion of Enriched Progenitor cells And Infarct Remodeling in Acute Myocardial Infarction) trial, and showed that contamination by red blood cells affected the functionality of isolated bone marrow-derived progenitor cells, and ultimately inhibited recovery from acute myocardial infarction (Assmus et al., 2010). An increasing number of clinical trials applying stem cell therapies for cerebral infarction will be started in the near future, and cell preparation will play a vital role for proper interpretation of the results.

2.2 Enhancement of endogenous stem cells

2.2.1 Long-term potentiation (LTP)

Another useful approach for regenerative medicine in cerebral infarction cases is to enhance endogenous stem cells. LTP is thought to be a cellular and molecular mechanism of hippocampal learning and memory (Bliss & Collingridge, 1993). LTP is observed as a long-lasting enhancement in the efficacy of synaptic transmissions, which requires NMDA receptor activation and increased Ca^{2+} influx. LTP can be induced by brief high-frequency stimulation. Chen et al. showed that high-frequency stimulation or tetanic stimulation induced the release of Wnt3a from hippocampal neurons (Chen et al., 2006). Wnt3a has been shown to be a major regulator of neurogenesis *in vivo* and *in vitro*, and blocking Wnt3a

expression has been reported to cause a significant decline in neuronal generation (Davidson et al., 2007). Moreover, recent papers suggest that LTP *per se* enhances neurogenesis (Bruel-Jungerman et al., 2006; Chun et al., 2006, 2009). These findings, linking LTP stimulation to the activation of a large latent neural precursor pool in the dentate gyrus, could explain the ability of specific environmental stimuli to increase the rate of neurogenesis in the hippocampus over prolonged periods.

2.2.2 Exercise

It is now widely accepted that exercise (van Praag et al., 1999), enriched environments (Kempermann et al., 1997), and learning tasks (Gould et al., 1999), can enhance the neurogenesis of endogenous stem cells, and affect regulatory mechanisms that may be linked to LTP. Exercise has been shown to enhance neurogenesis in both intact and disease animal models. Tajiri et al. showed that exercise had neuroprotective effects on a Parkinson's disease model in rats, with enhanced neurogenesis and migration toward the lesioned striatum observed. Furthermore, brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF) showed increases in the striatum as a consequence of exercise (Tajiri et al., 2010). Li et al. showed that whisker stimulation, as a peripheral stimulation after focal barrel cortex ischemia, enhanced migration from the subventricular zone, and increased the neurogenesis of endogenous stem cells, due to increased vascular endothelial growth factor (VEGF) and stromal-derived factor-1 expression (SDF-1) in the penumbra. They also showed that local cerebral blood flow recovered to a greater degree due to whisker stimulation (Li et al., 2008). This indicates that increased peripheral stimulation and afferent signals to the ischemic cortex can activate endogenous neural stem cells, cause them to migrate to the injured region, and differentiate into mature neurons. Thus, the beneficial aspects of rehabilitation are recognized as being vital to long-term recovery from ischemic stroke.

2.2.3 Electrical stimulation and repetitive transcranial magnetic stimulation

Electrical stimulation and repetitive transcranial magnetic stimulation have been used in clinical situations for treatment of many central nervous system diseases, for example Parkinson's disease (PD) (Fasano et al., 2010), epilepsy (Fisher et al., 2010), depression (Horvath et al.,2010) , and chronic pain (Rasche et al., 2006). Deep brain stimulation (DBS) has become a standard clinical therapy for PD patients and it can ameliorate motor function in such individuals, although the mechanism remains poorly understood. Toda et al. showed that DBS of the anterior nucleus of the thalamus (AN) enhanced the presence of endogenous stem cells in the hippocampal dentate gyrus and enhanced neurogenesis, which were associated with enhanced behavioral performance. Moreover, they showed that DBS of the AN reversed steroid-induced reductions in neurogenesis (Toda et al., 2008), implying that DBS can modulate synaptic plasticity and hippocampal neurogenesis.

Based on these reports, we have tried to evaluate whether electrical stimulation has a neuroprotective effect that mitigates cerebral infarction damage by the enhancement of endogenous stem cells and neurogenesis. We began with epidural stimulation because we wanted to stimulate the brain using a method that is less invasive compared with the use of exogenous stem cells for stem cell transplantation. In one of our experiments, rats received continuous electrical stimulation above the cerebral cortex during the acute phase of cerebral infarction. This stimulation increased cerebral blood flow, enhanced behavioral

recovery and reduced infarct volume. The neuroprotective effect was derived from anti-apoptotic, angiogenic and anti-inflammatory effects through the PI3K-Akt signaling pathway (Baba et al., 2009). As a next step, we hypothesized that electrical stimulation of the striatum could enhance the proliferation, migration, and neuronal differentiation of endogenous stem cells in the subventricular zone even during the chronic phase of the ischemic brain. Striatal electrical stimulation during the chronic phase of cerebral infarction was observed to enhance behavioral recovery and reduce infarct size. This neuroprotective effect was derived from stimulation of endogenous angiogenesis and neurogenesis with GDNF and VEGF upregulation (Morimoto et al., 2010). Machado et al. showed that chronic contralesional electrical stimulation of the lateral cerebellar nucleus improved motor recovery in rats following ischemic strokes, an effect derived from increased perilesional cortical excitability via chronic activation of the dentatothalamocortical pathway (Machado et al., 2009).

Transcranial direct current stimulation (tDCS) has been used in animal experiments and for chronic stroke patients. tDCS is thought to strengthen synaptic connections (Cheeran et al., 2008; Hummel et al., 2005; Nitsche et al., 2003, 2004), through a mechanism similar to that of LTP. Fritsch et al. showed that tDCS improved motor skill learning through enhanced synaptic plasticity that required brain-derived neurotrophic factor (BDNF) secretion and TrkB activation (Fritsch et al., 2010).

Vagus nerve stimulation (VNS) has been used in an animal model of ischemia, and patients given this therapy have demonstrated enhanced behavioral recovery and reduced infarction size (Ay et al., 2009). The potential mechanisms for the observed beneficial effects of VNS are thought to be the suppression of increased neuronal excitability, and the reduction of cytokine overproduction and inflammation. Collectively, electrical stimulation has been shown to have therapeutic benefit in cases of cerebral infarction not only in the acute phase but also in the chronic phase, which suggests that electrical stimulation has considerable therapeutic potential.

In addition to electrical stimulation, repetitive transcranial magnetic stimulation (rTMS) has been used in animal models of ischemia (Kaga et al., 2003), and in infarct patients with aphasia (Weiduschat et al., 2011), and has shown enhanced functional recovery. Compared with electrical stimulation, rTMS is more widely used because patients can avoid the surgery required for electrode implantation. It is presumed that the mechanism of its neuroprotective effect derives from increased glucose metabolism, inhibition of apoptosis in the ischemic hemisphere (Gao et al., 2010), and increased expression of c-fos, which is followed by upregulation of BDNF (Zhang et al., 2007).

2.2.4 Rehabilitation combined with electrical stimulation

Currently, after cerebral infarction, electrical stimulation (especially epidural electrical stimulation) is mainly performed together with rehabilitation, to enhance the functional recovery that normally occurs during rehabilitation. Northstar Neuroscience has performed clinical trials using epidural electrical stimulation for infarct patients with upper extremity hemiparesis (Northstar Neuroscience, formerly of Seattle, WA, U.S.A.). Unfortunately, the results of a Phase III randomized trial were unsuccessful, but the Phase II study showed that this therapeutic intervention is both safe and effective. Recently, preliminary study results from the same group showed that patients with non-fluent aphasia benefitted from speech-language therapy in combination with epidural electrical stimulation of the premotor cortex,

identified by fMRI. Patients with moderate as well as severe aphasia showed functional improvements after epidural electrical stimulation (Cherney et al., 2010).

2.2.5 Parameters and stimulation patterns

As mentioned above, electrical stimulation and transcranial magnetic stimulation can be of significant functional benefit to individuals who have suffered a cerebral infarction. However, stimulation parameters can vary widely even for the same stimulation method. For example, in some of our research on epidural stimulation, we used continuous stimulation with 2Hz pulses of 1ms width at an intensity of 100μA. On the other hand, Moon et al. used intermittent stimulation with 50Hz pulses of 194ms width whose intensity was flexibly adjusted to evoke movement of a forelimb. They also compared the duration of stimulation, and observed that compared to continuous stimulation, intermittent stimulation enhanced functional recovery more effectively (Moon et al., 2009).

The neuroprotective and neurorestorative effects of electromagnetic stimulation depend on the stimulation parameters and pattern. Moon et al. mentioned that the pattern and intensity of stimulation should be modified on an individual basis depending on the extent of the infarct. The efficacy of the results is affected by a large number of parameters, such as the frequency, intensity, pulse width, and duration of the stimulation (i.e., whether it is continuous or intermittent), and the stimulation target area and electrode resistance. Since the best combination of stimulation parameters and pattern are unknown at the outset, researchers tend to stimulate the ischemic brain using different stimulation parameters and patterns, searching for the combination that best enhances the neuroprotective and neurorestorative effects.

Regarding the frequency of stimulation, the difference in effect between high-frequency stimulation and low-frequency stimulation is usually explained as a consequence of different cellular and molecular mechanisms, LTP versus long-term depression (LTD), because synaptic plasticity is one of the mechanisms responsible for enhanced functional recovery due to electrical stimulation. Based on numerous previous reports, brief high-frequency stimulation (100Hz or higher) can induce long-term potentiation (LTP). On the other hand, brief low-frequency stimulation (1 or 2Hz) can induce long-term depression (LTD), which impairs long-lasting enhancement of synaptic transmission. Thus, the mechanism of enhanced recovery observed in response to high-frequency stimulation is discussed in terms of LTP, whereas low-frequency stimulation fails to induce functional recovery.

The duration of stimulation also affects the outcome. Brief high-frequency stimulation induces LTP, but this does not mean that continuous high-frequency stimulation will do the same. In a preliminary study, we could not confirm reductions in infarction volume after continuous high-frequency stimulation, compared with application of low-frequency stimulation (Baba et al., 2009). This implies that inappropriate parameters and stimulation patterns may simply cause tissue damage, and provide no therapeutic effect.

The condition of the brain also affects the results. Most LTP experiments conducted in the field of electrophysiological research are performed using intact rats and mice. As described above, NMDA receptor activation and increased Ca^{2+} influx are required for the induction of LTP. Increased Ca^{2+} influx is also observed in ischemia and because the ischemic brain has already been exposed to increased Ca^{2+} influx, the response to high-frequency

stimulation that can induce LTP in intact animals would be different in animals with cerebral infarction.

Although LTP is a possible mechanism whereby electrical stimulation enhances functional recovery, it is likely that other mechanisms are also involved. Electrical stimulation can induce increased regional cerebral blood flow, suppress inflammatory responses, induce anti-apoptotic responses, and enhance angiogenesis, which, individually and in combination, modulate the microenvironment of the infarct brain to enable functional recovery. This implies that electrical stimulation should be performed using appropriate parameters and stimulation patterns that are tailored for the condition of the brain.

2.2.6 Future directions

Due to a recent finding, that aged mice contain a larger pool of latent stem cells than can be activated (Walker et al., 2008), determining the best parameter settings and pattern of electromagnetic stimulation that will yield the best possible functional outcomes in patients with cerebral infarction is of paramount importance. To find ideal parameter values and patterns, the mechanism of electrical and magnetic stimulation must be elucidated in more detail. Given the failure of the Northstar Neuroscience Phase III trial in which epidural electric stimulation was used, rTMS will likely play a more important role for cerebral infarction patients in the future, because it is a less invasive technique. And, although improving cerebral infarction treatment procedures is of vital importance, primary stroke prevention is also essential. Simvastatin enhances hippocampal LTP in mice and causes a significant increase in Akt phosphorylation (Mans et al., 2010), and since LTP *per se* can enhance neurogenesis, as mentioned earlier, this medication should be effective for preventing primary stroke as well as hyperlipidemia. In short, the protection and enhancement of endogenous stem cells may be a key factor in the maintenance and prolongation of health.

2.3 Progress in ischemia analysis methods

Thus far, we have outlined basic therapeutic strategies for treating cerebral ischemia, based on the use of exogenous stem cells and the enhancement of endogenous stem cells. Improvement in therapeutic strategies and further elucidation of the ischemia mechanism in greater detail are both important.

To elucidate the mechanism of ischemia, and the actions of regenerative medicine, we need to analyze the neuronal activity in the ischemic brain by examining the response of single cells, as well as the response of large populations of neurons. For this purpose, the combination of MRI examinations (especially fMRI) and electrophysiological analysis are useful, because fMRI signals are thought to be proportional to the local average of neuronal activity.

The use of fMRI provides a major breakthrough not only in animal experiments but also in treatment of patients. As mentioned above, fMRI enables the enhancement of patient rehabilitation after stroke, via epidural electrical stimulation and detection of premotor cortex function. Using fMRI techniques, functional recovery after ischemia can be monitored, as originally functional areas are reactivated, with preservation of neurovascular coupling (Weber et al., 2008). fMRI also can reveal ipsilateral cortical fMRI responses after peripheral nerve damage, so that increased interneuron activity can be observed. Thus, fMRI enables analysis of modifications in fiber connections, such as callosal

interhemispheric projections (Pelled et al., 2009). The use of voltage-sensitive dyes also provides a similar correlation with extracellular direct current potential recording, which enables the analysis of molecular mechanisms of ischemia from an electrophysiological point of view (Farkas et al., 2008). Voltage-sensitive dye techniques allow sensory-evoked depolarization after cerebral infarction to be analyzed in considerable detail (Siglera et al., 2009).

The comparison of results derived from MRI examinations with those obtained from electrophysiological analysis would also be useful. The ischemic penumbra is a major target when attempting to treat cerebral infarction. From an electrophysiological point of view, depolarization is induced in the ischemic core and brief depolarization is induced in peri-infarct areas. Unlike electrophysiological analysis, diffusion-weighted imaging (DWI) in MRI does not include peri-infarct areas, defined as areas where a brief depolarization is seen during an electrophysiological examination. Thus, electrophysiological analysis can detect wider areas of damage than those detectable using histological or MRI techniques (Breschi et al., 2010). Behavioral analysis and fMRI analysis are typically usually used when analyzing and evaluating functional recovery, but electrophysiological analysis is seldom performed. The pursuit of cross-sectional analysis in greater depth should help to clarify the mechanism of cerebral infarction.

3. Conclusion

We have reviewed the therapeutic effect of stem cell transplantation and techniques for the enhancement of endogenous stem cells. As described above, previous studies have shown that functional recovery after cerebral infarction can be enhanced by stem cell transplantation, and that electromagnetic stimulation can provide neuroprotective and/or neurorestorative effects in animal models of ischemia. These results will stimulate additional clinical studies, but the development of more effective and reliable therapies will require further analysis.

4. Acknowledgments

We deeply appreciate the valuable support provided by Prof. Perry Bartlett, Prof. Cliff Abraham, Dr. Tara Walker, and Dr. Takao Yasuhara. We also appreciate the effort and contributions of Drs. Tanefumi Baba, Naoki Tajiri, Feifei Wang, and Takamasa Morimoto.

5. References

Adams, Jr, HP.; Zoppo, Gd.; Alberts, MJ.; Bhatt, DL.; Brass, L.; Furlan, A.; Grubb, RL.; Higashida, RT.; Jauch, EC.; Kidwell, C.; Lyden, PD.; Morgenstern, LB.; Qureshi, AI.; Rosenwasser, RH.; Scott, PA.; & Wijdicks, EFM. (2007). Guidelines for the Early Management of Adults With Ischemic Stroke. *Stroke*, 38, pp.1655-1711.

Anderova, M.; Kubinova, S.; Jelitai, M.; Neprasova, H.; Glogarova, K.; Prajerova, I.; Urdzikova, L.; Chvatal, A.; & Sykova, E. (2006). Transplantation of embryonic neuroectodermal progenitor cells into the site of a photochemical lesion: immunohistochemical and electrophysiological analysis. *J Neurobiol.*, 66(10), pp. 1084-1100.

Assmus, B.; Tonn, T.; Seeger, FH.; Yoon, CH.; Leistner, D.; Klotsche, J.; Schächinger, V.; Seifried, E.; Zeiher, AM.; & Dimmeler, S. (2010). Red Blood Cell Contamination of the Final Cell Product Impairs the Efficacy of Autologous Bone Marrow Mononuclear Cell Therapy. *Journal of the American College of Cardiology*, Vol. 55, No. 13, ISSN 0735-1097/10/$36.00, doi:10.1016/j.jacc.2009.10.059

Ay, I.; Lu, J.; Ay, H.; Sorensen, AG. (2009). Vagus nerve stimulation reduces infarct size in rat focal cerebral ischemia. *Neuroscience Letters*, 459, pp. 147–151.

Baba, T.; Kameda, M.; Yasuhara, T.; Morimoto T.; Kondo, A.; Shingo, T.; Tajiri, N.; Wang, F.; Miyoshi, Y.; Borlongan, CV.; Matsumae, M.; Date, I. (2009). Electrical Stimulation of the Cerebral Cortex Exerts Antiapoptotic, Angiogenic, and Anti-Inflammatory Effects in Ischemic Stroke Rats Through Phosphoinositide 3-Kinase/Akt Signaling Pathway. *Stroke*, 40, pp. e598-e605.

Bliss, TV.; & Collingridge, GL. (1993). A synaptic model of memory: long-term potentiation in the hippocampus. *Nature*, 361, pp. 31-39.

Breschi, GL.; Librizzi, L.; Pastori, C.; Zucca, I.; Mastropietro, M.; Cattalini, A. & Curtis, Md. (2010). Functional and structural correlates of magnetic resonance patterns in a new in vitro model of cerebral ischemia by transient occlusion of the medial cerebral artery, *Neurobiology of Disease*, 39, pp. 181–191.

Bruel-Jungerman, E.; Davis, S.; Rampon, C.; & Laroche, S. (2006). Long-term potentiation enhances neurogenesis in the adult dentate gyrus. *The Journal of Neuroscience,* 26, pp. 5888-5893.

Cabrer, PR.; Justicia, C.; Wiedermann, D.; & Hoehn, M. (2010). Stem Cell Mediation of Functional Recovery after Stroke in the Rat. *PLos ONE,* Volume 5, Issue 9, e12779.

Cheeran, B.; Talelli, P.; Mori, F.; Koch, G.; Suppa, A.; Edwards, M.; Houlden, H.; Bhatia, K.; Greenwood, R.; & Rothwell, JC. (2008). A common polymorphism in the brain-derived neurotrophic factor gene (BDNF) modulates human cortical plasticity and the response to rTMS. *J. Physiol.*, 586, pp. 5717–5725.

Chen, J.; Park, CS.; & Tang, SJ. (2006). Activity-dependent synaptic Wnt release regulates hippocampal long term potentiation. *J Biol Chem*., 281, pp. 11910-11916.

Cherney, LR.; Erickson, RK.; & Small, SL. (2010). Epidural cortical stimulation as adjunctive treatment for non-fluent aphasia: preliminary findings. *J Neurol Neurosurg Psychiatry*, 81, pp.1014e1021, doi:10.1136/jnnp.2009.184036.

Chun, SK.; Sun, W.; Park, JJ.; & Jung, MW. (2006). Enhanced proliferation of progenitor cells following long-term potentiation induction in the rat dentate gyrus. *Neurobiol Learn Mem*, 86, pp. 322-329.

Chun, SK.; Sun, W.; & Jung, MW. (2009). LTD induction suppresses LTP-induced hippocampal adult neurogenesis. *Neuroreport*, 23, 20(14), pp 1279-1283.

Davidson, KC.; Jamshidi, P.; Daly, R.; Hearn, MT.; Pera, MF.; & Dottori, M. (2007). Wnt3a regulates survival, expansion, and maintenance of neural progenitors derived from human embryonic stem cells. *Mol Cell Neurosci*., 36, pp. 408-415.

Detante, O.; Intravenous Stem Cells After Ischemic Stroke (ISIS), Available from http://clinicaltrials.gov/ct2/show/NCT00875654?term=mesenchymal+stem+cell+infarction&rank=10 de Vasconcelos Dos Santos, A.; da Costa Reis, J.; Diaz Paredes, B.; Moraes, L.; Jasmin.; Giraldi-Guimaraes, A.; & Mendez-Otero, R. (2011). Therapeutic window for treatment of cortical ischemia with bone marrow-derived cells in rats. *Brain Research*, 1306, pp. 149-158.

Farkas, E.; Pratt, R.; Sengpiel, F.; & Obrenovitch, TP. (2008). Direct, live imaging of cortical spreading depression and anoxic depolarisation using a fluorescent, voltage-sensitive dye. *J Cereb Blood Flow Metab.,* 28(2), pp.251–262, doi:10.1038/sj.jcbfm.9600569

Fasano, A.; Romito,LM.; Daniele, A.; Piano, C.; Zinno, M.; Bentivoglio, AR.; & Albanese, A. (2010). Motor and cognitive outcome in patients with Parkinson's disease 8 years after subthalamic implants. *Brain*, 133(9), pp 2664-2676.

Fisher, R.; Salanova, V.; Witt, T.; Worth, R.; Henry, T.; Gross, R.; Oommen, K.; Osorio, I.; Nazzaro, J.; Labar, D.; Kaplitt, M.; Sperling, M.; Sandok, E.; Neal, J.; Handforth, A.; Stern, J.; DeSalles, A.; Chung, S.; Shetter, A.; Bergen, D.; Bakay, R.; Henderson, J.; French, J.; Baltuch, G.; Rosenfeld, W.; Youkilis, A.; Marks, W.; Garcia, P.; Barbaro, N.; Fountain, N.; Bazil, C.; Goodman, R.; McKhann, G.; Babu, Krishnamurthy, K.; Papavassiliou, S.; Epstein, C.; Pollard, J.; Tonder, L.; Grebin, J.; Coffey, R.; Graves, N.; & SANTE Study Group. (2010). Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. *Epilepsia*, 51(5), pp. 899-908.

Fritsch, B.; Reis, J.; Martinowich, K.; Schambra, HM.; Ji, Y.; Cohen, LG.; & Lu, B. (2010). Direct Current Stimulation Promotes BDNF-Dependent Synaptic Plasticity: Potential Implications for Motor Learning. *Neuron,* 66, pp.198–204.

Fujita, Y.; Ihara, M.; Ushiki, T.; Hirai, H.; Kizaka-Kondoh, S.; Hiraoka, M.; Ito, H.; Takahashi, R. (2010). Early Protective Effect of Bone Marrow Mononuclear Cells Against Ischemic White Matter Damage Through Augmentation of Cerebral Blood Flow. *Stroke*, 41, pp.2938-2943.

Gage, FH. (2000). Mammalian neural stem cells. *Science*, 287, pp. 1433–1438.

Gao, F.; Wang, S.; Guo, Y.; Wang, J.; Lou, M.; Wu, J.; Ding, M.; Tian, M.; & Zhang, H. (2010). Protective effects of repetitive transcranial magnetic stimulation in a rat model of transient cerebral ischaemia: a microPET study. *Eur J Nucl Med Mol Imaging*, 37, pp. 954–961

Gould, E.; Beylin, A.; Tanapat, P.; Reeves, A.; & Shors, TJ. (1999). Learning enhances adult neurogenesis in the hippocampal formation. *Nat Neurosci.,* 2, 260-265.

Honmou, O.; Houkin, K.; Matsunaga, T.; Niitsu, Y.; Ishiai, S.; Onodera, R.; Waxman, SG.; & Kocsis, JD. (2011). Intravenous administration of auto serum-expanded autologous mesenchymal stem cells in stroke. *Brain*, 134(Pt 6), pp. 1790-1807.

Horvath, JC.; Mathews, J.; Demitrack, MA.; Pascual-Leone, A. (2010). The NeuroStar TMS device: conducting the FDA approved protocol for treatment of depression. *J Vis Exp.*, 45, pii: 2345, doi: 10.3791/2345.

Hummel, F.; Celnik, P.; Giraux, P.; Floel, A.; Wu, WH.; Gerloff, C.; & Cohen, LG. (2005). Effects of non-invasive cortical stimulation on skilled motor function in chronic stroke. *Brain,* 128, pp. 490–499.

Jin, K.; Mao, XO.; Xie, L.; Galvan, V.; Lai, B.; Wang, Y.; Gorostiza, O.; Wang, X.; & Greenberg, DA. (2010). Transplantation of Human Neural Precursor Cells in Matrigel Scaffolding Improves Outcome from Focal Cerebral Ischemia after Delayed Postischemic Treatment in Rats. *J Cereb Blood Flow Metab.*, 30(3), pp. 534–544, doi:10.1038/jcbfm.2009.219.

Kaga, A.; Fujiki, M.; Hori, S.; Nakano, T.; & Isono, M. (2003). Motor evoked potentials following transcranial magnetic stimulation after middle cerebral artery and/or basilar artery occlusions in rats. *Journal of Clinical Neuroscience,* 10(4), pp. 470–475

Kameda, M.; Shingo, T.; Takahashi, K.; Muraoka, K.; Kurozumi, K.; Yasuhara, T.; Maruo, T.; Tsuboi, T.; Uozumi, T.; Matsui, T.; Miyoshi, Y.; Hamada, H.; & Date, I. (2007). Adult neural stem and progenitor cells modified to secrete GDNF can protect, migrate and integrate after intracerebral transplantation in rats with transient forebrain ischemia. *European Journal of Neuroscience*, Vol. 26, pp. 1462–1478.

Kempermann, G.; Kuhn, H.G.; & Gage, FH. (1997). More hippocampal neurons in adult mice living in an enriched environment. *Nature* 386, pp. 493-495.

Kleinman, HK.; & Martin, GR. (2005). Matrigel: basement membrane matrix with biological activity. *Seminars in Cancer Biology*, 15:5, pp. 378-386.

Kurozumi, K.; Nakamura, K.; Tamiya, T.; Kawano, Y.; Kobune, M.; Hirai, S.; Uchida, H.; Sasaki, K.; Ito, Y.; Kato, K.; Honmou, O.; Houkin, K.; Date, I.; & Hamada, H. (2004). BDNF gene-modified mesenchymal stem cells promote functional recovery and reduce infarct size in the rat middle cerebral artery occlusion model. Mol Ther., 9(2), pp. 189-197.

Lappalainena, RS.; Narkilahti, S.; Huhtal, T.; Liimatainen, T.; Suuronen. T.; N¨arv¨anen, A.; Suuronena, R.; Hovatta, O.; & Jolkkonend, J. (2008). The SPECT imaging shows the accumulation of neural progenitor cells into internal organs after systemic administration in middle cerebral artery occlusion rats. *Neuroscience Letters*, 440, pp. 246–250.

Li, WL.; Yu, SP.; Ogle, ME.; Ding, XS.; & Wei, L. (2008). Enhanced Neurogenesis and Cell Migration following Focal Ischemia and Peripheral Stimulation in Mice. *Dev Neurobiol*., 68(13), pp.1474–1486, doi:10.1002/dneu.20674.

Lindvall, O.; Kokaia, Z.; & Martinez-Serrano, A. (2004). Stem cell therapy for human Neurodegenerative disorders–how to make it work. *Nature Medicine,* 10, pp. S42–S50

Lindvall, O.; & Kokaia, Z. (2006). Stem cells for the treatment of neurological disorders. *Nature,* Vol 441, doi:10.1038/nature04960

Liu, XS.; Chopp, M.; Zhang, XG.; Zhang, RL.; Buller, B.; Hozeska-Solgot, A.; Gregg, SR.; & Zhang. ZG. (2009). Gene profiles and electrophysiology of doublecortin-expressing cells in the subventricular zone after ischemic stroke. *J Cereb Blood Flow Metab*., 29(2), pp. 297–307., doi:10.1038/jcbfm.2008.119.

Lundberg J, Södersten E, Sundström E, Blanc KL, Andersson T, Hermanson O, Holmin S. (2011) Targeted Intra-arterial Transplantation of Stem Cells to the Injured CNS is More Effective than Intravenous Administration - Engraftment is Dependent on Cell Type and Adhesion Molecule Expression. *Cell Transplant*., Epub ahead of print.

Maekawa M, Yamaguchi K, Nakamura T, Shibukawa R, Kodanaka I, Ichisaka T, Kawamura Y, Mochizuki H, Goshima N, Yamanaka S. (2011). Direct reprogramming of somatic cells is promoted by maternal transcription factor Glis1. *Nature*, 474(7350), pp. 225-229.

Mans, RA.; Chowdhury, N.; Cap, D.; McMahon, LL.; & Li, L. (2010). Simvastatin enhances hippocampal long-term potentiation in C57BL/6 mice. *Neuroscience*, 166, pp. 435–444.

Moon, SK.; Shin, YI.; Kim, HI.; Kim, H.; Lee, JO.; & Lee, MC. (2009). Effect of prolonged cortical stimulation differs with size of infarct after sensorimotor cortical lesions in rats. *Neuroscience Letters*, 460, pp. 152–155

Morimoto, T.; Yasuhara, T.; Kameda, M.; Baba, T.; Kuramoto, S.; Kondo, A.; Takahashi, K.; Tajiri, N.; Wang, F.; Meng, J.; Ji, YW.; Kadota, T.; Maruo, T.; Kinugasa, K.; Miyoshi, Y.; Shingo, T.; Borlongan, CV.; & Date, I. (2010). Striatal stimulation nurtures endogenous neurogenesis and angiogenesis in chronic-phase ischemic stroke rats. DOI: 10.3727/096368910X544915

Muraoka, K.; Shingo, T.; Yasuhara, T.; Kameda, M.; Yuan, W.; Hayase, H.; Matsui, T.; Miyoshi, Y.; & Date, I. (2006). The high integration and differentiation potential of autologous neural stem cell transplantation compared with allogeneic transplantation in adult rat hippocampus. *Experimental Neurology*, 199, pp. 311–327.

Muraoka, K.; Shingo, T.; Yasuhara, T.; Kameda, M.; Yuen, WJ.; Uozumi, T.; Matsui, T.; Miyoshi, Y.; & Date, I. (2008). Comparison of the therapeutic potential of adult and embryonic neural precursor cells in a rat model of Parkinson disease. *J Neurosurg*, 108, pp. 149–159.

Nicole, O.; Ali, C.; Docagne, F.; Plawinski, L.; MacKenzie, ET.; Vivien, D.; & Buisson, A. (2001). Neuroprotection mediated by glial cell line-derived neurotrophic factor: involvement of a reduction of NMDA-induced calcium influx by the mitogen-activated protein kinase pathway. *J Neurosci.,* 21(9), pp. 3024-3033.

Nitsche, MA.; Fricke, K.; Henschke, U.; Schlitterlau, A.; Liebetanz, D.; Lang, N.; Henning, S.; Tergau, F.; & Paulus, W. (2003). Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. *J. Physiol.*, 553, pp. 293–301.

Nitsche, MA.; Liebetanz, D.; Schlitterlau, A.; Henschke, U.; Fricke, K.; Frommann, K.; Lang, N.; Henning, S.; Paulus, W.; & Tergau, F. (2004). GABAergic modulation of DC stimulation-induced motor cortex excitability shifts in humans. *Eur. J. Neurosci.*, 19, pp. 2720–2726

Northstar Neuroscience.; Safety and Effectiveness of Cortical Stimulation in the Treatment of Stroke Patients With Upper Extremity Hemiparesis (EVEREST), available from http://clinicaltrials.gov/ct2/show/NCT00170716?term=epidural+stimulation&rank=5

Okano, H. (2002) Neural stem cells: progression of basic research and perspective for clinical application. *Keio J. Med.*, 51, pp. 115–128.

Onda, T.; Honmou, O.; Harada, K.; Houkin, K.; Hamada, H.; & Kocsis, JD. (2008). Therapeutic benefits by human mesenchymal stem cells (hMSCs) and Ang-1 gene-modified hMSCs after cerebral ischemia. *J Cereb Blood Flow Metab.,* 28(2), pp. 329-340.

Pelled, G.; Bergstrom, DA.; Tierney, PL.; Conroy, RS.; Chuanga, KH.; Yud, D.; Leopolde, DA.; Waltersb, JR.; & Koretskya, AP. (2009). Ipsilateral cortical fMRI responses after peripheral nerve damage in rats reflect increased interneuron activity. *PNAS,* vol. 106, no. 33, pp. 14114–14119.

Ramos-Cabrer, P.; Justicia, C.; Wiedermann, D.; & Hoehn, M. (2010). Stem Cell Mediation of Functional Recovery after Stroke in the Rat. *PLoS one,* 5(9), e12779

Rasche, D.; Rinaldi, PC.; Young, RF.; & Tronnier, VM. (2006). Deep brain stimulation for the treatment of various chronic pain syndromes. *Neurosurg Focus,* 21(6), E8.

Shimada, IS.; & Spees, JL. (2011). Stem and Progenitor Cells for Neurological Repair: Minor Issues, Major Hurdles, and Exciting Opportunities for Paracrine-Based Therapeutics. *Journal of Cellular Biochemistry*, 112, pp. 374–380.

Shyu, WC.; Lin, SZ.; Chiang, MF.; Su, CY.; & Li, H. (2006). Intracerebral peripheral blood stem cell (CD34+) implantation induces neuroplasticity by enhancing beta1 integrin-mediated angiogenesis in chronic stroke rats. *The Journal of Neuroscience,* 29,26(13), pp. 3444-3453.

Siglera, A.; Mohajerania, MH.; & Murphya, TH. (2009). Imaging rapid redistribution of sensory-evoked depolarization through existing cortical pathways after targeted stroke in mice. *PNAS* ,vol. 106, no. 28, pp. 11759–11764.

Steindler, DA. (2002). Neural stem cells, scaffolds, and chaperones. *Nat Biotechnol*., 20(11), pp. 1091-1093.

Sun, C.; Zhang, H.; Li, J.; Huang, H.; Cheng, H.; Wang, Y.; Li, P.; & An, Y.(2010). Modulation of the major histocompatibility complex by neural stem cell-derived neurotrophic factors used for regenerative therapy in a rat model of stroke. *Journal of Translational Medicine*, 8, 77, http://www.translational-medicine.com/content/8/1/77

Takahashi, K.; Yamanaka, S. (2006). Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell,* 25, 126(4), pp. 663-676.

Takahashi, K.; Yasuhara, T.; Shingo, T.; Muraoka, K.; Kameda, M.; Takeuchi, A.; Yano, A.; Kurozumi, K.; Agari, T.; Miyoshi, Y.; Kinugasa, K.; & Date, I. (2008). Embryonic neural stem cells transplanted in middle cerebral artery occlusion model of rats demonstrated potent therapeutic effects, compared to adult neural stem cells. *Brain Research*, 1234, pp. 172-82.

Tajiri, N.; Yasuhara, T.; Shingo ,T.; Kondo, A.; Yuan, W.; Kadota, T.; Wang, F.; Baba, T.; Tayra, JT.; Morimoto, T.; Jing, M.; Kikuchi, Y.; Kuramoto, S.; Agari, T.; Miyoshi, Y.; Fujino, H.; Obata, F.; Takeda, I.; Furuta, T.; & Date, I. (2010). Exercise exerts neuroprotective effects on Parkinson's disease model of rats. *Brain Research,* Volume 1310, pp. 200-207

Temple, S. (2001). The development of neural stem cells. *Nature*, 414, pp. 112–117.

Toda, H.; Hamani, C.; Fawcett, A.; Hutchison, W.; & Lozano, A. (2008). The regulation of adult rodent hippocampal neurogenesis by deep brain stimulation. *J Neurosurg*., 108, pp. 132–138.

Treanor, JJ.; Goodman, L.; de Sauvage, F.; Stone, DM.; Poulsen, KT.; Beck, CD.; Gray, C.; Armanini, MP.; Pollock, RA.; Hefti, F.; Phillips, HS.; Goddard, A.; Moore, MW.; Buj-Bello, A.; Davies, AM.; Asai, N.; Takahashi, M.; Vandlen, R.; Henderson, CE.; & Rosenthal, A. (1996). Characterization of a multicomponent receptor for GDNF. *Nature*, 382(6586), pp. 80-83. van Praag, H.; Christie, BR.; Sejnowski, TJ.; & and Gage, FH. (1999). Running enhancesneurogenesis, learning, and long-term potentiation in mice. *Proc Natl Acad Sci U S A*, 96, pp. 13427-13431.

Walker, TL.; White, A.; Black, DM.; Wallace, RH.; Sah, P.; & Bartlett, PF. (2008). Latent Stem and Progenitor Cells in the Hippocampus Are Activated by Neural Excitation. *The Journal of Neuroscience*, 28(20), pp. 5240 –5247.

Wang F, Yasuhara T, Shingo T, Kameda M, Tajiri N, Yuan WJ, Kondo A, Kadota T, Baba T, Tayra JT, Kikuchi Y, Miyoshi Y, Date I. (2010). Intravenous administration of mesenchymal stem cells exerts therapeutic effects on parkinsonian model of rats: focusing on neuroprotective effects of stromal cell-derived factor-1alpha. *BMC Neuroscience*, 11, 52, doi:10.1186/1471-2202-11-52

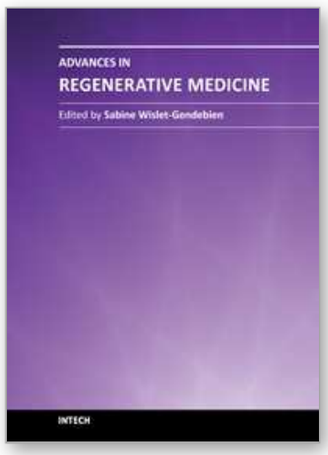
Wang, F.; Kameda, M.; Yasuhara, T.; Tajiri, N.; Kikuchi, Y.; Liang, HB.; Tayra, JT.; Shinko, A.; Wakamori, T.; Agari, T.; Miyoshi, Y.; & Date, I. (2011). GDNF pretreatment enhances the survival of neural stem cell following transplantation in Parkinson's disease model of rats. *Accepted by Neuroscience research*

Weber, R.; Ramos-Cabrer, P.; Justicia, C.; Wiedermann, D.; Strecker, C.; Sprenger, C.; & Hoehn, M. (2008). Early Prediction of Functional Recovery after Experimental Stroke: Functional Magnetic Resonance Imaging, Electrophysiology, and Behavioral Testing in Rats. *J. Neurosci*., 28(5), pp.1022–1029.

Weiduschat, N.; Thiel, A.; Rubi-Fessen, I.; Hartmann, A.; Kessler, J.; Merl, P.; Kracht, L.; Rommel, T.; & Heiss, WD. (2011). Effects of repetitive transcranial magnetic stimulation in aphasic stroke: a randomized controlled pilot study. *Stroke*, 42(2), pp. 409-15.

Yilmaz, G.; Alexander, JS.; Yilmaz, CE.; & Granger, DN. (2010). Induction of neuro-protective/regenerative genes in stem cells infiltrating post-ischemic brain tissue. *Experimental & Translational Stroke Medicine*, 2,11. http://www.etsmjournal.com/content/2/1/11

Zhang, X.; Mei, Y.; Liu, C.; & Yu, S. (2007). Effect of Transcranial Magnetic Stimulation on the Expression of c-Fos and Brain-derived Neurotrophic Factor of the Cerebral Cortex in Rats with Cerebral Infarct. *Journal of Huazhong University of Science and Technology*, 27 (4), pp. 415-418.



Advances in Regenerative Medicine

Edited by Dr Sabine Wislet-Gendebien

ISBN 978-953-307-732-1
Hard cover, 404 pages
Publisher InTech
Published online 21, November, 2011
Published in print edition November, 2011

Even if the origins of regenerative medicine can be found in Greek mythology, as attested by the story of Prometheus, the Greek god whose immortal liver was feasted on day after day by Zeus' eagle; many challenges persist in order to successfully regenerate lost cells, tissues or organs and rebuild all connections and functions. In this book, we will cover a few aspects of regenerative medicine highlighting major advances and remaining challenges in cellular therapy and tissue/organ engineering.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Masahiro Kameda and Isao Date (2011). Regenerative Medicine for Cerebral Infarction, Advances in Regenerative Medicine, Dr Sabine Wislet-Gendebien (Ed.), ISBN: 978-953-307-732-1, InTech, Available from: http://www.intechopen.com/books/advances-in-regenerative-medicine/regenerative-medicine-for-cerebral-infarction

INTECH
open science | open minds

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2011 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the Creative Commons Attribution 3.0 License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen