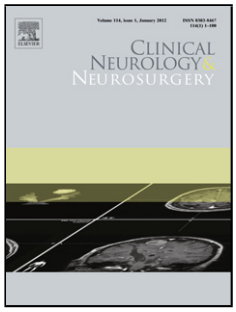

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Neural stem cell therapy - brief review.

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Highlights

- Extraction methods of neural stem cells.
- Description of those methods.
- Therapeutical use of neural stem cells.

Abstract:

Adult mammalian neural stem cells are unique because of their properties, such as differentiation capacity, self-renewal, quiescence, and also because they exist in specific niches, which are the subventricular zone (SVZ) and subgranular zone (SGZ) - the dentate gyrus of the hippocampus. SVZ is situated along the ependymal cell layer, dividing the ventricular area and subventricular zone. There are several sources of neural stem cells such as human embryonic stem cells, human fetal brain-derived neural stem/progenitor cells, human induced pluripotent stem cells, direct reprogrammed astrocytes. Stem cell sciences are a promising tool for research purposes as well as therapy. Induced pluripotent stem cells appear to be very useful for human neuron studies, allowing the creation of defined neuron populations, particularly for neurodevelopmental and neurodegenerative diseases as well as ischemic events.
Neural stem cell sciences have a promising future in terms of stem cell therapy as well as research. There is, however, still a great need for further research to overcome obstacles.
keywords: neural stem cell; NSC therapy; neural stem cell therapy

1. Introduction

Two classes of neural stem cells (NSCs) can be distinguished, notably embryonic stem cells (pluripotent, which create cells from each of the three embryonic germ layers) and adult stem cells (multipotent, which can create lineage-specific cell types). In 1961, Leblond et al. reported that glial cells were dividing throughout the parenchyma [1]. It was in 1965 when Altman and Das presented the first strong evidence for neurogenesis in the adult brain [2], but it was Goldman and Nottebohm, who in 1983 first detected the process of neurogenesis in adult birds [3]. The process of neurogenesis consists of four phases: cell proliferation, migration, cell survival and neuronal differentiation.
Adult mammalian neural stem cells are unique because of their properties such as differentiation capacity, self-renewal, quiescence, and because they exist in specific niches, which are the subventricular zone (SVZ) and subgranular zone (SGZ) - the dentate gyrus of the hippocampus. The SVZ is situated along the ependymal cell layer, dividing the ventricular area and SVZ. Neural stem cells situated in the SVZ are also known as type B cells. Type B cells are extending the basal process and the apical process with a primary cilium that goes through the ependymal cell layer and contacts the cerebrospinal fluid in the ventricle [4]; they give birth to transient amplifying progenitors, called C cells, and thereafter they divide a few times before becoming neuroblasts (A cells). Neuroblasts are migrating radially into the olfactory bulb and they evolve into different subtypes of

interneurons. Cells located at the SGZ (at the border with the inner granulate layer) are called radial glia-like neural stem cells (RGL, type 1 cells). They differentiate into intermediate progenitor cells (IPCs), which after proliferation become neuroblasts [5]. The next step is the migration of the neuroblasts along the SGZ and their transition into immature neurons, migrating radially into the granular cell layer and forming the dentate granular neurons [6].

Another interesting feature of adult NSCs is the fact that through entering and leaving the cell cycle NSCs are able to switch from quiescent into being active. Due to their quiescent state, adult NSCs are able to withstand metabolic stress and maintain their genomic integrity. Moreover, a recent study shows expression of receptors responsible for niche signals and downstream signaling components after NSC activation in the subgranular zone [7], which can be evidence of active processes resulting in quiescence [8]. Wnt inhibitor expression [7] as well as decreasing GABA [9] result in activation of quiescent NSC.

Once the cells are activated, they can follow different division paths: the asymmetric division, where a NCS and a committed progenitor cell are the result or a symmetric division, where two NSCs or two committed progenitor cells are created.

Christian et al. conclude that the primary function of adult NCSs is to support the brain with an additional layer of plasticity [10].

Neurons created by adult NSCs have different properties than mature neurons and it takes several months for them to become an equivalent of mature neurons during a process called maturation. Newborn neurons achieve their morphological maturity in about 2 months, whereas in adult-born neurons the process is delayed [11], which is essential for their functioning.

Because of being hyper-excitable and having a lower threshold for long-term potentiation induction [12], NCS-generated neurons are able to make new synaptic connections and contribute to information coding with mature neurons [13]. Adult NSCs situated in the subventricular zone are able to stimulate proliferation of neuroblasts by decreasing GABA signaling with the use of diazepam binding inhibitor (DBI) [14]They can also produce oligodendrocytes, which are able to myelinate axons after migration to the corpus callosum [15]. Another feature of adult NSCs is their capacity to produce astrocytes as well as glia. The function of astrocytes, which are generated by the NSCs located in subgranular zone, is to modify the surrounding neural circuit, which is possible due to the gap junctions created by astrocytes. Moreover, they release adenosine triphosphate (ATP), D-serine and glutamate (known as gliotransmitters) allowing to affect plasticity, excitability and synaptic activity [16]. Neural stem cells are instructed *in vivo* through extracellular signals or cell-to-cell contacts with ependymal cells, the extracellular matrix, neuronal inputs, immune cells, local vasculature and the cerebrospinal fluid [17], however NSC in SVZ and SGZ and NSC obtained from other sources are distinct populations of NSC [18,19].

Adult NSCs can influence the vasculature by activating pericytes (through released vasodilatating substances) and increasing blood flow [20]. The cells can affect one another through gap junctions [21] and expressing VEGF receptor 3 and VEGF-C, thus promoting activation of NSCs [22].

2. Sources of neural stem cells.

2.1 Human embryonic stem cells and Human induced pluripotent stem cells (hiPSC)

Human embryonic stem cells (hESCs) are capable of self-renewal and have pluripotent properties, which allow them to fully reproduce the phenotype of fetal neural precursors [23], as proven by several Parkinson’s disease and Huntington’s disease therapies. The method was established in 1998 by Thomson et al., who were first to devise the technique to recruit human embryonic stem cells from the inner cell mass of human blastocysts [24]. Being pluripotent, hESCs, are able to produce neural cells such as neurons, oligodendrocytes and glial cells, depending on the specific circumstances. Production of

contaminants is an issue and therefore efforts are made to produce a neural progenitor cell, capable of self-renewing and the production of a pure population of regionally specified cell types. The circumstances mentioned above are the specific factors that push the hESCs into a differentiation path of neural progenitor cells. The presence of stromal cells and stromal-derived induction activity promotes neural differentiation when co-cultured with hESCs [25]. Another factor inducing neural development is retinoic acid, that stimulates axon regeneration in the adult, patterning of the neural plate and neural tube in the early embryos and neuronal differentiation especially of the posterior hindbrain and anterior spinal cord formation as well as generating neural progenitor cell populations [26]. Differentiation stimulated by retinoic acid is possible because it activates transcription factors such as SOX6, SOX1,BRN2, cell structures (MAP2, ceramide), extracellular molecules (WNT) and cell signaling molecules.

Bone Morphogenetic Protein signaling is another neural differentiation technique. BMP signaling promotes astro-glial and neuronal cell production, however it prevents the differentiation into oligo-glial cells. It turned out that inhibiting BMP before or during gastrulation induces neural differentiation, so BMP-antagonists like noggin were used to cause neural differentiation [27]

Fibroblast Growth Factor 2 was found to help isolating and maintaining neural progenitor cells [28].

In 2007 Takahashi and Yamanaka published a method to dedifferentiate mouse somatic cells into embryonic-like cells [29] and soon it was found that induced pluripotent stem cells could be created from human somatic cells [30].

Fibroblasts or peripheral blood mononuclear cells can be converted into human induced pluripotent stem cells (hiPSCs) using this technique of direct reprogramming. The process has 3 phases: initiation, maturation and stabilization [31]. The loss of cell-type background is the main aim of the initiation phase and allows to continue the reprogramming process. Functioning of the other two phases rely on activation of pluripotency genes (SOX2 locus) [32] and requires four transcription factors (KLF4, c-MYC, OCT4 and SOX2) [33]. HiPSCs are able to transform into any class of neurons and glia in the brain. The transformation of HiPSCs to neural progenitor cells is similar to the transformation of embryonic stem cells [34] and it has two different ways to arrive at neural progenitors. The first one is viaembryoid bodies [35, 36], 3D dimensional cellular aggregates consisting of different cell types, including neurons. The second one is via adherent monolayers [37], which has a more homogeneous neuron population, a faster differentiation rate, but lower cell-to-cell connectivity [38]. Once specific factors are combined, cellular differentiation of neural progenitors is initiated and thereafter the neural development process takes place in vivo [39]. During the process of neural development, the expression of neural markers and the acquisition of electrophysiological activity is observed [40]. Although the electrophysiological features of created cells appear immature, Wakeman et al. proved that those cells are able to connect with existing, functional neural circuits [41]. Vierbuchen et al. established the technique that allows to skip the de-differentiation process and that enables to transform fibroblasts directly into neurons by adding Asc11, Brn2 and Myt1l transcription factors [42].

2.2 Human fetal brain-derived neural stem/progenitor cells.

Human fetal brain tissue is collected from cadavers and then isolated in cultures. Kim et al. presented a technique of culturing. In their study, they harvested the brain tissue from six different regions : telencephalon, mesencephalon, diencephalon, cerebellum, pons, medulla and spinal cord. The tissue was dissociated in tripsin and seeded into culture-treated plates. In order to stimulate mitogenic activity, FGF2 and leukemia inhibitor factor were added. Cultures were held in a humidified incubator at 37 degrees Celsius and 5% CO2 concentration in the air [43]. All harvested cells created neurospheres which contained cells of different subtypes. The mentioned cells can differentiate into neurons,

oligodendrocytes and astrocytes. It was found that forebrain-derived neurospheres created significantly more neurons than those from other regions. A study performed by Lee et al., who used this method, revealed that ca. 61% of the stem cells had differentiated into TUJ1+ neurons, ca. 2% into PDGFR-a+ oligodendrocyte progenitors and ca. 5% into GFAP+ astrocytes. They further found out that ca. 26% of neural stem/progenitor cell (NSPC)-derived differentiated cells expressed GABA and ca. 37% of NSPC-derived TUJ1+ neurons expressed GABA with small bipolar processes [44].

2.3 Direct reprogramming of astrocytes

Efforts have been made in order to obtain neural stem cells and neurons directly from reprogrammed astrocytes. Astrocytes harvested from murine cerebral cortex were used in the studies to be directly differentiated into neurons by forcing expression of a single transcription factor (PAX6, Neurog2, Mash1, Dlx2) [45, 46]. Corti et al. used this technique in a human model, reprogramming the human astrocytes using the expression of reprogramming factors such as OCT4, SOX2 and NANOG [47]. They proved that expression of a single key stem cell transcription factor is sufficient for astrocyte conversion using fully mature astrocytes. Created neural stem/precursor cells were self-renewing and multipotent. Moreover they presented marker expression and responded to growth factors characteristic of NSCs. Also, it was suggested that a specific desired phenotype can be acquired using a combination of multiple neurogenic transcription factors.

They discovered that overexpression of a single factor (OCT4) can induce full reprogramming of the cell [48] or start the formation of another phenotype [49] and came to the interesting conclusion that in conditions required for the iPSC reprogramming, these cells can obtain a specific, well-defined lineage phenotype, they are safer to use for therapy.

3. Clinical use

Stem cell sciences are a promising tool for research purposes as well as therapy. Induced pluripotent stem cells appeared to be very useful for human neuron studies, allowing the creation of defined neuron populations, particularly among neurodevelopmental and neurodegenerative diseases as well as ischemic events. Using iPSC, researchers have the possibility to study patient's genomics and the etiology of disease.

Many preclinical trials resulted in a positive outcome of neurogenesis after NSC transplantation in rodent stroke models. After stroke, a damaged tissue is being replaced by immature neuronal cells or neuroblasts, which were transformed from endogenous neural stem cells and migrated from the subventricular zone [50]. Treatment with the use of hESCs and fetal-derived NSCs turned out to promote cell proliferation and migration in the subventricular zone, dental gryus and striatum The cells also produced regenerative trophic factors promoting angiogenesis, reducing the level of inflammation and supporting tissue regeneration after stroke [51, 52]. It was also noted that treatment promoted endogenous neurogenesis mediated by NSC transplantation, which was based on the existence of a neuroblast marker (DCX and mature neuron marker (Fox3) [53, 54, 55] Baker et al. recently carried out a first iNSC study on a stroke pig model, which showed a significant tissue recovery, decreased microglia response, increased neuroblast migration and long-term integration with robust cell differentiation into neurons and oligodendrocytes [56]. They found out that the treatment with iNCS promotes neurogenesis and the migration of doublecortin (DCX+) neuroblasts from the subventricular zone to the lesion border. Moreover, the treatment promotes endogenous cell proliferation and migration, which is consistent with the results of the rodent studies. The explanation of this effect is enhanced trophic factor signaling (BDNF and NOG gene upregulation, encoding Noggin) mediated by transplanted iNCS. Also an increased expression of neurotrophic factors BDNF, GDNF and NTF3 was found, responsible for neuron protection [57] and increased expression of the gene encoding neurite branch mediator (Rtn4) that is associated with

neural repair mechanisms after stroke. The therapy turned out to decrease the microglia number at the lesion border, weakening the proinflammatory signaling, especially the expression on pro-inflammatory cytokines
(CSF2, IL-1B, IL-6) [58], which was also seen in rodent studies after fetal-derived and iPSC-derived NSC [59, 60].
Neural stem cell therapies were found to have a positive impact on cerebral blood perfusion, promoting angiogenesis through the increased expression of VEGF, Ang1 and angiogenic activity both in rodent and pig models [56, 61, 62].
The therapy also supports white matter reorganization, improves myelination, axonal sprouting, neural connectivity and white matter bundle thickness [63, 64, 65].
Transplantation therapy with the use of dopamine (DA) phenotype neurons turned out to have positive effects in Parkinson's disease animal models. The mentioned neurons are generated from ESCs, iPOCSs, mesenchymal stem cells or NSCs. Mouse ESCs were followed by stimulation using fibroblast growth factor 8 (FGF8) and sonic hedgehog [66], overexpression of Nurr1 [67], Bcl-xL [68] or co-cultured with a mouse bone marrow stromal cell line [69], which also worked with monkey-derived ESCs [70]. Redemond et al. managed to generate DA neurons form fetal brain-derived NPCs and found the induction of functional brain tissue recovery in Parkinson's disease monkey models [71]. Similar effects were found in studies performed by Cho et al., Chung et al. and Kriks et al., who obtained human DA neurons using human embryonal stem cells. After cell transplantation in rat Parkinson's disease models, induction of behavioral recovery was noted [72, 73, 74]. Best source of human DA neurons seems to be iPSCs therapy, because of the fact that neurons can be generated from the patient's fibroblasts and they do not cause an immune rejection. However, this must be done with caution because there is a risk of teratoma formation and optimization of in vitro DA neuron production is a precondition. Behavioral improvement was found in PD rat models after iPSC therapy [75]. Moreover iPSC-derived DA neurons were found to be best suited for the transplantation because of gene expression induction and their physiological and electrophysiological properties, which are similar to human DA midbrain neurons [76]. A recent study performed by Cho et al. showed enhanced functional recovery after mouse fibroblast-derived iNSC transplantation. iNSCs were found to reduce apomorphine-induced rotational asymmetry in the striatum and migrate around the medial forebrain bundle and pars compacta [77].
The neural stem cell therapy may also have a positive outcome in Huntington's disease (HD) treatment. HD is an autosomal dominant neurodegenerative disorder, which is caused by the expansion of CAG repeats at the Htt gene, leading to the loss of GABAergic medium spiny neurons in the striatum. The aim of the NCS therapy is to differentiate the neural stem cells into striatal GABAergic medium spiny neurons, in order to achieve proper connection with the globus pallidus and to receive the correct input from the substantia nigra and cortex. Bachoud-Levi et al. noted an improvement in motor and cognitive function after fetal cell transplantation [78] and showed the integration of fetal striatal cells within the striatum, which was previously reported in animal studies [79, 80, 81]. Later on, techniques such as hESC were used in studies, but because of the low differentiation efficiency, overgrowth (study performed in 2009 by Keene et al. showed neural overgrowth (neurons and glia composite) within the tissue graft [82], tumor formation as well as ethical and safety concerns [83] they were considered as not suitable for therapeutic purposes.
An idea of using autologous fibroblasts as a source of hiPSC-derived neurons has emerged as a treatment therapy for Huntington's disease. hiPSC-derived neurons were found as having similar features as human neurons, when it comes to morphology, electrophysiological features and gene expression profiles. The differentiation of iPSC into GABAergic medium spiny neurons consists of three steps: induction of neural precursor cells, differentiation and specification of neural precursor cells and specialization of striatal GABAergic medium spiny neurons. Recently, a novel gene correction technique has been

found using the clustered, regularly interspaced, short palindromic repeats (CRISPR/Cas-9),, as a method for genetic correction of HD patient-derived iNSC [84]. In conjunction with the direct fibroblast conversion techniques this may enable the clinical application in treatment of Huntington's disease.
Stem cell therapy was also used in adult mouse models with motor coordination disorders caused by degeneration of Purkinje neurons (PN). Several studies have already reported successful implantation of ES-derived cells exclusively in embryonic and late postnatal cerebella [85,86]. In a recent study performed by Higuera et al. a successful maturation of ES-derived PNs is reported in early postnatal as well as mature cerebella [87]. The acquisition of fully functional Purkinje Cells from ES-derived NPCs, capable of being integrated with downstream and cortical circuits may be considered as a future therapy method, however further research in this area is required.
Amyotropic lateral sclerosis (ALS) is a neurodegenerative disease caused by progressive degeneration of motor neurones in the spinal cord, brainstem, primary motor cortex and corticospinal tracts. ALS occurrence is mostly sporadic but circa 5-10% of all cases are familiar (caused by the SOD1 gene in about 20% of those cases and TARDBP gene mutation in 2-5% of those cases). There were many animal studies, which mostly gave information regarding the pathiphysiology of ALS, however no therapeutic routes have yet been established because of lack of success in translating these findings to therapies. Knowing the mechanisms of the disease Wang et al. generated two human iPSC lines from ALS patient-specific fibroblasts bearing heterozygous disease-causing mutations (FUS +/G1566A and SOD1 +/A272C) and generated isogenic gene-corrected iPSCs using CRISPR/Cas9 system with ssODN as repair template for correcting SOD1 +/A272C and FUS +/G1566A into wildtypes [88]. On the other hand, Bhinge et al. corrected the SOD1 mutation in patient-derived iPSCs with deep RNA-seq and found the higher expression of JUN (AP1 complex member) in motor neurons, suggesting its crucial role in motor neuron homeostasis. They came to a conclusion that hyperactivatiob of JUN may be a factor causing motor neuron degeneration. [89].

Alzheimer's disease is caused by chronic inflammation and neuronal loss due to neurofibrillary tangles (NFTs) of abnormally hyperphosphorylated tau, plaques of β-amyloid (Aβ). Moreover, it still remains not only a crucial medical but also social and economic problem. There are several studies, showing positive effect of stem cell therapy in mouse models [90, 91, 92, 93, 94, 95], however those methods turned out to be ineffective in human trials. Recently the results of phase I clinical trial (Trial identifier: NCT01297218, NCT01696591)

were presented, in which nine patients with AD were enrolled. They received bilateral stereotactic injection of human umbilical cord blood-derived MSCs into the hippocampus and precuneus. Unfortunately, after 24 months of the follow-up, no improvement was found neither in cognitive state nor AD pathology [96].
A study published by Karussis et al. reports the use of mesenchymal stem cells in multiple sclerosis among human participants. They confirmed the systemic immunomodulatory effects of MSC transplantation [97] previously described in animal models [98], which could be related to positive treatment effects in those patients. They also suggest the migration of stem cells from the site injection to the brain ventricles and spinal cord parenchyma.
Cohen et al. decided to deliver autologous bone-marrow-derived MSCs intravenously, despite the fact that lungs trap many of the

administered cells, but this route turned out to be effective in animal models [99]. The study confirmed feasibility, safety, and tolerability of autologous MSC transplantation [100],

however the authors suggest that transplantation from non-MS donor would be more efficient. [101] [102] [103].
Traumatic brain injury (TBI) is another disease, in which stem cell therapy may be potentially administered. There are many different administration routes presented by different authors, such as: injection into bone marrow [104], implantation into the lateral ventricle [105], implantation into hippocampus [106], intravenous injection [107], application to the surface of the brain [108], infusion in myicardial infarction and sham-MI [109]. In TBI rat models, mesenchymal stem cells turned out to be capable of differentiating into neuron- and astrocyte-like cells [110], thus enhancing neural growth and promoting sensory and motor functions improvement, which was confirmed by different studies [110] [111] [112]. Williams et al. report that treatment with mesenchymal stem cell-derived exosomes attenuates the severity of neurologic injury and allows for faster neurologic recovery in a clinically realistic large animal model of TBI [113]. Jahanbazi et al. isolated human neural stem/progenitor cells (hNS/PCs) from epileptic human brain during epilepsy surgery. They performed a transplantation of hNS/PCs and human adipose-derived stromal/stem cells (hADSCs) seeded in PuraMatrix hydrogel into TBI rat models. It turned out that the therapy decreased lesion volume, inhibited neuroinflammation, improved functional recovery and reduced the reactive gliosis at the injury site [114]. MSC therapy was also used in clinical trials. Cox et al. treated 10 children after TBI, and among 7 of them Glasgow Coma Scale score showed improvement after administration of therapy [115]. Tian et al. suggested in their study that a positive effect of MSC administration depends on the time between the moment of injury and stem cell transplantation [116].

Conclusions:
Neural stem cell sciences have a promising, yet distant future in terms of stem cell therapy as well as research. It enables a better understanding of the disease pathology and in the future may become a treatment option not only in neurodegenerative disease such as Parkinson’s disease or Huntington’s disease, but also in a post-stroke therapy, increasing the quality of life. Despite many human trials are still being planned, none of them have been successful so far. Moreover, many clinical trials are based on MSC, however researchers report that the number of MSC-derived neurons is extremely low and irrelevant for potential clinical use. There is still a great need for further research to overcome obstacles such as cell overgrowth and tumor growth as well as technical problems such as establishment of proper stem cell sources, appropriate quantity of stem cell transplants, choosing proper programming protocols and selection of the most profitable disease stage for treatment.

Ethics
The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.
Conflict of interest
None declared.

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