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Stem Cells in Drug Screening for Neurodegenerative Disease

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Because the average human life span has recently increased, the number of patients who are diagnosed with neurodegenerative diseases has escalated. Recent advances in stem cell research have given us access to unlimited numbers of multi-potent or pluripotent cells for screening for new drugs for neurodegenerative diseases. Neural stem cells (NSCs) are a good model with which to screen effective drugs that increase neurogenesis. Recent technologies for human embryonic stem cells (ESCs) or induced pluripotent stem cells (iPSCs) can provide human cells that harbour specific neurodegenerative disease. This article discusses the use of NSCs, ESCs and iPSCs for neurodegenerative drug screening and toxicity evaluation. In addition, we introduce drugs or natural products that are recently identified to affect the stem cell fate to generate neurons or glia.

Key Words: Stem cells, Neurodegeneration, Drug screening, IPS, ES cells

Stem cells have been considered as a good source for potential treatment of neurodegenerative diseases (reviewed in [1-7]). Stem cells have the ability to proliferate and differentiate into various cell types (reviewed in [8-21]). Human embryonic stem cells (ESCs) can be derived from the inner cell mass of blastocysts and be differentiated into all types of cells composing the human body [22-26]. However, using ESCs create ethical problems of destroying embryos and problems after transplantation such that cells derived from ESCs may be rejected from the recipient patients and immunosuppressants are required to be administered after transplantation [27-30]. Stem cells derived from further-developed embryos have relatively limited ability to differentiate and proliferate [31-38]. For example, neural stem cells (NSCs) can only be differentiated into cells comprising the nervous system such as neurons and glia [38-44]. Recent breakthroughs in the generation of induced pluripotent stem cells (iPSCs) showed that cells from patients can be converted into ESCs like pluripotent cells and if used in patients in the future, immunosuppressants may not be needed after transplantation [45-49]. Another advantage of iPSCs is that they can be induced to form differentiated types of cells including neurons and glia and the mechanisms involved in neurodegeneration of humans can be explored [50-53]. In addition, drug screening can be performed in the disease bearing cells that are differentiated from human iPSCs [53-57]. Therefore human stem cells including ESCs, adult stem cells and iPSCs provide a strategy in which these cells can be used for new drug screening or evaluating drug efficacies. In addition, potential toxicity can be predicted using human stem cells [58]. In this review, we focus on recent advances that deal with the concept that stem cells provide a good platform for drug screening in neurodegenerative diseases and evaluation of drug toxicities.

Degeneration of the nervous system results in diseases including Parkinson's disease, Alzheimer's disease, multiple sclerosis, Huntington's disease and so on. Since drugs or therapies that cure neurodegenerative diseases have not been developed yet, there is an enormous need for new drugs and better therapies. Until recently, emphasis has been on the potential use of stem cells in cell replacement/transplantation [59-62]. However, using stem cells as a model system to develop new drugs and evaluate toxicity has begun to receive increased attention [63,64]. This review first introduces recent findings identifying chemicals and natural products that induce differentiation of stem cells into neurons or glia. We also discuss advances in drug screening and in evaluating toxicities using human stem cells.

NSCs for Screening of Chemicals or Natural Products that Induce Neuronal or Glial Differentiation

An essential characteristic of NSCs is that, although

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ABBREVIATIONS: ESCs, embryonic stem cells; NSCs, neural stem cells; iPSCs, induced pluripotent stem cells; HDAC, histone deacetylase; BDNF, brain-derived neurotrophic factor; SVZ, subventricular zone; HC, hippocampus; SAR, structure-activity relationship; SSRIs, selective serotonin reuptake inhibitors; DG, dentate gyrus; HRP, horse radish peroxidise; SMA, spinal muscular atrophy.

somewhat restricted, they respond to environmental cues. For example, NSC differentiation into neurons can be induced by treatment of retinoic acid [65,66]. Similarly, histone deacetylase (HDAC) inhibitors can also cause NSCs to differentiate into astrocytes [67-69]. Retinoic acid treatment of NSC induced immediate up-regulation of a proneural gene, NeuroD, and increased p21 expression. Retinoic acid also affected the expression of trkA, trkB, trkC and $p75^{NGFR}$, causing better responses to neurotrophic factors and neuron maturation [65]. Modulation of ES cell differentiation was influenced by retinoic acid [66]. However, it was dependent on the concentration of retinoic acid and the developmental stage of the cells. An HDAC inhibitor, sodium butyrate, is reported to increase proliferation of NSCs and levels of brain derived neurotrophic factor (BDNF) in the ischemic brain of adult rodents [67]. Increases in new born neurons in ischemic regions of the brain by sodium butyrate appear to be mediated by BDNF, because BDNF receptor antagonists markedly reduced NSCs proliferation and attenuated behavioural benefits. Identification of new cell-fate modulators in NSCs provides several advantages. First, the chemicals or natural products that induce neurogenesis have the potential to be used in neurodegenerative diseases. In the adult human brain, it is known that NSCs exist in certain areas such as the subventricular zone (SVZ) and the hippocampus (HC) [38,70-73]. It would be beneficial for patients who suffer from neurodegeneration to take drugs or natural products that increase neurogenesis from endogenous NSCs (Fig. 1). In addition to potential use in the clinic, identification of new cell fate regulators may induce a homogeneous population, and provide a good model for drug screening. The underlying mechanisms of differentiation would also be useful to help understand stem cell biology and facilitate new drug development. A homogeneous population produced using chemicals that induce a certain type of cell may also be useful for transplantation in future potential cell replacement therapy.

As illustrated in Fig. 1, NSCs can be generated from either the fetus, the adult, ESCs or iPSCs. After treatment of chemical or natural product libraries, the levels of differentiation of NSC can be determined by image-based immunocytochemistry or immunostaining-based microplate reading quantitation methods. The chemicals or natural products that induce high levels of neurogenesis can further be used for studying structure-activity relationships (SAR) to generate more efficient but less toxic molecules as new drug candidates. Several laboratories have recognized the importance of identifying small molecules for controlling

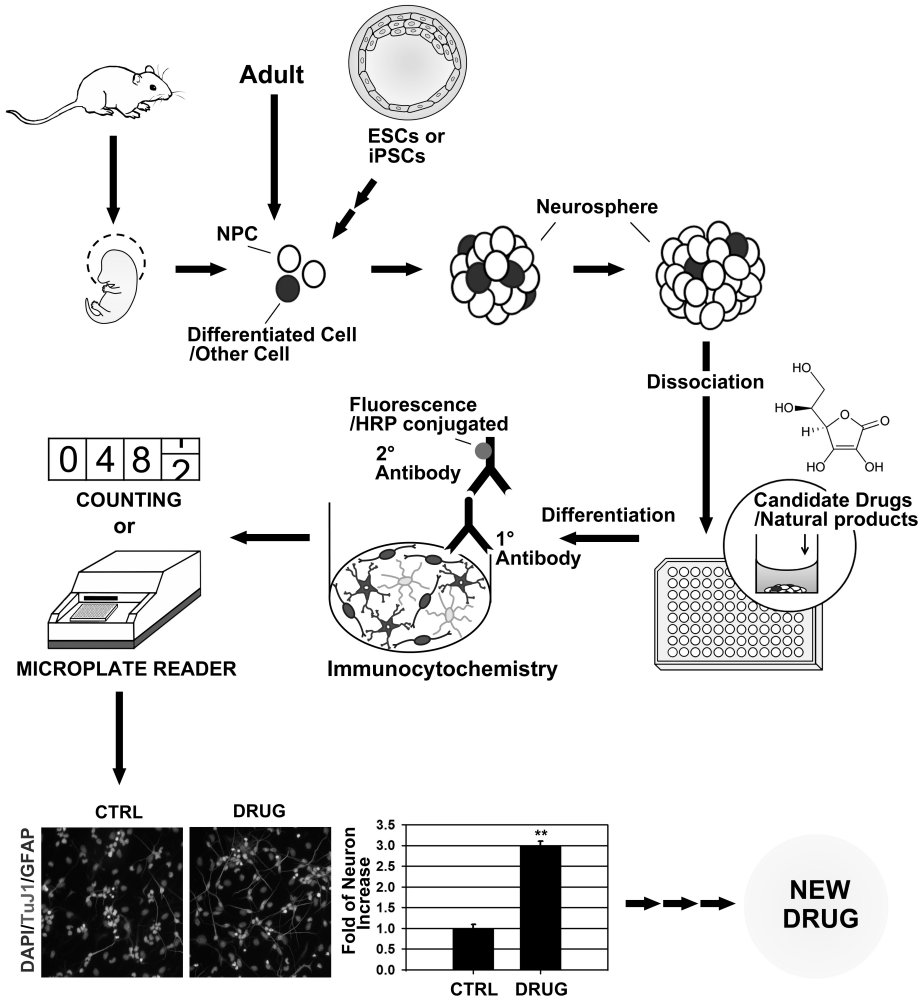


Fig. 1. High-throughput screening for the development of new drugs that are effective for the treatment of neurodegenerative diseases. NSC can be derived from adult cells, fetus cells, ESCs or iPSCs. After NSC plating, chemical or natural product libraries are treated. The effect of each drugs are detected by immunocytochemistry using cell type specific antibodies. If fluorescence conjugated secondary antibodies are used, cells can be visualized by fluorescence microscopy and the numbers of detected/differentiated cells are counted. If HRP conjugated secondary antibodies are used, cells can be treated with substrates and lysed to be measured by microplate reader. Once the chemicals or natural products that are effective are found, and structural activity relationship studies, animal studies and toxicity evaluations are done, promising agents can go on to clinical trials and may further be developed as new drugs.

NSCs fate [74,75]. Some widely used drugs such as antidepressants and anticonvulsants have been shown to regulate stem cell proliferation and differentiation [69,76-81]. Interesting clinical effects of selective serotonin reuptake inhibitors (SSRIs) in ameliorating cognition in Alzheimer's disease have been demonstrated [82]. Alzheimer's disease patients with depression have been treated with SSRIs in combination with cholinesterase inhibitors (donepezil, ravastigmine and galantamine) and showed better cognitive function than patients who were treated only with cholinesterase inhibitors [82]. Fluoxetine also increased neurogenesis by increasing NSCs proliferation and cell survival [79,80,83]. Administration of fluoxetine for 28 days significantly improved depression when measured in animals by a novelty-suppressed feeding test and an increase in neurogenesis in the HC was observed [81]. However, the use of fluoxetine to induce neurogenesis was challenged by recent data that chronic exposure to fluoxetine actually decreased neurogenesis in the adult SVZ [84]. The antidepressant sertraline increased neuronal differentiation through glucocorticoid receptors and increased both immature neuroblasts (double-cortin positive), and mature neurons (Map2 positive) [85]. Administration of tricyclic antidepressants such as amitriptyline caused cognitive benefits in patients suffering from Alzheimer's disease [86]. Amitriptyline increased neurotrophic factor levels in patients' serum. In cognitively impaired, aged, transgenic mice, amitriptyline treatment improved both short and long term memory retention and increased neurogenesis in the dentate gyrus (DG) [77]. It is also reported that a mood stabilizer, lithium, and carbamazepine increased neurogenesis but decreased astrocytogenesis [87]. Lithium and carbamazepine increased proliferation and decreased apoptosis of NSCs that are derived from HC [87,88]. When 3 month old double transgenic CRND8 mice (overexpressing the Swedish and Indiana mutations in the human amyloid precursor protein) were treated with lithium for 5 weeks, lithium induced proliferation of cells in the HC and induced neuronal fate specification [89]. However, when lithium was used to treat 7 month old transgenic CRND8 mice, the proliferative effects on NSCs and neurogenic effects of lithium were abolished, suggesting that lithium-induced facilitation of neurogenesis declines with Alzheimer disease progression.

The anticonvulsant valproate has effects on NSCs. Interestingly, the effects of valproate on neuronal differentiation appear to depend on the origin of the NSCs. Valproate enhanced neurogenesis in NSCs derived from either entire adult HC or forebrain [90-92]. However, in NSCs from DG of the HC, valproate induces astrocytogenesis while reducing neuronal differentiation [87]. A recent article suggested that valproate protected NSCs by reducing NSCs death by upregulating the antiapototic gene Bcl-XL and activating NF-kB signalling pathways [93]. In the early 2000s, VPA was known to function as a HDAC inhibitor [69]. As mentioned above, HDAC activity has an important role in enhancing neurogenesis by upregulation of the proneural gene NeuroD while inhibiting astrocytogenesis. Activation of ERK signalling has been implicated in VPA-induced neurogenesis [90,92]. Through the beta-catenin-Ras-ERK-$p21^{Cip/WAF1}$ pathway, NSC proliferation was inhibited while differentiation into neurons was increased [92].

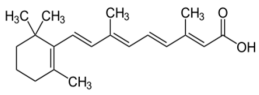
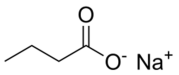
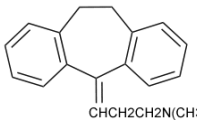
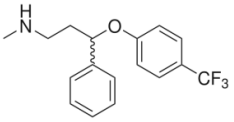
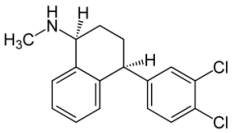
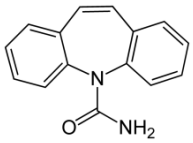
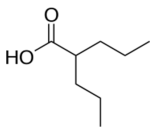
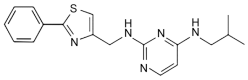
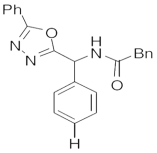
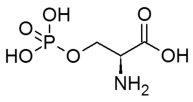
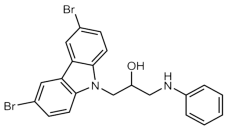
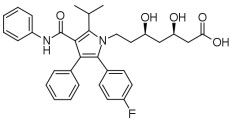
Schultz and colleagues described several synthetic molecules (for example KHS101) that induce neuronal differentiation of adult hippocampal NSCs by image-based screening [94]. KHS101 increased neurogenesis while reducing astrocytogenesis. In a search for its target, the authors found that KHS101 specifically interacts with the TACC3 protein and knockdown of TACC3 increased neuronal differentiation. TACC3 regulates progenitor cell expansion and terminal cell differentiation in hematopoietic and neural stem cells and appears to mediate the functioning of KHS101. We also identified oxadiazol compounds as inducers of astrocytogenesis by image based screening [95]. In a study of NSCs derived from developing rat (embryonic day 14), we found that oxadiazol derivatives specifically increased numbers of astrocytes while not affecting those of neurons.

For high throughput screening, Saxe and his colleagues used a chemiluminescence-based method on primary neurospheres and identified phosphoserine as an enhancer of neurogenesis [96]. Since cell counting after immunostaining requires skills and time, the authors used horse radish peroxidise (HRP)-conjugated secondary antibody and chemiluminescence detection was performed by microplate reader after HRP substrate treatment. Phosphoserine inhibited NSC proliferation, enhanced neurogenesis, and increased cell survival. It was suggested that the metabotropic glutamate receptor 4 mediated such effects. In addition to *in vitro* assays, *in vivo* screening was done in search of chemicals that enhance neurogenesis in the HC of adult mice [97]. The authors identified 8 chemicals out of 1000 tested that induce neurogenesis. An aminopropyl carbazole named P7C3 showed proneurogenic activity by protecting newborn neurons from apoptosis and by enhancing neurogenesis in the DG.

Considering that research has not been done for very long to develop drugs that modulate NSC fate or stem cell fate, it is amazing to find quite a lot of synthetic chemicals that have effects on neurogenesis (Table 1). This may be due to the ability of NSCs to respond to the environment and to differentiate into multiple cell types. Besides the chemicals mentioned above, recent patent applications report drugs that modulate melanocortin receptors, PPAR-γ, angiotensin, and 5-HT, and HMG coenzyme A reductase inhibitors were also neurogenic {reviewed in [74] and patents and references therein}. For example, in rats with traumatic brain injury, when atorvastatin and simvastatin were given for 14 days, these statins improved spatial learning measured by Morris water maze tests [98,99]. Interestingly, newly generated neurons and vessels were detected in statin-treated brain-injured rats [99]. With further screening, we should find efficient chemicals that enhance neuronal differentiation from NSCs. It will be beneficial to develop chemicals that have both neurogenic activity and neuron protecting effects for treatment of neurodegenerative diseases.

In addition to synthetic chemicals, recent results show that some natural products also affect cell fate determination of NSCs (Table 2). Until recently, neuroprotective effects of natural products have been intensely studied [100-102]. Methanol extracts of Jeju Native plants protected apoptosis induced by hydrogen peroxides [100]. Visnagin, an active component extracted from the fruits of *Ammi visnaga*, which has been used as a treatment for low blood-pressure, showed protective effects on kainic acid induced mouse hippocampal cell death by reducing inflammation [101]. BF-7 extracted from a sericultural product has significant protective effects on amyloid β peptide induced apoptosis through reduction of ROS generation and

Table 1. Synthetic compounds that are known to regulate stem cell fate

Name	Structural formula	Effects	Cells/system	Refs
Retinoic acid		-Increase neurogenesis	NSCs	65, 66
Sodium butyrate		-Increase neurogenesis -Increase neural proliferation	*In vivo*	67, 68
Amitriptyline		-Increase neurotrophic factor levels in DG	NSCs	77
Fluoxetine		-Increase neurogenesis	*In vivo* NSCs	79-81, 83
Sertraline		-Increase neurogenesis -Attenuate cellular damage	NSCs	85
Carbamazepine		-Increase neurogenesis -Decrease astrocytogenesis	NSCs	87
Valproate		-Increase neurogenesis -Reduce NSCs death -Neuroprotection	NSCs	90-93
KHS101		-Increase neurogenesis	NSCs	94
Oxadiazol compounds		-Enhance astrocyte differentiation	NSCs	95
Phosphoserine		-Inhibit NSCs proliferation -Enhance neurogenesis -Increase cell survival	hESCs NSCs	96
P7C3		-Protect newborn neurons from apoptosis -Enhance neurogenesis	NSCs	97
Atorvastatin		-Increase neurogenesis -Reduce neuronal death	*In vivo*	98, 99

diminished caspase activity [102]. *Glycyrrhizae radix* is reported to cause improvements in spatial learning, memory and stress-induced anxiety [103]. Garcinol, a polyisoprenylated benzophenone derivative in *Garcinia indica* fruit rind, is known to increase the numbers of neurons in EGF responsive neurospheres by increasing survival [104]. The survival enhancing effects of Garcinol were mediated by ERK activation and ERK activation modulated neurite outgrowth. Ginsenosides that are derived from *Panax notoginseng* were also identified as enhancers of neurogenesis in EGF-responsive NSCs [105]. Interestingly, ginsenosides induced neurogenesis at the expense of astrogliogenesis.

Table 2. Natural products that are known to affect stem cell survival, proliferation and differentiation

Name	Plant origin	Effects	Cells	Refs
Saururus chinesis extract	*Saururus chinesis*	-Protective effect on apoptotic cell death	SH-SY5Y cells	100
Smilax china extract	*Smilax china*	-Protective effect on apoptotic cell death	SH-SY5Y cells	100
Visnagin	*Ammi visnaga*	-Protect neuronal cell	*In vivo*	101
BF-7	Silkworm	-Neuroprotection -Enhance cognitive function	SKN-SH cells	102
Glycyrrhizae radix	*Glycyrrhiza Uralensis*	-Anti-stress effects	*In vivo*	103
Garcinol	*Garcinia indica*	-Promote proliferation -Increase neurogenesis	NSCs	104
Ginsenoside Rg5	*Panax notoginseng*	-Increase neurogenesis -Decrease astrocytogenesis	NSCs	105
Casticin	*Croton betulaster*	-Increase neurogenesis -Decrease neuronal cell death	NSCs	106
Curcumin	Indian spice turmeric	-Increase neurogenesis -Decrease neuronal cell death and glial cell activation	NSCs	107, 108
Nelumbo nucifera rhizome extract	*Nelumbo nucifera*	-Increase neurogenesis	*In vivo*	109, 110

The neurogenic effect of the ginsenosides was abolished completely by treatment with the Ca^{2+} channel antagonist nifedipine. A flavonoid, casticin, extracted from *Croton betulaster* also increased neuronal differentiation and decreased neuronal cell death [106]. Casticin increased neuronal transcription factor Tbr2 and did not affect gliogenesis when detected by immunocytochemistry with GFAP, S100β, Olig2 and NG2. NSCs cultured on top of astrocytes that were treated with casticin induced neurogenesis and conditioned media from casticin-treated astrocytes reproduced such effects. Curcumin, a natural phenolic component of yellow curry spice attenuates astroglial and microglial activation in kainic acid induced seizure [107]. In NSCs, curcumin has proliferation-promoting effects [108]. It was reported that administration of curcumin to adult mice increased HC neurogenesis. Methanol extracts of *Nelumbo nucifera*, a rhizome, increased NSC proliferation and increased neurogenesis *in vivo* [109,110].

Human Stem Cells for Drug Screening

Recent advances in screening technologies have enabled scientists to identify effective small molecules that induce neurogenesis. However, many studies were done using rodent NSCs as mentioned above or with highly proliferative immortalized or cancerous cell lines that do not accurately reflect the human pathophysiological condition. It is thus desirable to test or screen drugs with human cells to observe the effects and mechanisms of drugs. However, until very recently, it was almost impossible to obtain enough human tissues or cells that represent human neurodegenerative conditions. A recent breakthrough made in the stem cell research field is the generation of iPSCs from human fibroblasts or other somatic cells [45-48]. Using numerous combinations of stemness genes, Takahashi and his colleagues found that Oct4, Sox2, Klf4 and c-myc could reprogram mice fibroblasts into ES like cells [45]. Human somatic cells could also be converted into ES like cells by introduction of a few stemness genes [46,111,112]. Furthermore iPSCs were generated from fibroblasts taken from patients suffering from neurodegenerative diseases [52,53,113]. Thus the disease mechanism can be studied in these cells and drug screening for specific diseases can be done. Recent advances in gene editing such as zinc finger nuclease mediated and helper-dependent adenoviral vector approaches were able to cause insertion or deletion of specific target genes and cause iPSCs to produce isogenic lines [114,115]. Thus disease bearing iPSCs and appropriate control cells could be used for the study of pathological mechanisms of diseases and drug effects can also be more accurately tested in these cells.

Since neurodegeneration occurs late in adulthood, it is likely that iPSCs generated from patients would not represent true pathological conditions. Svendsen and his colleagues reported that iPSCs can be generated from spinal muscular atrophy (SMA) patients [53]. Although early produced motor neuron numbers were not affected, long term culture showed degeneration of motor neurons that had differentiated from iPSCs generated from an SMA patient. Interestingly, when iPSCs were generated from a patient with Parkinson's disease, there was not much loss of dopamine neurons [50]. The cells probably needed more time to develop Parkinson's disease that they are harbouring. Although much more research is needed to develop a system for drug screening, human iPSCs that are generated from patients with specific disease are a good model with which to test and screen drugs.

In addition to screening drugs that are effective in treatment, it seems apparent that human stem cells are an excellent model to evaluate drug toxicity. Before moving on to phase I clinical trials, it would be safer to test toxicity on human ESCs derived cardiomyocytes or other sources to predict adverse effects (Maybe this step could be called clinical trial phase 0.5). Since cellular contents of human cells are different from those of rodent or other animal cells, toxicities that are not identified in animal models could be detected in human stem cell derived differentiated cells.

CONCLUSION

Screening for drugs that modulate stem cell self-renewal and differentiation, or protect cell death, can be performed

to develop new drugs to treat human neurodegenerative disease. Stem cells provide a good platform with which to perform drug screening and evaluation of toxicity. In this review, we have introduced drugs and natural products that modulate stem cell fate to neurons or glia. With the ability of stem cells to respond to the environment, we expect to see, in the near future, more progress in identifying new drugs that regulate stem cell proliferation and differentiation and are used in neurodegenerative diseases.

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