Drug treatments that optimize endogenous neurogenesis as a therapeutic option for stroke

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Abstract:
Cell death and neurogenesis have been examined after stroke in the subventricular zone of the adult mammalian brain. New research focuses on the use of drugs to improve the viability of neural progenitor cells in rats after stroke. The aim of the drugs is to lengthen the timeframe for stroke therapy by targeting the endogenous repair mechanism that follows injury. In this paper, we look at the broad state of stroke therapy to assess the effectiveness of endogenous neurogenesis-enhancing drugs on stroke. This paper is a review article. Referred literature in this paper has been listed in the reference section. The data sets supporting the conclusions of this article are available online by searching various databases, including PubMed. Some original points in this article come from the laboratory practice in our research center and the authors’ experiences.

Keywords:
Central nervous system disorders, endogenous neural progenitor cells, neurogenesis, neurogenesis-enhancing drugs, regenerative medicine, stroke

Introductions
At the occurrence of an ischemic brain injury, bodily responses include apoptosis, leakage of the blood–brain barrier, inflammation cell death, excitotoxicity, as well as endogenous neural repair (see the study by Brouns and De Deyn1 for further details).[1] Many of these reactions occur following stroke lasting anywhere from hours to 2 days. An occurrence of these responses includes the apoptosis at the ischemic site.[2] It has been demonstrated that the p53 messenger RNA (mRNA) or protein is upregulated following stroke in a rodent distal middle cerebral artery occlusion (MCAo) model, leading to p53-dependent apoptosis in the penumbra.[3,4] Furthermore, the density of the terminal deoxynucleotidyl transferase 20-deoxuryridine 50-triphosphate dUTP nick end labeling (TUNEL) located within the ischemic cortex peaks 2 days following MCAo and stabilizes within 6 days.[5] It was also demonstrated that animals have reduced brain infarction when given a p53 inhibitor treatment preceding or directly following MCAo.[6,7] No beneficial effects on neuronal loss[7] or locomotor behaviors were recorded when the p53 inhibitor treatment was administered 3 h or later following MCAo.[5] Clinical applications for these drugs have been limited by the limited therapeutic window caused by the short length of apoptosis/necrosis in the ischemic region. Because of the narrow therapeutic window treatments aiming at suppressing apoptosis in the ischemic region, treatments must occur soon after MCAo.

In a study of the adult mammalian brain, cerebral ischemia was found to induce novel neurogenesis within the subventricular zone (SVZ) several days following stroke, representing a late bodily repair mechanism.[8] Utilizing...
bromodeoxyuridine (BrdU) labeling to measure to proliferation of neural progenitor cells (NPCs), a rise in BrdU immunoreactivity was recorded as soon as 2 days post-MCAo within the SVZ posts ischemia. Immunoreactivity remained constant through day 4, then wanted from day 6 to day 8 returning to baseline around day 10. This trend demonstrates a divergence between cell death in the ischemic-lesioned area and cell propagation in the SVZ. A longer treatment window may be achieved by focusing on the viability of endogenous NPCs within the SVZ following stroke.

Endogenous Neurogenesis-Enhancing Drugs

Several drugs in development directed toward the endogenous repair mechanisms that follow stroke control the differentiation, migration, or procreation of NPCs in the SVZ. Several of these drugs which may have the potential to create a longer timeframe for stroke therapy are described below.

Pifithrin-a

While stroke can induce the propagation of NPCs in the SVZ, a majority of the cells die following injury. NPC cells within the SVZ express high levels of p53 protein. Amplified TUNEL activity was discovered within the SVZ of stroke rats demonstrating that apoptosis is a factor in the death of NPCs. Because initiation of NPC propagation in SVZ ensues at a later stage, beginning at 6-day post-MCAo, 12 treatments of pifithrin-a and p53 inhibitor were found to enhance motor function in stroke rats while also improving viability of endogenous NPCs in the SVZ. These results suggest that p53 inhibition may attenuate the survival of endogenous NPCs and change biological outcomes several days following stroke.

Trophic factors

Specific trophic factors have been revealed to improve neural reparative activity after stroke. Some of the trophic factors that have received much attention from stroke researchers are discussed below.

Bone morphogenetic protein 7

Bone morphogenetic protein 7 (BMP7) is a trophic protein in the transforming growth factor-b superfamily that can promote DNA synthesis. DNA synthesis was examined by BrdU incorporation in mesencephalic-cultured neurons. Treatment with BMP7 following MCAo improved sensorimotor function, lowered body asymmetry, and increased locomotor activity from 7-day postinjury to 14-day postinjury. BMP7 simultaneously increased BrdU immunoreactivity in the corpus callosum, lesioned cortex, and SVZ. BrdU-positive cells are colabeled with NeuN and nestin. These results back the idea that BMP7 ameliorates functional recovery through the propagation of neuronal precursors in the stroke brain.

Brain-derived neurotrophic factor

In stroke animals, systemic administration of brain-derived neurotrophic factor (BDNF) improved the movement of NPCs into the lesioned site while in nonstroke animals, BDNF has been shown to increase movement of NPCs from the SVZ to the olfactory bulbs. Atorvastatin (a BDNF-activating chemical) increased movement of SVZ cells. Furthermore, gene therapy through adeno-associated virus infection induces an overexpression of BDNF enabling improved functional recovery and NPC movement from the SVZ. The results suggest that treatment with BDNF or increasing endogenous BDNF expression improved the movement of NPCs from the SVZ and enabled behavioral recovery in stroke animals.

Other trophic factors

Multiple other trophic factors have been shown to enhance neurorepair in stroke animals.

One such trophic factor is GDNF which is overexpressed through the transplantation of human umbilical cord CD34+ or neural stem cells leading to enhanced neurogenesis. Increased GDNF concentration amplified cell propagation in the SVZ and the recruitment of novel neuroblasts into the striatum following MCAo. Additional trophic factors, such as basic fibroblast growth factor, epidermal growth factor, and hepatocyte growth factor, have been determined to raise the number of BrdU-positive cells in the SVZ and advance endogenous neurogenesis in the stroke brain.

Cocaine- and amphetamine-regulated transcript

Cocaine- and amphetamine-regulated transcript (CART) is a peptide found in the brain. The expression of CART can be increased by electroconvulsive shock or focal cerebral ischemia in vivo and oxygen–glucose deprivation in culture. Recent experimentation has exemplified that CART treatment administered intranasally 3 days following MCAo improved neuronal repair by facilitating NPC propagation and movement from the SVZ. The movement and propagation of NPCs enhanced reinnervation in lesioned cortex and improved the functional recovery of stroke animals and also reduced cerebral infarction. Within the SVZ, CART improved the proliferating cell nuclear antigen, NPC marker Musashi-1, immunolabeling of BrdU, while upregulated BDNF mRNA. CART treatment increased neurosphere formation in an SVZ culture while anti-BDNF-blocking antibodies provoked CART-mediated cell movement from the SVZ. Increased
expression of Fluoro-Ruby fluorescence and GAP43 in the injured cortex was triggered by CART. CART treatment was also found to increase N-acetylaspartate levels in the injured cortex using 1H-magnetic resonance spectroscopy. These results show that neuroregeneration in the stroke brain can be improved through intranasal CART treatment.[9,34]

**Naturally Occurring Compounds as Agents for Enhancing Endogenous Neurogenesis in Stroke**

During the prestrike period, dietary supplementation has been shown to exhibit neuroprotective properties by reducing inflammation and increasing neurogenesis. By stimulating endogenous brain restoration, dietary supplementation can prevent the brain from undergoing further insult and injury.[35,36] Certain foods high in antioxidants such as polyphenols from blueberries, green tea, and amino acids such as carnosine exhibit anti-inflammatory properties and could, therefore, lessen the harmful effects of reactive oxygen species in the blood, brain, and other body tissues.[35,36] Further research should consider the effectiveness of a poststroke dietary treatment in dampening the secondary cell death cascade that follows stroke. It may also be clinically relevant to examine the use of dietary supplement as an additional treatment for prevention and chronic disease treatment in stroke and other diseases. We see the future of dietary supplements as an assisting treatment for treating stroke acutely, subacutely, and chronically.

**An Overview of Recent Advances in Stroke Therapeutics**

At present, tissue plasminogen activator (tPA) is the standard for treating ischemic stroke. The use case of tPA is narrowed by its 4.5-hour poststroke therapeutic window, and hemorrhagic transformation (HT) affects if administered outside of the therapeutic window. An effective stroke treatment is possible if the risk of HT and other drawbacks associated with delayed tPA is reduced. Drugs that maintain the patency of the cerebrovasculature to prevent delayed tPA-induced HT have promise as a treatment for ischemic stroke and have been the focus of much pharmaceutically oriented preclinical research. Drugs examined for HT ameliorating and endogenous neurogenerative properties include those discussed above as well as brain vasculature enhancing and blood brain barrier preserving drugs.[9,19,21,23,25,34] Hurdles regarding optimization of the drug regimen exist before clinical application can be reached. Uncertainties regarding the dose, timing, and route of the drug must be resolved for these drugs to be presented as effective treatment options.

**Conclusion**

At present, the narrow therapeutic window for stroke limits the scope of drugs usable for treatment. Multiple peptides, chemicals, and trophic factors that target the endogenous repair originating in the NPCs in the SVZ have been shown to improve behavioral performance poststroke.[38-37] The experimental method discussed proposes a possible treatment strategy for increasing the treatment window for stroke. Stroke is often difficult to treat directly following injury; therefore, this approach could increase further treatment opportunity.

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**Conflicts of interest**

There are no conflicts of interest.

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