Understanding neurogenesis in the adult human brain

The process of neurogenesis is most active during embryonic development and continues after birth for a year or 2 in humans. In the first stage (42 embryonic days), neural progenitor cells, which are mitotic are formed in a symmetrical fashion, after which the mode of cell division shifts from symmetrical to asymmetrical. During asymmetrical division, 1 neural progenitor and 1 neuron is produced.[1] Neurogenesis mostly occurs in the ventricular zone, and the newly formed progenitor neurons remain in the proliferative zone, while the neurons migrate radially out to the neocortex. The cortical neurogenesis completes by about 108 embryonic days.[2] A nonpathological process that is essential in the establishment of complex networks of the developing brain involves loss of about 50% of the neurons. There are approximately 100 billion neurons in a mature human brain. The naturally occurring neuronal cell death occurs prena tally, and elimination of about 50% of unwarranted connections among neurons occurs postnatally. Each neuron can make connections with more than 1000 other neurons, thus an adult brain has approximately 60 trillion neuronal connections.

Endothelin-B (ETB) receptors are a necessary component of the developing nervous system. ETB receptors act as regulators in differentiation, proliferation, and migration of neural cells during pre and postnatal development, assisting the formation of melanocytes, neurons, and glia of the enteric nervous system as well as the central nervous system (CNS).[3] We have demonstrated that stimulation of ETB receptors increases the expression of various growth factors, such as vascular endothelial growth factor (VEGF) and nerve growth factor, and plays an important role in the vascular and neuronal development of the CNS.[4-7]

It is now known that neurogenesis persists throughout the human lifespan, and new neurons are being formed in the adult brain. The first direct evidence for adult neurogenesis in humans was provided in 1998, when a thymidine analog, bromodeoxyuridine (BrdU) was administered to 5 cancer patients, and their postmortem brain tissue was obtained and compared to a similar patient without BrdU treatment. It was found that new neurons are being formed from dividing progenitor cells in the dentate gyrus of adult humans.[8] Follow-up studies could not be carried out because injecting BrdU in humans is not an option anymore, because of safety concerns of injecting a chemical that incorporates into the DNA of dividing brain cells. A landmark study was then conducted by measuring the 14C concentration in the DNA of brain cells of deceased patients that were previously exposed to atmospheric 14C released due to above-ground nuclear tests, and it showed significant neurogenesis in the human hippocampus.[9]

In the adult brain, there is an endogenous mechanism, which attempts to repair and reduce damage to the brain following insults such as head trauma and cerebrovascular accidents. The neurorestorative process involves neurogenesis, angiogenesis, and oligodendrogenesis. It is possible that stimulation of ETB receptors in the brain can lead to neurovascular remodeling and enhance the neurorestorative processes that are inherent in the adult brain. There are many pharmacological agents such as antidepressants, cannabinoids through CB1 receptors, granulocyte colony stimulating factor, and VEGF have been identified to modulate neurogenesis, and can provide new therapeutic strategies.

A large number of late stage clinical trials for indications such as stroke and Alzheimer’s disease have failed. This has led to reconsidering of the entire strategy, and now, the emphasis is being given to move away from acute neuroprotection and go toward delayed neurorestoration. In the United States, the National Institute of Neurological Disorders and Stroke is supporting mechanistic studies of neuroplasticity, which are relevant to stroke recovery. Stroke progress review group has also identified neurorestoration after stroke as a major priority area for stroke research. Many laboratories across the world are aggressively moving forward with compounds that can induce neurogenesis in the adult brain and potentially be used as therapeutic agents for the treatment of cerebrovascular accidents, Alzheimer’s disease, and brain injuries.

We have shown that selectively activating ETB receptors, with IRL-1620, in a focal stroke model is effective in reducing the infarct volume (by 83.66% in the acute study and 69.49% in the chronic study), and improved all neurological and motor function parameters when compared to the vehicle-treated group.[10-12] We also found that protection and recovery from the ischemic condition were due to reduction in apoptosis, and an increase in angiogenesis and neurogenesis within 7 days following infarct and treatment with IRL-1620. VEGF-positive vessels/30 µm brain slice in the IRL-1620 group numbered 11.33 ± 2.13 versus 4.19 ± 0.79 in the vehicle group.[12] IRL-1620 was also found to be highly effective in a rat model of Alzheimer’s disease.[5,13]

Several clinical studies have been initiated to evaluate adult neurogenesis using dietary supplements, pregnenolone, 583

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gut-derived peptides (ghrelin, glucagon-like-peptide-1), and drugs used for the treatment of depression. A trial of the antidepressant drug, fluoxetine given for the first 3 months to patients with stroke (FLAME study) showed much less impairment compared to control and this beneficial effect has been attributed to fluoxetine-induced neurogenesis. Other agents such as ET<sub>B</sub> receptor agonist, IRL-1620 are likely to enter clinical efficacy trials in the near future.

It can be concluded that angiogenesis and neurogenesis can be pharmacologically induced in the adult damaged brain. Therefore, pharmacological neurorestoration is likely to become a priority area of research for diseases such as stroke, Alzheimer’s disease, amyotrophic lateral sclerosis, and brain and spinal cord injuries.

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