



Brain Injury & Stem Cells

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Consciousness

- What is consciousness? Consciousness is self-awareness that occurs when cerebral cortex activity is synchronized by a rhythmic 30-90 Hz signal from the thalamus.
- Interrupting the thalamic rhythm causes loss of consciousness. Unconsciousness occurs during anesthesia, deep sleep, post-traumatic coma, and *gran mal* epileptic seizures.

Memory

- What is memory? Memory is storage and recall of previous activity in the brain. It is stored in all parts of the brain. Its formation and recall requires the hippocampus.
- Without memory, brain activity cannot interact over time. If memory storage or recall is compromised, consciousness is impaired. Short and long term memory are distinct.

Sensation

- What is sensation? Sensation is brain activity resulting from incoming or afferent signals. Consciousness is necessary for sensation but sensation is meaningless without memory.
- Most sensations (except auditory) reach the cortex through the thalamus. Subcortical visual and other sensory systems exist. For example, the amygdala can "see", i.e. "blind" sight.

Movement

- Movement result from muscle activity initiated by nervous signals from the central nervous system (CNS). They may be voluntary (conscious) or involuntary (reflexive).
- Motor activities are programmed in the spinal cord, brainstem and subcortical structures. The basal ganglia initiates motor programs that are modulated by motor cortex and reflexes.

Unilateral & Central

- The brain has two sides. Damage to one side usually does not cause coma or memory loss. For example, Congresswoman Gabriela Gifford did not have coma or memory loss.
- Damage to the midbrain can caused "locked-in" syndrome, blocking both input and output to the cortex, without eliminating memory or consciousness.

Neural Stem Cells

- For over a century, neuroscientists have believed that no new neurons are made after birth. However, much data have refuted belief and that neurogenesis occurs in adult brains.
- Originating in the subventricular zone (SVZ), adult neural stem cells (NSC) migrate to the hippocampus and olfactory bulb, providing a source of new neurons for these structures.

Stem Cell Transplants

- Neural stem cell transplants (from fetal sources or subventricular zone) produce mostly astrocytes (60%), oligodendroglia (25%), and neurons (15%).
- Intravenously administered bone marrow stem cells (autologous) generally do not enter the brain but may release growth factors and cytokines that seem to improve recovery.

Embryonic Stem Cells

- Embryonic stem cells (ESC) are obtained from blastocysts (2 weeks after fertilization) and are pluripotent (can make all cell types) but must be differentiated before transplantation.
- ESC form teratomas, stem cell tumors composed of many types of cells. Adult or neonatal stem cells usually do not make teratomas. Fetal stem cells sometimes do.

Umbilical Cord Blood

- Umbilical cord blood contains more stem cells than bone marrow and can be HLA-matched for immune compatibility.
- Cord blood has been used for over 20 years to replace bone marrow and is effective for treating genetic brain diseases.
- Most of the stem cells in cord blood is in the mononuclear cell fraction (buffy-coat layer). This is usually what is transplanted into the brain.

Other Stem Cells

- Mesenchymal stem cells been isolated from fat, peripheral blood, umbilical cord, and even baby teeth. They make mesenchymal tissues.
- MUSE cells were discovered by Mari Dezawa. About 1:300,000 adult mesenchymal stem cells express SSEA3/4 and are pluripotent.
- Other sources of pluripotent stem cells have been reported, from intestine, olfactory mucosa, umbilical cord lining, testiother and other germ cell sources.

Endogenous Sources

- The brain has its own stem cells. Why don't we stimulate the brain's own neural stem cells to grow and produce more neurons?
- GCSF (granular colony stimulating factor) stimulate bone marrow stem cells and has been used to treat stroke.
- Lithium stimulates neural stem cells to proliferate, to produce more neurons, and to secrete neurotrophins known to facilitate regeneration.

Mononuclear Cells

- Mononuclear cells from bone marrow or umbilical cord blood contain 1-2% CD34+ cells (endothelial progenitors) and CD133+ (pluripotent stem cells).
- Injections of these into the brains of animals after stroke and other forms of brain injury can facilitate behavioral recovery and regeneration in animals.
- Clinical trials of these cells are being done in Taiwan, Korea, China, Middle East, and Europe.

Lithium & Stem Cells

- In concentrations of 1 mM, lithium carbonate stimulates bone marrow, cord blood, neural, and embryonic stem cells to proliferate, increasing cell number of 3-4x within a week.
- It also causes cord blood mononuclear cells to produce neurotrophins, particularly nerve growth factor (NGF), neurotrophin-3 (NT-3), and glia-derived neurotrophic factor (GDNF).

Lithium & Gray Matter

- In 2003, Sasso and others reported patients who take lithium for manic depression have more gray matter and more neuronal markers than normal people.
- By 2008, a meta-analysis of 87 MRI studies by Kimmell, et al. indicated that 4-6 week course of lithium significantly increased gray matter, particularly hippocampus and cingulate gyrus.

Lithium Mechanisms

- Lithium act by blocking glycogen synthetase kinase 3-beta (GSK3b) which normally inhibits nuclear factors responsible for stimulating cell growth. Therefore, lithium disinhibits growth.
- These nuclear factors include nuclear factor of activated T-cells (NFAT) and beta-catenin, well known to increase neural stem cell proliferation and neuronal differentiation.

Deep Brain Stimulation

- Thalamic activity mediates consciousness. Many investigators do deep brain stimulation (DBS) of the thalamus to arouse people in coma or minimally conscious states.
- While some spectacular successes have been reported, the success rate of "waking patients" has been low, probably less than 15% of cases.

Other Drugs

- Zolpedem (a GABA receptor blocker) and Citicol (a acetylcholine stimulant) may help some patients but rates of clinically significant improvements are >10%
- Provigil has been used to increase wakefulness and alertness in people but again the effects of the drug have been limited at best.
- To my knowledge, there is little evidence that growth hormone, Chinese herbs, acupuncture, intravenous bone marrow cells, or other alternative therapies work.

What Can We Do?

- Our country has slowed down brain injury research over the past decade. Less brain injury research is going on now than 1995.
- We don't have a good animal model of brain injury that includes unconsciousness or memory loss as major features of the model.
- Clinical trials of treatments for chronic brain injury are as rare as hen's teeth. It is critical that the research be restarted.

Summary

- Loss of consciousness and memory are the two most devastating effects of traumatic brain injury and we have no effective therapies for either.
- Neural stem cells may repair brain damage but a reliable source of immune-compatible stem cells still has to be identified.
- GCSF and lithium stimulates endogenous stem cells to grow and may represent a reasonably safe and easy to give therapy for the time being.