Outline

- Define Traumatic Brain Injury.
- Define and discuss Apoptosis vs. Necrosis.
- List the different causes of TBI.
- Discuss the various challenges presented by different forms of traumatic injury.
- Describe the Mechanisms of TBI damage.
- Define the Theories of Recovery.
- Discuss the current Research on Treatments for TBI.
- Discuss other factors that affect TBI recovery.
What is TBI?

- Traumatic Brain Injury is anything that suddenly causes significant neuron death.

- This process has the potential to inhibit or eliminate the brain’s ability to coordinate or direct a specific bodily function.
How often does TBI occur in the U.S.?

CDC statistics on reported incidents of TBI from 2001 to 2010

Why the Rise in total incidents of TBI in 2007?
Economic Crash

Why the Plunge in Deaths?
New Standard of Treatment manual published. Braintrauma.org
Apoptosis vs. Necrosis

- Apoptosis:
  - Also known as Programed Cell Death, this is brought about by the expressions of “Suicide Genes” which generate proteins that begin to break apart the cell.

- Necrosis:
  - Something outside the cell infecting, damaging, or otherwise rendering the cell unable to repair itself, leading to cell death.
Apoptosis and Traumatic Brain Injury

- The Tumor Suppressor Gene P$_{53}$ acts as the commander in chief when the neuron is damaged due to:
  - DNA damage, oxidative stress, hypoxia, withdrawal of trophic support, hypoglycemia, metabolic compromise, oxidative stress, viral infections, and cellular calcium overload.

- P$_{53}$ triggers the transcription of proteins that either fix the damage, or cause cell death.

- In 2003, Charles Gilman + found that P$_{53}$ can and does act directly on the mitochondria.

Apoptotic Pathways in Neurons

Lifted From: https://www.uni-marburg.de/fb16/ipkp/gruppen/ag_culmsee/research
Apoptotic Pathways in Neurons

- Calcium overload
- Hypoxia (O\(_2\) loss)
- Immune Response/Osmotic Shock

  - Calpain enzyme activation
  - HIF Protein activation
  - Cytokine Signaling
  - P\(_53\) activation
  - JNK protein activation

  - PUMA Transcription
  - Bax Transcription

  - Inhibition of Bcl-2
  - Mitochondrial Membrane Damage

  - Cytochrome C release

- Apoptotic Proteins

  - Caspases activation

  - Cell Degradation
What Causes TBI?

- Physical Trauma
  - Open Head Injury
  - Closed Head Injury
- Stroke
  - When a blood vessel feeding the brain is blocked or broken
- Brain Surgery
- Drug Use
  - Alcohol
  - “Recreational” drugs
- Exposure to certain heavy metals
  - Lead
  - Mercury
Physical Trauma

- **Open Head Trauma:**
  - Any injury that exposes brain tissue to the air and damages the brain.

- **Complications:**
  - Extreme force injuries can cause bone fragments and foreign materials to enter the skull cavity.

- **Closed Head Trauma:**
  - Anything that damages the brain without opening the skull.

- **Complications:**
  - Excess damage can be caused by Pressure build up.
Stroke

- A stroke can occur anywhere in the brain, and varies greatly in the amount of damage it can produce.

- Ischemic stroke: About 80% of strokes are ischemic strokes. This type happens when a blood vessel in the brain develops a clot that cuts off blood flow to cells.

- Hemorrhagic stroke: The remaining 20% are hemorrhagic strokes, which happen when a weakened blood vessel in the brain bursts. When the vessel bleeds or hemorrhages suddenly, surrounding brain tissue can become damaged.

Brain Surgery

- Brain Surgery has the potential to cause less functional damage, because the damage is controlled, and treatment to aid in recovery can be administered at the time of injury.
Drugs

- Alcohol
  - Damage to the Cerebellum

- MPTP
  - Induces apoptosis in dopaminergic neurons of the Substantia Nigra.

- Methamphetamines
  - Reduces the binding of dopamine, increases risk of stroke.

- These, and other drugs have been shown to cause some of the same effects in the brain as Traumatic Brain Injury, and the effects can be as permanent.
Exposure to Heavy Metals

- **Lead**
  - Lead impairs cognitive function, but we didn’t know how until 2012. That year a team at the University of Massachusetts published their research indicating that Lead Blocks the production of BDNF or Brain-Derived Neurotrophic Factor.
  
  http://www.sciencedaily.com/releases/2012/02/120229105141.htm

- **Mercury**
  - Binds to the Tubulin proteins that make up the microtubules of the neuron and prevents them from binding together. This can cause retrograde degradation and eventually cell death.
  
  https://www.youtube.com/watch?v=XU8nSn5Ezd8
When the Brain is Damaged…

- Neurons Die.
- Neurotransmitters and Ion spill.
- Glial cell responses.
- Brain swelling.
- Anomalous Projections.
When Neurons Die.

- When neurons die, the loss of stimulus to the neurons they were connected to can, in some cases, be enough to cause those secondary, undamaged, neurons to die.

  - Deafferented:
    - Target structure loses all neuronal input.

  - Denervated:
    - Target structure loses some neuronal input.
Effects of a Neuronal Chemical Spill

- After a Brain Injury, Neurotransmitters and Ions are released into the local cerebrospinal fluid. This can cause the fluid space to become toxic to otherwise undamaged Neurons.

- This toxicity can act through:
  - Over-Excitation of the cell
  - Osmotic shock
Neurotransmitter and Ion release

Ca$^{2+}$
Na$^{+}$
K$^{+}$
Cl$^{-}$
Glutamate

Ca$^{2+}$
Na$^{+}$
K$^{+}$
Cl$^{-}$
Glutamate

Ca$^{2+}$
Na$^{+}$
K$^{+}$
Cl$^{-}$
Glutamate
Excitotoxicity

- Glutamate is a neurotransmitter that acts as a ligand for the Ion-Gated Ca\(^+\) Channel NMDA.

- When an excess of Glutamate is present, it will bind to the ligand receptors for too long, causing an unhealthy influx of Calcium into the cell.

- The Ca\(^+\) then causes the generation of Free Radicals, ATPases, proteases, and Phospholipases which start to chew up the cell wall.
Active Calpain Protein  Non-active Calpain Protein  Bax
NMDA Receptor  Glutamate  Calcium Ion  Cytochrome C
P53  Apoptosis
Osmotic Shock

- When an excess of ions are allowed into a neuron, the osmotic pressure will change relative to the change in charged ion within the cell. Water will then flow into the cell to balance the ion concentration, which can result in cell membrane rupture if enough fluid flows in.
When the Brain Swells

- The damaged area of the Brain Swells, which can pinch off neighboring capillaries, depriving undamaged areas of Oxygen and glucose.

- Because the brain is completely encased, injuries can arise when inflamed tissue presses against the rigid wall of the skull, increasing pressure against the otherwise undamaged areas of the brain.
Glial Cells

- Glial Cells are the support cells of the Brain.
- Astrocytes control ion concentration.
- Oligodendrocytes form the myelin sheaths.
  - Schwann cells in the peripheral nervous system.
- Microglia are the brains immune cells.
Glial Scar

- Astrocytes gather at a point of injury and can form a scar that blocks toxic chemicals from reaching undamaged neurons.
Glial Cells in Healing

- Oligodendrocytes produce Neurotrophic Factors.
- This family of chemicals has been found to promote new growth in neurons with damaged axon and/or dendrite regions.
- Nerve Growth Factor was the first discovered and is specific to Cholinergic neurons.
Glial Cells in defense

- Microglia absorb toxic chemicals and foreign particles, but after injury they also recruit White Blood Cells from neighboring capillaries into the area of damage.
Anomalous Projections

Even if an area of damage is encouraged to make new connections, they might not be the right ones, causing greater loss of function than the initial injury.

Before:

After:
Recovery from TBI

- Define Recovery
- Is Recovery Possible?
- Theories on Recovery mechanisms.
- Modern Research
  - Neurons Die.
  - Neurotransmitters and Ion spill.
  - Glial cell responses.
  - Brain swelling.
  - Anomalous Projections.
Definition: TBI Recovery

- Traumatic Brain Injury usually causes mild to severe disability. The level of recovery experienced by a patient is determined by the level of disability they experience after treatment or time from the injury.

- Full Recovery means that the individual can function as independently in society as they could prior to the injury.

- Partial Recovery (or mild TBI) means that a person experiences some disability, but is still able to care for themselves.
Recovery

- Santiago Ramon y Cajal was one of the first to demonstrate that the adult brain has the ability to repair itself.

- Back in 1913 he published his work demonstrating that Neurons Regenerate, and his work is still influencing research in Traumatic Brain Injury Repair to this day.
Theories of Recovery

- **Vicariance**: One tissue of the Brain “took over” the processing of information normally send to the now damaged tissue. Either a structure that already preforms a function, or a dormant “backup system” that becomes active when the primary system is damaged.

- **Functional Substitution**: The patient develops alternative behaviors or neural processing to perform the lost function.

- **Diaschisis**: This describes when no damage occurred to the non-functioning region, it merely received a temporary blockage or inhibition signal and function returns when the “shock” wares off.
Replacing lost neurons

- Stem cells and fetal brain tissue have been used to try and replace neurons lost from TBI.

- However, embryonic stem cell use is very controversial because naturally aborted tissue can’t be used due to preexisting problems, so the only donors for this treatment are selective abortions.
Alternatives?

- Shinya Yamanaka discovered that the alteration of a few genes will cause an adult, specialized cell to revert back to an undifferentiated pluripotent stem cell.

- Neural Progenitor Cells (NPC) have been found in the Ventricles and the Hippocampus, and retain the ability to differentiate. Goldman SA, Sim F. Neural progenitor cells of the adult brain. Novartis Found Symp. 2005;265:66–80. discussion 82-97.
Nerve Growth Factor Treatment

- Eugene Johnson and his team raised neurons in a culture dish found that the addition of Neuronal Growth Factor prevented cell death if it was administered within 72 hours.

- They also found that removing NGF caused cell death.

- When they blocked protein synthesis in addition to removing NGF, the cells remained alive.
TBI Treated with Glial-Cell-Derived Neurotrophic Factors

Fig. 4. AdGDNF is neuroprotective. AdGDNF treated animals had significantly more neurons remaining in the FL-SMC when compared to CCI only animals. (†significantly different from CCI p < 0.05; *significantly different from Sham p < 0.05).

Graph; found on p301
Microglia Regulation

- Microglia are the principal factor cause swelling in the region of neuronal injury. Initially positive healing response, but too much swelling is bad.

- Modern research is focusing on finding methods for selectively inhibiting or removing the Microglia after a certain time has passed after the initial injury.
Swelling Reduction

- For many years, Barbiturates were used to reduce swelling in TBI patients, because they reduce the metabolic rate of brain tissue and blood pressure. However, this tended to ultimately lower the patients chances for functional recovery.

- Recently “Mild Hypothermia Treatment” has been shown to have some of the same effects without the damaging side effects (Jiang, Ji-Yao, et al., 2000).
Other Factors Affecting TBI Recovery

- Age
- Gender
  - Hormonal State
- Specifics of Damage
  - Location
  - Rate
  - Frequency
- Environmental Stimulation during Recovery
- Social Support
Age and TBI

- It is logical to assume that a young brain might recover from TBI better than an old brain, but this isn’t necessarily true.

Different areas of the brain develop at different rates, damage in an undeveloped area may cause less long term functional deficits.
Gender and TBI

- Male and Female brains are different, and subject to different types and concentrations of Hormones.
- Most animal research is done on male animals.
- Females respond differently to TBI based on where they are in their menstrual cycle.

- Animal studies have shown greater recovery rates in females, but most human observational studies have shown no clear difference.
- Females have shown greater cognitive recovery after a similar injury to males.  
Specifics of Injury

- Location:
  - Damage to the Motor Cortex may cause physical disability, where damage to the Frontal Cortex, may cause mental disability.

- Rate:
  - Sudden Traumatic Injury tends to cause more functional loss than a slow growing tumor.

- Frequency:
  - Some research has indicated that numerous small amounts of damage, may cause less disability than one large injury.
Environmental Factors

- Cognitive stimulation and participation aid in recovery.
- Rats placed in stimulating environments full of toys, multiple levels, treats etc. recovered better from surgical TBI, than those placed in a sterile lab cage.
- Patients placed in a room with a view after brain surgery recovered more function than those in a room with no window or a window facing a wall.
Social Support

- All other things being equal, those with more social support, tend to regain more function than those without these advantages.

- Rats placed in cages with other rats after brain surgery recovered greater function than those placed alone.
References


- Restorative Neurology & Neuroscience, 2010, Vol. 28 Issue 3, p293-309, 17p, 3 Diagrams, 1 Chart, 4 Graphs Graph; found on p301

