Decrease of Post-Traumatic Brain Injury by Early Use of Butein, A Sirtuin-Activator

Mutombo Kankonde, M.D., MPH

What happens in TBI?
After a severe episode of ischemia, traumatic brain injury (TBI) or epilepsy, it is typical to find necrotic cell death within the injury core. In addition, a substantial number of neurons in regions surrounding the injury core have been observed to die via the programmed cell death (PCD) pathways due to secondary effects derived from the various types of insults. Apart from the cell loss in the injury core, cell death in regions surrounding the injury core may also contribute to significant losses in neurological functions.

Irreversible, the neuronal cell death contributes significantly to the pathology of traumatic brain injury (TBI) irrespective of the mode or severity of the injury. It is a priority to preserve the injured neurons in the regions around the injury core as quickly as possible. For neurons, to die or not to die depends on the stress-activated signaling pathways and apoptotic pathways.

Cell chemistry in TBI
When trauma to the brain or stress are the initiating events, a particular member of the MAPK family called the C-jun, is amplified. The C-Jun terminal protein (JNK) will lead to phosphorylation of various substrates in the Nucleus, the Mitochondrion and the Cytosol. In the Mitochondrion, the stress and toxic induced C-jun lead to loss of MMP and induce Cytochrome C release into the Cytosol with resulting in the activation of the Caspase cascade which leads to Apoptosis, or NEURONAL DEATH. At Nuclear and Cytoplasmic levels, C-jun downregulates Bcl-2, and MCL-1, upregulates BAX which are pro-Apoptotic, but it also induces pro-inflammatory (TNF alpha, Interleukin 6,8) Cyclins to cause death by Necrosis.

Hypothesis
Sirtuins protect against neuronal death. The study objective is to show that a sirtuin activator like BUTEIN can help protect against further neuronal death after a trauma to the brain and improve rehabilitation programs offered to TBI victims.

Should BUTEIN prove to be a sufficiently strong Sirtuin activator, the earliest possible administration of butein after a TBI could help slow down damage to the nerve cells and improve the efficiency of all subsequent brain and nerve cell function preserving medical and therapeutic measures.

- SIR2 = Protein Deacetylase (Epigenetic Effect) => Site of Cytokine production
- SIR1 = Co-activate Retinoic RARβ => Up-regulate ADAM10 => Increases the NOTCH which is known to “repair” neuronal damage

Butein
Butein, a chalconoid, has many effects on the cell:

- Inhibition of EGFR and SARC tyrosine kinase and c-AMP dependent processes;
- It is also an anti-inflammatory agent and aromatase inhibitor.
- It controls downregulation of NFkB and therefore the TNF by inactivating IKK;
- It inhibits glutathione reductase, but most importantly, it is one of the rare activators of Sirtuin compounds.

Butein, a plant polyphenol isolated from Rhus verniciflua, is able to inhibit the activation of protein tyrosine kinase, NF-κB and STAT3, and it also inhibits EGFR.

Sirtuins
Sirtuins or Sir2 proteins are a class of proteins that possess either mono-ribosyltransferase, or deacylase activity. They regulate important biological pathways in bacteria, archaea and eukaryotes. The name Sir2 comes from the yeast gene ‘silent mating-type information regulation 2’, the gene responsible for cellular regulation in yeast. Sirtuins play a capital role in aging, transcription, apoptosis, inflammation and stress resistance, as well as energy efficiency and alertness during low-caloric situations. Circadian clocks and mitochondrial biogenesis are also regulated by Sirtuins. Mammals possess seven sirtuins (SIRT1-7) that occupy different subcellular compartments such as the nucleus (SIRT1, -2, -6, -7), cytoplasm (SIRT1 and SIRT2) and the mitochondria (SIRT3, -4 and -5).

Downregulation of NF-κB
Activation of NF-κB transcription factors by receptors of the innate or adaptive immune system is essential for host defense. However, after danger is eliminated, NF-κB signaling needs to

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be tightly downregulated for the maintenance of tissue homeostasis. We will measure the negative regulatory effects in regard to the amount, localization or conformational properties of NF-κB-activating proteins to attenuate the NF-κB response. These mechanisms are needed to prevent inflammation, autoimmune disease and oncogenesis.

Methods & Materials
The standard evaluation is to simulate TBI in compliance with NIH guidelines in a mouse model with 50 individuals that are subsequently fed with Butein laced standard mouse chow and a second group of 50 lindividuals with TBI that are fed the same standard protocol diet but without addition of Butein. We will then follow their status and the preservation of neurologic performance based on the standard NIH parameters for brain and nerve function.

Performance will be measured and differences recorded daily during the first week, then after 1 week, at 1 month, 3 months and 6 months. The negative regulatory effects in regard to the amount, localization or conformational properties of NF-κB-activating proteins to attenuate the NF-κB response will also be measured.

Cost for this research project: $190,000 for Phase 1.

Traumatic Brain Injury Statistics
- Emergency Department Visits: 1,365,000 (3,740 per day)
- Hospitalizations: 275,000 (753 per day)
- Deaths: 52,000 (142 per day)
- Nearly 1/3 of all injury-related deaths in the US involve a traumatic brain injury
- About 75% of TBIs that occur each year are concussions or other forms of mild traumatic brain injury
- Direct medical costs and indirect costs of TBI, such as lost productivity, totaled an estimated $60 billion in the United States in the year 2000
- Ages 0-4, 15-19 and 65+ are most likely to sustain a traumatic brain injury
- Traumatic brain injury rates are higher for males than for females
- Falls are the leading cause of traumatic brain injury
- Motor vehicle accidents are the leading cause of traumatic brain injury related death


Common Symptoms of Concussions:
- Imbalance
- Headache
- Confusion
- Memory loss
- Loss of consciousness
- Vision change
- Hearing change
- Mood change

Fatigue
Malaise

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- For a comprehensive list of all references, please send your request to: drkcanerclinic@gmail.com
- Principal Investigator: Mutombo Kankonde, MD, MPH, Director of Grifols Plasma Lab El Paso 2
- Information and contact Office: 915-307-3354, Cell: 915-730-4535, drkcanerclinic@gmail.com
- For more research hypothesis and discussions visit: crbcm.blogspot.com
- The outline of Phase 2 of the project is available by simple request.

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Mutombo Kankonde, M.D., MPH, Greater East Cancer Center & CRBCM, El Paso, Texas.