The Neurometabolic Cascade of Concussion

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This article has 116 references.

Data Sources: Over 100 articles from both basic science and clinical medical literature selected for relevance to concussive brain injury, post-injury pathophysiology, and recovery of function.

1) "Concussion is defined as any transient neurologic dysfunction resulting from a biomechanical force."

2) "Loss of consciousness is a clinical hallmark of concussion but is not required to make the diagnosis."

3) Typical symptoms of concussion include confusion, disorientation, unsteadiness, dizziness, headache, and visual disturbances.

4) The primary elements of the pathophysiologic cascade following concussive brain injury are:
- Abrupt massive neuronal depolarization
- The massive release of excitatory neurotransmitters [*glutamate*, *aspartate*]
- Massive ionic shifts [Calcium (Ca++) ***in***flux, Potassium ***ef***flux (K+)]
- Changes in glucose metabolism
- Reduced cerebral blood flow
- Impaired axonal function [Ca++ ***in***flux, swelling, axonal death]

5) "Immediately after biomechanical injury to the brain, abrupt, indiscriminant release of neurotransmitters [*glutamate*, *aspartate*] and unchecked ionic fluxes [K+ ***ef***flux, Ca++ ***in***flux] occur."

6) "The binding of excitatory transmitters, such as glutamate, to the N-methyl-D-aspartate (NMDA) receptor leads to further neuronal depolarization with efflux of potassium and influx of calcium." These ionic shifts cause substantial changes in neuronal physiology.

7) In an effort to restore the neuronal membrane potential, the sodium-potassium (Na-K) pump works overtime. The Na-K pump requires increased amounts of adenosine triphosphate (ATP), triggering a dramatic jump in glucose metabolism. "This 'hypermetabolism' occurs in the setting of diminished cerebral blood flow, and the disparity between glucose supply and demand triggers a cellular energy crisis."

8) The increase in calcium also impairs mitochondrial oxidative metabolism, worsening the energy crisis.

9) Cytochrome oxidase is a measure of oxidative metabolism, and is reduced for 10 days post-injury. **[Important for low-level-laser therapy applications]**

10) Other important components of posttraumatic cerebral pathophysiology include the "generation of lactic acid, decreased intracellular magnesium, free radical production, inflammatory responses, and altered neurotransmission." **[This argues for the rationale of supplementing with Mg++, increasing antioxidants, and increasing EPA (antiinflammatory) omega-3 fatty acids]**

11) Immediately after biomechanical injury to the brain, there is massive nonspecific depolarization, leading to a massive release of the excitatory amino acid (EAA) glutamate. **[Reducing consumption of glutamate (MSG) and aspartame (half of aspartate artificial sweetener) could improve clinical outcomes]**

12) The massive excitation is then followed by a wave of neuronal suppression termed *spreading depression.* Early loss of consciousness, amnesia, or other cognitive dysfunction may be manifestations of this posttraumatic spreading depression.

13) "In an effort to restore ionic homeostasis, energy-requiring membrane pumps are activated and trigger an increase in glucose use." This abrupt increase in energy requirements is met by an increase in glycolysis [enzymatically increasing the conversion of glucose into pyruvate]. Accelerated glycolysis increases lactate production, resulting in lactate accumulation.

14) "Elevated lactate levels can result in neuronal dysfunction by inducing acidosis, membrane damage, altered blood brain barrier permeability, and cerebral edema."

Cerebral Blood Flow

15) Traumatic brain injury may reduce cerebral blood flow (CBF) by 50% of normal. **[Important]**

16) The posttraumatic decrease in CBF, in a setting of increased glucose use (hyperglycolysis), creates a mismatch in supply and demand causing a damaging energy crisis.

Calcium Accumulation

17) Activated NMDA receptors form a pore through which calcium (Ca++) enters the cell, and neuronal Ca++ accumulation occurs within hours of concussion.

18) "Intra-axonal calcium flux has been shown to disrupt neurofilaments and microtubules, impairing posttraumatic neural connectivity." **[Mg++ is *neuroprotective*]**

19) "Unchecked calcium accumulation can directly activate pathways leading to cell death." **[Magnesium (Mg++) is *neuroprotective*]**

20) Ca++ channel blockers "significantly reduce post-concussive Ca++ accumulation." **[Mg++ is Mother-Nature's Ca++ channel blocker; Mg++ is *neuroprotective*]**

21) Cannabinoids have been shown to block the NMDA receptor with an associated reduction in post-TBI Ca++ accumulation.

22) Excess intracellular Ca++ impairs mitochondrial function, resulting in impaired oxidative metabolism and energy failure. The Ca++ influx "corresponds to neuronal death."

23) Increased axonal Ca++ levels lead to microtubule breakdown.

24) Intracellular Ca++ may trigger cell death by leading to free radical overproduction and activation of apoptotic genetic signals.
[This serves the rationale for increasing antioxidants]

Reductions in Magnesium

25) Intracellular Mg++ levels are immediately reduced after TBI and remain low for up to 4 days.

26) Reduction in Mg++ correlates with post-injury neurologic deficits, and *posttreatment* to restore Mg++ levels results in improved protection and recovery.

27) Decreased Mg++ levels leads to neuronal dysfunction.

28) Mg++ is necessary for maintaining the cellular membrane potential and initiating protein synthesis.

29) Low levels of Mg++ leads to greater influx of Ca++ and its deleterious intracellular consequences.

Second Impact

30) Injured cells may be capable of recovering after an initial injury, but a second concussion during this energy crisis can lead to cell death.

31) "Athletic trainers and athletes feel significant pressure to return athletes to practice and play as soon as possible after injury."

32) "Repeated injury within a particular time frame can lead to a much larger anatomical or behavioral impairment than 2 isolated injuries."

33) "The resulting energy crisis [from the first impact] is a likely mechanism for post-concussive vulnerability, making the brain less able to respond adequately to a second injury and potentially leading to longer-lasting deficits."

34) During rehabilitation, it is possible to over-stimulate the injured brain and this excessive activation can lead to longer-lasting deficits.
[Do not exceed the neuron's metabolic threshold]

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35) Mechanical stretching of axons result in membrane depolarization and perhaps membrane disruption.

36) "Long-term deficits in memory and cognition in a setting of minimal anatomic change are often seen after concussion." These result from post-concussive alterations in glutamatergic (NMDA), adrenergic, and cholinergic systems.
[This is why the use of "anti-cholinergic" drugs is problematic, and the consumption of acetylcholine enhancing supplements is encouraged: See *Article Review 17-16*]

37) Inhibitory neurotransmission is altered after TBI. The loss of gamma amino butyric acid (GABA) can predispose the traumatized brain to subsequent development of *seizures*.

38) Long-term follow-up studies demonstrate persistent neurocognitive deficits after pediatric TBI. **[Important]**

39) "Steps in the physiologic cascade involve increased intracellular calcium, mitochondrial dysfunction, impaired oxidative metabolism, decreased glycolysis, diminished CBF, axonal disconnection, neurotransmitter disturbances, and delayed cell death."

40) "It is during this post-injury period, when cellular metabolism is already stretched to its limits, that the cell is more vulnerable to further insults."

41) Increased intracellular Ca++ accumulation "impairs mitochondrial metabolism at the time when the cell can least tolerate a reduction in ATP production."

42) Alterations in NMDA receptor composition can persist, and a second injury in this period can lead to further impairment of excitatory neurotransmission with a greater degree of cognitive dysfunction.

43) Post-TBI changes in inhibitory neurotransmission can "leave neurons more susceptible to massive depolarization and excitatory amino acid (EAAs) [glutamate/aspartate] release after a recurrent concussion."

44) Posttraumatic derangements in glucose metabolism persist for 2 to 4 weeks after injury.

45) Secondary axotomy (ongoing axonal damage and death) occurs in human brain tissue weeks after trauma.

Summary From Authors

46) "Cerebral concussion is followed by a complex cascade of ionic, metabolic, and physiologic events."

47) "The earliest changes are an indiscriminate release of EAAs and a massive efflux of K+, triggering a brief period of hyperglycolysis."

48) This is followed by more persistent Ca++ influx, mitochondrial dysfunction with decreased oxidative metabolism, diminished cerebral glucose metabolism, reduced CBF, and axonal injury.

49) "Late events in the cascade include recovery of glucose metabolism and CBF, delayed cell death, chronic alterations in neurotransmission, and axonal disconnection. Clinical signs and symptoms of impaired coordination, attention, memory, and cognition are manifestations of underlying neuronal dysfunction, most likely due to some of the processes described above."

50) "Traumatic injury to the developing brain may lead to long-lasting changes in cognitive potential, perhaps even with little evidence of an initial deficit."

51) "Children and adolescents who sustain a concussive brain injury should be closely monitored over time for the later appearance of neurobehavioral abnormalities."

Summary Points From Dan Murphy

The Traumatic Brian Injury Cascade Occurs in the Presence of Reduced Cerebral Blood Flow

Hyperglycolysis is the Conversion of Glucose to *Pyruvate* for Anaerobic Glycolysis, Resulting in a Build up of *Lactic Acid*

Traumatic Brain Injury Has Major Events at 2 Sites, the ***Synapse*** and the ***Axon***

Traumatic Brain Injury Cascade at the *Synapse*

1) Massive Nonspecific Neuronal Depolarization and Initiation of Action Potentials

2) Massive Release of Excitatory Neurotransmitters, primarily glutamate [NMDA]

3) Massive **Ef**flux of Potassium K+ / Massive **In**flux of Calcium Ca++

4) Increased Activity of Membrane Ionic Pumps to Restore Potassium Homeostasis

5) Increased Glucose Utilization (*hyperglycolysis*) in the Mitochondria to meet the increased need to generate more adenosine triphosphate (ATP)

6) Lactate accumulation as a Consequence of Hyperglycolysis

7) Increased Calcium Mitochondrial Influx also Impairs Mitochondrial Oxidative Metabolism, Reducing Availability of ATP

8) Decreased energy (ATP) production

9) Calcium Activation of Free Radical Nerve Cell Death [Calcium Driven *Calpain* Protein Cascade]

[*Calpain* is a protein found in many tissues, including the brain. *Calpain* breaks down protein and neurons. *Calpain* is activated by Ca++. Excessive amounts of *calpain* are activated following the Ca++ influx after cerebrovascular accident (during the ischemic cascade) and/or following traumatic brain injury. "Increase in concentration of calcium in the cell results in calpain activation, which leads to unregulated proteolysis of both target and non-target proteins and consequent irreversible tissue damage." *Calpain* is released in the brain for up to a month after a head injury, and "may be responsible for a shrinkage of the brain sometimes found after such injuries."]

Traumatic Brain Injury Cascade at the *Axon*

1) Traumatic Disruption of the Axon

2) Massive Axonal Calcium (Ca++) **In**flux **[Mg++ is *neuroprotective*]**

3) Axonal Neurofilament Compaction

4) Axonal Microtubule Disassembly

5) Axonal Swelling and Eventual Axonal Death (axotomy)

Clinical Suggestion From Dan Murphy

1) Improve cerebral blood flow:
   Cervical Spine Chiropractic Adjustment [see *Article Review 07-13*]

2) Avoid dietary consumption of excitatory amino acids glutamate and aspartate

3) Increase ATP production:
   Cervical Spine Chiropractic Adjustment
   Trans-cranial Low-Level Laser Therapy
   Consume Medium-Chain Saturated Triglycerides (coconut oil)
   Supplement with Acetyl-l-Carnitine + Alpha-Lipoic Acid

4) Take supplemental magnesium, about 900 mg/day

5) Take *ex*ogenous anti-oxidants (quality multiple vitamin-mineral supplement)
   [watch the copper]

6) Increase *en*dogenous anti-oxidants, especially glutathione
   (undenatured whey protein, NAC, Alpha-Lipoic Acid, etc.]

7) Manage Post-Concussive Syndrome [*Article Review 45-13*]:

- Omega-3s EPA+DHA
- Curcumin
- Magnesium
- Vitamin D3
- Resveratrol
- Green Tea (EGCGs)

8) Consume Acetylcholine enhancing supplements

9) *DO NOT* have a second brain injury, especially within the next 30-60 days