

The neurophysiology of brain injury

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FROM ABSTRACT

Objective: This article reviews the mechanisms and pathophysiology of traumatic brain injury (TBI).

Methods: Research on the pathophysiology of diffuse and focal TBI is reviewed with an emphasis on damage that occurs at the cellular level.

The mechanisms of injury are discussed in detail including the factors and time course associated with mild to severe diffuse injury as well as the pathophysiology of focal injuries.

Examples of electrophysiologic procedures consistent with recent theory and research evidence are presented.

Results: Acceleration/deceleration (A/D) forces rarely cause shearing of nervous tissue, but instead, initiate a pathophysiologic process with a well defined temporal progression.

The injury foci are considered to be diffuse trauma to white matter with damage occurring at the superficial layers of the brain, and extending inward as A/D forces increase.

Focal injuries result in primary injuries to neurons and the surrounding cerebrovasculature, with secondary damage occurring due to ischemia and a cytotoxic cascade.

A subset of electrophysiologic procedures consistent with current TBI research is briefly reviewed.

Conclusions: The pathophysiology of TBI occurs over time, in a pattern consistent with the physics of injury.

The development of electrophysiologic procedures designed to detect specific patterns of change related to TBI may be of most use to the neurophysiologist.

Significance: This article provides an up-to-date review of the mechanisms and pathophysiology of TBI and attempts to address misconceptions in the existing literature.

THIS AUTHOR ALSO NOTES:

Significant advances have been made regarding the ability to accurately detect and classify various forms of neurotrauma.

"Acceleration/deceleration (A/D) forces are considered to be an important factor in the genesis of TBI."

In 1943 it was learned that rotational acceleration forces are the "primary cause of injury producing predictable damage to the brain."

By 1961, it was observed that the "primary microscopic feature observed in neural tissue was diffuse degeneration of white matter without obvious damage to cortex."

"The nerve fibers were torn or stretched at the time of injury."

"Dominant theories of TBI considered the brainstem to be the focus of injury since even mild A/D forces could cause LOC [loss of consciousness]." **[IMPORTANT]**

The reticular nuclei and pontine cholinergic neurons in brainstem might be the primary site of damage and dysfunction related to TBI.

"Numerous clinicians and researchers conclude that A/D injuries result in sheer strains within the cranial vault, and these in turn lead to sheering of neurons and blood vessels occurring principally in the brainstem."

Acceleration /deceleration forces first injure the surface of the brain and progressively affects deeper structures as forces become more severe.

Grades I and II cause cortical and subcortical disconnection, and may involve memory disturbance, partially impaired awareness, without loss of motor control.

Grades II and III involved cortical, subcortical and diencephalic [thalamus and hypothalamus] disconnection.

Grades IV and V involving cortical, subcortical, diencephalic [thalamus and hypothalamus], and mesencephalic [top of brainstem] disconnection.

When the degree of trauma is sufficient to produce LOC, cortex and subcortical systems will be primarily affected, and less damage will be found in the rostral [top portion] of the brainstem.

The mesencephalon (rostral brainstem) is the last area to suffer trauma. [This area contains cranial nerve III that moves the eye and constricts the pupil. Therefore, a problem with these functions always indicates severe brain trauma.].

“Cognitive symptoms such as confusion and disturbance of memory can occur without LOC, however, the reverse cannot occur.”

Rotational forces cause the most severe injuries to the brain.

Sagittal (front-to-back) injuries result in good recovery.

Lateral injuries (side-to-side) result in persistent coma or severe disability

Oblique injuries fall between sagittal and lateral injuries.

“Severe injuries do not always involve actual trauma to the head.” **[IMPORTANT]**

Significant non-impact brain trauma occurs in motor vehicle accidents and in infants with shaken baby syndrome.

Large diameter neurons are often injured more than smaller neurons that surround them.

The depth of a traumatic brain lesion increases with increased force and thereby produces a more severe disturbance of consciousness.

One role of the neocortex is that it drives or activates the reticular system for consciousness.

Therefore, if the cortex plays a substantial role in maintaining consciousness, “trauma involving cortex and subcortical white matter will affect consciousness since brainstem reticular cells will be suppressed due to a lack of input.”

This “loss of function in the reticular formation was caused by traumatic neuronal depression or loss of afferent activity from sensory systems.” **[IMPORTANT]**

Following injury, small ion species enter the axons causing damage to axons in the following hours and days. **[This is an important treatment window].**

Consequently, traumatic brain injury is “a process, not an event.”

Within 1–2 h post-injury there is significant axonal swelling.

At 12–24 h post-injury, the swelling is so severe, that the axon begins to separate.

“From 30 h to 1 week, grossly swollen axonal segments were now commonly disconnected in humans.”

Further axonal disconnection occurred over the next 60 days, with Wallerian degeneration and macrophage activity and some new sprouting.

“Studies have demonstrated a functional link between the pathophysiology associated with TBI and deficits observed using visual Eps.” **[IMPORTANT diagnostic hint]**

There is a “relationship between TBI and Alzheimer’s disease.”

Researchers have observed that following injury there is reduced regional blood flow.

[This is another important diagnostic hint].

Calcium is the primary factor responsible for reactive axonal change.

“There appears to be an intricate cascade that begins with axonal stretch, followed by calcium influx,” resulting in neuronal injury.

Mechanical strain is the primary mediator of axonal injury.

Calcium enters the cell following stretch injury in a process called “mechanoporation,” which is a mechanical deformation of the cell membrane, which causes the pores to increase membrane leakage.

This influx of calcium is cytotoxic, that causes a “break down in the cell membrane, resulting in the release of arachidonic acid.” **[IMPORTANT]**

“This could in turn lead to the production of oxygen free radicals.”

[Recall that arachidonic acid is the omega-6 fatty acid that is converted into prostaglandin E2, and prostaglandin E2 is quite pro inflammatory, and inflammation is the #2 generator of free radicals]

“Calcium influx initiates glutamate neurotoxicity in a positive feedback manner by further stimulating the release of the transmitter glutamate.” **[IMPORTANT]**

“Following a contusion or haemorrhage, blood extends into the adjacent cortex where neurons undergo secondary necrosis due to ischemia.”

“Ischemia may be considered the most significant factor related to secondary damage that occurs following brain injury.”

“Focal injuries produce zones of profoundly reduced regional cerebral blood flow that may be a factor in ischemic neuronal necrosis.”

“In adjacent zones where ischemia may not reach critical levels, another process may occur that eventually leads to tissue damage and death.”

“Specifically, glutamate neurotoxicity may play a role in secondary ischemic damage.” **[IMPORTANT]**

Hypoxia-related neuronal depolarisation has been shown to increase extracellular levels of glutamate.

"Abnormally high levels of extracellular glutamate activate a wide variety of receptors that can cause depolarisation of the cell membrane, allowing for the activation of voltage dependent calcium channels."

The influx of calcium propagates "glutamate neurotoxicity in a positive feedback fashion by further stimulating the release of the transmitter glutamate."

[Glutamate Cascade, IMPORTANT]

"Increased levels of extracellular excitatory amino acids such as glutamate and aspartate are released from hippocampal regions immediately after moderate to severe" brain injury.

"In humans, increases as large as 10–15 times normal levels occur for glutamate and aspartate, lasting up to 4 days in the extracellular fluid adjacent to focal contusions." **[IMPORTANT]**

Moderate to severe injuries can disrupt the BBB. **[IMPORTANT]**

The presence of arachidonic acid causes increased endothelial cell permeability and induces edema.

Cytotoxic edema occurs when cells swell due to failure of the adenosine triphosphate (ATP) dependent Na⁺K⁺ pump. As a result, Na⁺ and water rapidly accumulates within cells.

A second cause of cytotoxic edema involves increased amounts of extracellular excitatory amino acid neurotransmitters such as glutamate that causes acute swelling in dendrites and cell bodies.

The presence of high extracellular glutamate levels causes membrane channels to open, which in turn leads to Na⁺ influx, membrane depolarisation, and excitotoxic swelling.

"This type of pathology, and the Ca²⁺ dependent late degeneration induced by glutamate, can act in isolation to produce irreversible neuronal injury."

Glutamate toxicity is more important at low levels of exposure and may "predominate under many pathological conditions."

Free radical production and associated damage has also been linked with edema.

"Severe deceleration forces associated with a high speed motor vehicle accident and no head impact may result in a pattern of predominantly diffuse injury, with several small traumatic foci related to petechial haemorrhage or tearing of small blood vessels."

"The electroencephalogram (EEG) is one of an increasingly large number of structural and functional procedures used to assess TBI," and has had varying amounts of success."

"Currently, structural imaging techniques and neurobehavioral procedures dominate the assessment and rehabilitation process following TBI."

"Computed tomography (CT) and MRI are useful for the detection of potentially life threatening focal trauma such as intracranial haemorrhage or haematoma."

"Neuropsychologic assessment is used to determine the severity and range of functional deficits and is used to plan appropriate rehabilitation strategies."

Some have concluded that EEG is "generally useless" as an assessment tool for mild TBI. **[IMPORTANT]**

"The BAEP has been used to assess changes in brainstem function associated with disturbed consciousness and coma following TBI."

"Patients with unfavourable outcomes almost always had abnormal BAEPs while only a portion of patients with normal BAEPs had favourable outcomes."

"Several studies have provided support for the position that SEPs are useful indicators of outcome following TBI and that they are superior to other EPs regarding sensitivity and specificity."

"SEPs have been shown to be better predictors of outcome compared to BAEPs and VEPs."

"BAEP is useful in the detection of functional damage while SEPs are useful for prognostic estimation."

Lower limb SEPs were of most use in the prediction of coma duration.

"Assessment of those who experience mild TBI is problematic."

"The standard protocol used to assess TBI severity and plan rehabilitation is dominated by CT, MRI, and neurobehavioral procedures. While these procedures may be effective for moderate to severe injury, they may be less useful for the assessment of mild TBI."

Negative CT findings are often interpreted by physicians when no significant neural trauma has occurred, which is often untrue.

MRI is more sensitive than CT in assessing mild TBI, but MRI is not able to detect damage to multiple individual axons that occurs among several normally functioning cells.

Changes in the latency and amplitude of the visual ERPs is a potentially useful methods for mild TBI assessment.

“Electrophysiologic procedures have demonstrated significant changes in brain function following mild TBI in athletes.”

Studies on athletes are important because they demonstrate that changes in brain function that occur following mild TBI are not always related to depression, PTSD, or malingering since these individuals are highly compliant and motivated to return to their sport.

“For patients with significant disturbances of consciousness resulting from severe TBI, EPs such as SEPs allow for an assessment of function in brainstem, thalamic, and cortical areas and can be used to assess outcome.”

“In patients who cannot communicate verbally or behaviorally following focal deficits to language or motor areas, an assessment of subcortical and cortical systems involved in language processing can be performed using computerized neuropsychologic tests combined with ERPs such as the N400.”

Mild TBI patients who are in litigation related to their injuries, or who are experiencing symptoms that can be attributed to brain injury, depression, or PTSD provide a significant challenge to clinicians, as these injuries are not necessarily transient without long-term cognitive sequelae.

“Patients who have sustained a mild TBI may be effectively assessed using cognitive ERPs that are generated from multiple cortical and subcortical areas, reflecting the diffuse nature of these injuries that occur primarily in white matter near the surface of the brain.”

“It is important for the neurophysiologist to understand the fact that impact is not required for significant damage to occur and that mild A/D forces can cause injury to axons and dendrites in the presence of non-injured neural tissue and cerebrovasculature.”

“It is important for the neurophysiologist to understand that there are no procedures available for the assessment of ‘brain injury’.”

“TBI comes in a variety of forms, ranging from diffuse injuries of white matter, to highly localized injuries.”

Most moderate to severe injuries consist of a combination of focal and diffuse injuries.

KEY POINTS FROM DAN MURPHY

- 1) Significant non-impact brain trauma occurs in motor vehicle accidents and in infants with shaken baby syndrome.
- 2) Severe brain injuries do not always involve actual trauma to the head.
- 3) Acceleration/deceleration (A/D) forces are an important cause of TBI.
- 4) Acceleration/deceleration (A/D) forces primarily affect the white matter of the superficial layers of the brain, and extend inward as A/D forces increase.
- 5) The mesencephalon (rostral brainstem) is the last area to suffer A/D trauma. The mesencephalon contains cranial nerve III that moves the eye and constricts the pupil. Therefore, a problem with these functions always indicates severe brain trauma.
- 6) Cognitive symptoms such as confusion and disturbance of memory can occur without LOC.
- 7) Lateral brain injuries (side-to-side) cause significantly more problems than sagittal (front-to-back) injuries.
- 8) Traumatic brain injury is not an event, but a process occurring over hours, days, weeks and months.
- 9) This article outlines the following cascade following TBI:
 - A) Axonal stretch.
 - B) Axonal stretch causes mechanical deformation of the cell membrane, causing membrane leakage.
 - C) Membrane leakage allows calcium influx into the neuron, resulting in neuronal injury.
 - D) This calcium is cytotoxic and causes a break down in the cell membrane, resulting in the release of arachidonic acid. Arachidonic acid is the omega-6 fatty acid that is converted into prostaglandin E₂, and prostaglandin E₂ is quite pro inflammatory. This inflammation is the #2 generator of free radicals. This increase in the production of free radicals further injures the neuron.
 - E) This increase of arachidonic acid causes increased membrane permeability and edema.
 - F) This calcium influx also stimulates the release of the transmitter glutamate, which initiates glutamate neurotoxicity.
 - G) This glutamate release causes depolarisation of the cell membrane, allowing for the influx of more calcium.
 - H) This influx of calcium propagates glutamate neurotoxicity in a positive feedback fashion by further stimulating the release of the transmitter glutamate. This is called the glutamate cascade of neuronal injury.

- 10) After brain trauma, glutamate and aspartate can increase as much as 10–15 times normal levels, lasting up to 4 days after injury.
- 11) Moderate to severe brain injuries can disrupt the BBB.
- 12) Computed tomography (CT) and MRI are useful for the detection of potentially life threatening focal trauma but are largely useless in mild traumatic brain injury.
- 13) EEG is also generally useless in the assessment of mild TBI.
- 14) The assessment of athletes with mild TBI show that these injuries are not always related to depression, PTSD, or malingering, and that they are not necessarily transient without long-term cognitive sequelae.
- 15) There is a relationship between TBI and Alzheimer's disease.

COMMENT

Based upon this and other articles on the pathophysiology of traumatic brain injury, I would argue that our management should include:

Mild traumatic Brain Injury Management

- 1) Magnesium, 600 mg / day. Magnesium is neuro-protective because it reduces calcium influx into the neuron.
- 2) Zinc 50 mg / day. Zinc is neuro-protective similar to magnesium.
- 3) Brain trauma creates damaging free radicals, so take antioxidants:

A	25,000 IU
C	1000 mg
E	1000 mg of mixed tocopherol
Selenium	400 mcg
Alpha Lipoic Acid	200 mg
CoQ10	100 mg
Riboflavin	100 mg
Folic Acid	800 mcg
B6	75 mg
B12	400 mcg (methylcobalamin)
- 4) Avoid excitotoxins in the diet.
- 5) EPA / DHA essential Fatty Acids
2 / 1 ratio, 5000 mg / day

I am currently taking the essential fatty acids and antioxidant network co-factors from Nutri-West nutritional company, primarily because they consulted me in putting their products together.

My favorite additional reading on the excitotoxin glutamate cascade are:

Excitotoxins Books

1997

Excitotoxins, The Taste That Kills by Russell Blaylock (University of Mississippi neurosurgeon), Health Press

1999

In Bad Taste, The MSG Symptom Complex, by George Schwartz, Health Press

2000

The Crazy Makers, How the Food Industry Is Destroying Our Brains and Harming Our Children, by Carol Simontacchi, Tarcher Putnam

Food Allergies by William Walsh, Wiley

2001

Fast Food Nation by Eric Schlosser, Houghton Mifflin

2002

Health and Nutrition Secrets by Russell Blaylock, Health Press, 2002

Two Good Articles

1) Stuart Lipton and PA Rosenberg. Mechanisms of Disease: Excitatory Amino Acids as a Final Common Pathway for Neurologic Disorders. *New England Journal Of Medicine*, 1994; 330:613-622, Mar 3, 1994.

2) Jerry D Smith, Chris M Terpening, Siegfried OF Schmidt and John G Gums; Relief of Fibromyalgia Symptoms Following Discontinuation of Dietary Excitotoxins; *The Annals of Pharmacotherapy*: Vol. 35, No. 6, pp. 702-706. June 2001.