

A Clinician's Guide to the Pathophysiology of Traumatic Brain Injury

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Abstract: Traumatic brain injury induces a complex pathophysiological cascade of cellular events. Central components of this response include increases in cerebral glucose uptake, reductions in cerebral blood flow, indiscriminate excitatory neurotransmitter release, ionic disequilibrium, and intracellular calcium accumulation. Acute glutamate release and nonspecific neuronal depolarization induce threatening perturbations in neuronal function. Restoration of homeostasis requires significant increases in glucose metabolism; however, there is often a concomitant reduction in cerebral blood flow, resulting in an uncoupling of supply and demand. Understanding the nature and timing of these processes provides the practicing clinician with a mechanistic rationale for acute physiological monitoring, aggressive interventions to address and minimize secondary injuries, implementation of advanced neuroimaging techniques, and careful monitoring return to normal activity in head injured patients.

Keywords: cerebral blood flow, glucose metabolism, glutamate, monitoring, positron emission tomography (pet)

INTRODUCTION

Traumatic brain injury (TBI) is a major cause of death and disability in children and young adults and has been identified as an important public health problem in the United States and worldwide¹⁻⁶. When head injuries of all severities are included, the age-related incidence has been estimated to be as high as 670/100,000⁷. Over the past 15-20 years the reported incidence of TBI resulting from motor vehicle accidents has been declining steadily in the United States; whereas brain injury resulting from firearms has been on the rise, somewhat negating the benefits of better public education and improved motor vehicle safety⁸. Worldwide, motor vehicle accidents remain a major cause of TBI, and this problem is actually increasing, particularly in developing nations. TBI remains a major cause of trauma-related death and hospitalization. Approximately 2 million persons suffer TBI in the United States annually and of these about 70,000 to 90,000 will have permanent long-term disability, creating a significant socioeconomic and emotional burden on the families and society. The most commonly affected group is males 15-24 years of age, but children under the age of five and adults above the age of 65 also tend to be at increased risk⁶. In the U.S., pediatric

TBI (under 14 years of age) is responsible for an estimated 3000 deaths, 29,000 hospitalizations and 400,000 emergency department visits annually⁴.

The etiology of TBI varies with age. The elderly experience an increased proportion of TBIs as a result of falls. Motor vehicle accidents, and, to a lesser degree, assaults, are predominant injury mechanism in adults and adolescents. Adolescents may also experience a higher rate of sports-related concussions. Preadolescent children are also frequent victims of motor vehicle accidents, but more often as a pedestrian or while riding a bicycle. Those under the age of 5 years are more prone to falls⁴, while infants are particularly vulnerable to repeated severe TBI in the form of nonaccidental trauma (child abuse). Boys are more likely than girls to sustain TBI, and this gender difference becomes increasingly apparent in the older pediatric and young adult population^{9,10}.

Over the past 20 years, basic science studies have provided significant insight into the underlying pathophysiological changes associated with TBI, making it distinct from other types of brain injury such as ischemia and seizures^{11,12,13}. First and foremost, TBI causes neural dysfunction and cell death as the result of a biomechanical load being imparted to the brain. This force results in indiscriminate neurotransmitter release and ionic flux shortly after the injury. Subsequently, there are significant alterations of cerebral metabolism and blood flow that result in cellular dysfunction and vulnerability to secondary

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injuries (such as hypoxia, hypotension, seizures or repeated TBI). Using advanced monitoring techniques in the neuro-ICU, many of the pathophysiological changes originally described in animal models have now been reported following severe human TBI⁹⁻¹⁷. Better understanding of these underlying perturbations should result in improved ICU care and lead the way for future clinical and translational research to develop effective guidelines and brain-specific therapy following TBI.

In this paper we will provide an overview of neurometabolic changes that take place following TBI (Figure 1). Furthermore, we will discuss the clinical relevance of these basic pathophysiological mechanisms from the standpoint of ICU management.

BIOMECHANICAL FACTORS

The biomechanics of traumatic brain injury involve both linear and rotational forces. Linear forces result from straight ahead acceleration-deceleration and can be associated with coup injury (at the site of contact) and contra-coup injury (distant, usually opposite the site of contact). While most high-speed head injuries involve some linear component, rotational forces will almost always also play a role. It is these rotational forces that lead to twisting and shearing injuries in the brain parenchyma, particularly in the white matter fiber tracts (resulting in diffuse axonal injury). Rotational forces of lower magnitude are also present in milder forms of TBI such as sports-related concussion.

Biomechanical forces in the pediatric population can be distinct from those in the adults. Some of these differences result from the relatively large head size, reduced muscular strength, and increased flexibility in the neck, which may allow larger forces to be transmitted to the brain. On the other hand, there is less CSF space around the younger brain, and the prominent bony ridges of the anterior and middle cranial fossae are less developed. These factors may contribute to the lower occurrence of focal lesions in pediatric TBI¹⁸⁻²¹. The developing skull is thinner as compared to an adult skull and therefore, more vulnerable to diffuse deformation²². The open fontanelles and the flexibility of the sutures may help dampen the traumatic forces; where the adult skull is lacking this luxury. The open fontanelles and sutures also help accommodate slower growing space-occupying lesions (such as chronic subdurals). On the other hand, the lower water content of the adult brain renders it more compliant²³⁻²⁴. Clearly, the biomechanics of the injury should be carefully considered in the evaluation of any TBI patient, and the etiology of trauma as well as the patient's age are important factors in the understanding these forces.

PATHOPHYSIOLOGY GLUCOSE METABOLISM

Experimental models have shown that TBI results in a significant increase of glucose utilization within the first 30 minutes post-injury, after which glucose uptake diminishes and then remains low for about 5-10 days^{25,13}. Clinical studies in humans using Positron Emission Tomography (PET) have demonstrated comparable results. Although it is difficult to capture the acute period of hyperglycolysis in a critically ill TBI patient, globally decreased glucose metabolism has been demonstrated persisting chronically for weeks to months post-injury in human patients¹⁵. In the subacute phase, another study showed no correlation between the level of consciousness as measured by Glasgow Coma Scale (GCS) and glucose metabolism²⁶. Diminished cerebral glucose metabolism was seen in both comatose (severe) and relatively intact (mild) TBI patients, implying marked global neurometabolic abnormalities may be present with or without significant clinical symptoms²⁶. Importantly, a follow-up study revealed that reduced glucose uptake in subcortical structures (including brainstem) did correlate with the presence of coma, suggesting that regional differences in physiology are relevant to clinical exam measures²⁷.

The initial hyperglycolysis described above results from disruption of ionic gradients across the neuronal cell membrane, activating energy-dependent ionic pumps²⁸⁻³². In experimental animal models the increase in glucose utilization is almost instantaneous following injury and lasts up to 30 minutes in the ipsilateral cortex and hippocampus^{25,33}. In more severe types of injury such as cortical contusion, the rise in glucose metabolism may last up to 4 hours in the outlying areas of the contused segment³⁴. As cerebral oxidative metabolism at baseline is already near or at maximum levels, this increased energy demand may be dealt with by augmenting glycolysis^{35,36} which in turn increases lactate production³⁷. Increased lactate levels are seen after both ischemic and concussive brain injuries³⁸⁻⁴⁴. However, the mechanism of lactate accumulation has traditionally been ascribed to reduced oxidative metabolism after ischemia, while, at least acutely after trauma, increased glycolysis may play a more prominent role. More recently, a mechanism of alternative metabolic substrate production has been proposed, whereby lactate originates from astrocytes and is shuttled to the neuron to facilitate energy production at a time of need⁴⁵⁻⁴⁷. This idea has received further support from experimental TBI studies utilizing ketone bodies as an alternative substrate⁴⁸ and clinical studies that show increased brain uptake of lactate following TBI⁴⁹.

In addition to the glycolytic disturbances mentioned above, there is also increasing evidence for impairment of oxidative metabolism following brain trauma⁵⁰⁻⁵³. This may lead to depletion of high-energy phosphates (adenosine triphosphate, ATP)⁵⁴⁻⁵⁶, with a subsequent rise in anaerobic metabolism, and yet further accumulation of lactate^{41, 57-59}. Increased lactate may generate neuronal dysfunction as a result of acidosis, membrane damage, disruption of the blood brain barrier and cerebral edema⁶⁰⁻⁶³. There is also some evidence suggesting lactate accumulation post-injury may render the neurons more susceptible to secondary ischemic insults⁶⁴.

Severely head injured patients frequently show cerebral lactic acidosis^{65, 66}. Post-injury cerebral lactate production is marked by an acute and extended increase in cerebrospinal fluid, and a negative arteriovenous difference in lactate content (higher jugular venous than arterial concentration)⁶⁵⁻⁶⁷. Several investigators^{41, 68} have shown a rise in lactate concentration in cerebrospinal fluid and in brain tissue within the initial 60 minutes following mild to moderate fluid percussion injury in rat models. Nilsson, et al., using a weight drop model of injury, showed a 4-to 5 fold increase in the dialysate concentration of lactate for about 80 minutes post injury; they also demonstrated a significantly higher elevation of lactate (7 fold) as injury severity increased^{69, 70}. The rise in extracellular lactate is partially presumed to be as a result of decreased cerebral blood flow in the face of increased energy demand from injury-induced ionic changes. However, as mentioned earlier, recent studies have suggested that the lactate story is not all bad. Lactate appears to serve as an alternative oxidative fuel in states of physiological stress or activation⁴⁵⁻⁴⁷. Furthermore, at least in patients with relatively preserved oxidative metabolism, brain uptake of lactate has been associated with improved outcome⁴⁹.

CEREBRAL BLOOD FLOW (CBF)

Cerebral hemodynamics change significantly post injury, and the pattern of these changes depends upon the type of injury and its severity^{71, 72}. Dietrich, in experimental animal models using mild to moderate TBI, showed a significant drop off in blood flow (70-80% of normal)⁷³, and with more severe injury the drop off neared ischemic levels⁷¹. Currently, there is an ongoing debate as to whether these low flow events are a contributing cause of cell injury, a consequence of the injured and dying tissue^{74, 75}, or a manifestation of a non-ischemic physiological perturbation. While studies after TBI have shown histopathological or neuroimaging changes compatible with hypoxia/ischemia^{72, 76} as well as marked acute reductions in CBF^{74, 76, 77}, the presence of true ischemia following clinical TBI has

been difficult to demonstrate. Diringier, et al., in clinical studies, has shown flow reduction to levels classically defined as "ischemic" following hyperventilation in severely head-injured patients; however, these flow reductions were not associated with a concomitant decrease of the cerebral metabolic rate for oxygen (CMRO₂) beyond that induced by TBI itself⁷⁵. Using a voxel-based method to identify a noncontiguous, physiological region of interest, Coles, et al., reported an ischemic brain volume of approximately 6%⁷⁸. In a different set of patients, Vespa, et al., reported an ischemic brain volume of only about 1.5%. They did find, however, that metabolic crisis, as defined by a lactate/pyruvate ratio (LPR) of >40, was present in 7/19 patients and this parameter (LPR) correlated negatively with CMRO₂, leading them to conclude that a "metabolic crisis without ischemia" was present after TBI⁷⁹.

In the pediatric population, increased blood flow (hyperemia) was once felt to be a common complication of TBI, resulting in increased intracranial pressure and cerebral edema. Current studies point out that post-injury hyperemia is not as common as once thought⁸⁰. Earlier studies of cerebral blood flow were done comparing brain-injured children to normal young adult values. It is now known that CBF undergoes significant changes through development and is significantly higher in children than adults⁸¹⁻⁸³. The newer studies, by comparing to age-appropriate controls, have not shown marked hyperemia^{84, 85}.

Kelly in 1996 and Vavilala in 2004 showed an association between outcome and cerebral blood flow that is dependent on the autoregulation. Intact autoregulation in the face of hyperemia is linked to better perfusion and subsequently a better outcome^{86, 87}, while hyperemia in a setting of impaired autoregulation is generally associated with intractable increases in intracranial pressure and ultimately, poorer cerebral perfusion and worse outcome. Thus, it appears that it is not only the magnitude of cerebral blood flow, but also the reactivity of the cerebral vasculature that determines tissue viability and prognosis.

IONIC FLUX AND GLUTAMATE

Acute injury to the brain causes a rapid release of glutamate^{88, 89}, the predominant excitatory neurotransmitter in the central nervous system. This indiscriminate release occurs as a result of extensive triggering of action potentials, synaptic neurotransmitter release, and membrane disruption. This massive release of glutamate is a major source of potassium efflux into the extracellular space^{70, 89}. The rise in the extracellular concentration of potassium also results from nonspecific breakdown of the plasma

membrane, especially in areas of the brain damaged by localized contusion^{90,91} or intracerebral hemorrhages⁹².

It is well known that experimental TBI triggers a rise in the extracellular potassium concentration^{89,90}. Both the fluid percussion and weight drop models of experimental brain injury transmit a substantial force to wide areas of the brain, resulting in diffuse dysfunction. This rise in the extracellular concentration of potassium occurs as the result of opening voltage-gated potassium channels by neuronal depolarization. Julian and Goldman demonstrated that deformation of neural tissue alone could produce enough depolarization to lead to neuronal firing⁹³. Importantly, glial cells play a prominent role in the re-uptake of extracellular potassium⁹⁴⁻⁹⁶ and are able maintain the concentration below the physiological ceiling in mildly abnormal states such as brief seizures or mild concussion^{89,97,98}. Nonetheless, some have shown that more severe concussive injury causes increases in extracellular potassium concentration up to 70 percent of the maximum level reached in ischemia (80 mM)⁹⁹⁻¹⁰¹. This significantly exceeds the physiological ceiling of 6-10 mM^{67,97,98,102}, and indicates that the normal glial uptake mechanisms have either been overwhelmed or somehow impaired^{94,103}. This increase in extracellular potassium, in turn, may lead to increased energy demand, causing greater rates of glycolysis with a parallel rise and accumulation of

lactate.

Glutamate also induces opening of ligand-gated channels that are permeable to calcium. A number of studies have shown an increase in intracellular calcium concentration following various experimental traumatic brain injury models^{52,104-107}. Fineman and colleagues have described a significant calcium accumulation for up to four days post fluid percussion injury in the ipsilateral cortex, hippocampus, striatum, and thalamus of the injured adult rat^{104,107}. Accumulation of calcium intracellularly has been an indicator for impending cell death. There are multiple means by which calcium exerts its apoptotic properties^{108,109}. For example, increased intracellular calcium can cause overstimulation of phospholipases¹¹⁰, plasmalogenase, caplains^{111,112}, protein kinases¹⁰⁸, guanylate cyclase¹¹³, nitric oxide synthetase, calcineurins, and endonucleases. As a result of these cellular changes there is overproduction of toxic reaction products, such as free radicals^{114,115}, significant disruption of the cytoskeletal organization^{116,117}, and activation of apoptotic genetic signals¹¹⁸. Accumulation of intracellular calcium does not always result in cell death, but affects the metabolic machinery of the mitochondria to such an extent that any secondary metabolic demand cannot be met, subsequently rendering the cell vulnerable to energy failure¹¹⁹. This becomes a significant issue in TBI patients, as in their initial phase of the injury they fight an uphill battle against secondary insults such as increased body temperature, seizures, hypotension and hypoxia. The need for meticulous monitoring to prevent or at least minimize the occurrence and/or repetition of the secondary injuries is clear.

Magnesium is one of the electrolytes that play a significant role in maintaining ionic balance within the injured cell. Several studies in experimental models of traumatic brain injury have shown a marked decrease in brain intracellular free and total magnesium concentration that lasts up to 4 days post injury¹²⁰⁻¹²². Vink and colleagues have shown in animal models that the decrease in free intracellular magnesium correlates with severity of injury¹²². Memon and colleagues demonstrated this finding in humans, where they showed a graded decrease in serum magnesium, correlating with severity of injury based on the CT scan and other diagnostic parameters¹²³.

Magnesium plays a pivotal role in maintaining the integrity of the mitochondrial inner membrane¹²⁴ and the functional reliability of the ATPase pump¹²⁵. Additionally, magnesium has a significant role in influencing the degree of excitotoxic damage as a result of TBI, as intra- and extracellular magnesium concentration affects the opening and closing of sodium and calcium ion channels, as well as

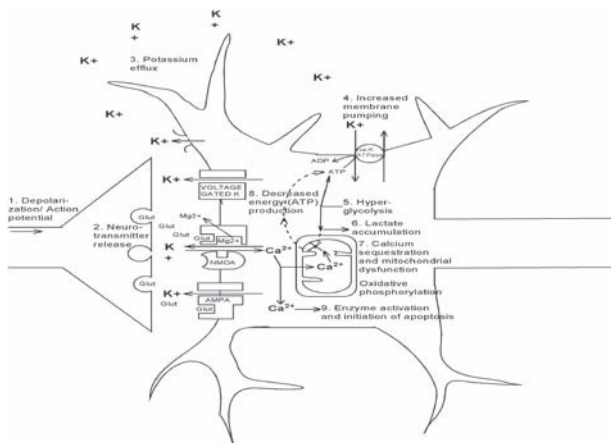


Fig 1: Neurometabolic cascade following traumatic injury. **CELLULAR EVENTS** 1) Nonspecific depolarization and initiation of action potentials. 2) Release of excitatory neurotransmitters (EAAs). 3) Massive efflux of potassium. 4) Increased activity of membrane ionic pumps to restore homeostasis. 5) Hyperglycolysis to generate more ATP. 6) Lactate accumulation. 7) Calcium influx and sequestration in mitochondria leading to impaired oxidative metabolism. 8) Decreased energy (ATP) production. 9) Calpain activation and initiation of apoptosis (modified from Giza and Hovda¹³⁴).

their ionic transporters¹²⁶. There is significant evidence pointing to a marked correlation between decreased magnesium levels and the outcome of TBI, such as cerebral edema, behavioral abnormalities, and impaired cognitive performance¹²⁷⁻¹²⁹.

Thus, ionic flux represents a fundamental cellular change induced by biomechanical injury. Direct potassium efflux and indiscriminate release of glutamate with subsequent neuronal depolarization may serve as the triggers for subsequent metabolic perturbation. Cellular metabolism and functional outcome also appear to be impaired by concomitant reductions in intracellular magnesium.

SUMMARY

Multiple physiological processes characterize the neurometabolic cascade of TBI. These include alterations in glucose metabolism, changes in blood flow and neurovascular coupling, release of excitatory neurotransmitters, efflux of potassium and accumulation of intracellular calcium. Attempts to restore ionic equilibrium require activation of energy-dependent membrane pumps. Increases in energy demand post-TBI may occur at a time of diminished cerebral blood flow and thus, a time of limited substrate availability. Using advanced monitoring and imaging techniques, many of the physiological processes originally described in experimental animals can now be detected and even followed in head-injured patients. These investigations have led to a more nuanced understanding of cerebral metabolism after brain injury. Conditions once felt to be associated with bad outcome (such as increased cerebral lactate and reduced cerebral blood flow) are not black-or-white indicators of cerebral distress. Increasingly, it appears that it is the relationship between these parameters that is more important in determining treatment response or outcome than the physiological values in isolation. Thus, being able to reliably monitor cerebral physiological changes in the intensive care setting is only the first step; understanding the complexity of post-injury pathophysiology is also critical for optimal management of head-injured patients.

REFERENCES

- Engberg A, Teasdale TW. Traumatic brain injury in children in Denmark: a national 15-year study. *Eur J Epidemiol* 1998;14:165-73.
- Murgio A, Andrade FA, Sanchez Munoz MA, Boetto S, Leung KM. International Multicenter Study of Head Injury in Children. ISHIP Group. *Childs Nerv Syst*. 1999;15:318-21.
- Tsai WC, Chiu WT, Chiou HY, Choy CS, Hung CC, Tsai SH. Pediatric traumatic brain injuries in Taiwan: an 8-year study. *J Clin Neurosci* 2004;11:126-9.
- Thurman,D.J. Traumatic Brain Injury (TBI) in the United States: Assessing Outcomes in Children - Appendix B. 2000. Internet Communication
- Weiner,H.L. & Weinberg,J.S. Head Injury. Cooper,P.R. & Golfinos,J.G. (eds.), pp. 419-456 (McGraw-Hill Medical Publishing Division, San Francisco, 2000).
- Kraus .JF., McArthur D.L., Silverman T.A., Jayaraman M. Epidemiology of Brain Injury. In: Narayan RK, Wilberger JE, Povlishock JT, editors. Neurotrauma. 1996. San Francisco: McGraw-Hill, 13-30.
- McCarthy,M.L., Serpi,T., Kufera,J.A., Demeter,L.A. & Paidas,C. Factors influencing admission among children with a traumatic brain injury. *Acad Emerg Med*. 2002; 9:684-93.
- Sosin DM, Sniezek JE, Waxweiler RJ. Trends in death associated with traumatic brain injury, 1979 through 1992. Success and failure. *JAMA*.1995;273:1778-80.
- Rivara FP. Epidemiology and prevention of pediatric traumatic brain injury. *Pediatr Ann* 1994;23:12-17.
- Kraus J.F., McArthur D.L.. Epidemiology of Head Injury. In: Cooper PR, Golfinos JG, editors. Head Injury. 2000. San Francisco: McGraw-Hill, 1-25.
- Nortje J, Menon DK. Traumatic brain injury: physiology, mechanisms, and outcome. *Curr Opin Neurol* 2004;17:711-8.
- Bramlett HM, Dietrich WD. Pathophysiology of cerebral ischemia and brain trauma: similarities and differences. *J Cereb Blood Flow Metab* 2004;24:133-50.
- Hovda, D.A. Metabolic Dysfunction. In: *Neurotrauma*, edited by Narayan, R.K., Wilberger, J.E. and Povlishock, J.T., San Francisco:McGraw-Hill, 1996; p. 1459-1478.
- Hillered L, Vespa PM, Hovda DA. Translational neurochemical research in acute human brain injury: the current status and potential future for cerebral microdialysis. *J Neurotrauma* 2005;22:3-41.
- Bergsneider M, Hovda DA, McArthur DL, et al. Metabolic recovery following human traumatic brain injury based on FDG-PET: time course and relationship to neurological disability. *J Head Trauma Rehabil* 2001;16:135-48.
- Reinert M, Hoelper B, Doppenberg E, Zauner A, Bullock R. Substrate delivery and ionic balance disturbance after severe human head injury. *Acta Neurochir Suppl* 2000;76:439-44.
- Vespa P, Prins M, Ronne-Engstrom E, et al. Increase in extracellular glutamate caused by reduced cerebral perfusion pressure and seizures after human traumatic brain injury: a microdialysis study. *J Neurosurg* 1998;89:971-82.
- Berney J, Froidevaux AC, Favier J. Paediatric head trauma: influence of age and sex. II. Biomechanical and anatomoclinical correlations. *Childs Nerv Syst* 1994;10:517-23.

19. Bruce DA, Raphaely RC, Goldberg AI, et al. Pathophysiology, treatment and outcome following severe head injury in children. *Childs Brain* 1979;5:174-91.
20. Levi L, Guilburd JN, Linn S, Feinsod M. The association between skull fracture, intracranial pathology and outcome in pediatric head injury. *Br J Neurosurg* 1991;5:617-25.
21. Luerssen TG, Klauber MR, Marshall LF. Outcome from head injury related to patient's age. A longitudinal prospective study of adult and pediatric head injury. *J Neurosurg* 1988;68:409-16.
22. Margulies SS, Thibault KL. Infant skull and suture properties: measurements and implications for mechanisms of pediatric brain injury. *J Biomech Eng* 2000;122:364-71.
23. Holland BA, Haas DK, Norman D, Brant-Zawadzki M, Newton TH. MRI of normal brain maturation. *AJNR* 1986;7:201-8.
24. Paus T, Collins DL, Evans AC, Leonard G, Pike B, Zijdenbos A. Maturation of white matter in the human brain: a review of magnetic resonance studies. *Brain Res Bull* 2001;54:255-66.
25. Yoshino A, Hovda DA, Kawamata T, Katayama Y, Becker DP. Dynamic changes in local cerebral glucose utilization following cerebral concussion in rats: evidence of a hyper- and subsequent hypometabolic state. *Brain Res* 1991;561:106-19.
26. Bergsneider M, Hovda DA, Lee SM, et al. Dissociation of cerebral glucose metabolism and level of consciousness during the period of metabolic depression following human traumatic brain injury. *J Neurotrauma* 2000;17:389-401.
27. Hattori N, Huang SC, Wu HM, et al. Correlation of regional metabolic rates of glucose with glasgow coma scale after traumatic brain injury. *J Nucl Med* 2003;44:1709-16.
28. Bull RJ, Lutkenhoff SD. Early changes in respiration, aerobic glycolysis and cellular NAD(P)H in slices of rat cerebral cortex exposed to elevated concentrations of potassium. *J Neurochem* 1973;21:913-22.
29. Lewis DV, Schuette WH. NADH fluorescence and [K⁺]_o changes during hippocampal electrical stimulation. *J Neurophysiol* 1975;38:405-17.
30. Lothman E, Lamanna J, Cordingley G, Rosenthal M, Somjen G. Responses of electrical potential, potassium levels, and oxidative metabolic activity of the cerebral neocortex of cats. *Brain Res* 1975;88:15-36.
31. Mayevsky A, Zeuthen T, Chance B. Measurements of extracellular potassium, ECoG and pyridine nucleotide levels during cortical spreading depression in rats. *Brain Res* 1974;76:347-9.
32. Rosenthal M, LaManna J, Yamada S, Younts W, Somjen G. Oxidative metabolism, extracellular potassium and sustained potential shifts in cat spinal cord in situ. *Brain Res* 1979;162:113-27.
33. Sunami K, Nakamura T, Ozawa Y, Kubota M, Namba H, Yamaura A. Hypermetabolic state following experimental head injury. *Neurosurg Rev* 1989;12(Suppl 1):400-11.
34. Samii, A., Lee, S.M. & Hovda, D.A. Delayed increases in glucose utilization following cortical impact injury. *Society for Neuroscience* 1998; 24: 738. Abstract.
35. Ackermann RF, Lear JL. Glycolysis-induced discordance between glucose metabolic rates measured with radiolabeled fluorodeoxyglucose and glucose. *J Cereb Blood Flow Metab* 1989;9:774-85.
36. Lear JL, Ackermann RF. Why the deoxyglucose method has proven so useful in cerebral activation studies: the unappreciated prevalence of stimulation-induced glycolysis. *J Cereb Blood Flow Metab* 1989;9:911-13.
37. Kawamata T, Katayama Y, Hovda DA, Yoshino A, Becker DP. Lactate accumulation following concussive brain injury: the role of ionic fluxes induced by excitatory amino acids. *Brain Res* 1995;674:196-204.
38. Biros MH, Dimlich RV. Brain lactate during partial global ischemia and reperfusion: effect of pretreatment with dichloroacetate in a rat model. *Am J Emerg Med* 1987;5:271-7.
39. Richards TL, Keniry MA, Weinstein PR, et al. Measurement of lactate accumulation by in vivo proton NMR spectroscopy during global cerebral ischemia in rats. *Magn Reson Med* 1987;5:353-7.
40. Nilsson B, Ponten U. Experimental head injury in the rat. Part 2: Regional brain energy metabolism in concussive trauma. *J Neurosurg* 1977;47:252-61.
41. Yang MS, DeWitt DS, Becker DP, Hayes RL. Regional brain metabolite levels following mild experimental head injury in the cat. *J Neurosurg* 1985;63:617-21.
42. Meyer JS, Kondo A, Nomura F, Sakamoto K, Teraura T. Cerebral hemodynamics and metabolism following experimental head injury. *J Neurosurg* 1970;32:304-19.
43. Corbett, R.J., Laptook, A.R., Nunnally, R.L., Hassan, A. & Jackson, J. Intracellular pH, lactate, and energy metabolism in neonatal brain during partial ischemia measured in vivo by ³¹P and ¹H nuclear magnetic resonance spectroscopy. *J Neurochem* 1988; 51: 1501-9.
44. Nelson, S.R., Lowry, O.H. & Passonneau, J.V. Head Injury. 1966; Caviness, W.F. & Walker, A.E. (eds.), JB Lippincott, Philadelphia, pp. 444-447.
45. Magistretti PJ, Sorg O, Yu N, Martin JL, Pellerin L. Neurotransmitters regulate energy metabolism in astrocytes: implications for the metabolic trafficking between neural cells. *Dev Neurosci* 1993;15:306-12.
46. Pellerin L, Magistretti PJ. Glutamate uptake into astrocytes stimulates aerobic glycolysis: a mechanism coupling neuronal activity to glucose utilization. *Proc Natl Acad Sci U S A*. 1994;91:10625-10629.
47. Pellerin L, Magistretti PJ. Neuroenergetics: calling upon astrocytes to satisfy hungry neurons. *Neuroscientist*. 2004;10:53-62.
48. Prins ML, Lee SM, Fujima LS, Hovda DA. Increased cerebral

- uptake and oxidation of exogenous betaHB improves ATP following traumatic brain injury in adult rats.
J Neurochem 2004;90:666-72.
49. Glenn TC, Kelly DF, Boscardin WJ, et al. Energy dysfunction as a predictor of outcome after moderate or severe head injury: indices of oxygen, glucose, and lactate metabolism.
J Cereb Blood Flow Metab 2003; 23:1239-50.
 50. Verweij BH, Muizelaar JP, Vinas FC, Peterson PL, Xiong Y, Lee CP. Impaired cerebral mitochondrial function after traumatic brain injury in humans.
J Neurosurg 2000;93:815-20.
 51. Verweij BH, Muizelaar JP, Vinas FC, Peterson PL, Xiong Y, Lee CP. Mitochondrial dysfunction after experimental and human brain injury and its possible reversal with a selective N-type calcium channel antagonist (SNX-111).
Neurol Res 1997;19:334-9.
 52. Xiong Y, Peterson PL, Muizelaar JP, Lee CP. Amelioration of mitochondrial function by a novel antioxidant U-101033E following traumatic brain injury in rats.
J Neurotrauma 1997;14:907-17.
 53. Xiong Y, Peterson PL, Verweij BH, Vinas FC, Muizelaar JP, Lee CP. Mitochondrial dysfunction after experimental traumatic brain injury: combined efficacy of SNX-111 and U-101033E.
J Neurotrauma 1998;15:531-44.
 54. Buczek M, Alvarez J, Azhar J, et al. Delayed changes in regional brain energy metabolism following cerebral concussion in rats.
Metab Brain Dis 2002;17:153-67.
 55. Mautes AE, Thome D, Steudel WI, Nacimiento AC, Yang Y, Shohami E. Changes in regional energy metabolism after closed head injury in the rat.
J Mol Neurosci 2001;16:33-9.
 56. Lee, S.M., Wong, M.D., Samii, A. & Hovda, D.A. Evidence for energy failure following irreversible traumatic brain injury.
Ann N Y Acad Sci 1999; 893: 337-40.
 57. Becker, D.P. Central Nervous System Trauma Status Report. 1985; Becker, D.P. & Povlishock, J.T. (eds.), Byrd Press, Richmond, pp. 229-242.
 58. Racker, E., Johnson, J.H. & Blackwell, M.T. The role of ATPase in glycolysis of Ehrlich ascites tumor cells.
J Biol Chem 1983; 258: 3702-5.
 59. Rose IA, Warms JV, O'Connell EL. Role of inorganic phosphate in stimulating the glucose utilization of human red blood cells.
Biochem Biophys Res Commun 1964; 15: 33-7.
 60. Gardiner M, Smith ML, Kagstrom E, Shohami E, Siesjo BK. Influence of blood glucose concentration on brain lactate accumulation during severe hypoxia and subsequent recovery of brain energy metabolism.
J Cereb Blood Flow Metab 1982;2:429-38.
 61. Kalimo H, Rehncrona S, Soderfeldt B, Olsson Y, Siesjo BK. Brain lactic acidosis and ischemic cell damage: 2. Histopathology.
J Cereb Blood Flow Metab 1981;1:313-27.
 62. Myers RE. A unitary theory of causation of anoxic and hypoxic brain pathology.
Adv Neurol 1979; 26: 195-213.
 63. Siemkowicz E, Hansen AJ. Clinical restitution following cerebral ischemia in hypo-, normo- and hyperglycemic rats.
Acta Neurol Scand 1978; 58: 1-8.
 64. Becker DP, Jenkins LW. The Physiological Basis of Modern Surgical Care. 1987; Miller TA, Rowlands B. (eds.), Mosby, St. Louis, pp. 763-788.
 65. DeSalles AA, Kontos HA, Ward JD, Marmarou A, Becker DP. Brain tissue pH in severely head-injured patients: a report of three cases.
Neurosurgery 1987;20:297-301.
 66. Robertson CS, Grossman RG, Goodman JC, Narayan RK. The predictive value of cerebral anaerobic metabolism with cerebral infarction after head injury.
J Neurosurg 1987;67:361-8.
 67. Hotson JR, Sybert GW, Ward AA, Jr. Extracellular potassium concentration changes during propagated seizures in neocortex.
Exp Neurol 1973;38:20-6.
 68. Inao S, Marmarou A, Clarke GD, Andersen BJ, Fatouros PP, Young HF. Production and clearance of lactate from brain tissue, cerebrospinal fluid, and serum following experimental brain injury.
J Neurosurg 1988;69:736-44.
 69. Nilsson P, Hillered L, Ponten U, Ungerstedt U. Changes in cortical extracellular levels of energy-related metabolites and amino acids following concussive brain injury in rats.
J Cereb Blood Flow Metab 1990;10:631-7.
 70. Nilsson P, Hillered L, Olsson Y, Sheardown MJ, Hansen AJ. Regional changes in interstitial K⁺ and Ca²⁺ levels following cortical compression contusion trauma in rats.
J Cereb Blood Flow Metab 1993;13:183-92.
 71. Dietrich WD, Alonso O, Busto R, et al. Posttraumatic cerebral ischemia after fluid percussion brain injury: an autoradiographic and histopathological study in rats.
Neurosurgery 1998;43:585-93.
 72. Graham DI, Adams JH. Ischaemic brain damage in fatal head injuries.
Lancet 1971;1:265-266.
 73. Dietrich WD, Alonso O, Busto R, et al. Widespread hemodynamic depression and focal platelet accumulation after fluid percussion brain injury: a double-label autoradiographic study in rats.
J Cereb Blood Flow Metab 1996;16:481-9.
 74. Bouma GJ, Muizelaar JP, Choi SC, Newlon PG, Young HF. Cerebral circulation and metabolism after severe traumatic brain injury: the elusive role of ischemia.
J Neurosurg 1991;75:685-93.
 75. Diringner MN, Videen TO, Yundt K, et al. Regional cerebrovascular and metabolic effects of hyperventilation after severe traumatic brain injury.
J Neurosurg 2002;96:103-8.
 76. von Oettingen G, Bergholt B, Gyldensted C, et al. Blood flow and ischemia within traumatic cerebral contusions.
Neurosurgery 2002; 50:781.
 77. Marion DW, Darby J, Yonas H. Acute regional cerebral blood flow changes caused by severe head injuries.

- J Neurosurg* 1991;74:407-14.
78. Coles JP, Fryer TD, Smielewski P, et al. Defining ischemic burden after traumatic brain injury using 15O PET imaging of cerebral physiology.
J Cereb Blood Flow Metab 2004; 24:191.
 79. Vespa P, Bergsneider M, Hattori N, et al. Metabolic crisis without brain ischemia is common after traumatic brain injury: a combined microdialysis and positron emission tomography study.
J Cereb Blood Flow Metab 2005; 25:763.
 80. Muizelaar JP, Marmarou A, DeSalles AA, et al. Cerebral blood flow and metabolism in severely head-injured children. Part I: Relationship with GCS score, outcome, ICP, and PVI.
J Neurosurg 1989;71:63-71.
 81. Chiron C, Raynaud C, Maziere B, et al. Changes in regional cerebral blood flow during brain maturation in children and adolescents.
J Nucl Med 1992;33:696-703.
 82. Zwienerberg M, Muizelaar JP. Severe pediatric head injury: the role of hyperemia revisited.
J Neurotrauma 1999;16:937-43.
 83. Suzuki K. The changes in regional cerebral blood flow with advancing age in normal children.
Nagoya Med J 1990; 34: 159-70.
 84. Adelson PD, Clyde B, Kochanek PM, Wisniewski SR, Marion DW, Yonas H. Cerebrovascular response in infants and young children following severe traumatic brain injury: a preliminary report.
Pediatr Neurosurg 1997;26:200-7.
 85. Sharples PM, Stuart AG, Matthews DS, Aynsley-Green A, Eyre JA. Cerebral blood flow and metabolism in children with severe head injury. Part 1: Relation to age, Glasgow coma score, outcome, intracranial pressure, and time after injury.
J Neurol Neurosurg Psychiatry 1995;58:145-52.
 86. Kelly DF, Kordestani RK, Martin NA, et al. Hyperemia following traumatic brain injury: relationship to intracranial hypertension and outcome.
J Neurosurg 1996;85:762-71.
 87. Vavilala MS, Lee LA, Boddu K, et al. Cerebral autoregulation in pediatric traumatic brain injury.
Pediatr Crit Care Med 2004;5:257-63.
 88. Bullock R, Zauner A, Woodward JJ, et al. Factors affecting excitatory amino acid release following severe human head injury.
J Neurosurg 1998;89:507-18.
 89. Katayama Y, Becker DP, Tamura T, Hovda DA. Massive increases in extracellular potassium and the indiscriminate release of glutamate following concussive brain injury.
J Neurosurg 1990;73:889-900.
 90. Takahashi H, Manaka S, Sano K. Changes in extracellular potassium concentration in cortex and brain stem during the acute phase of experimental closed head injury.
J Neurosurg 1981;55:708-17.
 91. Young W, Yen V, Blight A. Extracellular calcium ionic activity in experimental spinal cord contusion.
Brain Res 1982;253:105-13.
 92. Hubschmann OR, Kornhauser D. Effects of intraparenchymal hemorrhage on extracellular cortical potassium in experimental head trauma.
J Neurosurg 1983;59:289-93.
 93. Julian F, Goldman D. The effects of mechanical stimulation on some electrical properties of axons.
J Gen Physiol 1962; 46:297.
 94. Ballanyi K, Grafe P, ten Bruggencate G. Ion activities and potassium uptake mechanisms of glial cells in guinea-pig olfactory cortex slices.
J Physiol 1987;382:159-74.
 95. Kuffler SW. Neuroglial cells: physiological properties and a potassium mediated effect of neuronal activity on the glial membrane potential.
Proc R Soc Lond B Biol Sci. 1967;168:1-21.
 96. Paulson OB, Newman EA. Does the release of potassium from astrocyte endfeet regulate cerebral blood flow?
Science. 1987;237:896-8.
 97. Moody WJ, Futamachi KJ, Prince DA. Extracellular potassium activity during epileptogenesis.
Exp Neurol. 1974;42:248-63.
 98. Sybert GW, Ward AA, Jr. Changes in extracellular potassium activity during neocortical propagated seizures.
Exp Neurol. 1974;45:19-41.
 99. Astrup J, Rehncrona S, Siesjo BK. The increase in extracellular potassium concentration in the ischemic brain in relation to the preischemic functional activity and cerebral metabolic rate.
Brain Res 1980;199:161-74.
 100. Hansen AJ. Extracellular potassium concentration in juvenile and adult rat brain cortex during anoxia.
Acta Physiol Scand 1977;99:412-20.
 101. Hansen AJ. The extracellular potassium concentration in brain cortex following ischemia in hypo- and hyperglycemic rats.
Acta Physiol Scand 1978;102:324-9.
 102. Heinemann U, Lux HD. Ceiling of stimulus induced rises in extracellular potassium concentration in the cerebral cortex of cat.
Brain Res 1977;120:231-49.
 103. D'Ambrosio R, Maris DO, Grady MS, Winn HR, Janigro D. Impaired K(+) homeostasis and altered electrophysiological properties of post-traumatic hippocampal glia.
J Neurosci 1999;19:8152-62.
 104. Fineman I, Hovda DA, Smith M, Yoshino A, Becker DP. Concussive brain injury is associated with a prolonged accumulation of calcium: a ⁴⁵Ca autoradiographic study.
Brain Res 1993;624:94-102.
 105. Nadler V, Biegona A, Beit-Yannai E, Adamchik J, Shohami E. ⁴⁵Ca accumulation in rat brain after closed head injury; attenuation by the novel neuroprotective agent HU-211.
Brain Res 1995;685:1-11.
 106. Nilsson P, Laursen H, Hillered L, Hansen AJ. Calcium movements in traumatic brain injury: the role of glutamate receptor-operated ion channels.
J Cereb Blood Flow Metab 1996;16:262-70.
 107. Osteen CL, Moore AH, Prins ML, Hovda DA. Age-dependency

- of ^{45}Ca accumulation following lateral fluid percussion: acute and delayed patterns.
J Neurotrauma 2001;18:141-62.
108. Verity MA. Ca^{2+} -dependent processes as mediators of neurotoxicity.
Neurotoxicology. 1992;13:139-47.
 109. Tymianski M, Tator CH. Normal and abnormal calcium homeostasis in neurons: a basis for the pathophysiology of traumatic and ischemic central nervous system injury.
Neurosurgery 1996;38:1176-95.
 110. Farooqui AA, Horrocks LA. Excitatory amino acid receptors, neural membrane phospholipid metabolism and neurological disorders.
Brain Res Brain Res Rev 1991;16:171-91.
 111. Kampfl A, Posmantur RM, Zhao X, Schmutzhard E, Clifton GL, Hayes RL. Mechanisms of calpain proteolysis following traumatic brain injury: implications for pathology and therapy: implications for pathology and therapy: a review and update.
J Neurotrauma 1997;14:121-34.
 112. Roberts-Lewis JM, Marcy VR, Zhao Y, Vaught JL, Siman R, Lewis ME. Amino acid protects hippocampal neurons from NMDA- and ischemia-induced toxicity in vivo.
J Neurochem 1993;61:378-81.
 113. Carter CJ, Noel F, Scatton B. Ionic mechanisms implicated in the stimulation of cerebellar cyclic GMP levels by N-methyl-D-aspartate.
J Neurochem 1987;49:195-200.
 114. Schmidley JW. Free radicals in central nervous system ischemia.
Stroke 1990;21:1086-90.
 115. Siesjo BK. Pathophysiology and treatment of focal cerebral ischemia. Part II: Mechanisms of damage and treatment.
J Neurosurg 1992;77:337-54.
 116. Bignami A, Clark K. Non-phosphorylated and phosphorylated neurofilaments in hypothyroid rat cerebellum.
Brain Res 1987;409:143-5.
 117. Iwasaki Y, Yamamoto H, Iizuka H, Yamamoto T, Konno H. Suppression of neurofilament degradation by protease inhibitors in experimental spinal cord injury.
Brain Res 1987;406:99-104.
 118. Morgan JI, Curran T. Role of ion flux in the control of c-fos expression.
Nature 1986;322:552-5.
 119. Xiong Y, Gu Q, Peterson PL, Muizelaar JP, Lee CP. Mitochondrial dysfunction and calcium perturbation induced by traumatic brain injury.
J Neurotrauma 1997; 14: 23-34.
 120. Heath DL, Vink R. Traumatic brain axonal injury produces sustained decline in intracellular free magnesium concentration.
Brain Res 1996;738:150-3.
 121. Vink R, McIntosh TK, Demediuk P, Faden AI. Decrease in total and free magnesium concentration following traumatic brain injury in rats.
Biochem Biophys Res Commun 1987;149:594-9.
 122. Vink R, McIntosh TK, Demediuk P, Weiner MW, Faden AI. Decline in intracellular free Mg^{2+} is associated with irreversible tissue injury after brain trauma.
J Biol Chem 1988;263:757-61.
 123. Memon ZI, Altura BT, Benjamin JL, et al. Predictive value of serum ionized but not total magnesium levels in head injuries.
Scand J Clin Lab Invest 1995; 55:671.
 124. Binet A, Volfin P. Regulation by Mg^{2+} and Ca^{2+} of mitochondrial membrane integrity: study of the effects of a cytosolic molecule and Ca^{2+} antagonists.
Arch Biochem Biophys 1975;170:576-86.
 125. Ebel H, Gunther T. Magnesium metabolism: a review.
J Clin Chem Clin Biochem 1980;18:257-70.
 126. M. Bara, A. Guet-Bara, and J. Durlach. Regulation of sodium and potassium pathways by magnesium in cell membranes.
Magnes Res 1993; 6:167-77.
 127. Emerson CS, Vink R. Increased mortality in female rats after brain trauma is associated with lower free Mg^{2+} .
Neuroreport. 1992;3:957-60.
 128. Heath DL, Vink R. Neuroprotective effects of MgSO_4 and MgCl_2 in closed head injury: a comparative phosphorus NMR study.
J Neurotrauma 1998;15:183-9.
 129. McIntosh TK, Faden AI, Yamakami I, Vink R. Magnesium deficiency exacerbates and pretreatment improves outcome following traumatic brain injury in rats: ^{31}P magnetic resonance spectroscopy and behavioral studies.
J Neurotrauma 1988;5:17-31.
 130. DeSalles AA, Kontos HA, Becker DP, et al. Prognostic significance of ventricular CSF lactic acidosis in severe head injury.
J Neurosurg 1986; 65:615-24.
 131. Guerrero JL, Thurman DJ, Sniezek JE. Emergency department visits associated with traumatic brain injury: United States, 1995-1996.
Brain Inj 2000;14:181-6.
 132. Kury G, Weiner J, Duval JV. Multiple self-inflicted gunshot wounds to the head: report of a case and review of the literature.
Am J Forensic Med Pathol 2000;21:32-5.
 133. MacKenzie EJ, McCarthy ML, Ditunno JF, et al. Using the SF-36 for characterizing outcome after multiple trauma involving head injury.
J Trauma 2002;52:527-34.
 134. Giza CC, Hovda DA. The neurometabolic cascade of concussion.
Journal of Athletic Training 2001; 36:228-235.