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Commentary and Update on "The Mitochondrial Permeability Transition Pore Provides a Key to the Diagnosis and Treatment of Traumatic Brain Injury"

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Abstract

The etiology of traumatic brain injury involves opening of the mitochondrial permeability transition pore resulting in cessation of mitochondrial ATP synthesis by the electron transport system with conversion of the energy of the electron transport system from ATP synthesis to heat production causing an increase in brain temperature. Treatment of TBI can be directed to closing of the mitochondrial permeability transition pore by administration of cyclosporine, which binds cyclophilin, a specific protein component of the pore, or by provision of ketone bodies, whose metabolism increases the energy of ATP hydrolysis with closing of the mitochondrial pore.

Keywords: Traumatic brain injury; Mitochondrial permeability transition pore; ketone; pyruvate dehydrogenase; NIR spectroscopy; Reactive oxygen species; NADPH oxygenase; Brain temperature; ATP; Electron transport chain; Antioxidant

Introduction

The author of this commentary was asked to provide an update on the 2012 article [1], "The mitochondrial permeability transition pore provides a key to the diagnosis and treatment of traumatic brain injury". The history surrounding the original article will help the author update the reader on the status of ketones and TBI and the mitochondrial permeability transition pore, MPTP.

In the year 2001, George Cahill, Britton Chance, Henry Lardy, Yoshihiro Kashiwaya and Richard Veech suggested ketones in a bottle, ketone ester, may have many diverse medical uses [2]. Although, TBI was not specifically mentioned in that paper, the mechanism of reducing damage from reactive oxygen species would apply to traumatic brain injury, TBI. The event that caused this author to write a paper adding TBI to the list of maladies potentially treated with ketone ester came about in a conversation with the author's son, Thomas Veech, a physician at the VA. At the height of the Afghanistan and Iran conflicts, Thomas, attended a presentation on the current state of research on TBI. General David Petraeus was in attendance and had requested the input. In response to his son's report of little progress, Veech et al. wrote the paper entitled "The mitochondrial permeability transition pore provides a key to the diagnosis and treatment of traumatic brain injury" [1]. The hypothesis that MPTP provided the key to diagnosis was based on an observed temperature rise in the brain following TBI which was ostensibly caused because the mitochondria were uncoupled from ATP production due to the opening of the pore. The second hypothesis that MPTP provided a key to treatment was based on ketone metabolism counteracting the opening of the MPTP. This commentary will provide an update on both the diagnostic method and treatment suggested in the paper.

Progress on a NIR field diagnostic device

The diagnosis method proposed was to be used in the field by military personnel to measure the internal temperature of the brain with near-infrared (NIR) spectroscopy. Britton Chance, a co-author on the 2001 paper had built a similar device. Chance used NIR spectroscopy to measure hemoglobin. A student of Britton Chance, Clyde Barlow wrote a paper that suggested the same NIR spectroscopy could be used to measure water temperature [3]. There is a current display at the National Museum of Health and Medicine that is called: "Traumatic Brain Injury" [4]. In that display one can find the device shown in Figure 1, which uses near infrared to detect hematomas in the brain. The reader will note that one of the co- inventors was Britton Chance.

Figure 1: "Near Infrared (NIR) system for detection of brain hematomas, invented by Dr. Britton Chance (University of Pennsylvania) and Dr. Claudia Robertson (Baylor College of Medicine) and manufactured by InfraScan, Inc. The device is a notable advancement in combat casualty care as a triage tool for one of the most problematic diagnoses on the battlefield: traumatic brain injury with intracranial bleeding". The quote is from the display at the National Museum of Health and Medicine.

The invention of Chance and Robertson measured hemoglobin. The variation that Veech proposed would use two slightly different near infra-red frequencies that allow one to measure the temperature of water in the brain. In 2014 Bakhseshi et al. [5] demonstrated the feasibility of measuring temperatures inside the brain with time-resolved near infrared spectroscopy. The author is not aware of any other developments to measure brain temperature in the field with NIR.

Other methods of field diagnosis are now possible

In the years since the NIR device was proposed, other methods of field diagnosis have been developed. Some make use of the disruption of saccadic eye movement [6,7]. Other tests could make use of recent findings of biomarkers. These include the elevation of glial fibrillary acidic protein, GFAP, and ubiquitin C-terminal hydrolase, UCH-LI [8] either of which would appear to be candidates to make reliable field tests.

Glial fibrillary acidic protein, GFAP, is an astroglial protein released from astrocytes from white or grey matter into cerebrospinal fluid and blood after brain trauma. Also of use as a TBI diagnostic tool is the release into blood of the neuronal protein ubiquitin C-terminal hydrolyse L1, UCH-Li, which is elevated in blood even earlier after TBI than GFAP [8].

Progress in treating TBI with exogenous ketones

To begin to answer the question, "What progress has been made in treating TBI with exogenous ketones?", one begins by answering the question, "Does the MPTP play a role in TBI?

Does MPTP play a role in TBI?

The increase in brain temperature after TBI is most economically explained by the opening of the mitochondrial membrane permeability transition pore [1,9] with conversion of the energy of the electron transport system from ATP generation to heat production. This accounts for the decrease in brain phosphorylation potential during TBI and for the increase in mitochondrial Ca^{2+} and Mg^{2+} associated with this pore opening [10]. The opening of the pore destroys the mitochondrial proton gradient required from mitochondrial ATP synthesis with the energy of the electron transport system being converted into heat. The opening of the pore is associated with mitochondrial dysfunction resulting in loss of ATP synthesis and decrease in phosphorylation potential. A decrease in the energy of ATP hydrolysis can result in opening of the pore for a number of reasons, such as inhibition of pyruvate dehydrogenase, PDH [11].

A further substantiation of the role which opening of the MPTP plays in the origin of TBI is the observation that the antibiotic cyclosporine had some success in treating TBI [12–15]. Cyclosporine acts quite specifically in binding to the mitochondrial protein cyclophilin which forms a part of the MPTP [16].

Do ketones close the MPTP?

Closing of the MPTP can be achieved by increasing the energy of ATP hydrolysis by the metabolism of ketone bodies due to administration of ketone body esters or by feeding a ketogenic diet [9,17]. A ketone ester supplement is perhaps preferred to a ketogenic diet due to the difficulties and complications of the diet and the time it takes to enter a state of ketosis. Ketone esters are safe, and raise the blood D-ß-hydroxybutyrate levels quite rapidly [18].

What Cahill, Chance, Lardy, Kashiwaya and Veech knew about ketones, led Veech to propose that if one wanted to close the MPTP then D-ß-hydroxybutyrate given as a food supplement would have the same effect of closing the MPTP or at least have the effect of keeping the remaining mitochondria from opening the pore. The mechanisms invoked to justify these statements are beyond the scope of a commentary but they can be found explained best in Sato et al. [19] and Curtis et al. [20].

If ketones are a potential treatment, why have they not been tested?

The question remaining is what would ketones in a bottle do for TBI, and why haven't ketones been tested in patients as they have been in experimental animals [21]?

Perhaps this is the fault of the author assuming his audience was aware of the relevant biochemistry. There are three other benefits not mentioned in the 2012 article that would be relevant to TBI.

Ketones turn on the FOXO3a transcription factor increasing the production of important antioxidant enzymes such as superoxide dismutase and catalase. They do this perhaps by a mechanism described by Shimazu et al. [22]. They showed D-ß-hydroxybutyrate was a histone deacetylase inhibitor. Perhaps D-ß-hydroxybutyrate increases production of SOD and catalase by attaching directly to the lysine in histones [23].

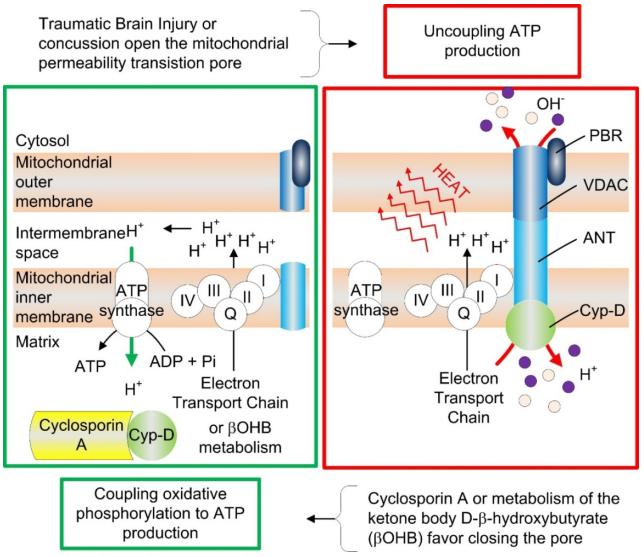

Figure 2: Traumatic brain injury leads to opening the mitochondrial permeability transition pore. Cyclosporin A or metabolism of the ketone body D-ß-hydroxybutyrate favors closing the pore.

Ketones raise the level of cytosolic NADPH [19]. NADPH is the ultimate source of reducing electrons to drive the antioxidant enzymes and the molecular antioxidants that must be reduced each time they quench a reactive oxygen species, ROS, or reactive nitrogen species, RNS (Figure 3).

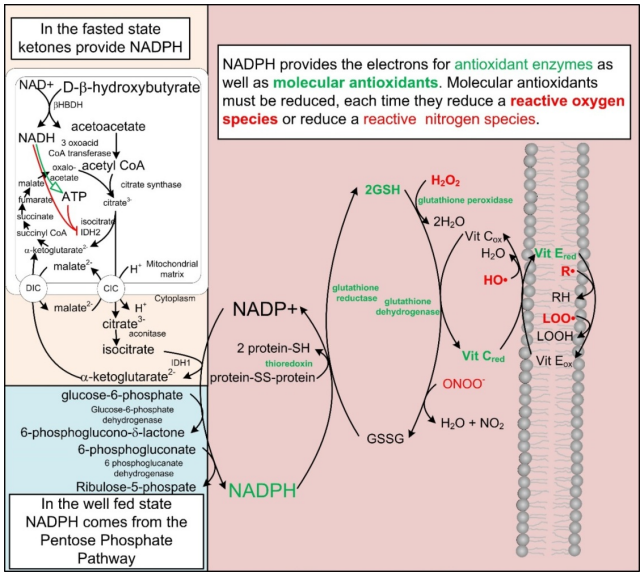

Figure 3: An ample supply of NADPH is needed to overcome the metabolic cascade of TBI. As glucose is depleted the pentose phosphate pathway would not be able to provide the needed NADPH. NADPH provides the reducing potential to counteract ROS and RNS through antioxidants that must be reduced each time they are oxidized as they quench by reduction a ROS or RNS. Abbreviations: IDH 1 and 2 – isocitrate dehydrogenase 1 and 2, DIC-dicarboxylate carrier, CIC – citrate carrier, NAD - nicotinamide adenine dinucleotide, NADH – reduced NAD+, NADP - nicotinamide adenine dinucleotide phosphate, NADPH – reduced $NADP^+$, GSH - glutathione, GSSG glutathione disulfide, Vit C – vitamin C or ascorbate, Vit E- vitamin E or α tocopherol, $R^{\bullet-}$ free radical on a carbon atom, RH – an organic molecule with C-H bond, $LOO^{\bullet-}$ lipid peroxyl radical, LOOH –lipid peroxide.

The entry of pyruvate into oxidative phosphorylation is inhibited in TBI by phosphorylation of pyruvate dehydrogenase [11]. Ketones can power the mitochondria under conditions of stress when PDH inhibition has limited the ability of mitochondria to run on pyruvate, a product of glycolysis (Figure 4).

The metabolic cascade that causes secondary injury in TBI is matched by the metabolic cascade of D-ß-hydroxybutyrate

TBI secondary damage due to the complex biochemical events that arise after injury is targeted on many fronts by the effect of D-ß-hydroxybutyrate. Not only does it resist opening of the MPTP it also upregulates survival gene products associated with FOXO3a.

D-ß-hydroxybutyrate generates NADPH when demands on glucose limit the NADPH available from the pentose phosphate pathway. NADPH powers both antioxidant molecules and antioxidant enzymes. The ATP desperately needed to rebalance homeostasis and make repairs is provided by D-ß-hydroxybutyrate even when pyruvate dehydrogenase has been inhibited.

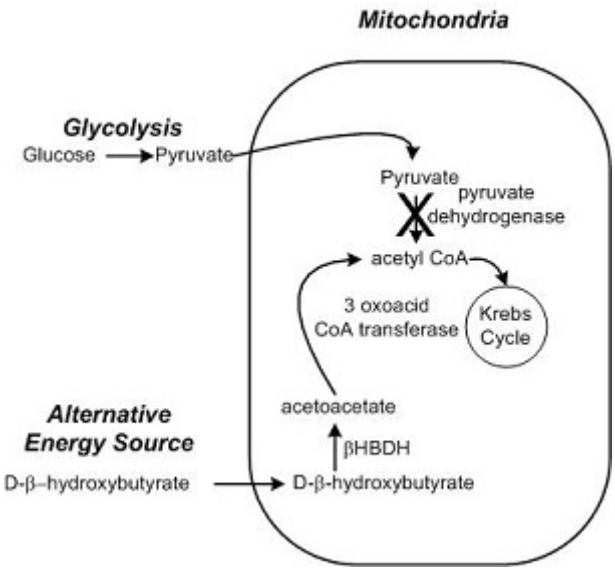

Figure 4: D-ß-hydroxybutyrate metabolism produces Acetyl CoA which enters the Krebs, tricarboxylic acid cycle by an alternative pathway that does not require the usual path through pyruvate dehydrogenase (PDH).

Potential to interrupt the vicious cycle of neurodegeneration

The finding that ROS/RNS lead to inflammation signals that results in NADPH oxidase, NOX, production points to a vicious cycle [24]. The superoxide produced by NOX is removed by the FOXO3a induced enzymes SOD and catalase. The requirement for additional NADPH is met by D-B-hydroxybutyrate [19] (Figure 3). By quenching ROS/RNS, ketone esters may possibly break the vicious cycle and allow the brain cells to return to a normal metabolic state.

Conclusion

Kabadi and Faden report on thirty unsuccessful clinical trials in seeking to find a neuroprotective treatment for TBI [25]. Hasn't the time come to add ketone esters as a metabolic cascade that counters the metabolic cascade of TBI to the list of clinical trials? The author recommends we add D-ß-hydroxybutyrate somewhere into the cocktail of treatment options and see if we can't change our record from zero for thirty.

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