Current Research in Diabetes & Obesity Journal
ISSN: 2476-1435

Juniper Publishers
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Research Article
Volume 16 Issue 3 - January 2023
DOI: 10.19080/CRDOJ.2023.16.555937

Curr Res Diabetes Obes J

Mild Traumatic Brain Injury, Hibernation, Type 2 Diabetes Common Etiopathophysiology Biomarkers and Function

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Submission: October 8, 2022; **Published:** January 17, 2023

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Abstract

The link between diabetes and traumatic brain injury (TBI) is an area worthy of exploration. TBI is a caused by bump, blow, jolt, or penetrating injury to the head. Mild (mTBI) and moderate TBI frequently result in chronic pervasive physical, cognitive, emotional and behavioral symptoms, which impact long-term outcome and functioning. Traumatic brain injury is associated with neuroendocrinopathies, including hypothalamic, pituitary, adrenal, pancreatic, pineal, and other hormonal dysfunctions. Increases in cortisol, cholesterol, and weight gain that can occur with some TBI survivors may contribute to development of Type II Diabetes, as can the medications they take. Many patients with TBI find physical activity, proper eating, sleeping and even hygiene difficult. They also often experience anxiety and stress, which contribute to hormonal dysregulation. Here we show that the most common symptoms of TBI and neuroendocrine dysfunction that overlap are fatigue, poor memory, anxiety, depression, weight change, emotional lability, lack of concentration, and attention difficulties. We also report on different hibernating animals as model of people with TBI.

Keywords: Diabetes; Traumatic brain injury; Hormonal dysregulation; Type II diabetes; Metabolic syndrome; Chronic cognitive; Emotional and behavioral symptoms

Introduction

Traumatic brain injuries (TBIs) and type II diabetes have much in common. They are both: among top causes of morbidity and mortality; neuroendocrine related disorders; have effects on metabolism and nerve processes; and, have effects on cognitive and sensory function. Just as a TBI can lead to having type II diabetes, having uncontrolled diabetes can lead to TBI. This paper provides evidence from our lab and others which demonstrates these effects.

Traumatic Brain Injury - Causes

Traumatic brain injury is a caused by bump, blow, jolt, or penetrating injury to the head. Brain injuries occur in motor vehicle or bicycle crashes, in sports and industrial accidents. They may be sustained from whiplash, falls, assaults, loud blast injuries, long periods of exposure to loud blasts at unexpected intervals, chemical exposure, or anoxia. The common all-cause effects of TBI are prevalent, disabling and treatment-resistant conditions due to focal impact to the head and/or sudden acceleration/deceleration of the brain within the skull (Figure 1). Shaken baby syndrome, falls, surgeries gone wrong or delayed, following pressure, blood or blockage of the brain, due to strokes, viruses, or injuries to the eye (or other body parts) can also produce TBI injuries. If not fatal, TBI are often life-changing and require the same kind of aggressive diagnosis and proper treatment that occurs with heart attacks and strokes. The first step in the treatment of intracranial brain injury is to recognize when it has occurred so that stroke medications can be used in the 3-hour window of a non-bleeding stroke, as necessary and appropriate. Many people are in denial that they have a traumatic brain injury and do not seek care. Others do not seek care because they do not have the resources for it. Lastly, those who are in motor vehicle accidents often do not seek care because of complications surrounding car insurance and liability issues or nationality status. Others are in denial, because a TBI causes confusion, activation of the sympathetic nervous system (the "fight-or-flight" response) and changes in one's self-identity. People are not ready to handle this while symptoms are masked by sympathetic over-load. The first phase of TBI is confusion [1]. The brain actively responds to neural insults immediately.

Traumatic Brain Injury - Incidence

Traumatic brain injury is a serious neurological disorder, which occurs at a rate of about 10,000,000 year. It surpasses many human diseases in terms of deaths or hospitalizations. It is

the 3rd leading cause of death and disability [2].

Traumatic Brain Injury - Diagnosis

The severity of TBI can be classified as mild and/or moderate (mTBI) or severe based upon the individual's clinical presentation and evaluation. Positive results on imaging tests, such as CAT scans or MRIs can be definitive of a traumatic brain injury. However, negative tests on such scans do not preclude there being a TBI. Some of the inherent challenges with TBI is that damage to the brain is often not evident on imaging with CAT scans or MRIs. CAT scans are used to evaluate whether: there has been compression of the brain, such that some of the sulci are compromised; whether there has been a midline shift; or a brain bleed has occurred. MRIs are also limited. They only show focal changes in the brain. They do not reveal damaged caused by diffuse axonal shearing, which is a major cause of injury in TBI. PET scan can evaluate axonal shearing, but they are so expensive or of limited availability that they are not typically utilized to evaluate TBIs. The secondary insult leads to degeneration of neurons, glial cells or axons, due to the biomolecular and physiological changes that follow the primary insult. In the absence of definitive damage on a scan, evaluation by a neuropsychologist is needed for diagnosis of TBI [3].

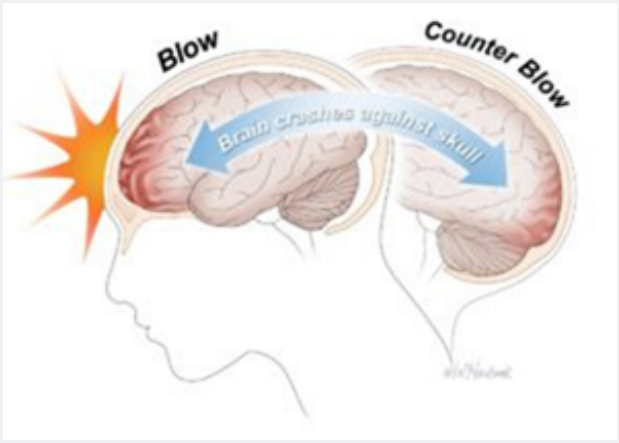

Figure 1: Sudden acceleration/deceleration of the brain within the skull.

Trajectory of mTBI

Mild (mTBI) and moderate to severe TBI frequently results in chronic cognitive, emotional and behavioral symptoms, which impact long-term outcome and functioning. These numbers will be increasing, because of Covid-19, which had its effects via an area in the brainstem, the pons, which controls breathing. We have already seen post-Covid 19 patients presenting with mTBI. Moderate TBI patients have difficulty ambulating, speaking, and they do not drive. Severe TBI cases are of individuals who are bedridden, on catheters, and have a limited capacity to communicate.

Prognosis of Traumatic Brain Injury

In the following pages, we list some of the symptoms a brain injury typically shows, first those that are likely to appear at the time of the injury, then those that may appear later. It should be noted that brain injuries are highly individualized. As such, the symptoms will vary widely from person to person. Healing in brain injury takes time, for some months and others' years. Much has to do with the individual's premorbid state and the health and plasticity of their hippocampus before the injury. Failure to appreciate this and forcing individuals back to their normal life activities before they are ready can severely retard their progress in recovery. It is important to identify a brain injury quickly and to be alert to both the initial symptoms and those that appear later (see Figure 2).

Common symptomatology -- such as headache, seizures, motor disorders, sleep disorders, dizziness, visual disturbances, mood changes, and cognitive, memory, speech and sleep difficulties --all resemble symptoms of post-traumatic stress disorder (PTSD), which is typically co-morbid with TBI. Some of the symptoms unique to TBI are persistent headaches, ringing in the ears, and sensitivity to light. Another challenge of TBI is that people often do not look different. So, it is hard for the individual with TBI and the people around them to adjust to profound changes associated with TBI. These, and other factors, may be associated with an increased vulnerability to certain psychological disorders, possibly accounting for the high rate of such disorders and suicide among survivors [4,5].

Hormones and TBI

Traumatic brain injury is associated with neuroendocrinopathies including hypothalamic, pituitary, adrenal, gonadal, pancreatic, pineal and other hormonal dysfunctions. Indeed, prior to the development of current technologies to image the brain, one of the means by which TBIs were defined was

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by verifying long term dysfunction of the endocrine axis a year following brain insult, which occurs in 30-80% of persons with TBI. Some of the challenges facing individuals with TBI include a list of up to 137 symptoms which focus on physical, cognitive, and emotional challenges, which are largely due to effects of hormonal targets (Table 1).

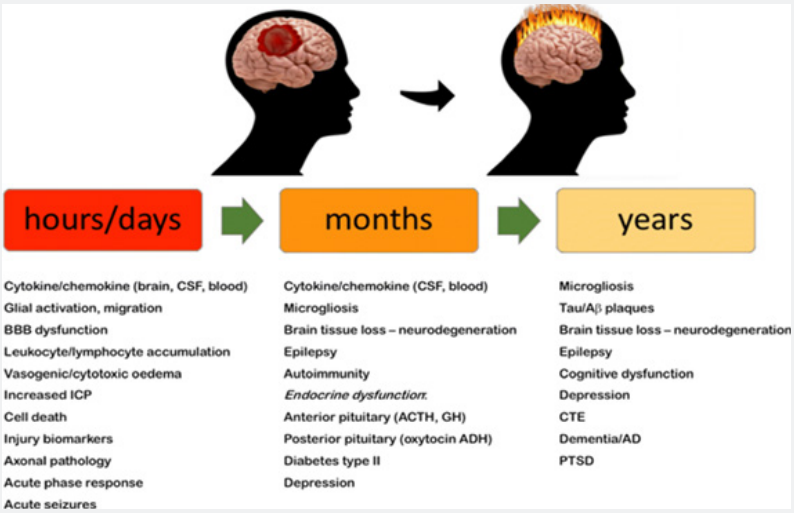

Figure 2: These steroids are released in the bloodstream and can have varied effects throughout the whole system given their lipophilic nature and many cellular targets.

Table 1: A list of all symptoms of traumatic brain injury.

Symptoms of Traumatic Brain Injury		
Physical	**Cognitive**	**Emotional**
Changes in consciousness, headache, lightheadedness, dizziness, vertigo, nausea, vomiting, difficulty swallowing, fatigue, lethargy, imbalance, gait disturbance, walking abnormalities, sleep disturbance, slurred speech, loss of smell, loss of taste, numbness, seizures, difficulty with coordination, muscle spasms, twitching, spatial disorientation, difficulty breathing, changes in appetite, weight gain or loss, loss of sex drive, sexual dysfunction, pain, blurred vision, light sensitivity, sensitivity to colors, difficulty with depth perception, tracking, scanning, hand-eye coordination, noise sensitivity, ringing in the ears, popping noises in the ears, spinal rigidity, decreased range of motion	confusion, disorientation, short term and long term memory deficits, distractibility, inattention, lack of concentration, slowed processing speed, inability to multi-task, difficulty reading, difficulty making decisions, difficulty initiating actions, difficulty with numbers and money, rigid thinking, poor judgement, difficulty putting thoughts to words, difficulty finding words, difficulty judging time	mood swings, impulsiveness, anger, agitation, anxiety, panic attacks, restlessness, depression, feelings of hopelessness, difficulty controlling emotions, impatience, discomfort with others, obsessiveness, compulsions

Results of Self Reports#

Participants at the 2015 Brain Injury Association of New York State Congress (BIANYS) annual congress, held at the Marriot Hotel in Latham, NY were asked to complete a survey. Gary Bussey was the keynote speaker. He is in many ways a personification of someone with a TBI, who has recovered and makes it work for him. He can function in the world, but it seems challenging for him in some ways; for example, emotional regulation, self-awareness, and impulsiveness can be difficult symptoms that are now part of his persona. # The data presented in this section were part of a graduate class in Experimental Methods taken at North Central University to Qualify for my License to Practice in NY State.

Neuroendocrine dysfunction, TBI, and diabetes share 20 overlapping symptoms.

During each session at the congress, questionnaires were left for participants. The questionnaires focused on the individual's level of TBI, the duration since their TBI, how they were functioning, the physical, cognitive and emotional symptoms associated with their TBI, and the degree to which individuals perceived their symptoms impaired their daily life. The cut off level for significant reliability was preset at 0.7. Of all 137 TBI symptoms (see Table 1), 12 symptoms had a Cronbach's alpha statistical loading of greater than 0.80 and another set of 8 particular symptoms had a Cronbach's alpha score above 0.85 concordance (see Figure 3). They all corresponded with symptoms of neuroendocrine dysfunction, diabetes and TBI.

What we find evaluating people in the clinic

It should be noted that there is a tell-tale factor in determining TBI that can be identified at the first opportunity for a neuropsychologist, no sooner than 3 months after injury.

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Sexual dysfunction has been reported in every man and woman with a mTBI that my clinic has treated. The reasons were for consummatory (performance) and amotivational (desire) dysfunction. It is so endemic in the disorder that most people have never been asked about it, or associated it with their injury, and those with mTBI typically do not report this symptom unless it is explicitly asked. The majority of my patients were never asked about erectile dysfunction post-TBI and were highly relieved to know this was likely due to pituitary dysfunction and they could be treated by a urologist with fast-acting, non-selective phosphodiesterase inhibitors, such as Viagra, or longer acting more selective phosphodiesterase inhibitors, such as Cialis (as long as their penile vasculature was healthy, as that is the canary in the coal mine for the heart, and they had no cardiac history).

TBI and diabetes – Incidence

During a traumatic brain injury, which is typically due to a blow to the head or a blast injury, the brain -- tethered to the spinal cord -- generally stays in place and the skull moves around the brain causing damage, including contra-cous impact to the brain and movement of the pituitary, which is held on by a nerve net to the hypothalamus (Figure 4). Of the patients in our clinic, those who are type 1 diabetics, long prior to their TBI, demonstrate the least variance in blood sugar levels, A1C, cortisol, and cholesterol. Many more patients (~33%) have become diabetic after their TBI.

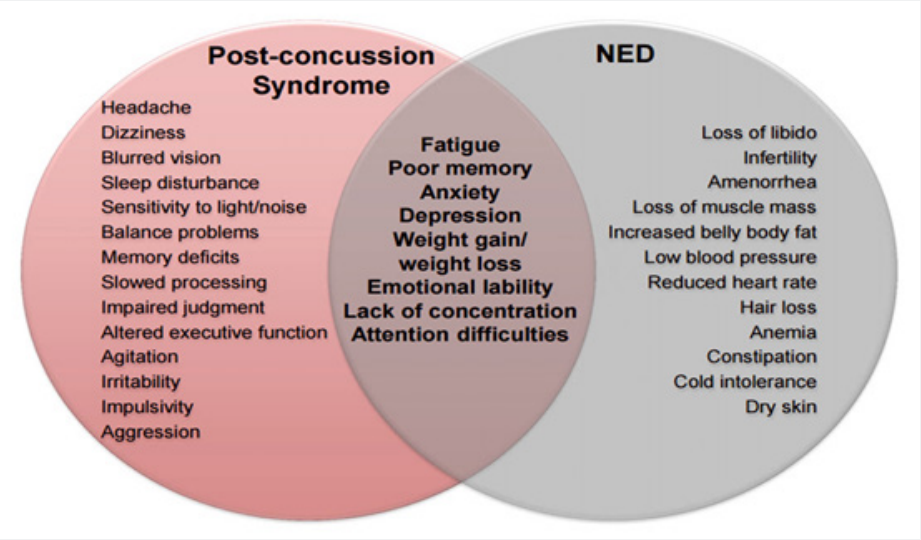

Figure 3: Post concussion syndrome and NED.

Those with TBI who become Type II diabetics are typically associated with the development of a lifestyle in which they become like "bears" in terms of their phenotype, behavior, metabolism and endocrinopathies. They eat sparsely and only when food is made available to them. They engage in very little physical activity; if able to they will spend a significant amount of time sleeping or at rest; they gain weight, develop metabolic syndrome and type 2 diabetes. Other patients, we may call "squirrels", with mTBI, are able to maintain some level of activity and remain on a daily schedule of eating, exercise, cognitive and social engagement, and do not seem to develop type 2 diabetes. However, they do typically experience an increase in cholesterol levels usually between 50 and 75 ng/mL higher than prior to their injury. Many are encouraged to take cholesterol lowering medications, which are contraindicated in TBI, due to their amnestic effects. Further, cholesterol goes up with TBI because it is a necessary building block for the brain. However, if total cholesterol levels exceed 300, it should be treated.

Boosts in cognitive performance with sugar

It is a well-known fact that Dr. Robert Flint (St. Rose College, Albany, NY) and Dr. Ewan McNay (UAlbany, NY) have shown that having a little sugar boost will enhance cognitive performance when college students have a candy before a test. Indeed, two decades ago, Dr. Robin Kanarek (Tufts University, Medford, MA) conducted a study funded by M&M Mars, showing better cognitive performance 2-3 hours following a Snickers bar snack compared to an isocalaric amount of grapes. The later was the basis of television commercials.

We have seen this in some of our TBI patients. There is a candy jar in our reception room filled with Lifesaver peppermints in individual wrapped packages. Those bears who have a mint did not do better on a simple go-no-go attentional task (push a button when green circle appears but not when patterned circle appears) than bears that do not have a mint. However, squirrels that have a mint perform better that those that do not have a mint. This ruled out age-related effects of the capacity for cognitive

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enhancement. The former studies were in college populations and were neurotypical. Our observations were pre-Covid 19, before telemed was so commonly used, and cognitive rehabilitation was offered for 1-2 hrs in person.

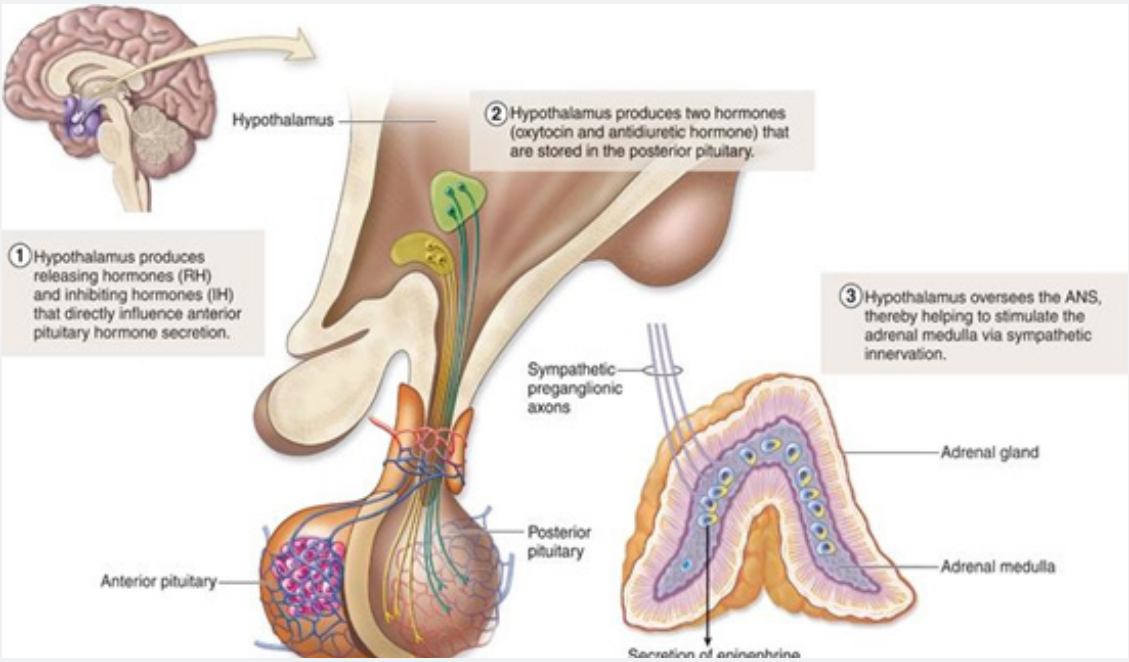

Figure 4: It is important to identify a brain injury quickly and to be alert to both the initial symptoms and those that appear later.

Hibernation as a model system for stress

To deal with stressors in their environment (defined as any stimuli that can alter the homeostatic state), animals in the Arctic have adapted neuroendocrine, behavioral and physiological patterns.

Other Model of Stress

Stress responses are generally modeled in the laboratory by limiting rats' and mice's life-sustaining resources (e.g. food) or setting up a harsh environment (e.g. social isolation, exposure to cold or footshock, or physical restraint). The neuroendocrine, behavioral, and autonomic responses to such stressors are then characterized [6-11]. A question is what is the pattern of such effects in an ecologically-relevant model, such as hibernation of mammals [12]?

What hibernation can tell us as an ethologically relevant model

Hibernation is an adaptation for mammals, which is characterized by severely reduced energy needs (i.e. lower metabolism and body temperature) in times when resources may be limited, such as in the Artic during winter [13,14]. As such, it may be similar to what we see in some of our patients with TBI, who have Type II diabetes and amotivation syndrome and cannot do much other than sleep and the minimum activites of daily living (ADLs) (Figure 5).

Hibernation is thought to have some conserved physiological mechanisms across different species [15,16]. For example, some similarities in increased tau phosphorylation has been demonstrated in the brains of hibernating species, such as arctic ground squirrels (Spermophilus parryii), Syrian hamsters (Mesocricetus auratus) and black bears (Ursus americanus), during torpor compared to arousal [17]. However, there are robust differences in hibernation patterns among these species. Unlike Syrian hamsters, black bears and arctic ground squirrels are obligate hibernators, with hibernation patterns under a strict circadian rhythm.

Different patterns of hibernation

There are different patterns of hibernation among black bears and artic ground squirrels. Black bears' hibernation is characterized by a metabolic rate that drops to about 25% of the euthermic condition and maximum reductions in body temperature to 30°C [18]. Among artic ground squirrels, metabolic rate can drop to 2% and body temperature can be at or below 0°C [19]. Unlike smaller mammals that hibernate, black bears enter a continuous state of torpor for 5-7 months that is not interrupted by periodic states of arousals [19]. A question then is the role of steroid, stress, and neural plasticity factors of this species, in comparison to smaller mammals (arctic ground squirrels).

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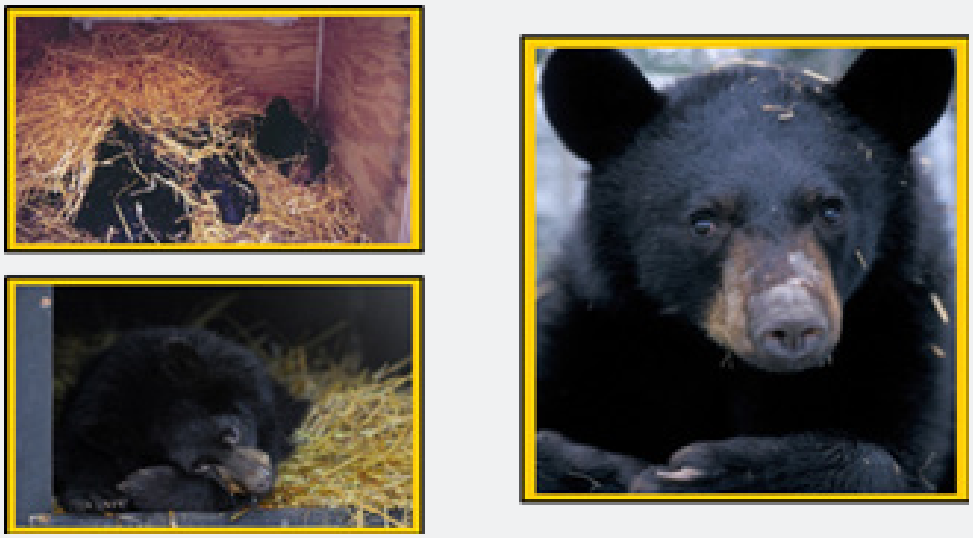

Figure 5: Upper left is in hibernation, below is one in emergence, on the right is during the summer when they are most active.

Results from the studies on black bears:

I. Glucose levels were lower in hibernation than emergence and summer

II. Cholesterol was higher during hibernation and emergence than in summer.

III. Cortisol levels were higher in females, than males, except during emergence.

Interpretation of our studies in black bears

These results support that there may be sex-specific endocrine effects associated with emergence from hibernation among Ursus americanus. There were differences in metabolic stress with emergence. We have observed similar differences among subsets of people with mTBI, who develop Type 2 diabetes as a result of weight gain and/or inactivity. Together, these finding suggest that development of metabolic syndrome and associated glucose dysregulation, cholesterol, hibernation or emergence, may be biomarkers of mTBI associated with dysthymia or amotivational syndrome. This may allow better monitoring and treatment of such individuals.

Metabolic factors in brain function

This monitoring and treatment is necessary because it has already been established that metabolic factors in brain function, links between type II diabetes and Alzheimer's, and the role of insulin in brain function, the hippocampus relies on insulin signaling, and measurement of the cognitive impact of recurrent hypoglycemia. For example, see some of the research coming out of the McNay lab described below [20].

Insulin affects spatial working memory

Researchers inhibited GluT4-mediated glucose uptake and found that glucose utilization in the dorsal hippocampus of male rats during hippocampally-mediated spatial working memory tasks. The data obtained suggested functional hippocampal GluT4 is not required for baseline hippocampal cognitive processing, but cognitive enhancement by supra-baseline insulin does, thus demonstrating a key role of GluT4 in transducing precognitive effects of elevated hippocampal insulin [20].

How does hypoglycemia impair cognition?

Cognition is impaired during hypoglycemia, but restoration of euglycemia is associated with improved hippocampally mediated memory. Increased glucocorticoid signaling during recurrent hypoglycemia produced changes in the dorsal hippocampus associated with hippocampus-dependent contextual learning. In addition to supporting cognition, these changes may reduce damage caused by repeated exposure to hypoglycemia [20].

Can you enhance cognitive performance in Alzheimer's?

Dyshomeostasis in zinc and copper have been observed in Alzheimer's disease to cause profound cognitive impairment. Insulin therapy enhances cognitive performance, but recent data suggest this may be due to the inclusion of zinc in insulin formation. Researchers looked to the spatial working memory of Sprague Dawley rats and found hippocampal zinc and copper, as well as plasma copper, increased with age, but plasma zinc decreased. Zinc supplementation improved cognitive performance, suggesting its use in cognitive impairment disorders [20].

Insulin resistance

Obesity and type II diabetes are both associated with decreased metabolism in the brain. Researchers found lower levels of glucose in the brains of individuals with obesity and type II diabetes. The authors of the study believe this may be why these individuals have

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an increased risk of developing eating disorders and Alzheimer's. Insulin resistance, which can be caused by obesity and physical inactivity, is linked to a rapid decline in cognitive abilities. Both diabetic and non-diabetic patients with insulin resistance showed an accelerated cognitive decline in memory and executive function. Researchers used a drug, 2-DG, to mimic the ketogenic diet in rats. Neuroscientists were able to prevent the development of epileptic activity in mice following a traumatic brain injury, suggesting a change in metabolism is key to its therapeutic effects. These findings suggest that there is a bidirectional relationship between glucose, diabetes and traumatic brain injury and the manifestations of their neuroendocrinopathies. This is similar to what has been reported in other neurodegenerative disorders such as epilepsy, Alzheimers, and dementia [20-22].

Our goal - Always more, always neurosteroids

We are interested in exploring the role of these changes in steroid levels in a natural model of stress and how this relates to brain plasticity. Neuropsychiatric disorders, such as depression, are considered to be highly stress-sensitive and impacted by circadian/seasonal effects. Moreover, neurosteroids play a role in depression. Progestogens can decrease depressive-like behavior among young and aged female rats or mice [32-37]. Men and women diagnosed with depression have lower levels of allopregnanolone in cerebrospinal fluid, and levels of allopregnanolone are increased with treatment with antidepressants, such as the selective serotonin reuptake inhibitors (reviewed in [38]). It has been proposed that depression may be related to the health of plasticity-prone areas of the brain, such as the hippocampus. Efficacy of antidepressant treatments has been associated with ability to enhance neural plasticity ([39]). The notion is that by investigating metabolic and trophic factors in hibernating animals (bears and squirrels), important information about the role of these factors for stress-related and TBI models will be elucidated and may provide further rationale for investigating neurosteroids.

Summary

We have demonstrated the following;

a) A common outcome of TBI is neuroendocrine dysfunction; type II diabetes is a common sequela of neuroendocrine dysfunction. Therefore, it carries as no surprise that many people with TBI develop type II diabetes; however, there is heterogeneity in the manifestation and course of diabetes among our TBI patients,

b) Some TBI patients with type II diabetes show a pattern that is akin to what we have observed previously in hibernating bears, others show a pattern that is more similar to that of squirrels,

c) How diabetes effects the brain to disrupt cognitive functioning may be by impairing or altering energy metabolism, energy utilization from the brain and/or hormonal metabolism and function.

It is also possible that diabetes affects the brain and disrupts cognitive functioning by impairing hormonal regulation and/or metabolism of peripheral or centrally acting steroids and/or their targets.

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How to cite this article: Cheryl A Frye, Luciana F Lembo, Jennifer T. Mild Traumatic Brain Injury, Hibernation, Type 2 Diabetes Common Etiopathophysiology Biomarkers and Function. Curre Res Diabetes & Obes J 2023; 16(3): 555937.DOI: 10.19080/CRDOJ.2023.16.555937

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