

UCLA

UCLA Previously Published Works

Title

Making sense of gut feelings in the traumatic brain injury pathogenesis.

Permalink

<https://escholarship.org/uc/item/6qd1k2vz>

Authors

Royes, Luiz Fernando Freire
Gomez-Pinilla, Fernando

Publication Date

2019-07-01

DOI

10.1016/j.neubiorev.2019.05.012

Peer reviewed



HHS Public Access

Author manuscript

Neurosci Biobehav Rev. Author manuscript; available in PMC 2020 July 01.

Published in final edited form as:

Neurosci Biobehav Rev. 2019 July ; 102: 345–361. doi:10.1016/j.neubiorev.2019.05.012.

Making Sense of Gut Feelings in the Traumatic Brain Injury Pathogenesis

Luiz Fernando Freire Royes^a and Fernando Gomez-Pinilla^{b,*}

^aExercise Biochemistry Laboratory, Center of Physical Education and Sports, Federal University of, Santa Maria – UFSM, Santa Maria-RS, Brazil

^bDepartments of Neurosurgery, and Integrative and Biology and Physiology, UCLA Brain Injury Research Center, University of California Los Angeles, USA

Abstract

Traumatic brain injury (TBI) is a devastating condition which often initiates a sequel of neurological disorders that can last throughout lifespan. From metabolic perspective, TBI also compromises systemic physiology including the function of body organs with subsequent malfunctions in metabolism. The emerging panorama is that the effects of TBI on the periphery strike back on the brain and exacerbate the overall TBI pathogenesis. An increasing number of clinical reports are alarming to show that metabolic dysfunction is associated with incidence of long-term neurological and psychiatric disorders. The autonomic nervous system, associated hypothalamic-pituitary axis, and the immune system are at the center of the interface between brain and body and are central to the regulation of overall homeostasis and disease. We review the strong association between mechanisms that regulate cell metabolism and inflammation which has important clinical implications for the communication between body and brain. We also discuss the integrative actions of lifestyle interventions such as diet and exercise on promoting brain and body health and cognition after TBI.

Keywords

Metabolic Syndrome; TBI; Inflammation; Autonomic Nervous System; brain plasticity

1. Introduction

Traumatic brain injury (TBI) is a devastating condition which often initiates a sequel of neurological and psychiatric disorders that can last for considerable time. TBI affects millions of Americans each year, resulting in approximately 2.5 million emergency department visits in 2013 (Taylor et al., 2017). Based on a series of large-scale population studies, a TBI incidence of 823.7 *per* 100,000 people is reported in USA. The situation in

*Corresponding author: Fernando Gomez-Pinilla, Ph.D., Department of Integrative Biology and Physiology, University of California Los Angeles, Los Angeles, California 90095, USA, fgomezpi@ucla.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

the European Union is also alarming with an overall incidence rate of 81.0-643.5 for admitted TBI per 100,000 people (Majdan et al., 2016). Most of the efforts to understand the TBI pathology have been centered on the brain, and we know that processes such as ischemia, hypoxemia, oxidative stress, and inflammation are intrinsic aspects of the TBI pathology (Ayton et al., 2014). However, we are just starting to understand that TBI also compromises systemic physiology and the function of body organs including liver, pancreas, and spleen with subsequent failures in metabolic and immune functions (Tables 1 and 2) (Plesnila, 2016). The emerging panorama is that the effects of TBI on the periphery initiate a pathological loop that can strike back on the brain and exacerbate the overall TBI pathogenesis. The consequences of dysfunctional cell metabolism on the outcome of brain trauma are particularly alarming for the Western society given the explosion of metabolic disorders. The magnitude of the problem is dreadful when considering that the incidence of TBI and associated cognitive disorders is on the rise, as is the prevalence of metabolic disease (Roozenbeek et al., 2013). A recent meta-analysis concluded that metabolic disorders such as diabetes and obesity complicate the healing prospect of TBI patients (Gharib et al., 2015). Therefore, it is crucial to understand how TBI impacts systemic physiology to have a thorough dimension of the TBI pathogenesis, which is necessary for the design of effective treatments to cope with the long-term burden of living with TBI.

The autonomic nervous system (ANS), associated hypothalamic-pituitary axis, and the immune system are at the center of the interface between brain and body and are central to the regulation of overall body homeostasis; therefore, they are primary intermediate for the action of TBI on systemic physiology (Figure 1). Indeed, clinical evidence indicates that injury-related alterations of the hypothalamic-pituitary system can have devastating consequences for body physiology. Here we discuss how the interaction between the ANS and the neuroendocrine system influences peripheral metabolism and the function of organ systems after TBI, and how the peripheral pathophysiology can exacerbate brain pathology. We also examine the strong association between mechanisms that regulate energy metabolism and inflammation given their implications for the communication between body and brain (Anthony and Pitossi, 2013). In addition, we discuss how the capacity of lifestyle to modulate brain-gut interaction can be pivotal for the prevention of secondary complications, and healing of patients affected by TBI.

2. Central Role of Autonomic Nervous System (ANS) and Hypothalamic-Pituitary Axis (HPA) in Maintaining Homeostasis

The HPA is often compromised in TBI patients and imbalances in the body's hormone homeostasis are one of the most important metabolic consequences of TBI (Bosarge et al., 2015; Tan et al., 2017). A large proportion of severe TBI patients (20-55%) present significant endocrine dysfunction, which reduces quality of life, rehabilitative outcome, and life expectancy (Roquilly et al., 2013). Post-traumatic hypopituitarism is a major sequel of TBI, in which hypophyseal vessels are particularly affected by direct injury or occlusion resulting in disruption of blood supply to the pituitary gland (Fernandez-Rodriguez et al., 2011). Endocrine dysfunction after TBI can result in neurobehavioral deficits that can last

for years. For example, chronic hypopituitarism associated with mild TBI has been associated with the pathogenesis of post-traumatic stress disorder (Undurti et al., 2018).

An increasing line of clinical and experimental evidence indicates that the disruptive effects of TBI on autonomic function are major contributors to the multiorgan failure that exacerbates the TBI pathophysiology. The ANS innervates smooth muscle and glands, and regulates all bodily functions such as circulation, digestion, body fluids, urination, and sexual arousal. The hypothalamus integrates diverse physiological processes involving the autonomic nervous system and the HPA, such that dysfunction of the hypothalamus is a major factor for the loss of body homeostasis (Shi et al., 2016).

2.1 TBI Promotes Dysfunction of the Hypothalamic-Pituitary-Adrenal Axis

Damage to the pituitary-adrenal axis can alter blood levels of catecholamines, cortisol, glucagon and growth hormone (GH), which in turn disrupt glycogenolysis and glucose production (Bulger et al., 2012) (Bosarge et al., 2015). The catecholamines epinephrine and norepinephrine, produced in the adrenal medulla, are involved in a fast stress response. Massive secretion of catecholamines into the circulation is a major player on the stress response to TBI (Desborough, 2000; Woolf, 1987), and a direct effect of sympathetic hyperactivation. As discussed below, a growing body of evidence supports a causative effect of sympathetic hyperactivity on the development of systemic organ dysfunction after TBI (Hinson et al., 2017; Lang et al., 2015). Epinephrine and Norepinephrine signal through α - and β -adrenergic receptors which are also expressed in leukocytes, which indicates that leukocytes have the potential to influence the production of inflammatory agents under stress conditions (see Figure 1) (Bierhaus et al., 2003; van der Poll and van Deventer, 1999). β -blocker therapy improves outcome in TBI patients (Alali et al., 2017), and attenuates the inflammatory response in animal studies (Villapol et al., 2015a). It is noteworthy that elevated stress has consequences for the regulation of other hormonal systems such as the hypothalamic-pituitary-gonadal (HPG). HPG dysfunction involves an adaptive process often involving an excess of stress hormones such as cortisol, and occurring at the early phase post-TBI (Ntali and Tsagarakis, 2019). Furthermore, prospective and longitudinal studies have shown high frequency (15% to 68%) of sex steroid hormone deficiency among TBI survivors. Izzo et al., (2016) demonstrated that the hypogonadism-induced sex steroid deficiency has implications beyond psychosexual and fertility for survivors of TBI (Izzo et al., 2016). Chronic hypogonadism also induces muscle weakness and osteoporosis exacerbating the immobility after neuronal injury (Agha and Thompson, 2004). Neuroendocrine dysfunction can last for many years after the original onset of brain injury (Alavi *et al.*, 2016).

The adrenal cortex produces the glucocorticoid cortisol which is involved in regulation of metabolism and immune function, and the mineralocorticoid aldosterone which is important for blood pressure control. Adrenal insufficiency can lead to life-threatening complications chiefly related to a drop in cortisol levels (Cohan et al., 2005; Molaie and Maguire, 2018). It is considered adrenal insufficiency when cortisol levels are lower than 15-18 μ g/dL in acutely ill patients or lower than 10 μ g/dL in chronic TBI patients (Kleindienst et al., 2009). Patients

with adrenal insufficiency lose their ability to maintain normal blood pressure and cardiovascular function (Quinkler et al., 2018).

The acute effects of TBI on the hypothalamic-pituitary-adrenal axis also can disrupt metabolic balance by the release of glucocorticoids, and sustained elevation in cortisol is associated with poor clinical outcomes (Santarsieri et al., 2014), particularly in TBI patients (Wagner et al., 2011). Hypercortisolemia increases the release of glucose from the liver, together with inhibiting insulin release from pancreatic beta cells (Lambillotte et al., 1997) and weakening the insulin-dependent transport of glucose into cells (Cree et al., 2010). It is noteworthy that the therapeutic benefit of targeting the action of glucocorticoids in TBI is controversial as while they can reduce inflammation (Campolo et al., 2013), they can also impair synaptic plasticity and promote neuronal degeneration (Rothman and Mattson, 2013).

2.2 The Impact of TBI on the Hypothalamic-Pituitary-growth hormone (GH) Axis

The hypothalamic-growth hormone axis has been one of the most studied in the context of TBI (Giuliano et al., 2017). GH produced by the anterior pituitary has a crucial action on the control of immune function, nitrogen and mineral retention, and lipid and protein synthesis, in addition to regulation of IGF-1 release by the liver (Simsek et al., 2015). Chronic growth hormone deficiency (GHD) is common among survivors of TBI which can last for several months or years following the original incident (Giuliano et al., 2017). GHD is associated with reductions in lean body mass (Mossberg et al., 2017), exercise capacity (Gonzalez et al., 2018) cardiac function (Cittadini et al., 2009), and bone mineral density (Bogdan et al., 2016). In addition, chronic GHD is characterized by metabolic abnormalities including visceral obesity and prevalence of non-alcoholic fatty liver disease (NAFLD)/non-alcoholic steatohepatitis (NASH) (see Figure 2) (Takahashi, 2017). GHD is associated with poor quality of life, being particularly detrimental for the well-being of TBI patients based on sleep disturbances, social isolation, and reduced physical capacity (Giuliano et al., 2017; Ranke and Wit, 2018). It is noteworthy that the GH and gonadotrophin systems are highly susceptible to TBI, as gonadotrope and somatotrope cells are proximal to the vascular territory of the long hypophyseal portal vessels. Indeed, HPG dysfunction can affect up to 80% of TBI patients (Alavi et al., 2016).

IGF-1 is largely produced in the liver (Tanriverdi and Kelestimur, 2015) and TBI patients often exhibit reduced circulating IGF-1 levels (Aimaretti et al., 2004b). A meta-analysis study showed a positive correlation between blood IGF-1 levels and cognitive function, in which adequate levels of IGF-1 seem necessary to maintain cognitive function (Fernandez and Torres-Aleman, 2012). Although the brain also synthesizes IGF-1, IGF-1 from the body can cross the blood-brain barrier and affect brain tissue. Contrary to peripheral IGF-1, brain IGF-1 levels tend to increase after TBI such that IGF-1 mRNA levels increase in the brain within days after brain injury in adult rats (Feeney et al., 2017) and developmental rats (Schober et al., 2012). IGF-1 has various isoforms that respond to TBI with a different time course and appear to have distinctive functions (Aperghis et al., 2004). For example, IGF-1A mRNA (encoding for the Eb peptide) peaks by 3 days post-TBI (Schober et al., 2012), whereas IGF-1B mRNA (encoding the Eb peptide) peaks by 2 days post-TBI.

TBI patients with hypopituitarism present alterations in glucose and lipid metabolism (Karamouzis et al., 2016) that are within the range of action of GH (Bartke, 2011b). GH/IGF-1 deficiency is associated with multiple physical and metabolic manifestations including diminished lean body mass, disrupted lipoprotein and carbohydrate metabolism (Mavalli et al., 2010). In addition, it has been shown that IGF-1 levels can vary as a function of hepatic insulin resistance and pancreatic beta cell dysfunction (Friedrich et al., 2012). Peripheral resistance to GH action is manifested by elevated plasma GH and low plasma IGF-1 (Agha et al., 2004). Considering that excessive amount of GH opposes to the effects of insulin in the liver and peripheral tissue, the TBI-induced down regulation of peripheral IGF-1 decreases the anabolic effects of GH, resulting in nitrogen wasting and hyperglycemia (see Figure 2) (Takahashi, 2017). The possibility that GH replacement can improve patient's outcome during the acute phase after TBI is still controversial (Garrahy et al., 2017). For example, GH may exacerbate pulmonary dysfunction, intracranial hypertension, and hyperglycemia which are common in TBI patients (Garrahy et al., 2017).

2.3 The Impact of TBI on the Hypothalamic-Neurohypophysial Axis: Dysfunctional Antidiuretic System Disrupts Water Homeostasis

Brain trauma often leads to dysfunction of the hypothalamic neurons secreting antidiuretic hormone (ADH) into the posterior pituitary gland. Proper action of the ADH system is vital for maintaining water homeostasis (Capatina et al., 2015). Inadequate ADH secretion after TBI leads to varying degrees of water dysregulation, and can evolve into several clinical manifestations (Behan et al., 2008). Continuous secretion of ADH causes reabsorption and retention of water by the kidneys, leading to concentrated urine and hyponatremia. Hyponatremia (low levels of sodium in blood) after TBI is the most common electrolyte problem resulting in edema and seizures (Capatina et al., 2015). In turn, post-traumatic diabetes insipidus (PTDI) is usually caused by damage to the posterior part of the pituitary gland from where ADH is secreted (Silva et al., 2015), such that patients with PTDI lose their ability to concentrate urine (polyuria). The lack of fluid consumption can result in severe dehydration and hypovolemic hypernatremia. Dehydration characterized by decreased skin turgor, dry mucous membranes, hypotension, tachypnea, tachycardia occurs most frequently in the first few days following the trauma episode posing elevated risk of mortality (Capatina et al., 2015). Hypernatraemic dehydration has been shown to increase morbidity and to reduce recovery after brain injury (Garrahy et al., 2017). PTDI occurs in up to 16% of all brain-injured patients usually 5 to 10 days after trauma (Hadjizacharia et al., 2008) and generally lasts for about a month; however, it can prolong up to 3 years post-TBI (Aimaretti et al., 2004a).

3. TBI Disrupts Function of Organ Systems (Figure 3)

3.1 TBI and Brain-Liver Axis.

The function of the liver in detoxification, synthesis of lipids and proteins is essential for the maintenance of homeostasis, such that liver dysfunction can have devastating consequences for overall performance of the whole organism. Experimental concussive brain injury has been shown to induce early inflammation by disrupting mitochondrial function and redox status in the liver (de Castro et al., 2017; Villapol et al., 2015c). In turn, signals derived from

the liver inflammatory reaction can exacerbate brain pathology (de Castro et al., 2017; Villapol et al., 2015c). Concussive brain injury in rodents causes major reductions in liver weight and protein production, with concomitant effects on body physiology (Moinard et al., 2008; Moinard et al., 2005). It seems plausibly that these deficits in protein homeostasis and degradation in liver are responsible for the muscle atrophy and locomotor deficits in TBI patients (Shahidi et al., 2018; Wright et al., 2017). The muscle wasting during the initial phase of injury has also been associated with muscle release of amino acids that are used for inflammatory protein synthesis in the liver (Moinard et al., 2005). In addition, brain-injured patients undergo rapid weight loss, with negative nitrogen balance and enhanced whole-body protein breakdown that seem secondary to inflammation and sympathetic activation (See Figure 1) (Mansoor et al., 1996).

The liver also reacts to TBI by displaying a systemic acute-phase response, involving leukocyte mobilization, and increase in cytokines which may be viewed as an attempt to regain homeostasis after trauma; however, this response may also be perceived as a way to enhance the multiorgan dysfunction syndrome. In particular, the post-injury hepatic inflammation results in higher levels of serum amyloid A1 (SAA1) and proinflammatory cytokines, infiltration of neutrophils and macrophages with detrimental effects on brain cells (Washington et al., 2016). Indeed, the production of cytokines and chemokines by the liver seems to act as an amplifier of the local brain injury inflammatory response (see Figure 1) (Anthony et al., 2012). The liver is highly susceptible to changes in energy metabolism and overproduction of reactive oxygen species based on its high demands for energy (Ray, 2012). Accordingly, the combination of high oxidative metabolism and ATP depletion in the liver has been shown to collapse the mitochondria machinery and to precipitate hepatic cells to a necrotic death (Sullivan et al., 2018). It has been recently reported that TBI collapses the ion gradient homeostasis followed by dysglycemia in the liver (de Castro et al., 2017). In addition, the involvement of liver in the events by which TBI disrupts glucose regulation emphasizes the risk posed by liver dysfunction for development of metabolic disorders such as type-2 diabetes (Tsatsoulis et al., 2013).

3.2 TBI and Brain-Spleen Axis: Inflammation and Sepsis

The spleen is deeply involved in synthesis and storage of immune cells and plays an important role in the systemic response to TBI, which is characterized by a reduction in splenic mass and an increase of immune cells in circulation (Das et al., 2011). The sepsis response to TBI is also reflected in translocation of bacteria to multiple organs with a subsequent increase in systemic inflammatory response and organ failure (Bansal et al., 2009b). As part of the inflammatory/sepsis response, elevated levels of tumor necrosis factor alpha (TNF- α), interleukin 1b (IL-1b), and IL-6 can affect tight junction permeability in the intestine (Al-Sadi et al., 2014). In turn, the secreted TNF- α binds TNF receptors (TNFRs) on intestinal epithelial cells and upregulates molecular pathways related to pro-inflammatory cytokines such as NF- κ B. Increased sympathetic activity post-TBI results in splanchnic hypoperfusion with subsequent alterations in the intestinal tight junction proteins ZO-1, occludin, and increased intestinal permeability (see Figure 1) (Zhang and Jiang, 2015b). Aberrant intestinal permeability can be evidenced as elevated ratio of orally ingested lactulose (a marker of paracellular permeability) to mannitol (a marker of transcellular

permeability) in urine (McHugh et al., 2007) of TBI patients. The disruption of the intestinal barrier blocks flow of ions, solutes, proteins, and bacterial products across the intestinal wall (Nighot et al., 2017), and may influence an array of metabolic functions (De-Souza and Greene, 2005).

Regarding the effect of TBI on periphery alterations, the spleen is important organ in the flux of monocytes and T cells into the peripheral circulation following injury (Rasouli et al., 2011). Microvesicles (MVs)/exosomes-based therapies offer promise in promoting neuroprotection by mitigating central neuroinflammation as well as modulating peripheral inflammation characterized by spleen-induced macrophages and monocytes release into circulation (Patel et al., 2018). This in turn lessens the infiltration of pro-inflammatory molecules into the brain and prevents the contribution of peripheral immune cells to the secondary injury.

3.3. TBI and Cardiovascular/heart interaction between brain and body

Loss of cardiovascular function is a common sequel in severe TBI patients occurring in 80-90% of patients admitted to intensive-care units, and is associated with high incidence in hospital mortality (Zygun et al., 2006); (Eric Nyam et al., 2019). The communication between the brain and heart is a highly integrative process involving neuroendocrine and immune factors under autonomic regulation. TBI patients exhibit paroxysmal sympathetic hyperactivity, characterized by periodic episodes of increased heart rate, blood pressure, and systemic inflammation (Schwulst et al., 2013). Pre-clinical evidence indicates the involvement of progressive cardiomyocyte oxidative stress and expression of pro-inflammatory chemokines in TBI-induced apoptosis (Chen et al., 2018). In turn, the spleen transfers resident leukocytes and secretes proinflammatory cytokines into the systemic circulation (Ajmo et al., 2008). Consequently, the immune cells and inflammatory factors may promote collagen deposition, proliferation of cardiac fibroblasts and cardiomyocyte death after TBI. In agreement with this idea, mice subjected to splenectomy after controlled cortical impact (CCI) showed significantly improved cardiac function, and decreased cardiac fibrosis, oxidative stress, cardiomyocyte apoptosis, and decreased infiltration of immune cells and inflammatory factors to the heart. (Zhao et al., 2019). Considering that systemic inflammatory response syndrome in TBI patients is associated with systolic cardiac dysfunction (Deepika et al., 2018) (Hasen et al., 2019), it is plausible that a paroxysmal sympathetic hyperactivity followed by immune response after brain injury may play a vital role in mediating brain-heart interaction. However, existing information with regards to the effects of TBI on myocardial function (Cuisinier et al., 2016);(Venkata and Kasal, 2018) is controversial given possible confounding factors such as multiple trauma, associated comorbidities and hemorrhagic shock that may induce a cardiac failure independently of the brain injury.

3.4. The Multiple Effects of TBI on the Gastro-Intestinal System

The bidirectional communication between the central and the enteric nervous systems is crucial for modulation of gastrointestinal functions such as motility, secretion, blood flow, intestinal permeability, mucosal immune activity, and visceral sensation including pain (Rhee et al., 2009). One commonly overlooked aspect of TBI is the disruption of the brain-

gut axis (Ma et al., 2017a; Sundman et al., 2017). In the first few weeks after TBI, most patients have reduced intestinal contractile activity and absorption, which is manifested by vomiting and abdominal distension (Sundman et al., 2017).

3.4.1. Alterations in Intestinal Permeability—Evidence from human and rodent studies indicate that acute TBI can disrupt the intestinal wall that functions to filter the flow of select ions, proteins, bacteria and their subproducts (Jin et al., 2010). When the gastrointestinal (GI) tract is compromised, substances can aberrantly penetrate the intestine leading to a chronic inflammatory sequel (Anthony et al., 2012). As discussed above, TNF- α is a central player in the regulation of intestinal permeability following TBI. TNF- α expression in mammals is induced by Toll-like receptor (TLR) signaling pathways in macrophages that are part of the defense mechanisms involved in the innate immune response (Verstrepen et al., 2008). Secreted TNF- α binds to TNF receptors (TNFRs) on intestinal epithelial cells and activates pro-inflammatory cytokines resulting in enhanced tight junction permeability in the intestine (Stoecklein et al., 2012). TBI elicits a positive feedback loop involving TNF- α and damage-associated molecular patterns (DAMPs, nucleic acids released from apoptotic and necrotic cells), which disrupt the intestinal barrier function (Anthony et al., 2012). It has been shown that treatment of mice with the hormone ghrelin blocks the TBI-related increase in TNF- α expression along with disruptions in intestinal permeability (Bansal et al., 2010). TBI also induces production of catecholamines which can lead to gastrointestinal dysfunction such that the sedative Propofol, that inhibits catecholamine release, counteracts the increase of TNF- α and intestinal permeability in rats (see Figure 3) (Jin et al., 2010).

TBI patients show an increase in the ratio of orally ingested lactulose (marker of paracellular permeability) to mannitol (marker of transcellular permeability) in urine (Hernandez et al., 2007). The use of the lactulose-mannitol test as well as a dye permeability test have revealed the effects of controlled cortical impact (CCI) in increasing paracellular permeability in rodents (Bansal et al., 2009b). TBI patients also show decreased levels of occludin and increased levels of myosin light chain kinase in the intestine (Bansal et al., 2009b; Zhang and Jiang, 2015b). Interestingly the pathogenesis of type 2 diabetes involves increased intestinal permeability (De-Souza and Greene, 2005), which encompasses with the higher clinical complications and mortality rates observed in brain trauma patients with diabetes or obesity (Ditillo et al., 2014). The altered gastrointestinal motility (Lu et al., 1997), splanchnic ischemia (Hernandez et al., 2007), gut hyperpermeability (Hang et al., 2003), followed by hyperglycemia, reinforce a role for glucose in a positive feedback loop after TBI.

3.4.2. Alterations in Intestinal Contractility—Preclinical and clinical studies indicate that inflammatory processes play a role on the alterations of contractility of the gut observed in the TBI pathogenesis (Sundman et al., 2017). TBI causes a delayed decrease in intestinal contractile activity which disturbs food intake and proper nutrition (Rauch et al., 2012). Experimental brain injury in rodents results in an exaggerated immune response to lipopolysaccharide (LPS) challenge, as manifested by elevated levels of inflammatory cytokines IL-1 β , TNF- α , and IL-6, and altered microglia phenotype (Ritzel et al., 2018). In

Author Manuscript

addition, the LPS challenge can cause depressive behavior in mice previously exposed to brain injuries (Fenn et al., 2014; Shitaka et al., 2011). The fact that these depressive symptoms emerge after thirty days post-injury (Fenn et al., 2014) suggests an involvement of chronic inflammation (Mayer et al., 2006). In agreement with this view, pre-clinical studies have shown that dysfunctional contractility of the smooth muscle within the GI tract correlates with both increased systemic inflammation and brain atrophy (Sun et al., 2015). In particular, it has been reported that a dysfunction in colon mucosal barrier develops over time after TBI, as evidenced by reduced expression of claudin-1 and increased activation of sub-epithelial enteric glial cells (EGCs) which regulate mucosal barrier homeostasis (Ma et al., 2017a). Interestingly, these alterations have been associated with inflammatory and degenerative processes in the injured cerebral cortex (see Figure 3) (Ma et al., 2017a).

Author Manuscript

3.4.3. Microbiota: Minding the Gap between Brain and Gut—As discussed above, gastrointestinal disorders are a notable complication in the TBI pathogenesis (Bansal et al., 2009a; Hang et al., 2003; Katzenberger et al., 2015). An increasing line of evidence indicates that gut microbiota plays an important role in brain-gut interaction and behavioral outcome by producing metabolites, hormones and immune factors (Schmidt, 2015). On the other hand, products of carbohydrate fermentation by gut bacteria such as the short chain fatty acid (SCFA) butyrate, have been shown to regulate brain plasticity and function, including hippocampal neurogenesis, synaptic plasticity, and neuronal repair. The gut microbes also synthesize a vast array of neuroactive molecules including neurotransmitters such as GABA, which have effects on the CNS (Patterson et al., 2014). The intestinal microbiota also affects the intestinal epithelium, local mucosal immune system, enteric nervous system and spinal and vagal nerves. Microbiome sub-products modulate CNS function using hormones such as cortisol and catecholamines, immune regulators such as cytokines, and neurotransmitters such as acetylcholine and serotonin (see Figure 3) (Schmidt, 2015). Gut microbiota also controls the amount of energy that is taken from foods playing an important role in weight regulation, particularly, increasing energy harvest from food in obesity (Ley, 2010). Since TBI patients develop signs of hyperglycemia (Shi et al., 2016) and gut microbiota are associated with metabolic alterations such as fat distribution and adipose tissue inflammation (Boulange et al., 2016), it is plausible that changes in the microbiota composition can contribute to glucose dysregulation after TBI. However, further experimental and longitudinal studies are needed to better understand causal or temporal associations between these events. Further understanding of the role of the gut microbiome and gut-brain axis during TBI may result in the novel application of probiotics, dietary therapeutics and pharmacological compounds in the prevention or reversal of secondary complications of TBI.

Author Manuscript

3.4.4. Role of microvesicles in the interplay between brain and body—Another way for cells and systems to communicate across body and brain is via microvesicles (MVs)/exosomes. Microvesicles (MVs)/exosomes are a heterogeneous group of extracellular vesicles (EVs) less than 1 μm in diameter released into the extracellular environment from virtually all cell types (Greening and Simpson, 2018). A number of interesting studies, using animal's models of TBI, and/or clinical samples suggest that (MVs)/exosomes serve as carriers of many bioactive molecules including cytosolic proteins, nucleic acids (mRNA,

miRNA), permitting, among others, the acquisition of new functional properties by recipient cells in the systemic TBI-induced pathophysiology (Shlosberg et al., 2010); (Nekludov et al., 2014); (Andrews et al., 2016); (Mondello et al., 2018). (MVs)/exosomes modulate inflammation, neuronal function and plasticity, BBB permeability and cellular responses to brain injury (Walker et al., 2012); (Zhang et al., 2015); (Kim et al., 2016). Furthermore, the higher stability followed by less invasiveness, easy delivery, low or no immunogenicity and tumorigenicity reinforces the potential of microvesicles-derived exosomes (i.e. cell-free exosome-based therapy) for the treatment of TBI pathophysiology (Mondello et al., 2018).

4. The Coalition between Metabolic dysfunction and Inflammation Fuels the TBI Pathogenesis

4.1. Disruption of Glucose Metabolism

Clinical evidence indicates that TBI patients often develop signs of hyperglycemia even on the absence of preexisting diabetes (Shi et al., 2016), and excessive glucose production has been correlated with the severity of the injury and clinical outcome (Asehnoune et al., 2017). TBI patients with hypopituitarism frequently present metabolic alterations in glucose levels, insulin resistance and hypertriglyceridemia (Tanriverdi et al., 2015). Animal studies have shown that hyperglycemia leads to a reduction of immune and bioenergetic functions resulting in inflammation and elevated susceptibility to infections (de Castro et al., 2017). In addition, systemic hyperglycemia contributes to anaerobic metabolism in the brain following acute injury, resulting in lactic acidosis and tissue damage (Kim et al., 2012). Animals (de Castro et al., 2017) and clinical (Asehnoune et al., 2017) studies have shown an association between hyperglycemia and increased morbidity and mortality after TBI. Hyperglycemia and insulin resistance are very common in critically ill patients with TBI, even affecting patients with no history of diabetes (Shi et al., 2016). Along this view, normalization of blood glucose levels in patients with severe TBI has been shown to decrease mortality and morbidity (including infection rate), to reduce stays in Intensive Care Unit, and to improve neurological outcome (Van den Berghe et al., 2006). In turn, hypoglycemia (<40 mg/dl or 2.2 mmol/l blood glucose level) induced by i.v. application of insulin increases stress hormones such as ACTH, cortisol, and GH (Hoffman et al., 1994). The insulin tolerance test (ITT) is often useful to diagnose dysregulation of the hypothalamic–pituitary–adrenal axis. As discussed above, GH plays a major role in the regulation of glucose metabolism (see Figure 2) (Bartke, 2011a).

4.2. Insulin Action across Body and Brain

Insulin produced by the pancreas gland is a major modulator of the effects of TBI on systemic and central physiology. Besides its hormonal action as main regulator of glucose metabolism and other aspects of body physiology (Bedinger and Adams, 2015; Gralle, 2017), insulin is surfacing as an important modulator of brain function and plasticity (Lima et al., 2002). The effect of insulin on neural cells is mediated by a family of receptors located in brain regions particularly associated with synaptic plasticity and cognitive processing such as the hippocampus (Agrawal et al., 2016c). Reduced insulin receptor signaling in the hippocampus impairs long-term potentiation and recognition memory

(Nistico et al., 2012). Insulin receptor signaling promotes neurogenesis, increases neuronal survival and reduces neuroinflammation (Adzovic et al., 2015; Bateman and McNeill, 2006). Experimental evidence showing that insulin influences mitochondrial function (Szendroedi et al., 2012) provides a general explanation for how insulin can influence a range of cellular processes highly dependent on metabolic energy. Indeed, reduced sensitivity to the action of insulin is considered a predictor of poor clinical outcome in TBI patients (Mowery et al., 2009b). Manipulation of the insulin signaling is getting recognition as a potential therapeutic target to reduce the burden of brain injury. For example, the anti-inflammatory effects of insulin (van der Heide et al., 2006) have led to the implementation of insulin sensitizing treatment to attenuate cell damage and to promote recovery following CNS insults (Eakin et al., 2013).

Disease states characterized by insulin resistance, such as obesity and type 2 diabetes, are risk factors for TBI complications (Agrawal et al., 2016a; Ley et al., 2011). In addition, insulin resistance is associated with increased mortality after TBI (Majdan et al., 2015). TBI patients suffering type 2 diabetes (T2D) or insulin-dependent T2D have a higher mortality rate compared to severe TBI patients without T2D (Majdan et al., 2015). These results indicate that insulin deficiency may contribute to the increased mortality observed in TBI patients, and that T2D may be an independent predictor of poor outcome and mortality after TBI (Ditillo et al., 2014). In addition, as discussed below, experimental metabolic syndrome (MetS) in rodents elicited by overconsumption of dietary fructose reduces signaling through the insulin receptor in the hippocampus and potentiates the effects of TBI on behavioral dysfunction (Agrawal et al., 2016c). These results additionally emphasize the metabolic impact of diet on TBI outcome (see below).

4.3. Diabetes and Obesity Exacerbate TBI Pathology

Increasing evidence indicates that metabolic disorders such as obesity and T2D that disrupt the regulatory action of insulin on glucose metabolism in the body can also influence the brain. For example, the occurrence of MetS, characterized by elevated levels of serum triglyceride and low glucose tolerance, reduces hippocampal insulin receptor signaling, which is commensurate to poor learning and memory performance (Agrawal and Gomez-Pinilla, 2012). This also implies that metabolic disorders such as obesity and diabetes have the potential to exacerbate the TBI pathology as the inability of brain to metabolize glucose is an intrinsic aspect of the TBI pathology (Ditillo et al., 2014).

It has been shown that obese Zucker rats have an exaggerated hyperglycemic response and insulin dysregulation after trauma as compared to lean rats (Xiang et al., 2014). These results in animals are consistent with clinical evidence that obese critically ill patients have an increased need for insulin (Pieracci et al., 2008). In addition, obese patients that suffer brain trauma have more clinical complications and higher mortality rates than lean patients with similar injuries (Stein et al., 2012). Clinical reports suggest that metabolic dysfunction is a predictor of poor outcome in TBI patients and can increase incidence of long-term neurological and psychiatric disorders (Ley et al., 2011; Mowery et al., 2009a; Stein et al., 2012). The occurrence of obesity has been associated with several neurological abnormalities including cell degeneration, reduced neurogenesis, and increased cognitive/

mood disorders (Yehuda et al., 2011). Experimental evidence indicates that obese mice exposed to TBI have higher levels of anxiety as determined in the open field test (Sherman et al., 2016). A separate line of studies denotes a negative correlation between obesity and neurocognitive function in collegiate and professional athletes (Mathews and Wagner, 2008). For example, a study of 38 overweight and 38 normal weight retired National Football League players found that the overweight group had greater cognitive impairment and lower blood flow in the prefrontal cortex as well as hypometabolism in the temporal pole (Willeumier et al., 2012).

4.4. Dysfunctional Metabolism Fosters a Pro-Inflammatory Milieu Across Body and Brain

There is a close association between metabolic dysfunction and inflammation in the TBI pathogenesis. For example, dysglycemia is followed by an increase in circulating cytokines, opening of the blood brain barrier, neutrophils infiltration and neuronal inflammation (de Castro et al., 2017). In addition, TNF- α seems to disturb functionality of glucose metabolism by affecting levels of adipocyte-specific genes and contributing to insulin resistance and hyperglycemia (see Figure 2) (Ruan et al., 2002). The inflammatory reaction after TBI also increases the level of corticotrophin-releasing hormone (CRH) which stimulates the release of adrenocorticotrophic hormone (ACTH) from the anterior pituitary, with subsequent elevation of blood glucose. Nitric oxide (NO), which is part of the inflammatory response, participates in signal transduction pathways that lead to the release of corticosterone from the adrenal gland, and subsequent hyperglycemia. While hyperglycemia is generally related to low Glasgow Coma Scale (GCS) score (Kobata et al., 2017), the association between hyperglycemia and poor outcome in TBI is transient (Zhou et al., 2017). Management of hyperglycemia with insulin protocol seems critical for improving TBI outcome, but further studies are needed to better determine the level of serum glucose that is harmful for patients with TBI. As discussed below, consumption of caloric diets, which produce inflammation and disrupt glucose metabolism, have been shown to reduce brain plasticity and cognitive ability (see Figure 4). Acute hyperglycemia is associated with a pro-inflammatory and pro-oxidant cell environment (Dandona et al., 2004b; Kadhim et al., 2008; Zhang et al., 2005). As discussed above, hypothalamus-pituitary axis dysfunction following experimental TBI results in long-term depletion in serum GH and persistent inflammation (Kasturi and Stein, 2009). Early hepatic inflammation in rodent TBI is characterized by an increase of TLR 4, JNK, TNF α , JKK (Villapol et al., 2015c), leading to reduced hepatic insulin sensitivity and loss of GH sensitivity (see Figure 2) (Berryman et al., 2013).

Widespread inflammation is becoming recognized as a common component of the neuropathophysiology of obesity (Dandona et al., 2004a; Kadhim et al., 2008). In humans, levels of fibrinogen (a marker of inflammation) in the amygdala have been shown to correlate with overweight and obesity (Cazettes et al., 2011). Adipose tissue collected from obese animals and humans show larger amount of pro-inflammatory factors (Shi et al., 2016), and this suggests that obese individuals are more prone to the inflammatory consequences of brain trauma. Indeed, obese individuals have higher levels of cytokines relative to lean subjects after trauma, which emphasizes the risk posed by metabolic dysfunction on TBI outcome (Andruszkow et al., 2013; Li and Sirko, 2018). In addition,

animal studies have shown that the obesity-associated release of pro-inflammatory cytokines is accompanied by activation of the immune system and a local inflammatory response (Kadhim et al., 2008).

5. Diet and Exercise: Green Technology for Managing TBI

Pathophysiology

5.1. The Impact of the Epidemic of Metabolic Syndrome (MetS) on the Brain

As discussed above, a particular aspect of the TBI pathophysiology is the inability of the brain to metabolize energy (Lakshmanan et al., 2010; Vespa et al., 2005). TBI patients experience sudden abnormalities in the control of brain glucose metabolism (Kato et al., 2007), which can increase the risk of secondary brain damage (Griesdale et al., 2009; Liu-DeRyke et al., 2009). Clinical reports indicate that metabolic dysfunction is a predictor of poor outcome in TBI patients (Klose and Feldt-Rasmussen, 2018). Overload of an already disrupted brain metabolic regulation may exacerbate pathophysiology (Di Pietro et al., 2010), and may increase incidence of long-term neurological and psychiatric disorders. As discussed below, the fact that the incidence of TBI (Roozenbeek et al., 2013) and metabolic disease (Padwal, 2014) are on the rise, makes the magnitude of the problem even worse.

MetS, characterized by abdominal obesity, hypertriglyceridemia, increased blood pressure, and elevated glucose level (Grundy, 2006) is a major and escalating public-health burden worldwide (Alberti et al., 2009). Insulin resistance is the hallmark of MetS, characterized by a decrease in sensitivity to the action of insulin and associated with oxidative stress and inflammation, is largely enhanced by sugary diets and physical inactivity (Booth et al., 2002). Insulin penetrates the brain blood barrier and has an impact on various neurological events such as feeding behavior, and learning and memory. In addition, animal studies indicate that the insulin resistance observed in the periphery also occurs in brain tissue (see Figure 4) (Agrawal and Gomez-Pinilla, 2012).

5.2. Fructose Consumption Exacerbates the Pathophysiology of TBI

Fructose consumption is considered an important contributor to the epidemic of MetS (Malik and Hu, 2012). Studies in rodents have shown that a high fructose diet results in hepatic oxidative damage and altered lipid (Kelley et al., 2004) and glucose (Agrawal et al., 2016b; Agrawal and Gomez-Pinilla, 2012) metabolism. In addition, high fructose consumption is portraying as a suitable animal model to assess the influence of metabolic disorders on the brain (Agrawal and Gomez-Pinilla, 2012). Fructose consumption increases the levels of the glucose transporter 5 (GLUT5) in glial cells in the hippocampus and cortex in rats (Gomez-Pinilla and Tyagi, 2013). The fact that GLUT5 is considered a specific transporter of fructose into cells, the results of the latter indicate that fructose facilitates its own transport into the brain. The fructose-induced MetS disrupts signaling through insulin receptors which are localized to brain areas involved in cognition processing such hippocampus (Cisternas et al., 2015). Research showing that a high fructose diet disrupts insulin signaling in the brain (Agrawal and Gomez-Pinilla, 2012), suggests that insulin is part of the pathway by which fructose impacts neuronal function. Indeed, insulin activates regulators of mitochondrial biogenesis, such as the peroxisome proliferator-activated

receptor gamma coactivator-1alpha (PGC-1 α). PGC-1 α is a member of a family of transcription co-activators (Ventura-Clapier et al., 2008), which in conjunction with the mitochondrial transcription factor A (TFAM) (Campbell et al., 2012; Ekstrand et al., 2004), and sirtuin 1 (SIRT1) regulate cellular energy metabolism. PGC-1 α can interact with brain-derived neurotrophic factor (BDNF) (Cheng et al., 2012), and reactive oxygen species in the regulation of brain plasticity (Chen et al., 2011).

It has been reported (Agrawal et al., 2016b; Agrawal et al., 2016c) that overconsumption of dietary fructose for duration sufficient to disrupt peripheral metabolism exacerbates cognitive dysfunction following TBI. These effects are concomitant to reductions in levels of proteins related to synaptic plasticity and cellular energy metabolism (Agrawal et al., 2016c). For example, fructose consumption aggravates the effects of TBI on molecular systems engaged in cell energy homeostasis (SIRT1, PGC-1 α) and synaptic plasticity (BDNF, TrkB, CREB, synaptophysin) in the hippocampus (Agrawal et al., 2016c). Fructose also aggravates the effects of TBI on spatial memory in association with a decrease in hippocampal insulin receptor signaling. Additionally, fructose consumption and TBI have been shown to promote plasma membrane lipid peroxidation, based on elevated protein and phenotypic expression of 4HNE. The results of this study indicate that high fructose consumption exacerbates the pathology of brain trauma by further disrupting energy metabolism and brain plasticity (see Figure 5) (Agrawal et al., 2016c).

5.3. Dietary Balance Essential to Preserve Metabolic Homeostasis

Consumption of healthy dietary components is a productive strategy to counteract metabolic dysfunction and to protect mental health. In particular, docosahexaenoic acid (DHA; C22:6n-3) is one of the major n-3 polyunsaturated fatty acids which is an integral component of plasma membranes in the brain. DHA is important for brain development and plasticity, and provides support to learning and memory in animal models of Alzheimer's disease (Hashimoto et al., 2002; Lim et al., 2005) and brain injury (Yin et al., 2018). The action of DHA has been associated to counteracting several peripheral metabolic disturbances such as diabetes (Coste et al., 2003). It has been found that fructose consumption, particularly under conditions of DHA deficiency, increases hippocampal insulin resistance, as evidenced by a decrease in the insulin receptor signaling (Agrawal and Gomez-Pinilla, 2012). Phosphorylation of insulin receptor and its signaling molecules Akt are diminished under conditions of n-3 deficiency, and these effects are aggravated by fructose consumption. These results indicate the importance of dietary DHA for maintaining proper insulin signaling in brain, and the necessity of adequate levels of n-3 in diet to cope with challenges imposed by fructose (Agrawal and Gomez-Pinilla, 2012). DHA supplementation in rodents exposed to TBI has been shown to normalize levels of BDNF and related synaptic and cell-metabolic modulators, in conjunction with improving learning ability. DHA may help to counteract the effects of TBI by providing resistance to oxidative stress and preserving plasma membrane homeostasis. In support of the neuroprotective action of diet, the supplementation of the Indian curry spice curcumin into the diet for 3 weeks before or after (Sharma et al., 2009) experimental concussive injury can lessen the consequences of the injury on synaptic plasticity markers and cognitive tasks. In addition to

having profound antioxidant and anti-inflammatory effects, curcumin prevents a reduction of DHA content in the brain following brain trauma (Wu et al., 2014).

5.4. Exercise Fosters Metabolic Homeostasis in the TBI Pathology

Together with overconsumption of high caloric diets, the lack of physical activity is considered an important contributor to the MetS epidemic. The lack of physical activity contributes to 6% of the burden of coronary heart disease, 7% of T2DM, 10% of breast cancer and 10% of colon cancer around the world (Geiss et al., 2017). According to the Centre for Disease Control and Prevention (CDC) and the American College of Sports Medicine, sedentary subjects are defined as those who do not engage in at least 150 minutes of physical activities per week (Pratt et al., 2016). Sedentary lifestyle has been shown to increase the risk of neurological disorders such as stroke, dementia and depression (Booth et al., 2012). The physical inactivity-induced blood pressure, HDL cholesterol, plasma fibrinogen and platelet aggregation, which are biomarkers of T2DM and obesity, are also important risk factors for stroke (Hu et al., 2001). On the other hand, regular exercise exerts a broad range of beneficial effects, including improvements in cardio-vascular function and provides resistance to several neurological diseases (Radak et al., 2008). A large amount of evidence in humans and animals indicates that physical activity enhances cognitive abilities (Gomez-Pinilla and Hillman, 2013). Systematic reviews and meta-analyses studies have provided compelling evidence that physical activity promotes low-to-moderate risk reductions of dementia (Hamer and Chida, 2009) (Stigger et al., 2018). The fact that obesity is associated with low levels of dopamine may provide cues to understand why obese individuals have a tendency to practice physical activity less frequently (Rueggsegger and Booth, 2017). Physical inactivity also tends to correlate with hippocampal atrophy in advanced age and may lead to cognitive and memory dysfunction (Vivar and van Praag, 2017). The fact that hippocampal atrophy is one of the biomarkers for Alzheimer disease (AD) is congruent with the view that physical inactivity is considered a crucial risk factor for AD (see Figure 4) (Gomez-Pinilla and Hillman, 2013).

Physical exercise facilitates endogenous repair mechanisms in the brain and enhances functional recovery after experimental TBI (Archer et al., 2012; Griesbach, 2011). Neuronal injury results in overproduction of reactive oxygen species that compromise cell function (McKee and Lukens, 2016). Aerobic physical exercise has neuroprotective properties through a large variety of mechanisms particularly by counteracting elevated oxidative stress (da Silva Fiorin et al., 2016; Lima et al., 2009) and by increasing production of BDNF (Gomez-Pinilla and Hillman, 2013). Physical activity enhances neuronal functions and delays or prevents cell damage and neurobehavioral disability after TBI (da Silva Fiorin et al., 2016; Silva et al., 2013). The effects of physical exercise on increasing antioxidant defenses (Marques-Aleixo et al., 2012), improving mitochondrial biogenesis (Navarro and Boveris, 2009), and upregulating the metabotrophin BDNF (Gomez-Pinilla and Hillman, 2013) are a vivid demonstration of the capacity of exercise to promote metabolic homeostasis. Interestingly, experimental studies in rodents have shown that exercise works in concert with a DHA-rich diet to influence molecular systems underlying cognitive function (Chytrova et al., 2010). A possible mechanism for this complementary action of exercise is exerted by acting on molecular systems associated with control of cell

metabolism, plasma membrane integrity, and synaptic plasticity, which are necessary for supporting synaptic plasticity and cognition (see Figure 4) (Wu et al., 2014)

5.5. Cell Metabolism and Neuronal Plasticity Provides Grounds for the Impact of Lifestyle on TBI Outcome

Bioenergetics abnormalities are getting recognition as a common feature of neurological disorders (Mattson et al., 2008), and a failure in mitochondrial function is as a major sequel of TBI (Singh et al., 2006). An increasing body of evidence indicates that diet-induced metabolic disease poses a threat for brain function and can increase the risk for neurological and psychiatric disorders (Farooqui et al., 2012). This comes to no surprise if we consider that energy conservation and bioenergetics are driving forces for biological adaptation and brain evolution (Gomez-Pinilla and Yang, 2018). A growing body of evidence indicates that mechanisms that regulate cell metabolism closely interact with those that regulate brain plasticity (Gomez-Pinilla and Yang, 2018). As discussed above, this association is illustrated by results showing that fructose and TBI affect the actions of key elements in the BDNF signaling cascade (Agrawal et al., 2016c). Disruption in BDNF function has been implicated in the pathophysiology of several psychiatric disorders such as depression (Levada and Troyan, 2018) and schizophrenia (Angelucci et al., 2005). Both signaling through the BDNF receptor trkB and the insulin receptor (Lee et al., 2005) have been reported to involve PI3K/Akt/mTOR pathways, which are essential for synaptic plasticity and cognition. CREB is an important step in BDNF signaling and a point of convergence of many signaling pathways regulating synaptic activity and learning and memory (Alonso et al., 2002). Through TrkB receptor, BDNF leads to the activation of CREB, which is a potent activator of PGC-1 α (Herzig et al., 2001). PGC-1 α is a transcription regulator deeply involved in energy metabolism and mitochondrial function (Romero et al., 2014). The interaction between CREB and PGC-1 α is reflected by results showing that phosphorylation of CREB changes in proportion to levels of PGC-1 α in response to TBI. Taking all together, the mechanisms underlying the actions of diet and exercise on the brain use common molecular elements of cell bioenergetics and plasticity (Gomez-Pinilla and Yang, 2018). Interestingly, the same molecular elements and systems involved with the positive actions of exercise and diet, are also part of the molecular machinery underlying cognitive functional recovery following TBI (see Figure 4) (Meng et al., 2017).

5.6. Epigenetic Alterations Prolong the Effects of TBI and Lifestyle on the Brain

An increasing line of evidence indicates that the action of lifestyle factors such as diet and exercise can be saved as epigenetic modifications with long-term consequences for neural resilience (Tyagi et al., 2015). In particular, early exposure to dietary omega-3 fatty acids appeared to be saved as changes in DNA methylation of the *Bdnf* gene. Methylation is one of the most stable forms of epigenetic variability. Results suggest that such epigenetic alterations may serve to create a reservoir of neuroplasticity that can protect the brain when needed, i.e., against the deleterious effects of switching to a western diet. It appears that exposure to a diet rich in omega-3 fatty acids during brain formation can help to build an “epigenetic memory” that confers resilience to metabolic perturbations occurring in adulthood. Systems biology approaches have been used in rodents to gain a thorough view of the impact of TBI on fundamental aspects of gene regulation, which have the potential to

alter the course of the TBI pathogenesis (Meng et al., 2017). Studies have shown that TBI perturbs epigenomic programming, transcriptional activities (expression level and alternative splicing) events in the hippocampus which are involved in neuronal signaling, metabolism, and inflammation. Many TBI signature genes and network regulators identified in the rodent model have been causally associated with brain disorders with link to TBI such as Alzheimer's disease, as shown by human genome-wide association studies. Fructose consumption has also been shown to impact several of the genes affected by TBI (Meng et al., 2017).

6. Adverse Consequences of Autonomic dysfunction in the TBI pathology (Table 2)

As discussed above, TBI compromises the function of body organs including liver, pancreas, and spleen with subsequent failures in metabolic and immune functions (Plesnila, 2016). The emerging panorama is that TBI initiates a pathological loop on systemic physiology that can exacerbate the TBI pathogenesis. Most TBI patients experience enhanced activity of the Sympathetic Nervous System (Meyfroidt et al., 2017) with subsequent episodes of increased heart rate and blood pressure, sweating, hyperthermia, and motor posturing. Sympathetic activation immediately post-TBI is essential for survival as early hypotension (systolic blood pressure <90 mm Hg) is associated with high mortality rate (Krishnamoorthy et al., 2017). Similarly, late hypotension is associated with 11-fold higher risk of death after severe TBI (Geeraerts et al., 2008). In addition, there is strong association between high catecholamine levels and severity of the brain injury, duration of mechanical ventilation, myocardial damage, endocrine abnormalities, length of hospital stay, and functional outcome (Rizoli et al., 2017; Woolf, 1987).

As a compensatory mechanism to restore vital homeostasis in the face of TBI, there is an early activation of the hypothalamic-pituitary axis which elevates blood levels of cortisol, glucagon and growth hormone, resulting on glycogenolysis, hypermetabolism, and excessive glucose production (Bosarge et al., 2015; Bulger et al., 2012). Sympathetic activation also results in a massive secretion of catecholamines into the periphery as part of a generalized stress response to trauma (Di Battista et al., 2016). By functioning on islet beta cells' alpha 2 receptor, the sympathetic activation can also stimulate glucagon production and decrease insulin secretion (López-Gamero et al., 2018). While sympathetic activation is an essential compensatory response to brain injury, excessive or prolonged hyperadrenergic state may have a negative impact on outcome. Excessive release of catecholamines can inhibit glucose transport *via* inhibition of insulin binding, leading to transient insulin resistance and glucose homeostasis impairment (Reilly and Saltiel, 2017). The secretion of glucocorticoids and catecholamines induced by excessive sympathetic activity is also linked to exacerbation of secondary brain injury and contributes to unfavorable patient outcome and mortality (Di Battista et al., 2016). Excessive catecholamines increases cytokine production and reduces GH and IGF-I production after TBI, and they are part of the metabolic changes observed in the acute phase of TBI characterized by hypermetabolism, hypercatabolism, refractory nitrogen wasting, and immunosuppression (Hatton et al., 2006). Reduced levels of GH and

IGF-1 in TBI patients is associated with poor recovery (Schneider et al., 2017), and increase in neuropsychiatric manifestations (Agha et al., 2004; Kelly et al., 2006).

7. Concluding Remarks

Clinical and experimental evidence reveals the pervasive effects of TBI on systemic physiology that can strike back on the brain with subsequent effects on brain plasticity and behavior. TBI disrupts the function of the hypothalamic-pituitary axis and autonomic nervous system with profound alterations in body physiology and brain function. TBI elicits a multiorgan inflammatory response including metabolic alterations, bacteria dysbiosis and translocation, immune dysfunction, anomalous protein synthesis and hormonal status -- which in turn, exacerbate the TBI pathogenesis in the brain. The failure of the brain to perform metabolic homeostasis after TBI increases the consequences of secondary brain damage. The magnitude of the burden posed by disrupted metabolism is exacerbated by lifestyle-induced metabolic disorders such as diabetes and obesity. An increasing body of evidence indicates that diet-induced metabolic dysfunction and the lack of exercise pose a threat for brain function and can exacerbate TBI pathogenesis. Clinical reports indicate that metabolic dysfunction can increase incidence of long-term neurological and psychiatric disorders, and that metabolic dysfunction can be used as predictor of poor outcome in TBI patients. Although alterations in the functions of the autonomic nervous system and hypothalamic-pituitary axis can have devastating consequences for proper maintenance of body homeostasis, their functions are often unreported in TBI patients, and poorly studied in animal models of TBI. Therefore, it is critical to better understand the function of the autonomic nervous system on the pathophysiology of TBI in order to help prevention and treatment of TBI.

Acknowledgements

This work was supported by The National Institute of Health award R01 NS50465 to FGP, and Conselho Nacional de Desenvolvimento Científico e Tecnológico award CNPq: #307382/2017-6 to LFR. Authors would like to thank Rafael Parciannelo Cipolat for reviewing the color artwork (Figures).

8. References

- Adzovic L, Lynn AE, D'Angelo HM, Crockett AM, Kaercher RM, Royer SE, Hopp SC, Wenk GL, 2015 Insulin improves memory and reduces chronic neuroinflammation in the hippocampus of young but not aged brains. *J Neuroinflammation* 12, 63. [PubMed: 25889938]
- Agha A, Rogers B, Mylotte D, Taleb F, Tormey W, Phillips J, Thompson CJ, 2004 Neuroendocrine dysfunction in the acute phase of traumatic brain injury. *Clin Endocrinol (Oxf)* 60, 584–591. [PubMed: 15104561]
- Agrawal D, Raghavendran K, Schaubel DE, Mishra MC, Rajajee V, 2016a A Propensity Score Analysis of the Impact of Invasive Intracranial Pressure Monitoring on Outcomes after Severe Traumatic Brain Injury. *J Neurotrauma* 33, 853–858. [PubMed: 26414629]
- Agrawal J, Kumar R, Malhi P, Dayal D, 2016b Prevalence of psychosocial morbidity in children with type 1 diabetes mellitus: a survey from Northern India. *J Pediatr Endocrinol Metab* 29, 893–899. [PubMed: 27226095]
- Agrawal R, Gomez-Pinilla F, 2012 'Metabolic syndrome' in the brain: deficiency in omega-3 fatty acid exacerbates dysfunctions in insulin receptor signalling and cognition. *J Physiol* 590, 2485–2499. [PubMed: 22473784]

- Agrawal R, Noble E, Vergnes L, Ying Z, Reue K, Gomez-Pinilla F, 2016c Dietary fructose aggravates the pathobiology of traumatic brain injury by influencing energy homeostasis and plasticity. *J Cereb Blood Flow Metab* 36, 941–953. [PubMed: 26661172]
- Aimaretti G, Ambrosio MR, Benvenga S, Borretta G, De Marinis L, De Menis E, Di Somma C, Faustini-Fustini M, Grottoli S, Gasco V, Gasperi M, Logoluso F, Scaroni C, Giordano G, Ghigo E, Italian Society of, E., 2004a Hypopituitarism and growth hormone deficiency (GHD) after traumatic brain injury (TBI). *Growth Horm IGF Res* 14 Suppl A, S114–117. [PubMed: 15135791]
- Aimaretti G, Ambrosio MR, Di Somma C, Fusco A, Cannavo S, Gasperi M, Scaroni C, De Marinis L, Benvenga S, degli Uberti EC, Lombardi G, Mantero F, Martino E, Giordano G, Ghigo E, 2004b Traumatic brain injury and subarachnoid haemorrhage are conditions at high risk for hypopituitarism: screening study at 3 months after the brain injury. *Clin Endocrinol (Oxf)* 61, 320–326. [PubMed: 15355447]
- Ajmo CT Jr., Vernon DO, Collier L, Hall AA, Garbuzova-Davis S, Willing A, Pennypacker KR, 2008 The spleen contributes to stroke-induced neurodegeneration. *J Neurosci Res* 86, 2227–2234. [PubMed: 18381759]
- Al-Sadi R, Ye D, Boivin M, Guo S, Hashimi M, Ereifej L, Ma TY, 2014 Interleukin-6 modulation of intestinal epithelial tight junction permeability is mediated by JNK pathway activation of claudin-2 gene. *PLoS One* 9, e85345. [PubMed: 24662742]
- Alali AS, Gomez D, McCredie V, Mainprize TG, Nathens AB, 2017 Understanding Hospital Volume-Outcome Relationship in Severe Traumatic Brain Injury. *Neurosurgery* 80, 534–542. [PubMed: 28362914]
- Alavi SA, Tan CL, Menon DK, Simpson HL, Hutchinson PJ, 2016 Incidence of pituitary dysfunction following traumatic brain injury: A prospective study from a regional neurosurgical centre. *Br J Neurosurg* 30, 302–306. [PubMed: 26610235]
- Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart JC, James WP, Loria CM, Smith SC Jr., International Diabetes Federation Task Force on, E., Prevention, National Heart, L., Blood, I., American Heart, A., World Heart, F., International Atherosclerosis, S., International Association for the Study of, O., 2009 Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation* 120, 1640–1645. [PubMed: 19805654]
- Alonso M, Vianna MR, Izquierdo I, Medina JH, 2002 Signaling mechanisms mediating BDNF modulation of memory formation in vivo in the hippocampus. *Cell Mol Neurobiol* 22, 663–674. [PubMed: 12585686]
- Anderson GD, Peterson TC, Vonder Haar C, Farin FM, Bammler TK, MacDonald JW, Kantor ED, Hoane MR, 2015 Effect of Traumatic Brain Injury, Erythropoietin, and Anakinra on Hepatic Metabolizing Enzymes and Transporters in an Experimental Rat Model. *AAPS J* 17, 1255–1267. [PubMed: 26068867]
- Andrews AM, Lutton EM, Merkel SF, Razmpour R, Ramirez SH, 2016 Mechanical Injury Induces Brain Endothelial-Derived Microvesicle Release: Implications for Cerebral Vascular Injury during Traumatic Brain Injury. *Front Cell Neurosci* 10, 43. [PubMed: 26973460]
- Andruszkow H, Veh J, Mommsen P, Zeckey C, Hildebrand F, Frink M, 2013 Impact of the body mass on complications and outcome in multiple trauma patients: what does the weight weigh? *Mediators Inflamm* 2013, 345702. [PubMed: 24023413]
- Angelucci F, Brene S, Mathe AA, 2005 BDNF in schizophrenia, depression and corresponding animal models. *Mol Psychiatry* 10, 345–352. [PubMed: 15655562]
- Anthony DC, Couch Y, Losey P, Evans MC, 2012 The systemic response to brain injury and disease. *Brain Behav Immun* 26, 534–540. [PubMed: 22085588]
- Anthony DC, Pitossi FJ, 2013 Special issue commentary: the changing face of inflammation in the brain. *Mol Cell Neurosci* 53, 1–5. [PubMed: 23147112]
- Aperghis M, Johnson IP, Cannon J, Yang SY, Goldspink G, 2004 Different levels of neuroprotection by two insulin-like growth factor-I splice variants. *Brain Res* 1009, 213–218. [PubMed: 15120599]

- Archer T, Svensson K, Alricsson M, 2012 Physical exercise ameliorates deficits induced by traumatic brain injury. *Acta Neurol Scand* 125, 293–302. [PubMed: 22233115]
- Asehnoune K, Balogh Z, Citerio G, Cap A, Billiar T, Stocchetti N, Cohen MJ, Pelosi P, Curry N, Gaarder C, Gruen R, Holcomb J, Hunt BJ, Juffermans NP, Maegele M, Midwinter M, Moore FA, O'Dwyer M, Pittet JF, Schochl H, Schreiber M, Spinella PC, Stanworth S, Winfield R, Brohi K, 2017 The research agenda for trauma critical care. *Intensive Care Med* 43, 1340–1351. [PubMed: 28756471]
- Ayton S, Zhang M, Roberts BR, Lam LQ, Lind M, McLean C, Bush AI, Frugier T, Crack PJ, Duce JA, 2014 Ceruloplasmin and beta-amyloid precursor protein confer neuroprotection in traumatic brain injury and lower neuronal iron. *Free Radic Biol Med* 69, 331–337. [PubMed: 24509156]
- Bansal D, Ave P, Kerneis S, Frileux P, Boche O, Baglin AC, Dubost G, Leguern AS, Prevost MC, Bracha R, Mirelman D, Guillen N, Labruyere E, 2009a An ex-vivo human intestinal model to study *Entamoeba histolytica* pathogenesis. *PLoS Negl Trop Dis* 3, e551. [PubMed: 19936071]
- Bansal V, Costantini T, Kroll L, Peterson C, Loomis W, Eliceiri B, Baird A, Wolf P, Coimbra R, 2009b Traumatic brain injury and intestinal dysfunction: uncovering the neuro-enteric axis. *J Neurotrauma* 26, 1353–1359. [PubMed: 19344293]
- Bansal V, Ryu SY, Blow C, Costantini T, Loomis W, Eliceiri B, Baird A, Wolf P, Coimbra R, 2010 The hormone ghrelin prevents traumatic brain injury induced intestinal dysfunction. *J Neurotrauma* 27, 2255–2260. [PubMed: 20858122]
- Bartke A, 2011a Growth hormone, insulin and aging: the benefits of endocrine defects. *Exp Gerontol* 46, 108–111. [PubMed: 20851173]
- Bartke A, 2011b Pleiotropic effects of growth hormone signaling in aging. *Trends Endocrinol Metab* 22, 437–442. [PubMed: 21852148]
- Bateman JM, McNeill H, 2006 Insulin/IGF signalling in neurogenesis. *Cell Mol Life Sci* 63, 1701–1705. [PubMed: 16786222]
- Bedinger DH, Adams SH, 2015 Metabolic, anabolic, and mitogenic insulin responses: A tissue-specific perspective for insulin receptor activators. *Mol Cell Endocrinol* 415, 143–156. [PubMed: 26277398]
- Behan LA, Phillips J, Thompson CJ, Agha A, 2008 Neuroendocrine disorders after traumatic brain injury. *J Neurol Neurosurg Psychiatry* 79, 753–759. [PubMed: 18559460]
- Berryman DE, Glad CA, List EO, Johannsson G, 2013 The GH/IGF-1 axis in obesity: pathophysiology and therapeutic considerations. *Nat Rev Endocrinol* 9, 346–356. [PubMed: 23568441]
- Bierhaus A, Wolf J, Andrassy M, Rohleder N, Humpert PM, Petrov D, Ferstl R, von Eynatten M, Wendt T, Rudofsky G, 2003 A mechanism converting psychosocial stress into mononuclear cell activation. *Proceedings of the National Academy of Sciences* 100, 1920–1925.
- Bogdan Y, Tornetta P 3rd, Einhorn TA, Guy P, Leveille L, Robinson J, Bosse MJ, Haines N, Horwitz D, Jones C, Schemitsch E, Sagi C, Thomas B, Stahl D, Ricci W, Brady M, Sanders D, Kain M, Higgins TF, Collinge C, Kottmeier S, Friess D, 2016 Healing Time and Complications in Operatively Treated Atypical Femur Fractures Associated With Bisphosphonate Use: A Multicenter Retrospective Cohort. *J Orthop Trauma* 30, 177–181. [PubMed: 26709814]
- Booth FW, Chakravarthy MV, Gordon SE, Spangenburg EE, 2002 Waging war on physical inactivity: using modern molecular ammunition against an ancient enemy. *J Appl Physiol* (1985) 93, 3–30. [PubMed: 12070181]
- Booth FW, Roberts CK, Laye MJ, 2012 Lack of exercise is a major cause of chronic diseases. *Compr Physiol* 2, 1143–1211. [PubMed: 23798298]
- Bosarge PL, Shoultz TH, Griffin RL, Kerby JD, 2015 Stress-induced hyperglycemia is associated with higher mortality in severe traumatic brain injury. *J Trauma Acute Care Surg* 79, 289–294. [PubMed: 26218699]
- Boulangé CL, Neves AL, Chilloux J, Nicholson JK, Dumas ME, 2016 Impact of the gut microbiota on inflammation, obesity, and metabolic disease. *Genome Med* 8, 42. [PubMed: 27098727]
- Bulger EM, Guffey D, Guyette FX, MacDonald RD, Brasel K, Kerby JD, Minei JP, Warden C, Rizoli S, Morrison LJ, Nichol G, Resuscitation Outcomes Consortium I, 2012 Impact of prehospital mode of transport after severe injury: a multicenter evaluation from the Resuscitation Outcomes

- Consortium. *J Trauma Acute Care Surg* 72, 567–573; discussion 573-565; quiz 803. [PubMed: 22491538]
- Campbell CT, Kolesar JE, Kaufman BA, 2012 Mitochondrial transcription factor A regulates mitochondrial transcription initiation, DNA packaging, and genome copy number. *Biochim Biophys Acta* 1819, 921–929. [PubMed: 22465614]
- Campolo M, Ahmad A, Crupi R, Impellizzeri D, Morabito R, Esposito E, Cuzzocrea S, 2013 Combination therapy with melatonin and dexamethasone in a mouse model of traumatic brain injury. *J Endocrinol* 217, 291–301. [PubMed: 23532863]
- Capatina C, Paluzzi A, Mitchell R, Karavitaki N, 2015 Diabetes Insipidus after Traumatic Brain Injury. *J Clin Med* 4, 1448–1462. [PubMed: 26239685]
- Cazettes F, Cohen JI, Yau PL, Talbot H, Convit A, 2011 Obesity-mediated inflammation may damage the brain circuit that regulates food intake. *Brain Res* 1373, 101–109. [PubMed: 21146506]
- Chen S-D, Yang D-I, Lin T-K, Shaw F-Z, Liou C-W, Chuang Y-C, 2011 Roles of oxidative stress, apoptosis, PGC-1 α and mitochondrial biogenesis in cerebral ischemia. *International journal of molecular sciences* 12, 7199–7215. [PubMed: 22072942]
- Chen X, Pan Z, Fang Z, Lin W, Wu S, Yang F, Li Y, Fu H, Gao H, Li S, 2018 Omega-3 polyunsaturated fatty acid attenuates traumatic brain injury-induced neuronal apoptosis by inducing autophagy through the upregulation of SIRT1-mediated deacetylation of Beclin-1. *J Neuroinflammation* 15, 310. [PubMed: 30409173]
- Cheng A, Wan R, Yang JL, Kamimura N, Son TG, Ouyang X, Luo Y, Okun E, Mattson MP, 2012 Involvement of PGC-1 α in the formation and maintenance of neuronal dendritic spines. *Nat Commun* 3, 1250. [PubMed: 23212379]
- Chu W, Li M, Li F, Hu R, Chen Z, Lin J, Feng H, 2013 Immediate splenectomy down-regulates the MAPK-NF-kappaB signaling pathway in rat brain after severe traumatic brain injury. *J Trauma Acute Care Surg* 74, 1446–1453. [PubMed: 23694871]
- Chytrova G, Ying Z, Gomez-Pinilla F, 2010 Exercise contributes to the effects of DHA dietary supplementation by acting on membrane-related synaptic systems. *Brain Res* 1341, 32–40. [PubMed: 19446534]
- Cisternas P, Salazar P, Serrano FG, Montecinos-Oliva C, Arredondo SB, Varela-Nallar L, Barja S, Vio CP, Gomez-Pinilla F, Inestrosa NC, 2015 Fructose consumption reduces hippocampal synaptic plasticity underlying cognitive performance. *Biochim Biophys Acta* 1852, 2379–2390. [PubMed: 26300486]
- Cittadini A, Saldamarco L, Marra AM, Arcopinto M, Carlomagno G, Imbriaco M, Del Forno D, Vigorito C, Merola B, Oliviero U, Fazio S, Sacca L, 2009 Growth hormone deficiency in patients with chronic heart failure and beneficial effects of its correction. *J Clin Endocrinol Metab* 94, 3329–3336. [PubMed: 19584187]
- Cohan P, Wang C, McArthur DL, Cook SW, Dusick JR, Armin B, Swerdloff R, Vespa P, Muizelaar JP, Cryer HG, Christenson PD, Kelly DF, 2005 Acute secondary adrenal insufficiency after traumatic brain injury: a prospective study. *Crit Care Med* 33, 2358–2366. [PubMed: 16215393]
- Coste TC, Gerbi A, Vague P, Pieroni G, Raccach D, 2003 Neuroprotective effect of docosahexaenoic acid-enriched phospholipids in experimental diabetic neuropathy. *Diabetes* 52, 2578–2585. [PubMed: 14514643]
- Cree MG, Paddon-Jones D, Newcomer BR, Ronsen O, Aarsland A, Wolfe RR, Ferrando A, 2010 Twenty-eight-day bed rest with hypercortisolemia induces peripheral insulin resistance and increases intramuscular triglycerides. *Metabolism* 59, 703–710. [PubMed: 19919871]
- Cuisinier A, Maufrais C, Payen JF, Nottin S, Walther G, Bouzat P, 2016 Myocardial function at the early phase of traumatic brain injury: a prospective controlled study. *Scand J Trauma Resusc Emerg Med* 24, 129. [PubMed: 27793208]
- Czorlich P, Dreimann M, Emami P, Westphal M, Lefering R, Hoffmann M, 2017 Body Mass Index >35 as Independent Predictor of Mortality in Severe Traumatic Brain Injury. *World Neurosurg* 107, 515–521. [PubMed: 28823658]
- da Silva Fiorin F, de Oliveira Ferreira AP, Ribeiro LR, Silva LF, de Castro MR, da Silva LR, da Silveira ME Jr., Zemolin AP, Dobrachinski F, Marchesan de Oliveira S, Franco JL, Soares FA, Furian AF, Oliveira MS, Figuera MR, Freire Royes LF, 2016 The Impact of Previous Physical

- Training on Redox Signaling after Traumatic Brain Injury in Rats: A Behavioral and Neurochemical Approach. *J Neurotrauma* 33, 1317–1330. [PubMed: 26651029]
- Dandona P, Aljada A, Bandyopadhyay A, 2004a Inflammation: the link between insulin resistance, obesity and diabetes. *Trends Immunol* 25, 4–7. [PubMed: 14698276]
- Dandona P, Chaudhuri A, Aljada A, 2004b Endothelial dysfunction and hypertension in diabetes mellitus. *Med Clin North Am* 88, 911–931, x-xi. [PubMed: 15308385]
- Das M, Leonardo CC, Rangooni S, Pennypacker KR, Mohapatra S, Mohapatra SS, 2011 Lateral fluid percussion injury of the brain induces CCL20 inflammatory chemokine expression in rats. *J Neuroinflammation* 8, 148. [PubMed: 22040257]
- De-Souza DA, Greene LJ, 2005 Intestinal permeability and systemic infections in critically ill patients: effect of glutamine. *Crit Care Med* 33, 1125–1135. [PubMed: 15891348]
- de Castro MRT, Ferreira A.P.d.O., Busanello GL, da Silva LRH, da Silveira MEP Junior, Fiorin F.d.S., Arrifano G, Crespo-López ME, Barcelos RP, Cuevas MJ, 2017 Previous physical exercise alters the hepatic profile of oxidative-inflammatory status and limits the secondary brain damage induced by severe traumatic brain injury in rats. *The Journal of physiology* 595, 6023–6044. [PubMed: 28726269]
- Deepika A, Devi BI, Shukla D, Sathyaprabha TN, Christopher R, Ramesh SS, 2018 Neuroimmunology of Traumatic Brain Injury: A Longitudinal Study of Interdependency of Inflammatory Markers and Heart Rate Variability in Severe Traumatic Brain Injury. *J Neurotrauma* 35, 1124–1131. [PubMed: 29304719]
- Desborough JP, 2000 The stress response to trauma and surgery. *Br J Anaesth* 85, 109–117. [PubMed: 10927999]
- Di Battista AP, Rizoli SB, Lejniaks B, Min A, Shiu MY, Peng HT, Baker AJ, Hutchison MG, Churchill N, Inaba K, 2016 Sympathoadrenal activation is associated with acute traumatic coagulopathy and endotheliopathy in isolated brain injury. *Shock (Augusta, Ga.)* 46, 96.
- Di Pietro V, Amin D, Pernagallo S, Lazzarino G, Tavazzi B, Vagnozzi R, Pringle A, Belli A, 2010 Transcriptomics of traumatic brain injury: gene expression and molecular pathways of different grades of insult in a rat organotypic hippocampal culture model. *J Neurotrauma* 27, 349–359. [PubMed: 19903084]
- Ditillo M, Pandit V, Rhee P, Aziz H, Hadeed S, Bhattacharya B, Friese RS, Davis K, Joseph B, 2014 Morbid obesity predisposes trauma patients to worse outcomes: a National Trauma Data Bank analysis. *J Trauma Acute Care Surg* 76, 176–179. [PubMed: 24368375]
- Eakin K, Li Y, Chiang YH, Hoffer BJ, Rosenheim H, Greig NH, Miller JP, 2013 Exendin-4 ameliorates traumatic brain injury-induced cognitive impairment in rats. *PLoS One* 8, e82016. [PubMed: 24312624]
- Ekstrand MI, Falkenberg M, Rantanen A, Park CB, Gaspari M, Hulthen K, Rustin P, Gustafsson CM, Larsson NG, 2004 Mitochondrial transcription factor A regulates mtDNA copy number in mammals. *Hum Mol Genet* 13, 935–944. [PubMed: 15016765]
- Eric Nyam TT, Ho CH, Chio CC, Lim SW, Wang JJ, Chang CH, Kuo JR, Wang CC, 2019 Traumatic Brain Injury Increases the Risk of Major Adverse Cardiovascular and Cerebrovascular Events: A 13-Year, Population-Based Study. *World Neurosurg* 122, e740–e753. [PubMed: 30391613]
- Farooqui AA, Farooqui T, Panza F, Frisardi V, 2012 Metabolic syndrome as a risk factor for neurological disorders. *Cell Mol Life Sci* 69, 741–762. [PubMed: 21997383]
- Feeney C, Sharp DJ, Hellyer PJ, Jolly AE, Cole JH, Scott G, Baxter D, Jilka S, Ross E, Ham TE, Jenkins PO, Li LM, Gorgoraptis N, Midwinter M, Goldstone AP, 2017 Serum insulin-like growth factor-I levels are associated with improved white matter recovery after traumatic brain injury. *Ann Neurol* 82, 30–43. [PubMed: 28574152]
- Feldman SF, Lapidus N, Dorival C, Diallo A, Amri I, Fontaine H, Pol S, Carrat F, group, A.A.H.s., 2018 Signal detection on a patient cohort: A disproportionality analysis of the ANRS CO22 HEPATHER cohort to identify associations between direct acting antivirals and adverse events in patients with hepatitis C virus chronic infection. *Pharmacoepidemiol Drug Saf* 27, 797–805. [PubMed: 29749668]

- Fenn AM, Gensel JC, Huang Y, Popovich PG, Lifshitz J, Godbout JP, 2014 Immune activation promotes depression 1 month after diffuse brain injury: a role for primed microglia. *Biol Psychiatry* 76, 575–584. [PubMed: 24289885]
- Fernandez-Rodriguez E, Bernabeu I, Castro AI, Kelestimur F, Casanueva FF, 2011 Hypopituitarism following traumatic brain injury: determining factors for diagnosis. *Front Endocrinol (Lausanne)* 2, 25. [PubMed: 22649368]
- Fernandez AM, Torres-Aleman I, 2012 The many faces of insulin-like peptide signalling in the brain. *Nat Rev Neurosci* 13, 225–239. [PubMed: 22430016]
- Friedrich N, Thuesen B, Jorgensen T, Juul A, Spielhagen C, Wallaschofski H, Linneberg A, 2012 The association between IGF-I and insulin resistance: a general population study in Danish adults. *Diabetes Care* 35, 768–773. [PubMed: 22374641]
- Garrahy A, Sherlock M, Thompson CJ, 2017 MANAGEMENT OF ENDOCRINE DISEASE: Neuroendocrine surveillance and management of neurosurgical patients. *Eur J Endocrinol* 176, R217–R233. [PubMed: 28193628]
- Geeraerts T, Friggeri A, Mazoit JX, Benhamou D, Duranteau J, Vigue B, 2008 Posttraumatic brain vulnerability to hypoxia-hypotension: the importance of the delay between brain trauma and secondary insult. *Intensive Care Med* 34, 551–560. [PubMed: 17938889]
- Geiss LS, Kirtland K, Lin J, Shrestha S, Thompson T, Albright A, Gregg EW, 2017 Changes in diagnosed diabetes, obesity, and physical inactivity prevalence in US counties, 2004–2012. *PLoS One* 12, e0173428. [PubMed: 28267760]
- Gharib M, Kaul S, LoCurto J, Perez M, Hajri T, 2015 The obesity factor in critical illness: Between consensus and controversy. *J Trauma Acute Care Surg* 78, 866–873. [PubMed: 25807411]
- Giuliano S, Talarico S, Bruno L, Nicoletti FB, Ceccotti C, Belfiore A, 2017 Growth hormone deficiency and hypopituitarism in adults after complicated mild traumatic brain injury. *Endocrine* 58, 115–123. [PubMed: 27878771]
- Gomez-Pinilla F, Tyagi E, 2013 Diet and cognition: interplay between cell metabolism and neuronal plasticity. *Current opinion in clinical nutrition and metabolic care* 16, 726. [PubMed: 24071781]
- Gomez-Pinilla F, Yang X, 2018 SYSTEM BIOLOGY APPROACH INTERSECTING DIET AND CELL METABOLISM WITH PATHOGENESIS OF BRAIN DISORDERS. *Progress in neurobiology*.
- Gomez-Pinilla F, Hillman C, 2013 The influence of exercise on cognitive abilities. *Comprehensive Physiology* 3, 403–428. [PubMed: 23720292]
- Gonzalez S, Sathyapalan T, Javed Z, Atkin SL, 2018 Effects of Growth Hormone Replacement on Peripheral Muscle and Exercise Capacity in Severe Growth Hormone Deficiency. *Front Endocrinol (Lausanne)* 9, 56. [PubMed: 29527190]
- Gralle M, 2017 The neuronal insulin receptor in its environment. *J Neurochem* 140, 359–367. [PubMed: 27889917]
- Greening DW, Simpson RJ, 2018 Understanding extracellular vesicle diversity - current status. *Expert Rev Proteomics* 15, 887–910. [PubMed: 30326765]
- Griesbach GS, 2011 Exercise after traumatic brain injury: is it a double-edged sword? *PM R* 3, S64–72. [PubMed: 21703583]
- Griesdale DE, Tremblay MH, McEwen J, Chittock DR, 2009 Glucose control and mortality in patients with severe traumatic brain injury. *Neurocrit Care* 11, 311–316. [PubMed: 19636972]
- Grundy SM, 2006 Atherogenic dyslipidemia associated with metabolic syndrome and insulin resistance. *Clin Cornerstone* 8 Suppl 1, S21–27. [PubMed: 16903166]
- Hadjizacharia P, Beale EO, Inaba K, Chan LS, Demetriades D, 2008 Acute diabetes insipidus in severe head injury: a prospective study. *Journal of the American College of Surgeons* 207, 477–484. [PubMed: 18926448]
- Hamer M, Chida Y, 2009 Physical activity and risk of neurodegenerative disease: a systematic review of prospective evidence. *Psychol Med* 39, 3–11. [PubMed: 18570697]
- Hang CH, Shi JX, Li JS, Wu W, Yin HX, 2003 Alterations of intestinal mucosa structure and barrier function following traumatic brain injury in rats. *World J Gastroenterol* 9, 2776–2781. [PubMed: 14669332]

- Hasen M, Almojuela A, Zeiler FA, 2019 Autonomic Dysfunction and Associations with Functional and Neurophysiological Outcome in Moderate/Severe Traumatic Brain Injury: A Scoping Review. *J Neurotrauma*.
- Hashimoto M, Hossain S, Shimada T, Sugioka K, Yamasaki H, Fujii Y, Ishibashi Y, Oka J, Shido O, 2002 Docosahexaenoic acid provides protection from impairment of learning ability in Alzheimer's disease model rats. *J Neurochem* 81, 1084–1091. [PubMed: 12065621]
- Hatton J, Kryscio R, Ryan M, Ott L, Young B, 2006 Systemic metabolic effects of combined insulin-like growth factor-I and growth hormone therapy in patients who have sustained acute traumatic brain injury. *Journal of neurosurgery* 105, 843–852. [PubMed: 17405254]
- Hendrick LE, Schroepfel TJ, Sharpe JP, Alsbrook D, Magnotti LJ, Weinberg JA, Johnson BP, Lewis RH, Clement LP, Croce MA, Fabian TC, 2016 Impact of Beta-Blockers on Nonhead Injured Trauma Patients. *Am Surg* 82, 575–579. [PubMed: 27457854]
- Hernandez G, Hasbun P, Velasco N, Wainstein C, Buggedo G, Bruhn A, Klaassen J, Castillo L, 2007 Splanchnic ischemia and gut permeability after acute brain injury secondary to intracranial hemorrhage. *Neurocrit Care* 7, 40–44. [PubMed: 17603761]
- Herzig S, Long F, Jhala US, Hedrick S, Quinn R, Bauer A, Rudolph D, Schutz G, Yoon C, Puigserver P, Spiegelman B, Montminy M, 2001 CREB regulates hepatic gluconeogenesis through the coactivator PGC-1. *Nature* 413, 179–183. [PubMed: 11557984]
- Hinson HE, Schreiber MA, Laurie AL, Baguley IJ, Bourdette D, Ling GS, 2017 Early fever as a predictor of paroxysmal sympathetic hyperactivity in traumatic brain injury. *Journal of Head Trauma Rehabilitation* 32, E50–E54.
- Hoffman DM, O'Sullivan AJ, Baxter RC, Ho KK, 1994 Diagnosis of growth-hormone deficiency in adults. *Lancet* 343, 1064–1068. [PubMed: 7512681]
- Hu G, Pekkarinen H, Hanninen O, Tian H, Guo Z, 2001 Relation between commuting, leisure time physical activity and serum lipids in a Chinese urban population. *Ann Hum Biol* 28, 412–421. [PubMed: 11459239]
- Hu YC, Wang F, Zhang DD, Sun Q, Li W, Dai YX, Zhou ML, Hang CH, 2013 Expression of intestinal CD40 after experimental traumatic brain injury in rats. *J Surg Res* 184, 1022–1027. [PubMed: 23647802]
- Izzo G, Tirelli A, Angrisani E, Cannaviello G, Cannaviello L, Puzziello A, Vatrella A, Vitale M, 2016 Pituitary dysfunction and its association with quality of life in traumatic brain injury. *Int J Surg Suppl* 1:S103–8.
- Jin P, Zhu L, Zhang J, Xie S, Pan D, Wen H, Meng W, Lin L, Chen D, 2014 A correlation study of the expression of resistin and glycometabolism in muscle tissue after traumatic brain injury in rats. *Chin J Traumatol* 17, 125–129. [PubMed: 24889973]
- Jin W, Ni H, Dai Y, Wang H, Lu T, Wu J, Jiang J, Liang W, 2010 Effects of tert-butylhydroquinone on intestinal inflammatory response and apoptosis following traumatic brain injury in mice. *Mediators Inflamm* 2010, 502564. [PubMed: 21274455]
- Kadhim HJ, Duchateau J, Sebire G, 2008 Cytokines and brain injury: invited review. *J Intensive Care Med* 23, 236–249. [PubMed: 18504260]
- Karamouzis I, Pagano L, Prodam F, Mele C, Zavattaro M, Busti A, Marzullo P, Aimaretti G, 2016 Clinical and diagnostic approach to patients with hypopituitarism due to traumatic brain injury (TBI), subarachnoid hemorrhage (SAH), and ischemic stroke (IS). *Endocrine* 52, 441–450. [PubMed: 26573924]
- Kasturi BS, Stein DG, 2009 Traumatic brain injury causes long-term reduction in serum growth hormone and persistent astrogliosis in the cortico-hypothalamo-pituitary axis of adult male rats. *J Neurotrauma* 26, 1315–1324. [PubMed: 19317601]
- Kato T, Nakayama N, Yasokawa Y, Okumura A, Shinoda J, Iwama T, 2007 Statistical image analysis of cerebral glucose metabolism in patients with cognitive impairment following diffuse traumatic brain injury. *J Neurotrauma* 24, 919–926. [PubMed: 17600509]
- Katzenberger RJ, Ganetzky B, Wassarman DA, 2015 The gut reaction to traumatic brain injury. *Fly (Austin)* 9, 68–74. [PubMed: 26291482]
- Kelley GL, Allan G, Azhar S, 2004 High dietary fructose induces a hepatic stress response resulting in cholesterol and lipid dysregulation. *Endocrinology* 145, 548–555. [PubMed: 14576175]

- Kelly DF, McArthur DL, Levin H, Swimmer S, Dusick JR, Cohan P, Wang C, Swerdloff R, 2006 Neurobehavioral and quality of life changes associated with growth hormone insufficiency after complicated mild, moderate, or severe traumatic brain injury. *J Neurotrauma* 23, 928–942. [PubMed: 16774477]
- Keshavarzi Z, Khaksari M, Shahrokhi N, 2014 The effects of cyclooxygenase inhibitors on the gastric emptying and small intestine transit in the male rats following traumatic brain injury. *Iran J Basic Med Sci* 17, 406–410. [PubMed: 25140201]
- Kim DK, Nishida H, An SY, Shetty AK, Bartosh TJ, Prockop DJ, 2016 Chromatographically isolated CD63+CD81+ extracellular vesicles from mesenchymal stromal cells rescue cognitive impairments after TBI. *Proc Natl Acad Sci U S A* 113, 170–175. [PubMed: 26699510]
- Kim GS, Jung JE, Narasimhan P, Sakata H, Chan PH, 2012 Induction of thioredoxin-interacting protein is mediated by oxidative stress, calcium, and glucose after brain injury in mice. *Neurobiology of disease* 46, 440–449. [PubMed: 22366181]
- Kleindienst A, Brabant G, Bock C, Maser-Gluth C, Buchfelder M, 2009 Neuroendocrine function following traumatic brain injury and subsequent intensive care treatment: a prospective longitudinal evaluation. *J Neurotrauma* 26, 1435–1446. [PubMed: 19459759]
- Klose M, Feldt-Rasmussen U, 2018 Chronic endocrine consequences of traumatic brain injury - what is the evidence? *Nat Rev Endocrinol* 14, 57–62. [PubMed: 28885623]
- Ko A, Harada MY, Barmparas G, Thomsen GM, Alban RF, Bloom MB, Chung R, Melo N, Margulies DR, Ley EJ, 2016 Early propranolol after traumatic brain injury is associated with lower mortality. *J Trauma Acute Care Surg* 80, 637–642. [PubMed: 26808028]
- Kobata H, Sugie A, Suehiro E, Dohi K, Kaneko T, Fujita M, Oda Y, Kuroda Y, Yamashita S, Maekawa T, 2017 Association between Blood Glucose Levels the Day after Targeted Temperature Initiation and Outcome in Traumatic Brain Injury: A Post-Hoc Analysis of the B-HYPO Study. *J Neurotrauma* 34, 987–995. [PubMed: 27673360]
- Krishnamoorthy V, Rowhani-Rahbar A, Chaikittisilpa N, Gibbons EF, Rivara FP, Temkin NR, Quistberg A, Vavilala MS, 2017 Association of Early Hemodynamic Profile and the Development of Systolic Dysfunction Following Traumatic Brain Injury. *Neurocrit Care* 26, 379–387. [PubMed: 28000133]
- Lakshmanan R, Loo JA, Drake T, Leblanc J, Ytterberg AJ, McArthur DL, Etchepare M, Vespa PM, 2010 Metabolic crisis after traumatic brain injury is associated with a novel microdialysis proteome. *Neurocrit Care* 12, 324–336. [PubMed: 20225002]
- Lambillotte C, Gilon P, Henquin JC, 1997 Direct glucocorticoid inhibition of insulin secretion. An in vitro study of dexamethasone effects in mouse islets. *J Clin Invest* 99, 414–423. [PubMed: 9022074]
- Lang Y, Fu F, Sun D, Xi C, Chen F, 2015 Labetalol prevents intestinal dysfunction induced by traumatic brain injury. *PLoS one* 10, e0133215. [PubMed: 26186619]
- Larson BE, Stockwell DW, Boas S, Andrews T, Wellman GC, Lockette W, Freeman K, 2012 Cardiac reactive oxygen species after traumatic brain injury. *J Surg Res* 173, e73–81. [PubMed: 22172132]
- Lee CC, Huang CC, Wu MY, Hsu KS, 2005 Insulin stimulates postsynaptic density-95 protein translation via the phosphoinositide 3-kinase-Akt-mammalian target of rapamycin signaling pathway. *J Biol Chem* 280, 18543–18550. [PubMed: 15755733]
- Levada OA, Troyan AS, 2018 Poststroke Depression Biomarkers: A Narrative Review. *Front Neurol* 9, 577. [PubMed: 30061860]
- Ley EJ, Srour MK, Clond MA, Barnajian M, Tillou A, Mirocha J, Salim A, 2011 Diabetic patients with traumatic brain injury: insulin deficiency is associated with increased mortality. *J Trauma* 70, 1141–1144. [PubMed: 21610428]
- Ley RE, 2010 Obesity and the human microbiome. *Curr Opin Gastroenterol* 26, 5–11. [PubMed: 19901833]
- Li M, Sirko S, 2018 Traumatic Brain Injury: At the Crossroads of Neuropathology and Common Metabolic Endocrinopathies. *J Clin Med* 7.

- Lim GP, Calon F, Morihara T, Yang F, Teter B, Ubeda O, Salem N Jr., Frautschy SA, Cole GM, 2005 A diet enriched with the omega-3 fatty acid docosahexaenoic acid reduces amyloid burden in an aged Alzheimer mouse model. *J Neurosci* 25, 3032–3040. [PubMed: 15788759]
- Lima FD, Oliveira MS, Furian AF, Souza MA, Rambo LM, Ribeiro LR, Silva LF, Retamoso LT, Hoffmann MS, Magni DV, Pereira L, Figuera MR, Mello CF, Royes LF, 2009 Adaptation to oxidative challenge induced by chronic physical exercise prevents Na⁺,K⁺-ATPase activity inhibition after traumatic brain injury. *Brain Res* 1279, 147–155. [PubMed: 19422810]
- Lima MH, Ueno M, Thirone AC, Rocha EM, Carvalho CR, Saad MJ, 2002 Regulation of IRS-1/SHP2 interaction and AKT phosphorylation in animal models of insulin resistance. *Endocrine* 18, 1–12. [PubMed: 12166618]
- Liu-DeRyke X, Collingridge DS, Orme J, Roller D, Zurasky J, Rhoney DH, 2009 Clinical impact of early hyperglycemia during acute phase of traumatic brain injury. *Neurocrit Care* 11, 151–157. [PubMed: 19479209]
- López-Gamero A, Martínez F, Salazar K, Cifuentes M, Nualart F, 2018 Brain Glucose-Sensing Mechanism and Energy Homeostasis. *Molecular Neurobiology*, 1–28.
- Lu K, Liang CL, Li PC, Liliang PC, Huang CY, Lee YC, Wang KW, Yang SN, Sun YT, Wang HK, 2017 Risk factors for myocardial dysfunction after traumatic brain injury: A one-year follow-up study. *Injury* 48, 1794–1800. [PubMed: 28701282]
- Lu YC, Liu S, Gong QZ, Hamm RJ, Lyeth BG, 1997 Inhibition of nitric oxide synthase potentiates hypertension and increases mortality in traumatically brain-injured rats. *Mol Chem Neuropathol* 30, 125–137. [PubMed: 9138424]
- Ma EL, Smith AD, Desai N, Cheung L, Hanscom M, Stoica BA, Loane DJ, Shea-Donohue T, Faden AI, 2017a Bidirectional brain-gut interactions and chronic pathological changes after traumatic brain injury in mice. *Brain Behav Immun* 66, 56–69. [PubMed: 28676351]
- Ma J, Wang J, Cheng J, Xiao W, Fan K, Gu J, Yu B, Yin G, Wu J, Ren J, Hou J, Jiang Y, Tan Y, Jin W, 2017b Impacts of Blast-Induced Traumatic Brain Injury on Expressions of Hepatic Cytochrome P450 1A2, 2B1, 2D1, and 3A2 in Rats. *Cell Mol Neurobiol* 37, 111–120. [PubMed: 26913515]
- Majdan M, Brazinova A, Wilbacher I, Rusnak M, Mauritz W, 2015 The impact of body mass index on severity, patterns and outcomes after traumatic brain injuries caused by low level falls. *Eur J Trauma Emerg Surg* 41, 651–656. [PubMed: 26038011]
- Majdan M, Plancikova D, Brazinova A, Rusnak M, Nieboer D, Feigin V, Maas A, 2016 Epidemiology of traumatic brain injuries in Europe: a cross-sectional analysis. *Lancet Public Health* 1, e76–e83. [PubMed: 29253420]
- Malik VS, Hu FB, 2012 Sweeteners and Risk of Obesity and Type 2 Diabetes: The Role of Sugar-Sweetened Beverages. *Curr Diab Rep*.
- Mansoor O, Beaufriere B, Boirie Y, Rallièr C, Taillandier D, Aourousseau E, Schoeffler P, Arnal M, Attaix D, 1996 Increased mRNA levels for components of the lysosomal, Ca²⁺-activated, and ATP-ubiquitin-dependent proteolytic pathways in skeletal muscle from head trauma patients. *Proc Natl Acad Sci U S A* 93, 2714–2718. [PubMed: 8610106]
- Marques-Aleixo I, Oliveira PJ, Moreira PI, Magalhaes J, Ascensao A, 2012 Physical exercise as a possible strategy for brain protection: evidence from mitochondrial-mediated mechanisms. *Prog Neurobiol* 99, 149–162. [PubMed: 22940590]
- Mathews EM, Wagner DR, 2008 Prevalence of overweight and obesity in collegiate American football players, by position. *J Am Coll Health* 57, 33–38. [PubMed: 18682343]
- Mattson MP, Gleichmann M, Cheng A, 2008 Mitochondria in neuroplasticity and neurological disorders. *Neuron* 60, 748–766. [PubMed: 19081372]
- Mavalli MD, DiGirolamo DJ, Fan Y, Riddle RC, Campbell KS, van Groen T, Frank SJ, Sperling MA, Esser KA, Bamman MM, Clemens TL, 2010 Distinct growth hormone receptor signaling modes regulate skeletal muscle development and insulin sensitivity in mice. *J Clin Invest* 120, 4007–4020. [PubMed: 20921627]
- Mayer LS, Bay RC, Politis A, Steinberg M, Steele C, Baker AS, Rabins PV, Lyketsos CG, 2006 Comparison of three rating scales as outcome measures for treatment trials of depression in Alzheimer disease: findings from DIADS. *Int J Geriatr Psychiatry* 21, 930–936. [PubMed: 16955427]

- McHugh GS, Engel DC, Butcher I, Steyerberg EW, Lu J, Mushkudiani N, Hernandez AV, Marmarou A, Maas AI, Murray GD, 2007 Prognostic value of secondary insults in traumatic brain injury: results from the IMPACT study. *J Neurotrauma* 24, 287–293. [PubMed: 17375993]
- McKee CA, Lukens JR, 2016 Emerging Roles for the Immune System in Traumatic Brain Injury. *Front Immunol* 7, 556. [PubMed: 27994591]
- Meng Q, Zhuang Y, Ying Z, Agrawal R, Yang X, Gomez-Pinilla F, 2017 Traumatic brain injury induces genome-wide transcriptomic, Methylomic, and network perturbations in brain and blood predicting neurological disorders. *EBioMedicine* 16, 184–194. [PubMed: 28174132]
- Meyfroidt G, Baguley IJ, Menon DK, 2017 Paroxysmal sympathetic hyperactivity: the storm after acute brain injury. *Lancet Neurol* 16, 721–729. [PubMed: 28816118]
- Moinard C, Gupta S, Besson V, Morio B, Marchand-Leroux C, Chaumeil JC, Cynober L, Charrueau C, 2008 Evidence for impairment of hepatic energy homeostasis in head-injured rat. *J Neurotrauma* 25, 124–129. [PubMed: 18260795]
- Moinard C, Neveux N, Royo N, Genthon C, Marchand-Verrecchia C, Plotkine M, Cynober L, 2005 Characterization of the alteration of nutritional state in brain injury induced by fluid percussion in rats. *Intensive Care Med* 31, 281–288. [PubMed: 15703899]
- Molaie AM, Maguire J, 2018 Neuroendocrine Abnormalities Following Traumatic Brain Injury: An Important Contributor to Neuropsychiatric Sequelae. *Front Endocrinol (Lausanne)* 9, 176. [PubMed: 29922224]
- Mondello S, Thelin EP, Shaw G, Salzet M, Visalli C, Cizkova D, Kobeissy F, Buki A, 2018 Extracellular vesicles: pathogenetic, diagnostic and therapeutic value in traumatic brain injury. *Expert Rev Proteomics* 15, 451–461. [PubMed: 29671356]
- Mossberg KA, Durham WJ, Zgaljardic DJ, Gilkison CR, Danesi CP, Sheffield-Moore M, Masel BE, Urban RJ, 2017 Functional Changes after Recombinant Human Growth Hormone Replacement in Patients with Chronic Traumatic Brain Injury and Abnormal Growth Hormone Secretion. *J Neurotrauma* 34, 845–852. [PubMed: 27627580]
- Mowery NT, Carnevale RJ, Gunter OL, Norris PR, Dossett LA, Dortch MJ, Morris JA Jr., May AK, 2009a Insulin resistance heralds positive cultures after severe injury. *Surg Infect (Larchmt)* 10, 503–509. [PubMed: 19877769]
- Mowery NT, Gunter OL, Guillamondegui O, Dossett LA, Dortch MJ, Morris JA Jr., May AK, 2009b Stress insulin resistance is a marker for mortality in traumatic brain injury. *J Trauma* 66, 145–151; discussion 151-143. [PubMed: 19131817]
- Navarro A, Boveris A, 2009 Brain mitochondrial dysfunction and oxidative damage in Parkinson's disease. *J Bioenerg Biomembr* 41, 517–521. [PubMed: 19915964]
- Nekludov M, Mobarrez F, Gryth D, Bellander BM, Wallen H, 2014 Formation of microparticles in the injured brain of patients with severe isolated traumatic brain injury. *J Neurotrauma* 31, 1927–1933. [PubMed: 24956150]
- Nighot M, Al-Sadi R, Guo S, Rawat M, Nighot P, Watterson MD, Ma TY, 2017 Lipopolysaccharide-Induced Increase in Intestinal Epithelial Tight Permeability Is Mediated by Toll-Like Receptor 4/Myeloid Differentiation Primary Response 88 (MyD88) Activation of Myosin Light Chain Kinase Expression. *Am J Pathol* 187, 2698–2710. [PubMed: 29157665]
- Nistico R, Cavallucci V, Piccinin S, Macri S, Pignatelli M, Mehdawy B, Blandini F, Laviola G, Lauro D, Mercuri NB, D'Amelio M, 2012 Insulin receptor beta-subunit haploinsufficiency impairs hippocampal late-phase LTP and recognition memory. *Neuromolecular Med* 14, 262–269. [PubMed: 22661254]
- Ntali G, Tsagarakis S, 2019 Traumatic brain injury induced neuroendocrine changes: acute hormonal changes of anterior pituitary function. *Pituitary*.
- Olsen AB, Hetz RA, Xue H, Aroom KR, Bhattarai D, Johnson E, Bedi S, Cox CS Jr., Uray K, 2013 Effects of traumatic brain injury on intestinal contractility. *Neurogastroenterol Motil* 25, 593–e463. [PubMed: 23551971]
- Padwal RS, 2014 Obesity, diabetes, and the metabolic syndrome: the global scourge. *Canadian Journal of Cardiology* 30, 467–472. [PubMed: 24530217]

- Park KD, Lim OK, Yoo CJ, Kim YW, Lee S, Park Y, Lee JK, 2016 Voxel-based statistical analysis of brain metabolism in patients with growth hormone deficiency after traumatic brain injury. *Brain Inj* 30, 407–413. [PubMed: 26910852]
- Patel NA, Moss LD, Lee JY, Tajiri N, Acosta S, Hudson C, Parag S, Cooper DR, Borlongan CV, Bickford PC, 2018 Long noncoding RNA MALAT1 in exosomes drives regenerative function and modulates inflammation-linked networks following traumatic brain injury. *J Neuroinflammation* 15, 204. [PubMed: 30001722]
- Patterson E, Cryan JF, Fitzgerald GF, Ross RP, Dinan TG, Stanton C, 2014 Gut microbiota, the pharmabiotics they produce and host health. *Proc Nutr Soc* 73, 477–489. [PubMed: 25196939]
- Pieracci F, Hydo L, Eachempati S, Pomp A, Shou J, Barie PS, 2008 Higher body mass index predicts need for insulin but not hyperglycemia, nosocomial infection, or death in critically ill surgical patients. *Surg Infect (Larchmt)* 9, 121–130. [PubMed: 18426344]
- Plesnila N, 2016 The immune system in traumatic brain injury. *Curr Opin Pharmacol* 26, 110–117. [PubMed: 26613129]
- Pratt SI, Jerome GJ, Schneider KL, Craft LL, Buman MP, Stoutenberg M, Daumit GL, Bartels SJ, Goodrich DE, 2016 Increasing US health plan coverage for exercise programming in community mental health settings for people with serious mental illness: a position statement from the Society of Behavior Medicine and the American College of Sports Medicine. *Transl Behav Med* 6, 478–481. [PubMed: 27146275]
- Quinkler M, Ekman B, Zhang P, Isidori AM, Murray RD, Investigators E-A, 2018 Mortality data from the European Adrenal Insufficiency Registry-Patient characterization and associations. *Clin Endocrinol (Oxf)* 89, 30–35. [PubMed: 29682773]
- Radak Z, Chung HY, Koltai E, Taylor AW, Goto S, 2008 Exercise, oxidative stress and hormesis. *Ageing Res Rev* 7, 34–42. [PubMed: 17869589]
- Ranke MB, Wit JM, 2018 Growth hormone - past, present and future. *Nat Rev Endocrinol* 14, 285–300. [PubMed: 29546874]
- Rasouli J, Lekhraj R, Ozbalik M, Lalezari P, Casper D, 2011 Brain-Spleen Inflammatory Coupling: A Literature Review. *Einstein J Biol Med* 27, 74–77. [PubMed: 22611344]
- Rau CS, Wu SC, Chen YC, Chien PC, Hsieh HY, Kuo PJ, Hsieh CH, 2017 Stress-Induced Hyperglycemia, but Not Diabetic Hyperglycemia, Is Associated with Higher Mortality in Patients with Isolated Moderate and Severe Traumatic Brain Injury: Analysis of a Propensity Score-Matched Population. *Int J Environ Res Public Health* 14.
- Rauch S, Krueger K, Turan A, You J, Roewer N, Sessler DI, 2012 Use of wireless motility capsule to determine gastric emptying and small intestinal transit times in critically ill trauma patients. *J Crit Care* 27, 534 e537–512.
- Ray K, 2012 Liver: Activation of NF-kappaB signaling in hepatocytes induces liver fibrosis. *Nat Rev Gastroenterol Hepatol* 9, 244.
- Reilly SM, Saltiel AR, 2017 Adapting to obesity with adipose tissue inflammation. *Nature Reviews Endocrinology* 13, 633.
- Rhee SH, Pothoulakis C, Mayer EA, 2009 Principles and clinical implications of the brain-gut-enteric microbiota axis. *Nat Rev Gastroenterol Hepatol* 6, 306–314. [PubMed: 19404271]
- Ritzel RM, Doran SJ, Barrett JP, Henry RJ, Ma EL, Faden AI, Loane DJ, 2018 Chronic Alterations in Systemic Immune Function after Traumatic Brain Injury. *J Neurotrauma* 35, 1419–1436. [PubMed: 29421977]
- Rizoli SB, Jaja BN, Di Battista AP, Rhind SG, Neto AC, da Costa L, Inaba K, da Luz LT, Nascimento B, Perez A, Baker AJ, de Oliveira Manoel AL, 2017 Catecholamines as outcome markers in isolated traumatic brain injury: the COMA-TBI study. *Crit Care* 21, 37. [PubMed: 28228155]
- Romero MC, Valero A, Navarro MC, Hierro I, Baron SD, Martin-Sanchez J, 2014 Experimental demonstration of pathogenic potential of *Anisakis physeteris* and *Anisakis paggiae* in Wistar rats. *Parasitol Res* 113, 4377–4386. [PubMed: 25240961]
- Roozenbeek B, Maas AI, Menon DK, 2013 Changing patterns in the epidemiology of traumatic brain injury. *Nat Rev Neurol* 9, 231–236. [PubMed: 23443846]
- Roquilly A, Vourc'h M, Cinotti R, Asehnoune K, 2013 A new way of thinking: hydrocortisone in traumatic brain-injured patients. *Crit Care* 17, 1016. [PubMed: 24313953]

- Rothman SM, Mattson MP, 2013 Activity-dependent, stress-responsive BDNF signaling and the quest for optimal brain health and resilience throughout the lifespan. *Neuroscience* 239, 228–240. [PubMed: 23079624]
- Ruan H, Miles PD, Ladd CM, Ross K, Golub TR, Olefsky JM, Lodish HF, 2002 Profiling gene transcription in vivo reveals adipose tissue as an immediate target of tumor necrosis factor- α : implications for insulin resistance. *Diabetes* 51, 3176–3188. [PubMed: 12401708]
- Rueggsegger GN, Booth FW, 2017 Running from Disease: Molecular Mechanisms Associating Dopamine and Leptin Signaling in the Brain with Physical Inactivity, Obesity, and Type 2 Diabetes. *Front Endocrinol (Lausanne)* 8, 109. [PubMed: 28588553]
- Santarsieri M, Niyonkuru C, McCullough EH, Dobos JA, Dixon CE, Berga SL, Wagner AK, 2014 Cerebrospinal fluid cortisol and progesterone profiles and outcomes prognostication after severe traumatic brain injury. *J Neurotrauma* 31, 699–712. [PubMed: 24354775]
- Schmidt C, 2015 Mental health: thinking from the gut. *Nature* 518, S12–15. [PubMed: 25715275]
- Schneider KJ, Leddy JJ, Guskiewicz KM, Seifert T, McCreary M, Silverberg ND, Feddermann-Demont N, Iverson GL, Hayden A, Makdissi M, 2017 Rest and treatment/rehabilitation following sport-related concussion: a systematic review. *Br J Sports Med* 51, 930–934. [PubMed: 28341726]
- Schober ME, Ke X, Xing B, Block BP, Requena DF, McKnight R, Lane RH, 2012 Traumatic brain injury increased IGF-1B mRNA and altered IGF-1 exon 5 and promoter region epigenetic characteristics in the rat pup hippocampus. *J Neurotrauma* 29, 2075–2085. [PubMed: 22413999]
- Schwulst SJ, Trahanas DM, Saber R, Perlman H, 2013 Traumatic brain injury-induced alterations in peripheral immunity. *J Trauma Acute Care Surg* 75, 780–788. [PubMed: 24158195]
- Shahidi B, Shah SB, Esparza M, Head BP, Ward SR, 2018 Skeletal Muscle Atrophy and Degeneration in a Mouse Model of Traumatic Brain Injury. *J Neurotrauma* 35, 398–401. [PubMed: 28895461]
- Sharma S, Zhuang Y, Ying Z, Wu A, Gomez-Pinilla F, 2009 Dietary curcumin supplementation counteracts reduction in levels of molecules involved in energy homeostasis after brain trauma. *Neuroscience* 161, 1037–1044. [PubMed: 19393301]
- Sherman M, Liu MM, Birnbaum S, Wolf SE, Minei JP, Gatson JW, 2016 Adult obese mice suffer from chronic secondary brain injury after mild TBI. *J Neuroinflammation* 13, 171. [PubMed: 27357503]
- Shi J, Dong B, Mao Y, Guan W, Cao J, Zhu R, Wang S, 2016 Review: Traumatic brain injury and hyperglycemia, a potentially modifiable risk factor. *Oncotarget* 7, 71052–71061. [PubMed: 27626493]
- Shibahashi K, Sugiyama K, Kashiura M, Hamabe Y, 2017 Decreasing skeletal muscle as a risk factor for mortality in elderly patients with sepsis: a retrospective cohort study. *J Intensive Care* 5, 8. [PubMed: 28096999]
- Shitaka Y, Tran HT, Bennett RE, Sanchez L, Levy MA, Dikranian K, Brody DL, 2011 Repetitive closed-skull traumatic brain injury in mice causes persistent multifocal axonal injury and microglial reactivity. *J Neuropathol Exp Neurol* 70, 551–567. [PubMed: 21666502]
- Shlosberg D, Benifla M, Kaufer D, Friedman A, 2010 Blood-brain barrier breakdown as a therapeutic target in traumatic brain injury. *Nat Rev Neurol* 6, 393–403. [PubMed: 20551947]
- Silva LF, Hoffmann MS, Gerbatin Rda R, Fiorin Fda S, Dobrachinski F, Mota BC, Wouters AT, Pavarini SP, Soares FA, Figuera MR, Royes LF, 2013 Treadmill exercise protects against pentylenetetrazol-induced seizures and oxidative stress after traumatic brain injury. *Journal of neurotrauma* 30, 1278–1287. [PubMed: 23530735]
- Silva PE, Maldaner V, Vieira L, de Carvalho KL, Gomes H, Melo P, Babault N, Cipriano G Jr., Durigan JLQ, 2018 Neuromuscular electrophysiological disorders and muscle atrophy in mechanically-ventilated traumatic brain injury patients: New insights from a prospective observational study. *J Crit Care* 44, 87–94. [PubMed: 29078131]
- Silva PP, Bhatnagar S, Herman SD, Zafonte R, Klibanski A, Miller KK, Tritos NA, 2015 Predictors of Hypopituitarism in Patients with Traumatic Brain Injury. *J Neurotrauma* 32, 1789–1795. [PubMed: 26413767]
- Simsek Y, Karaca Z, Tanriverdi F, Unluhizarci K, Selcuklu A, Kelestimur F, 2015 A comparison of low-dose ACTH, glucagon stimulation and insulin tolerance test in patients with pituitary disorders. *Clin Endocrinol (Oxf)* 82, 45–52. [PubMed: 24953859]

- Singh IN, Sullivan PG, Deng Y, Mbye LH, Hall ED, 2006 Time course of post-traumatic mitochondrial oxidative damage and dysfunction in a mouse model of focal traumatic brain injury: implications for neuroprotective therapy. *J Cereb Blood Flow Metab* 26, 1407–1418. [PubMed: 16538231]
- Stein DM, Lindel AL, Murdock KR, Kufera JA, Menaker J, Scalea TM, 2012 Use of serum biomarkers to predict secondary insults following severe traumatic brain injury. *Shock* 37, 563–568. [PubMed: 22552017]
- Stigger F, Marcolino MAZ, Portela KM, Plentz RDM, 2018 Effects of Exercise on Inflammatory, Oxidative and Neurotrophic Biomarkers on Cognitively Impaired Individuals Diagnosed with Dementia or Mild Cognitive Impairment: A Systematic Review and Meta-Analysis. *J Gerontol A Biol Sci Med Sci*.
- Stoecklein VM, Osuka A, Lederer JA, 2012 Trauma equals danger--damage control by the immune system. *J Leukoc Biol* 92, 539–551. [PubMed: 22654121]
- Sullivan EM, Pennington ER, Green WD, Beck MA, Brown DA, Shaikh SR, 2018 Mechanisms by Which Dietary Fatty Acids Regulate Mitochondrial Structure-Function in Health and Disease. *Advances in Nutrition* 9, 247–262. [PubMed: 29767698]
- Sun B, Hu C, Fang H, Zhu L, Gao N, Zhu J, 2015 The effects of *Lactobacillus acidophilus* on the intestinal smooth muscle contraction through PKC/MLCK/MLC signaling pathway in TBI mouse model. *PLoS one* 10, e0128214. [PubMed: 26030918]
- Sundman MH, Chen NK, Subbian V, Chou YH, 2017 The bidirectional gut-brain-microbiota axis as a potential nexus between traumatic brain injury, inflammation, and disease. *Brain Behav Immun* 66, 31–44. [PubMed: 28526435]
- Szendroedi J, Frossard M, Klein N, Bieglmayer C, Wagner O, Pacini G, Decker J, Nowotny P, Muller M, Roden M, 2012 Lipid-induced insulin resistance is not mediated by impaired transcapillary transport of insulin and glucose in humans. *Diabetes* 61, 3176–3180. [PubMed: 22891212]
- Takahashi Y, 2017 The Role of Growth Hormone and Insulin-Like Growth Factor-I in the Liver. *Int J Mol Sci* 18.
- Tan H, Yang W, Wu C, Liu B, Lu H, Wang H, Yan H, 2017 Assessment of the role of intracranial hypertension and stress on hippocampal cell apoptosis and hypothalamic-pituitary dysfunction after TBI. *Sci Rep* 7, 3805. [PubMed: 28630478]
- Tanriverdi F, Kelestimir F, 2015 Neuroendocrine Disturbances after Brain Damage: An Important and Often Undiagnosed Disorder. *J Clin Med* 4, 847–857. [PubMed: 26239451]
- Tanriverdi F, Schneider HJ, Aimaretti G, Masel BE, Casanueva FF, Kelestimir F, 2015 Pituitary dysfunction after traumatic brain injury: a clinical and pathophysiological approach. *Endocr Rev* 36, 305–342. [PubMed: 25950715]
- Taylor BC, Hagel Campbell E, Nugent S, Bidelspach DE, Kehle-Forbes SM, Scholten J, Stroupe KT, Sayer NA, 2017 Three Year Trends in Veterans Health Administration Utilization and Costs after Traumatic Brain Injury Screening among Veterans with Mild Traumatic Brain Injury. *J Neurotrauma* 34, 2567–2574. [PubMed: 28482747]
- Tsatsoulis A, Mantzaris MD, Bellou S, Andrikoula M, 2013 Insulin resistance: an adaptive mechanism becomes maladaptive in the current environment - an evolutionary perspective. *Metabolism* 62, 622–633. [PubMed: 23260798]
- Tyagi E, Zhuang Y, Agrawal R, Ying Z, Gomez-Pinilla F, 2015 Interactive actions of Bdnf methylation and cell metabolism for building neural resilience under the influence of diet. *Neurobiology of disease* 73, 307–318. [PubMed: 25283985]
- Undurti A, Colasurdo EA, Sikkema CL, Schultz JS, Peskind ER, Pagulayan KF, Wilkinson CW, 2018 Chronic hypopituitarism associated with increased postconcussive symptoms is prevalent after blast-induced mild traumatic brain injury. *Frontiers in neurology* 9, 72. [PubMed: 29515515]
- Van den Berghe G, Wilmer A, Milants I, Wouters PJ, Bouckaert B, Bruyninckx F, Bouillon R, Schetz M, 2006 Intensive insulin therapy in mixed medical/surgical intensive care units: benefit versus harm. *Diabetes* 55, 3151–3159. [PubMed: 17065355]
- van der Heide LP, Ramakers GM, Smidt MP, 2006 Insulin signaling in the central nervous system: learning to survive. *Prog Neurobiol* 79, 205–221. [PubMed: 16916571]

- van der Poll T, van Deventer SJ, 1999 Cytokines and anticytokines in the pathogenesis of sepsis. *Infectious disease clinics of North America* 13, 413–426. [PubMed: 10340175]
- Venkata C, Kasal J, 2018 Cardiac Dysfunction in Adult Patients with Traumatic Brain Injury: A Prospective Cohort Study. *Clin Med Res* 16, 57–65. [PubMed: 30587559]
- Ventura-Clapier R, Garnier A, Veksler V, 2008 Transcriptional control of mitochondrial biogenesis: the central role of PGC-1alpha. *Cardiovasc Res* 79, 208–217. [PubMed: 18430751]
- Verstrepen L, Bekaert T, Chau TL, Tavernier J, Chariot A, Beyaert R, 2008 TLR-4, IL-1R and TNF-R signaling to NF-kappaB: variations on a common theme. *Cell Mol Life Sci* 65, 2964–2978. [PubMed: 18535784]
- Vespa P, Bergsneider M, Hattori N, Wu H-M, Huang S-C, Martin NA, Glenn TC, McArthur DL, Hovda DA, 2005 Metabolic crisis without brain ischemia is common after traumatic brain injury: a combined microdialysis and positron emission tomography study. *Journal of Cerebral Blood Flow & Metabolism* 25, 763–774. [PubMed: 15716852]
- Villapol S, Balarezo MG, Affram K, Saavedra JM, Symes AJ, 2015a Neurorestoration after traumatic brain injury through angiotensin II receptor blockage. *Brain* 138, 3299–3315. [PubMed: 26115674]
- Villapol S, Kryndushkin D, Balarezo MG, Campbell AM, Saavedra JM, Shewmaker FP, Symes AJ, 2015b Hepatic expression of serum amyloid A1 is induced by traumatic brain injury and modulated by telmisartan. *The American journal of pathology* 185, 2641–2652. [PubMed: 26435412]
- Villapol S, Kryndushkin D, Balarezo MG, Campbell AM, Saavedra JM, Shewmaker FP, Symes AJ, 2015c Hepatic expression of serum amyloid A1 is induced by traumatic brain injury and modulated by telmisartan. *Am J Pathol* 185, 2641–2652. [PubMed: 26435412]
- Vivar C, van Praag H, 2017 Running changes the brain: the long and the short of it. *Physiology* 32, 410–424. [PubMed: 29021361]
- Wagner AK, Amin KB, Niyonkuru C, Postal BA, McCullough EH, Ozawa H, Dixon CE, Bayir H, Clark RS, Kochanek PM, Fabio A, 2011 CSF Bcl-2 and cytochrome C temporal profiles in outcome prediction for adults with severe TBI. *J Cereb Blood Flow Metab* 31, 1886–1896. [PubMed: 21448217]
- Walker PA, Shah SK, Jimenez F, Aroom KR, Harting MT, Cox CS Jr., 2012 Bone marrow-derived stromal cell therapy for traumatic brain injury is neuroprotective via stimulation of non-neurologic organ systems. *Surgery* 152, 790–793. [PubMed: 22853856]
- Washington PM, Villapol S, Burns MP, 2016 Polypathology and dementia after brain trauma: Does brain injury trigger distinct neurodegenerative diseases, or should they be classified together as traumatic encephalopathy? *Exp Neurol* 275 Pt 3, 381–388. [PubMed: 26091850]
- Willeumier K, Taylor DV, Amen DG, 2012 Elevated body mass in National Football League players linked to cognitive impairment and decreased prefrontal cortex and temporal pole activity. *Transl Psychiatry* 2, e68. [PubMed: 22832730]
- Woolf CJ, 1987 Excitatory amino acids increase glycogen phosphorylase activity in the rat spinal cord. *Neurosci Lett* 73, 209–214. [PubMed: 2882447]
- Wright DK, Liu S, van der Poel C, McDonald SJ, Brady RD, Taylor L, Yang L, Gardner AJ, Ordidge R, O'Brien TJ, Johnston LA, Shultz SR, 2017 Traumatic Brain Injury Results in Cellular, Structural and Functional Changes Resembling Motor Neuron Disease. *Cereb Cortex* 27, 4503–4515. [PubMed: 27566977]
- Wu A, Ying Z, Gomez-Pinilla F, 2014 Dietary strategy to repair plasma membrane after brain trauma: implications for plasticity and cognition. *Neurorehabil Neural Repair* 28, 75–84. [PubMed: 23911971]
- Xiang L, Lu S, Mittwede PN, Clemmer JS, Hester RL, 2014 Inhibition of NADPH oxidase prevents acute lung injury in obese rats following severe trauma. *Am J Physiol Heart Circ Physiol* 306, H684–689. [PubMed: 24414071]
- Yehuda H, Szuchman-Sapir A, Khatib S, Musa R, Tamir S, 2011 Human atherosclerotic plaque lipid extract promotes expression of proinflammatory factors in human monocytes and macrophage-like cells. *Atherosclerosis* 218, 339–343. [PubMed: 21862015]

- Yin Y, Li E, Sun G, Yan HQ, Foley LM, Andrzejczuk LA, Attarwala IY, Hitchens TK, Kiselyov K, Dixon CE, Sun D, 2018 Effects of DHA on Hippocampal Autophagy and Lysosome Function After Traumatic Brain Injury. *Mol Neurobiol* 55, 2454–2470. [PubMed: 28365875]
- Zhang X, Dong F, Ren J, Driscoll MJ, Culver B, 2005 High dietary fat induces NADPH oxidase-associated oxidative stress and inflammation in rat cerebral cortex. *Exp Neurol* 191, 318–325. [PubMed: 15649487]
- Zhang X, Jiang X, 2015a Effects of enteral nutrition on the barrier function of the intestinal mucosa and dopamine receptor expression in rats with traumatic brain injury. *Journal of Parenteral and Enteral Nutrition* 39, 114–123. [PubMed: 24047867]
- Zhang X, Jiang X, 2015b Effects of enteral nutrition on the barrier function of the intestinal mucosa and dopamine receptor expression in rats with traumatic brain injury. *JPEN J Parenter Enteral Nutr* 39, 114–123. [PubMed: 24047867]
- Zhang Y, Chopp M, Meng Y, Katakowski M, Xin H, Mahmood A, Xiong Y, 2015 Effect of exosomes derived from multipotent mesenchymal stromal cells on functional recovery and neurovascular plasticity in rats after traumatic brain injury. *J Neurosurg* 122, 856–867. [PubMed: 25594326]
- Zhao Q, Yan T, Li L, Chopp M, Venkat P, Qian Y, Li R, Wu R, Li W, Lu M, Zhang T, Chen J, 2019 Immune Response Mediates Cardiac Dysfunction after Traumatic Brain Injury. *J Neurotrauma* 36, 619–629. [PubMed: 30045672]
- Zhou J, Burns MP, Huynh L, Villapol S, Taub DD, Saavedra JM, Blackman MR, 2017 Temporal Changes in Cortical and Hippocampal Expression of Genes Important for Brain Glucose Metabolism Following Controlled Cortical Impact Injury in Mice. *Front Endocrinol (Lausanne)* 8, 231. [PubMed: 28955302]
- Zhu KJ, Huang H, Chu H, Yu H, Zhang SM, 2014 Alterations in enterocyte mitochondrial respiratory function and enzyme activities in gastrointestinal dysfunction following brain injury. *World J Gastroenterol* 20, 9585–9591. [PubMed: 25071356]
- Zlotnik A, Klin Y, Gruenbaum BF, Gruenbaum SE, Ohayon S, Leibowitz A, Kotz R, Dubilet M, Boyko M, Shapira Y, Teichberg VI, 2012 beta2 adrenergic-mediated reduction of blood glutamate levels and improved neurological outcome after traumatic brain injury in rats. *J Neurosurg Anesthesiol* 24, 30–38. [PubMed: 21979171]
- Zygun DA, Zuege DJ, Boiteau PJ, Laupland KB, Henderson EA, Kortbeek JB, Doig CJ, 2006 Ventilator-associated pneumonia in severe traumatic brain injury. *Neurocrit Care* 5, 108–114. [PubMed: 17099256]

Highlights

- Brain pathology impacts the body via autonomic nervous system, endocrine and immune pathways
- Peripheral metabolic dysfunction after TBI exacerbates brain pathology
- Metabolic dysfunction increases incidence of long-term neurological disorders after TBI
- Metabolic dysfunction is a predictor of poor outcome in TBI patients

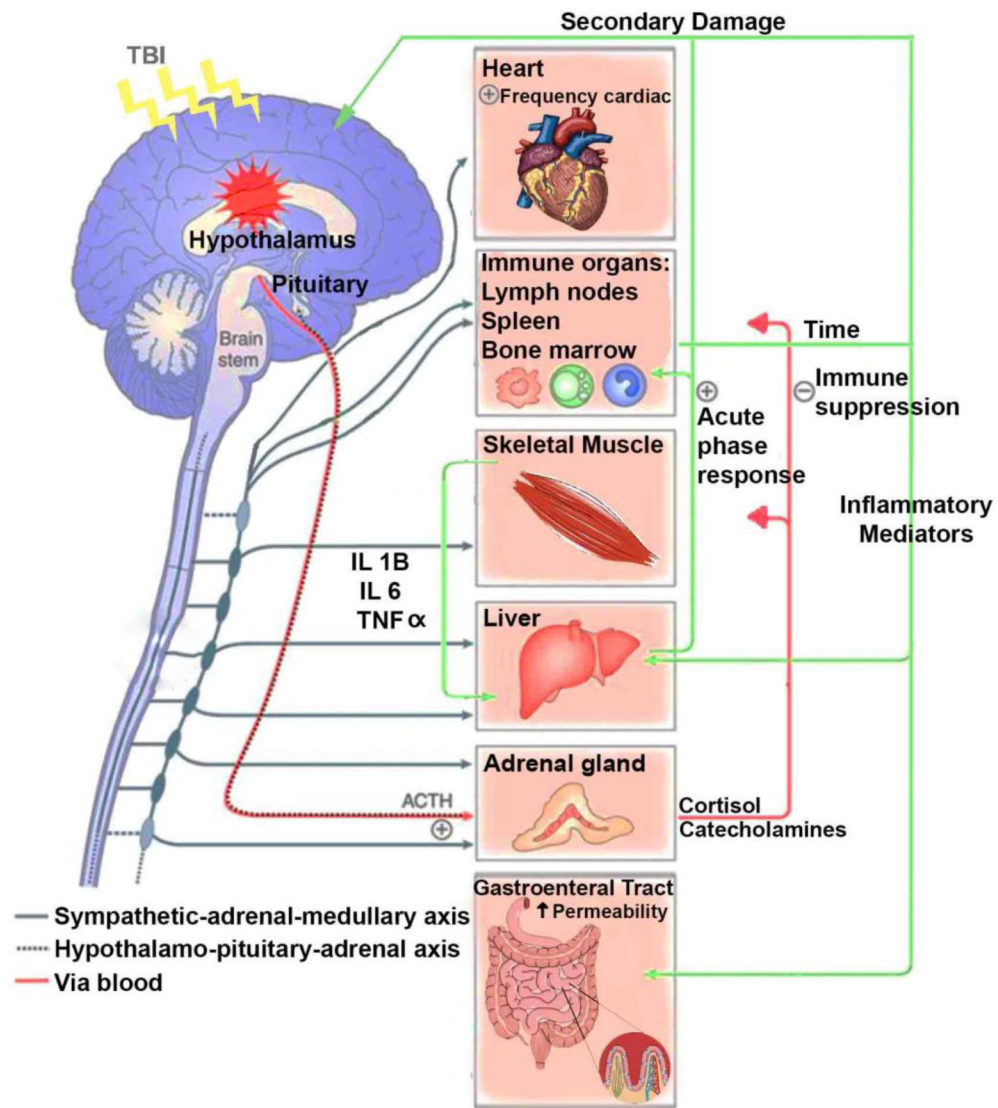


Figure 1.

The diagram illustrates the main organ components for the interaction between the brain and periphery after TBI. TBI induces central inflammation and triggers a multiorgan inflammatory response, involving the action of the autonomic nervous system and hypothalamic-pituitary axis. Autonomic dysregulation and subsequent secretion of catecholamines into the periphery are major players on the generalized host stress response after TBI. For instance: Sympathetic hyperactivity after TBI results in an elevated heart rate and blood pressure. Catecholamine signal through α - and β -adrenergic receptors which are expressed in immune organs like lymph nodes, spleen and bone marrow have the potential to influence the production of inflammatory mediators that alter the redox status in the liver and increase the intestinal permeability after TBI. The generalized sepsis response caused by translocation of bacteria induces a systemic inflammatory sequel with subsequent secondary inflammation in the brain. The liver reacts to sympathetic activation after TBI by displaying a systemic acute-phase response, involving leukocyte mobilization, and increase in cytokines

that penetrate the leaky BBB, and become a major player of the secondary brain damage. Indeed, the muscle wasting during the initial phase of injury has been associated with ACTH and catecholamine release since muscle release of amino acids are used for inflammatory protein synthesis in the liver. The Catecholamine and cortisol effects on immune organs like lymph nodes, spleen and bone marrow also contribute to secondary damage after TBI.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

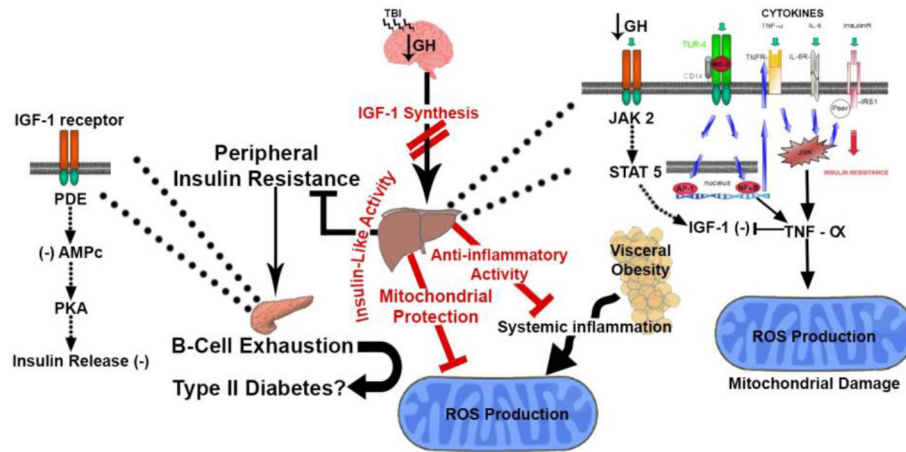


Figure 2. Proposed mechanism by which TBI alters hypothalamic-pituitary growth hormone (GH) Axis. TBI-induced chronic growth hormone deficiency (GHD) is characterized by metabolic abnormalities associated with decreased IGF-1 synthesis. The presence of low plasma GH decreases the hepatic IGF-1 synthesis via dysregulation of the GH receptor, JAK2 and STAT5 pathways. Early hepatic inflammation after TBI also activates the hepatic toll like receptors (TLR-4) that leads to nuclear translocation of the transcription factor NF- κ B, TNF- α receptor upregulation and TNF- α increase. This systemic inflammation could induce insulin resistance by stimulating cytokines receptors and JNK pathway that leads to serine/threonine phosphorylation of IRS1, TNF- α and mitochondrial ROS production. It is recognized that the growth hormone GH/IGF system is involved in metabolism manifestations. In turn, TBI-induced GH/IGF-1 deficiency may be associated with visceral obesity that leads to systemic inflammation and ROS production. Low plasma IGF-1 induces β -cell exhaustion and consequently peripheral insulin resistance by dysregulation of the IGF-1 receptor, PDE and PKA pathway.

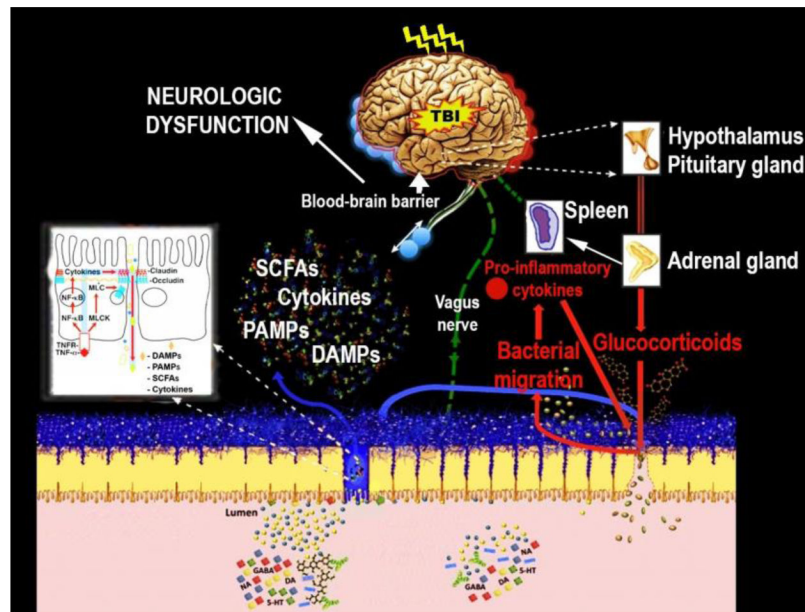


Figure 3. Proposed mechanism by which TBI alters the brain-gut axis, and in turn, how peripheral pathological signals impact the brain. Right after TBI, dysfunctional hypothalamic-pituitary-adrenal axis disrupts metabolic balance and increases stress hormones such as adrenocorticotropic and cortisol. It is postulated that the ACTH-induced Epinephrine (E) and norepinephrine (NE) by adrenal gland together with efferent vagal output promote splanchnic hypoperfusion, thereby increasing Cytokines and chemokines. The secreted TNF- α by spleen macrophages after TBI binds TNF receptors (TNFRs) on intestinal epithelial cells and activates several pathways, including the NF- κ B pathway that upregulates genes encoding pro-inflammatory cytokines and myosin light chain kinase (MLCK). These signals enhance tight junction permeability in the intestine involving damage-associated molecular patterns (DAMPs), Pathogen-associated molecular patterns (PAMPs), and cytokines. The Cytokines produced increases intestinal permeability and then penetrate the leaky BBB to contribute to secondary brain damage characterized by fatigue, and learning and memory dysfunctions.

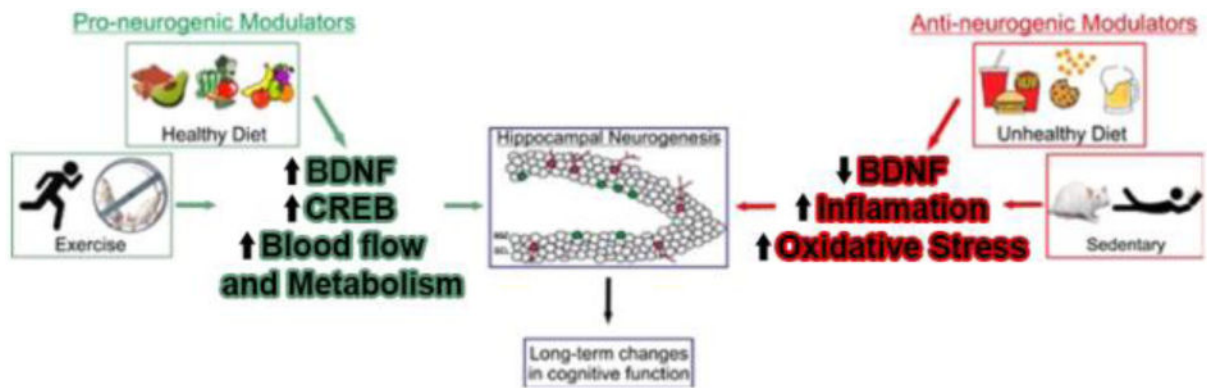


Figure 4.

Lifestyle factors influence neuronal plasticity such as neurogenesis, and cognition. Elevated levels of inflammatory metabolic agents elicited by Unhealthy Diet and sedentary lifestyle can negatively influence hippocampal neurogenesis. Since Reactive oxygen species (ROS) play an important role in the progression of inflammatory disorders, the ROS induced by chronic {Yamin, 2008 #396} {Yamin, 2008 #396} exposure to inflammatory mediators disrupts the endothelial barrier and allows the transfer of immune cells and pro-inflammatory cytokines into the brain parenchyma that, in turn, disrupts production of BDNF and the delicate balance needed for synaptic plasticity. This has detrimental consequences for neural precursor cells (neurogenesis), as well as for the normal neuronal functioning. On the other hand, Healthy diet and Physical exercise has pro-neurogenic properties through a variety of mechanisms, particularly by increasing blood flow, cell metabolism, and synaptic plasticity. These pro-neurogenic modulators promote hippocampal plasticity and long-term changes in cognitive function.

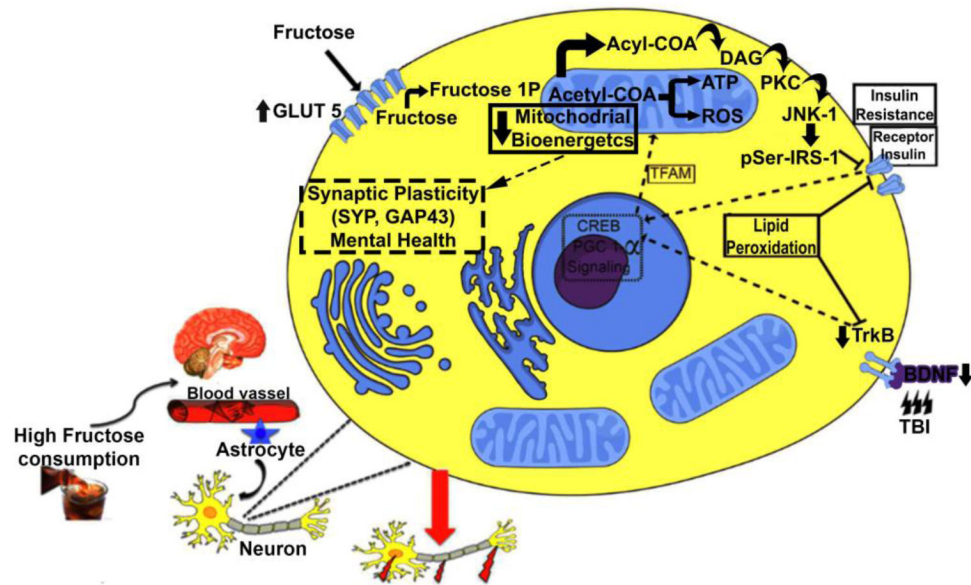


Figure 5.

Proposed mechanism by which metabolic disorders like the one elicited by high fructose consumption may aggravate the pathophysiology of TBI. In CNS, fructose increases levels of the fructose transporter GLUT5 suggesting that fructose consumption enhances its own transport into the brain. We propose that intracellular fructose accumulation induces the formation of acetyl-CoA and acyl-CoA. High levels of acyl-CoA can be converted to diacylglycerol (DAG) that activates the protein kinase C epsilon (PKCε), which, in turn, activates the protein c-jun-*N*terminal kinase-1 (JNK1). This protein leads to insulin resistance through the phosphorylation of IRS-1 on Serine307 residue (IRS-1Ser307). It is well known that the TrkB BDNF receptor and InR receptors are involved in regulation of cell metabolism and synaptic plasticity in neurons. Along this line of thought, the actions of fructose and TBI converge and inhibit pathways associated with management of cell energy metabolism like cAMP response element-binding protein (CREB) and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α). Considering the interactive actions of PGC-1α and mitochondrial transcription factor A (TFAM) on mitochondrial biogenesis, it is plausible to propose that fructose and TBI decrease oxidative phosphorylation and bioenergetics. It is important to note fructosylation releases large amounts of superoxide anions, leading to disproportionate formation of reactive oxygen species in mitochondria. Moreover, the loss in energy homeostasis results in ROS, and the harmful by-product of lipid peroxidation 4-hydroxynonenal (4HNE), thereby compromising plasma membrane function. Therefore, a high fructose diet and TBI disrupt the interplay between energy metabolism and synaptic plasticity with profound consequences for brain function.

Table 1.

Summary of clinical studies and Main Outcomes Addressing the effect of TBI on Peripheral Metabolism

Study (year)	Subjects	Purpose	Measurements	Main results
(Silva et al., 2018) (Silva et al., 2018)	Mechanically ventilated patients with severe TBI	Relationship between neuromuscular electrophysiological disorders (NED) and muscle atrophy in TBI patients.	The muscle structure (thickness and echogenicity) was assessed by B-mode ultrasound.	Mechanically-ventilated patients with TBI developed NED and muscle atrophy
(Shibahashi et al., 2017) (Shibahashi et al., 2017)	Olderpatients (age 60 years) with TBI	Evaluate skeletal muscle mass as predictive marker for TBI outcome.	Skeletal muscle mass and clinical outcomes (Glasgow scale)	Reduced skeletal muscle mass was associated with poorer outcome after TBI
(Rizoli et al., 2017) (Rizoli et al., 2017)	Patients with isolated moderate-to-severe TBI	Association between catecholamine levels post-trauma and functional outcome.	Epinephrine (Epi) and norepinephrine (NE) and clinical outcomes (Glasgow scale)	Elevated circulating catecholamines, are independently associated with functional outcome and mortality after TBI
(Czorlich et al., 2017) (Czorlich et al., 2017)	Patients with severe TBI	Evaluate the impact of body mass index (BMI) on mortality and early neurologic outcome	Patients were categorized into underweight, normal, pre-obese and obese based on BMI. Early neurologic outcome was classified using the Glasgow Outcome Scale.	The BMI 35 is an independent predictor of mortality and is associated with an inferior early functional neurologic outcome.
(Mossberg et al., 2017) (Mossberg et al., 2017)	Patients with isolated moderate to severe TBI	The effects of recombinant human growth hormone (rhGH) replacement on physical and cognitive functioning in TBI patients.	Peak cardiorespiratory capacity, body composition, muscle force testing and neuropsychological tests.	The rhGH replacement has a positive impact on cardiorespiratory fitness and a positive impact on perceptual fatigue in survivors of TBI with altered GH secretion.
(Rau et al., 2017) (Rau et al., 2017)	Patients with isolated moderate to severe TBI	Analyze whether hyperglycemia is associated with higher morbidity and mortality in TBI patients.	TBI patients were allocated into four groups: Stress-induced hyperglycemia (SIH), diabetic hyperglycemia (DH), diabetes normoglycemia, and non-diabetic normoglycemia (NDN)	Patients with SIH and DH had significantly higher mortality than patients with NDN. The mortality was significantly higher in patients with SIH and but not with DH.
(Lu et al., 2017) (Lu et al., 2017)	Patients with isolated moderate to severe TBI	Determine if TBI patients have a higher risk of myocardial dysfunction than the general population and to identify the risk factors of myocardial dysfunction in TBI patients.	Patients who visited ambulatory care centers or were hospitalized with a diagnosis of TBI.	Diabetes, hypertension, peptic ulcer disease, chronic liver disease and chronic renal disease were risk factors of myocardial dysfunction in TBI patients
(Hendrick et al., 2016) (Hendrick et al., 2016)	Nonhead injured trauma patients	Impact of beta-blockers on Nonhead injured trauma patients	Mortality, length stay in intensive care unit (ICU)	Beta-blockers had not effect on mortality and ICU in TBI patients
(Park et al., 2016) (Park et al., 2016)	Patients with diffuse axonal injury.	Investigate the regional cerebral metabolism related to growth hormone deficiency (GHD) after traumatic brain injury (TBI)	Patients underwent brain F-18 FDG PET study and an insulin tolerance test (ITT).	Compared with subjects with TBI but normal GH, patients with GHD after TBI showed decreased cerebral glucose metabolism.
(Giuliano et al., 2017) (Giuliano et al., 2017)	Patients with complicated mild TBI	Evaluate whether mild TBI patients with GH deficiency had developed alterations in the glycolipid profile and clinical indices of injury severity and neurological outcome.	GH deficiency was investigated by the combined test (GH releasing hormone + arginine). The glycolipid and clinical outcomes (Glasgow scale) were also evaluated.	TBI Patients had high occurrence of isolated GH deficiency, which was associated with visceral adiposity and metabolic alterations.
(Di Battista et al., 2016) (Di Battista et al., 2016)	Patients with moderate-to-severe TBI	Early dynamic profile of circulating inflammatory cytokines/chemokines and interrelationships between these	Plasma cytokine, chemokine, catecholamines. Neurological outcome was assessed using	Positive association between catecholamines, cytokines and chemokine with poor

Study (year)	Subjects	Purpose	Measurements	Main results
		mediators with catecholamines and clinical indices of injury severity and neurological outcome.	the extended Glasgow outcome scale (GOSE)	outcome at 6 months after TBI.
(Ko et al., 2016) (Ko et al., 2016)	Patients with moderate-to-severe TBI	The effect of β -Adrenergic receptor blockers (BBs) on TBI-induced cascade of immune and inflammatory.	Patients who received early propranolol after TBI (Feldman et al.) were compared with those who did not (non-EPAT). Data including demographics, hospital length of stay (LOS) and mortality were collected.	Early administration of propranolol after TBI was associated with improved survival.
(Majdan et al., 2015) (Majdan et al., 2015)	Patients with severe TBI	Analyze whether BMI, height and weight of patients were related to severity, patterns and outcomes of TBI caused by low level falls.	Patients were categorized into underweight, normal, pre-obese and obese based on BMI and demographic characteristics, injury severity, patterns and outcomes were compared.	The patients in all BMI groups were of similar injury severity and neurological status. Obese and pre-obese patients required longer stay at ICU.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 2

Summary of preclinical studies and Main Outcomes Addressing the effect of TBI on Peripheral Metabolism

Study (year)	Experimental model/sample	Purpose	Main results
(Shahidi et al., 2018) (Shahidi et al., 2018)	Controlled cortical impact model (CCI)	investigate skeletal muscle-related changes (atrophy and degeneration/regeneration) resulting from CCI	CCI induces degeneration in Soleus and atrophy in tibialis anterior muscle.
(Ma et al., 2017b) (Ma et al., 2017b)	Controlled cerebral blast injury model	Correlation between cytokines and hepatic cytochrome P450 (CYP450) enzyme superfamily after TBI	The cytokines in serum have a negative correlation with the expressions of CYP450 enzymes.
(de Castro et al., 2017)	Fluid Percussion Injury model (FPI)	Investigate whether a peripheral oxidative/inflammatory response contributes to neuronal dysfunction after TBI, as well as the prophylactic role of exercise training.	Exercise training alters the profile of oxidative-inflammatory status in liver and protects against acute hyperglycaemia and a cerebral inflammatory response after TBI
(Lang et al., 2015) (Lang et al., 2015)	weight drop model of TBI	Evaluate the impact of body mass index (BMI) on mortality and early neurologic outcome in patients suffering from severe TBI.	Beta-adrenergic blockade reduced TBI-induced sympathetic hyperactivity, and prevented histopathological intestinal injury, gut permeability after TBI
(Sun et al., 2015) (Sun et al., 2015)	Feeney's weight-drop method	The effects of probiotic <i>Lactobacillus acidophilus</i> on the intestinal smooth muscle contraction in TBI mouse model.	PKC/MLCK/MLC signaling pathway plays an important role in <i>Lactobacillus acidophilus</i> -mediated improvement of contractile properties of intestinal smooth muscle after TBI. .
(Villapol et al., 2015) (Villapol et al., 2015b)	Controlled cerebral blast injury model	Investigate whether systemic response to trauma is associated with the hepatic acute-phase response.	TBI induces an increase in expression of the acute-phase protein, SAA1, and also AT1R mRNA, together with several other inflammatory changes in liver.
(Anderson et al., 2015) (Anderson et al., 2015)	Cortical contusion impact (CCI) injury model.	Determine the effects of TBI alone on the gene expression of hepatic inflammatory proteins, drug-metabolizing enzymes, and transporters in CCI model	In contrast to clinical TBI, there was not a significant effect of experimental TBI on CYP or UGT2B7 metabolic enzymes.
(Zhang et al., 2014) (Zhang and Jiang, 2015a)	Fluid Percussion Injury model(FPI)	The investigate the expression of Resistin in subcutaneous adipose tissue of rats with traumatic brain injury	FPI increased the gene expression of Resistin in subcutaneous fat 12 h, 24 h, 72 h, 1 week, 2 weeks, and 4 weeks after TBI.
(Jin et al., 2014) (Jin et al., 2014)	Fluid Percussion Injury model(FPI)	The investigate the expression of Resistin in muscle of rats after TBI	Compared with control, the muscular resistin expression in FPI increased the gene expression of Resistin in muscle
(Zhu et al., 2014) (Zhu et al., 2014)	Feeney's weight-drop method	Alterations in rat enterocyte mitochondrial respiratory function and enzyme activities in gastrointestinal after traumatic brain injury (TBI).	Rat enterocyte mitochondrial respiratory function and enzyme activities are inhibited following TBI.
(Keshavarzi et al., 2014) (Keshavarzi et al., 2014)	Controlled cerebral blast injury model	Assess the alteration of gastric function and barrier function of gastrointestinal (GI) tract following TBI.	TBI induced Inflammation, congestion, ulcer and intragastric pressure reduction
(Hu et al., 2013)(Hu et al., 2013)	Cortical contusion impact (CCI) injury model	Effect of TBI on intestinal expression pattern of CD40	The positive relationship between the expression of CD40 and that of TNF- α , VCAM-1, and ICAM-1 in jejunum after TBI.
(Olsen et al., 2013) (Olsen et al., 2013)	Controlled cortical impact injury (TBI)	Determine whether TBI affects intestinal smooth muscle function.	TBI decreased intestinal contractile activity, delayed transit that is attributed

Study (year)	Experimental model/sample	Purpose	Main results
			to inflammatory injury in the intestinal smooth.
(Chu et al., 2013) (Chu et al., 2013)	Controlled cortical impact injury (TBI)	The effect of TBI on molecular mechanisms in spleen and local brain inflammation.	Immediate splenectomy down-regulates the MAPKYNF-JB signaling pathway in rat brain after severe TBI.
(Larson et al., 2012) (Larson et al., 2012)	Fluid Percussion Injury model (FPI)	The effect of β -adrenergic blockade on blood pressure and left ventricle contractility after TBI	Treatment with propranolol protected against TBI-induced blood pressure, cardiac contractility and ROS generation increase.
(Zlotnik et al., 2012) (Zlotnik et al., 2012)	Controlled cortical impact injury (TBI)	The effect of nonselective β -adrenergic block antagonists on blood glutamate levels and on the neurological outcomes of rats after TBI	Systemic glutamate reduction after TBI is the result of a stress response and of the activation of the sympathetic nervous system through the β 2 adrenergic receptors.
(Bansal et al., 2009) (Bansal et al., 2009b)	Weight drop TBI model	The effect of vagal nerve stimulation intestinal permeability after TBI.	The central vagal stimulation regulates intestinal permeability after TBI.
(Moinard et al., 2008) (Moinard et al., 2008)	Fluid Percussion Injury model (FPI)	The effect of TBI on liver energy homeostasis.	TBI is responsible for an impairment of liver energy homeostasis.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript