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Making sense of gut feelings in the traumatic brain injury pathogenesis

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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.

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 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 (Fig. 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 interation can be pivotal for the prevention of secondary complications, and healing of patients

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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)	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)	Older patients (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)	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)	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)	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)	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)	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)	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)	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)	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)	Patients with moderate-to-severe TBI	Early dynamic profile of circulating inflammatory cytokines/chemokines and interrelationships between these mediators with catecholamines and clinical indices of injury severity and neurological outcome.	Plasma cytokine, chemokin, catecholamines. Neurological outcome was assessed using the extended Glasgow outcome scale (GOSE)	Positive association between catecholamines, cytokines and chemokine with poor outcome at 6 months after TBI.
(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., 2018) 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)	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.

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)	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)	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)	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)	Feeney's weight-drop method	The effects of probiotic *Lactobacillus acidophilus* on the intestinal smooth muscle contraction in TBI mouse model.	PKC/MLCK/MLC signaling pathway plays an important role in *Lactobacillus acidophilus*-mediated improvement of contractile properties of intestinal smooth muscle after TBI.
(Villapol et al., 2015a;b)	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)	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 UGT27B7 metabolic enzymes.
(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)	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)	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)	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)	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)	Controlled cortical impact injury (TBI)	Determine whether TBI affects intestinal smooth muscle function.	TBI decreased intestinal contractile activity, delayed transit that is attributed to inflammatory injury in the intestinal smooth.
(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)	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)	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 β2 adrenergic receptors.
(Bansal et al., 2009a,b)	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)	Fluid Percussion Injury model (FPI)	The effect of TBI on liver energy homeostasis.	TBI is responsible for an impairment of liver energy homeostasis.

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 Fig. 1) (Bierhaus et al., 2003; van der Poll and van Deventer, 1999). β-blocker therapy

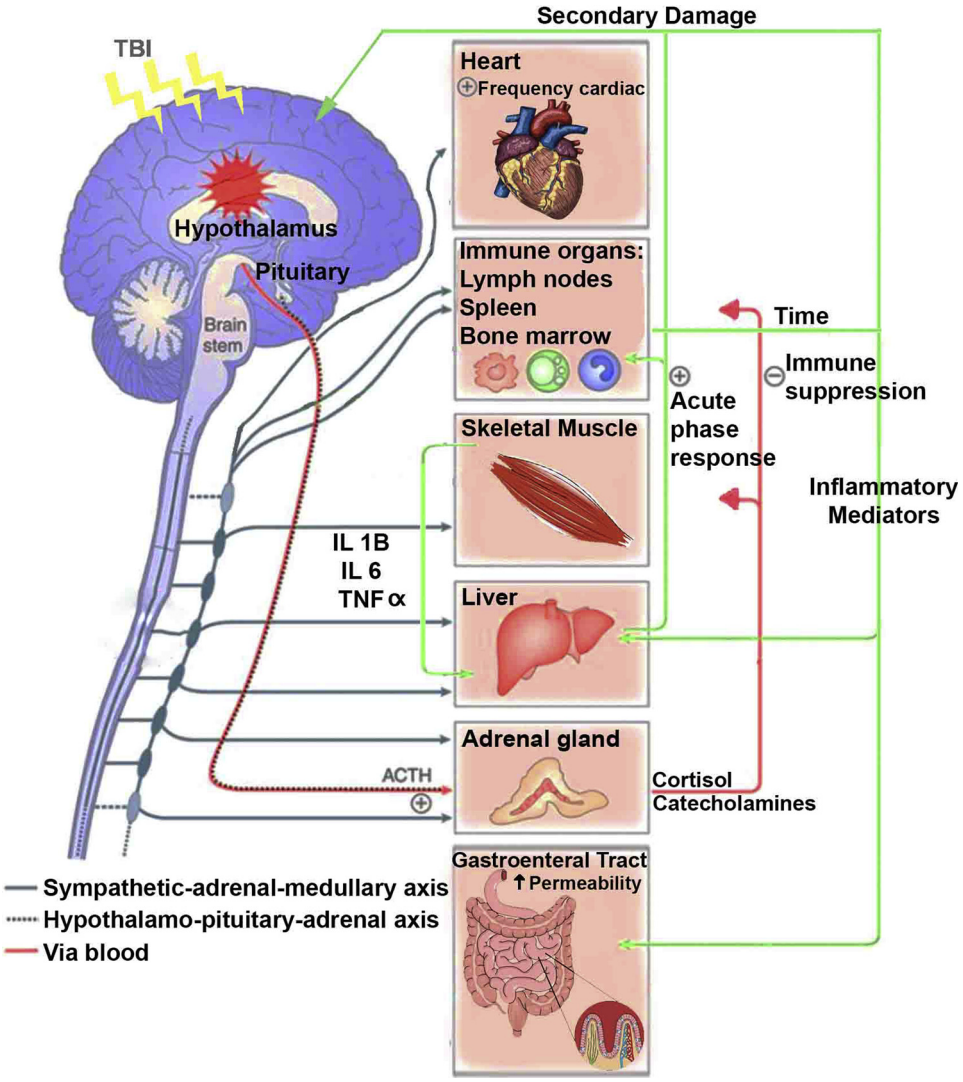


Fig. 1. The diagram illustrates the main organ components for the interaction between the brain and periphery after TBI. TBI induces central inflammation and triggers a multiorgan inflammatory response, involving the action of the autonomic nervous system and hypothalamic-pituitary axis. Autonomic dysregulation 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.

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%–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 function 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 et al., 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 μg/dL in acutely ill patients or lower than 10 μg/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

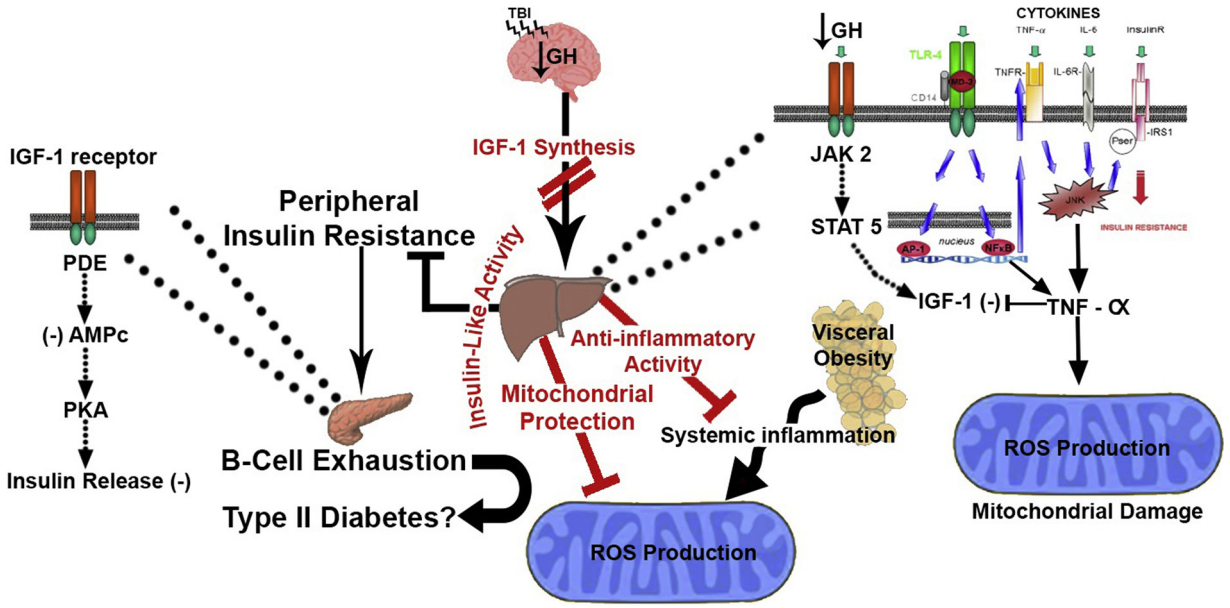


Fig. 2. Proposed mechanism by which TBI alters hypothalamic-pituitary growth hormone (GH) Axis. TBI-induced chronic growth hormone deficiency (GHD) is characterized by metabolic abnormalities associated with decreased IGF-1 synthesis. The presence of low plasma GH decreases the hepatic IGF-1 synthesis 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-κB, TNF-αreceptor 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.

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 Fig. 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 Fig. 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 5–10 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 (Fig. 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., 2015b). In turn, signals derived from the liver inflammatory reaction can exacerbate brain pathology (de Castro et al., 2017; Villapol et al., 2015b). Concussive brain injury in rodents causes major reductions in liver weight and protein production, with concomitant effects on body physiology (Moinard et al., 2008, 2005). It seems plausibly that these deficits in protein homeostasis and degradation in liver are responsible for the muscle athrophy 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 Fig. 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 Fig. 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-kB. 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 Fig. 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 incidency 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 co-morbidities 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 Fig. 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-1β, TNF-α, and IL-6, and altered microglia phenotype (Ritzel et al., 2018). In 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 Fig. 3) (Ma et al., 2017a).

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

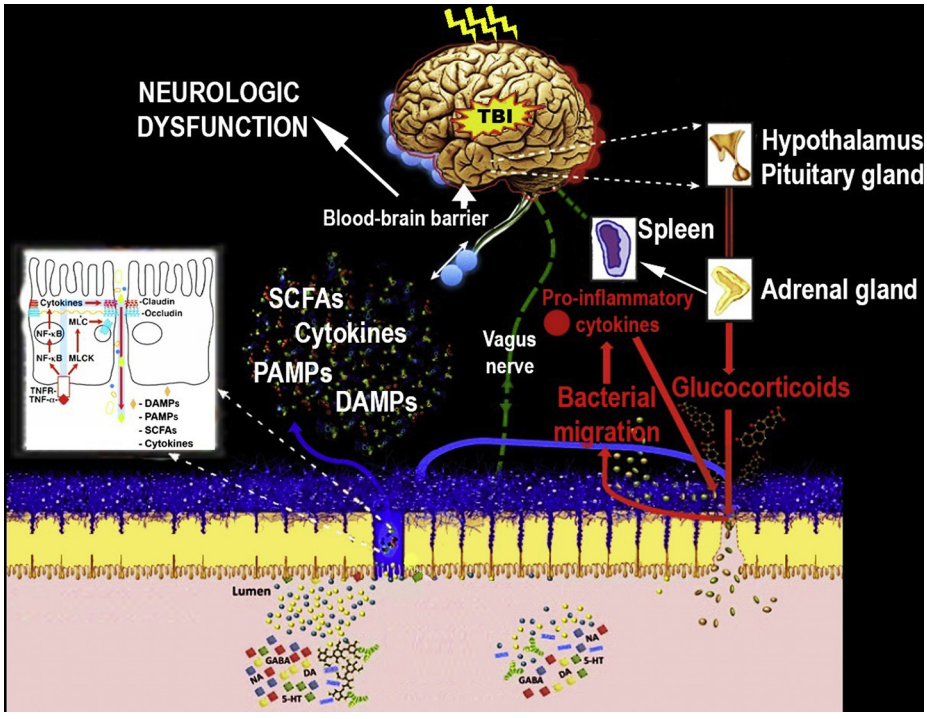


Fig. 3. Proposed mechanism by which TBI alters the brain-gut axis, and in turn, how peripheral pathological signals impact the brain. Right after TBI, dysfunctional hypothalamic-pituitary-adrenal axis disrupts metabolic balance and increases stress hormones such adrenocorticotrophic and cortisol. It 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-κB 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.

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 Fig. 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.

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 Fig. 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 commensurable 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 Fig. 2) (Ruan et al., 2002). The inflammatory reaction after TBI also increases the level of corticotrophin-releasing hormone (CRH) which stimulates the release of adrenocorticotropic 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 Fig. 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., 2015b), leading to reduced hepatic insulin sensitivity and loss of GH sensitivity (see Fig. 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., 1985). 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

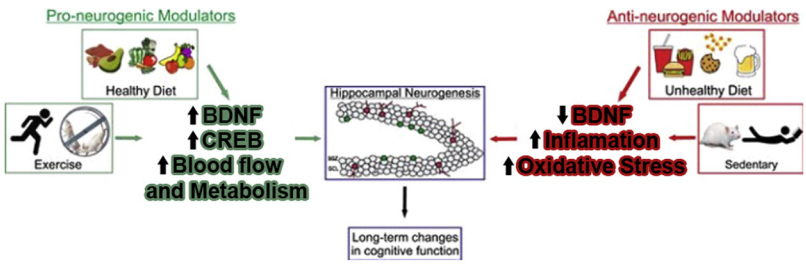


Fig. 4. Lifestyle factors influence neuronal plasticity such as neurogenesis, and cognition. Elevated levels of inflammatory metabolic agents elicited by Unhealthy Diet and sedentary lifestyle can negatively influence hippocampal neurogenesis. Since Reactive oxygen species (ROS) play an important role in the progression of inflammatory disorders, the ROS induced by chronic 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.

indicate that the insulin resistance observed in the periphery also occurs in brain tissue (see Fig. 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-1α). PGC-1α is a member of a family of transcription co-activators (Ventura-Clapier et al., 2008), which in conjunction with the mitocho2ndrial transcription factor A (TFAM) (Campbell et al., 2012; Ekstrand et al., 2004), and sirtuin 1 (SIRT1) regulate cellular energy metabolism. PGC-1α 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,c) 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-1α) 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 Fig. 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 min 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 cardiovascular 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 (Ruegsegger 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 Fig. 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

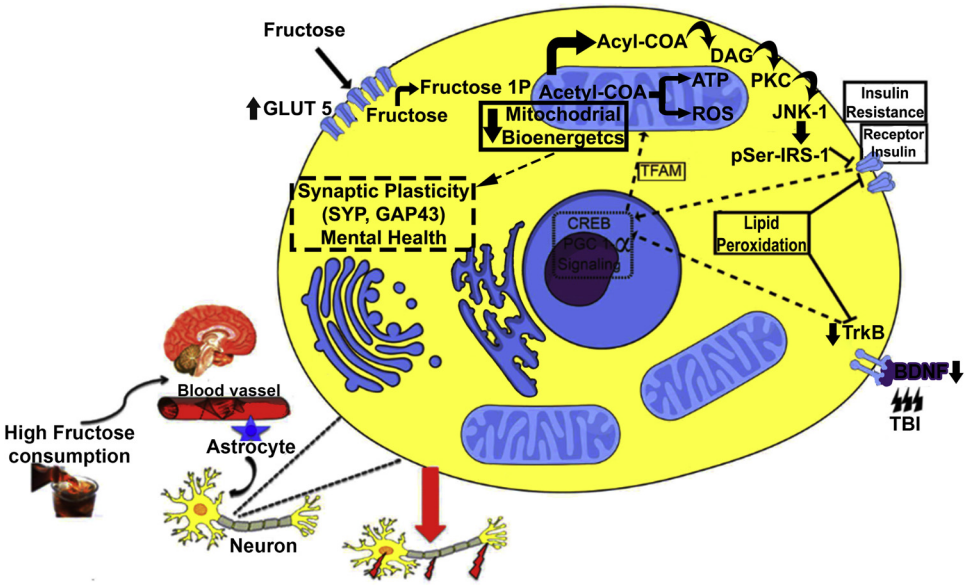


Fig. 5. Proposed mechanism by which metabolic disorders like the one elicited by high fructose consumption may aggravate the pathophysiology of TBI. In CNS, fructose increases levels of the fructose transporter GLUT5 suggesting that fructose consumption enhances its own transport into the brain. We propose 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 know 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 import 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.

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 Fig. 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-1α (Herzig et al., 2001). PGC-1α is a transcription regulator deeply involved in energy metabolism and mitochondrial function (Romero et al., 2014). The interaction between CREB and PGC-1α is reflected by results showing that phosphorylation of CREB changes in proportion to levels of PGC-1α 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 Fig. 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-Gambero 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.

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