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Review

Western diet aggravates neuronal insult in post-traumatic brain injury: Proposed pathways for interplay

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ABSTRACT

Traumatic brain injury (TBI) is a global health burden and a major cause of disability and mortality. An early cascade of physical and structural damaging events starts immediately post-TBI. This primary injury event initiates a series of neuropathological molecular and biochemical secondary injury sequelae, that last much longer and involve disruption of cerebral metabolism, mitochondrial dysfunction, oxidative stress, neuroinflammation, and can lead to neuronal damage and death. Coupled to these events, recent studies have shown that lifestyle factors, including diet, constitute additional risk affecting TBI consequences and neuropathophysiological outcomes. There exists molecular cross-talk among the pathways involved in neuronal survival, neuroinflammation, and behavioral outcomes, that are shared among western diet (WD) intake and TBI pathophysiology. As such, poor dietary intake would be expected to exacerbate the secondary damage in TBI. Hence, the aim of this review is to discuss the pathophysiological consequences of WD that can lead to the exacerbation of TBI outcomes. We dissect the role of mitochondrial dysfunction, oxidative stress, neuroinflammation, and neuronal injury in this context. We show that currently available data conclude that intake of a diet saturated in fats, pre- or post-TBI, aggravates TBI, precludes recovery from brain trauma, and reduces the response to treatment.

1. A healthy metabolic state is required for normal brain function

1.1. Brain metabolism: a unique metabolic profile

The brain is an energy-intensive organ that can utilize glucose or ketone bodies as energy sources according to metabolite availability. Therefore, regulation of metabolic rates is especially vital in the central nervous system (CNS). Consequently, a rapid distortion of cerebral function could result from any metabolic imbalance compromising the availability of glucose without a compensatory ketogenic response as in the case of hyperinsulinemia or insulin resistance, for instance [1]. Interestingly, metabolic dysfunction is a direct risk factor for behavioral, cognitive and mood disorders [2]. As well, obesity has been linked to a higher risk of neurodegenerative disorders such as Alzheimer's disease [3]. Notably, these metabolic disorders and neuronal changes have been linked to common pathways involving inflammation, mitochondrial dysfunction and insulin resistance as will be discussed below.

1.2. Mitochondria: impact on brain function and cognition

Mitochondria are unique cytoplasmic energy production organelles with a separate genome, the mitochondrial DNA (mtDNA) [4]. Due to its proximity to increased reactive oxygen species (ROS) levels, its lack of histones, and its limited DNA proofreading and repair

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Abbreviations

(AMPK)	adenosine monophosphate activated protein kinase
(ATP)	adenosine triphosphate
(BBB)	blood-brain barrier
(BMI)	body mass index
(BDNF)	brain-derived neurotrophic factor
(CR)	caloric-restricted
(CREB)	cAMP-response element-binding protein
(CNS)	central nervous system
(CBF)	cerebral blood flow
(WD)	western diet
(IL)	interleukin
(mTOR)	mammalian target of rapamycin
(RNS)	reactive nitrogen species
(ROS)	reactive oxygen species
(TLR-4)	Toll-Like Receptor 4
(TBI)	traumatic brain injury
(TCA)	tricarboxylic acid
(T2DM)	type 2 diabetes mellitus.

capacities, mtDNA is more susceptible to damage than nuclear DNA [5]. mtDNA damage can be caused by metabolic insults such as redox homeostasis imbalance resulting from overconsumption of diets rich in fats, for instance. Interestingly, mitochondrial dysfunction may lead to the development of insulin resistance, which will be discussed in the next section [6]. The brain is vulnerable to mitochondrial defects given its dependence on mitochondrial function for neurogenesis, neurotransmitter synthesis, calcium homeostasis, and neuronal survival, plasticity, and excitability [7]. In fact, literature shows that mitochondrial dysfunction underlies the etiology of several neurodegenerative diseases such as Alzheimer's disease [8].

1.3. Insulin regulates metabolism and affects cognition

Insulin is the main hormone regulating blood-glucose levels and tissue glucose uptake . An abnormal blood insulin level, is a major marker of the metabolic syndrome [9]. Due to its ability to cross the blood brain barrier (BBB), insulin acts as a neuropeptide and activates neuronal insulin receptor signaling, which is critical for neuronal growth, survival, and differentiation [10]. Additionally, neuronal insulin signaling enhances neurogenesis, increases neuronal survival and reduces neuroinflammation [11]. Mounting evidence correlates insulin resistance in the brain to neurological diseases [12] and cognitive deficits [13]. In fact, insulin-mediated signaling pathways play important roles in the regulation of brain functions under normal and disease states [9]. For instance, insulin treatment in individuals with Alzheimer's disease improved memory performance [14]. These observations led to the notion that enhancing insulin signaling can be an attractive therapeutic target following brain injury.

2. Western diet (WD) alters brain metabolism

2.1. The western diet can lead to obesity, inflammation, and mitochondrial dysfunction

The shift towards WD (*i.e.* a diet rich in saturated fats and refined sugars) is correlated with an increased incidence of metabolic disorders including obesity and type 2 diabetes [15]. Of specific interest, WD has been shown to impair cognitive performance and synaptic plasticity, as well as increase the risk of dementia [16]. A large body of evidence correlates obesity with cognitive decline [17]. This is further compounded by the finding that obesity negatively impacts the outcome of a frontal head collision where obese patients had a higher likelihood of increased injury severity or death [18]. Remarkably, obesity can compromise and delay patient recovery post brain injury and can pose a burden to rehabilitation [19].

Mechanistically, WD intake and obesity have been shown to be accompanied by systemic inflammatory responses, which can cause cognitive decline and worsen brain injury outcomes [17, 20]. Adipocytes secrete pro-inflammatory mediators, which can promote metabolic dysregulation and insulin resistance [21]. Interestingly, WD-induced hyperinsulinemia and insulin resistance are thought to reciprocally drive this process via the trophic effect of insulin on adipocytes as the ensuing hypertrophy, in response to excess caloric intake, leads to hypoxia and inflammatory cell infiltration [22]. Pro-inflammatory cytokines usually induced by WD such as IL-1β and IL-6 can disrupt neural circuits involved in cognition and memory [23]. Moreover, evidence shows that WD consumption leads to inflammatory changes leading to brain insulin resistance [20]. Alongside, WD-induced neuronal pathologies are exacerbated by mitochondrial dysfunction including reduced activities of citrate synthase and complexes I and III [24] and increased mitochondrial ROS production [25].

2.2. High-fat diets are not created equal

Although the present review focuses on the effects of WD, it is prudent to differentiate its detrimental effects from the protective effects of another type of high-fat diet, the ketogenic diet (KD). KD is a fat-rich diet low in proteins and carbohydrates. Unlike WD, KD has low obesogenic and addictive potentials, and is neuroprotective [26, 27]. Reduced carbohydrate content, in the KD, mimics the beneficial effects of caloric restriction or fasting [28]. Under such conditions, sugar stores of the body are exhausted and the rate of gluconeogenesis is insufficient to provide glucose fast enough to meet brain energy needs. Metabolism is shifted towards the use of fats as the primary fuel source and liver catabolism of fatty acids is increased leading to subsequent rises in ketone bodies levels, which serve as an alternative energy supply for the brain [29]. Contrary to WD, the KD can reduce neuronal inflammation [30], decrease behavioral patterns of depression in animal models [31], ameliorate cognitive defects [32], and mitigate neuronal injury [33].

2.3. Low-fat traditional diets promote brain health

A large body of evidence supports the efficacy of low-fat dietary patterns in ameliorating age-related cognitive dysfunction and reducing risk of Alzheimer's dementia [34]. A recent longitudinal investigation of the effect of one such diet, the Mediterranean diet (MD), on cognitive health indicated that MD consumption was associated with reduced risk of dementia and better memory and language performance [35]. Smaller clinical trials had supported the conclusions regarding the cognitive impact of MD [36, 37].

Animal studies indicated that antioxidants and flavonoids from fruits and vegetables in these diets suppress neuro-inflammation by reducing oxidative stress and apoptosis via inhibiting NF-$_\kappa$B-dependent inflammatory signaling [34]. In direct contrast to WD, the MD was shown to reduce systemic insulin resistance in humans, not necessarily as a consequence of body weight modulation [38]. Other low fat dietary patterns have also been associated with an insulin sensitizing effect [39]. However, there is a paucity of studies investigating the direct impact of these dietary patterns on brain cognitive functions.

3. Traumatic brain injury: classification, secondary injury, and disruption of brain metabolism

3.1. TBI severity and secondary injury

Traumatic brain injury (TBI) is a life-threatening progressive brain insult, following a mechanical impact, leading to neurobehavioral dysfunction. Yearly, it is estimated that ~ 50 million TBIs occur worldwide with an overall cost reaching USD 400 billion [40]. TBI can be classified into focal injury due to blunt or penetrating impact or diffuse non-penetrating injury due to blast waves or inertial loading. Clinically, TBI severity is classified using the Glasgow Coma Scale coupled with neuroimaging techniques [40]. Typically, severe and moderate TBIs exhibit overt gross structural damage and "focal" abnormalities including subarachnoid hemorrhage, hematomas, and bleeding detected using neuroimaging. However, mild TBI (mTBI) or concussion injury shows negative neuroimaging results; nevertheless, this does not preclude future neurological defects [40].

The pathophysiological events in TBI occur as primary and secondary brain injuries. Primary injury represents the immediate direct mechanical damage at the site of injury including tissue damage, impaired regulation of cerebral blood flow (CBF), subarachnoid hemorrhage, epidural hematoma, subdural hematoma, and contusion. The secondary injury (non-mechanical damage) involves a cascade of downstream interacting cellular, and molecular events initiated by the primary insult [41]. The secondary brain injury involves diffuse axonal injury, inflammation, ischemia, excitotoxicity, and energy failure. Both, primary and secondary injuries interact to produce a complex pattern of evolving damage [42].

In the focal, open head injury, the primary and secondary brain injury phases are quite discernible. This penetrating brain trauma is associated with blood-brain barrier (BBB) disruption, recruitment of blood borne immune cells, and thus, a rapid inflammatory response at the injured neuronal site [43]. Contrarily, mTBI injury phases are more obscure with no spatial separation when compared to open head injury. This is commonly observed in sports injury where rotational and linear acceleration forces are applied to the brain with no penetrating injury [44, 45]. As a result, around 10–40% of mTBIs evolve into post-concussion syndrome and long-term cognitive and behavioral deficits associated with white matter injury without apparent neural cell degeneration [46].

3.2. TBI induces metabolic and oxidative stress: implications for mitochondrial dysfunction

An energy crisis emerges post-TBI as the increased energetic demand cannot be met due to mitochondrial dysfunction contributing to the progression of secondary injury [47]. Moreover, following TBI, glucose metabolism is altered, in part due to oxygen deprivation [48]. An elevation in the Lactate/Pyruvate ratio is observed post-TBI indicating a shift towards anaerobic metabolism in animal models [49, 50] and human subjects [51]. As such, shortly following TBI, the brain experiences a period of hyperglycolysis, during which glucose utilization is increased so as to meet the metabolic demands compounded by mitochondrial dysfunction [52]. The latter could result from the reduced activity of several mitochondrial enzymes post-TBI. Indeed, mitochondrial pyruvate dehydrogenase complex activity is decreased post-TBI [53], as well as the enzymatic activities of mitochondrial complexes I and IV, which compromises oxidative metabolism and leads to a decreased ATP/ADP ratio [53].

Mitochondrial dysfunction post-TBI may also result from its Ca^{2+} buffering function. Under normal physiological conditions, neuronal Ca^{2+}homeostasis is maintained by mitochondria [7]. Following TBI, aberrant release of neurotransmitters takes place, including the excitatory glutamate, leading to excitotoxicity [54]. Excitotoxicity is mainly mediated by the pathophysiological activation of voltage-gated calcium channels and the subsequent Ca^{2+} build up within neural cells. Consequently, excessive uptake of Ca^{2+} by mitochondria occurs, causing Ca^{2+} toxicity. This can lead to increased mitochondrial membrane permeability, dysfunctional mitochondrial enzymes and mitochondrial DNA damage [55]. Moreover, following TBI aberrant translocation of the mitochondrial-encoded protein dynamin-related protein 1 (DRP 1) to the outer mitochondrial membrane leads to excessive mitochondrial fission. This effectively decreases mitochondrial count possibly leading to neurodegeneration [56].

3.3. Individual differences in response to TBI

Differences in response to TBI have been noted among patients, where some may suffer from severe and persistent outcomes while others do not [57]. Several physiological and psychological factors can predispose individuals to the likelihood of these symptoms. These include: pre-existing psychological problems, gender, being older, and having previous head injuries [58–60].

A prospective cohort study conducted among patients with mTBI concluded that patients with negative mTBI perceptions, stress, anxiety and depression had worse outcomes [57]. Several studies were conducted in regards to age as a risk factor for poor prognosis post-TBI. In one study, adults aged > 60 had the highest rates of TBI-related hospitalization and death [59, 60].

Many studies reported a sex difference in the outcomes of TBI. Considering that the incidence of TBI is higher in males, most of the animal and clinical studies focus on the male population [61]. In fact, many studies have reported that females exhibit better outcomes post-TBI. This observation was related to female hormones and their ability to act as neuroprotective agents [62, 63]. Nevertheless, other studies reported worse outcomes of TBI in females following a concussion, with more symptoms and more persistent sequelae [59, 60].

4. WD, but not KD, worsens brain functional and metabolic outcomes post-TBI

4.1. WD exacerbates TBI-induced injury

Most studies evaluating the impact of altered dietary composition on TBI focused on its neuropathological and behavioral outcomes independent of the brain injury modes or severity context, i.e. whether it is mTBI or more pronounced penetrating head injury, or even on the level and timing of intervention, which represent key elements in defining a specific TBI model [64–66]. The lack of these correlational studies depicts major caveats in the field of nutritional supplementation/needs in TBI. In one study, the outcomes of secondary injury outcomes from a closed head injury with single hit (mTBI) were evaluated in WD-fed obese C57 BL/6 mice as compared to lean mice. At a chronic time point (30 days), the obese mice showed marked microglial activation along with a chronic inflammatory state, attributed to perturbation of the hypothalamic-pituitary adrenal axis [67]. Another study assessed the effect of chronic fructose consumption on hippocampal molecular changes and mitochondrial bioenergetics following diffuse brain injury. The authors did not notice differences one week after injury, whereas a more chronic time point (~one month) showed the secondary injury characteristic in this mTBI model [65]. Along the same lines, a high-fat/sucrose diet induced behavioral changes post-open head injury, where outcomes were assessed at 21 days post-injury. Brain-injured rats on the high fat/sucrose diet had more severe somatosensory dysfunction compared to rats in the sham group. Furthermore, the experimental group exhibited working memory impairment in addition to having significantly higher loss of cortical tissue post-injury. Nevertheless, the neurobehavioral outcomes were correlated primarily to the dietary intake rather than the open head TBI pathophysiology [64]. Similarly, four weeks of high-fat/sucrose feeding followed by experimental mild

diffused brain injury led to exacerbation of the TBI-induced impairment of spatial learning capacity. This decline in learning ability was confirmed by decreases in the levels of brain-derived neurotrophic factor (BDNF) in the CA3 and dentate gyrus of the hippocampus. Also, pronounced decreases were observed in the levels of active phosphorylated synapsin I protein, a major pre-synaptic protein, and cAMP-response element-binding protein (CREB), a downstream transcription factor that modulates synaptic transmission. Yet again, these changes were assessed only one week post-injury overlooking the secondary pathophysiological injury that needs to be checked at chronic time points relevant to the model used [66]. Similar results were obtained in other studies [68, 69]. Nevertheless, these results still suggest that WD can affect the molecular machinery responsible for maintaining neuronal function and homeostasis following brain injury.

It is noteworthy that all WD combinations associated with detrimental outcomes post-TBI (Table 1) have a non-ketogenic composition [27]; high in refined sugar and carbohydrate content, an essential factor contributing to the induction of hyperinsulinemia and insulin resistance. Significantly, obese mice subjected to repeated TBI showed prolonged reduction in PKB/ Akt activation, a downstream effector pathway of insulin signaling [70]. In this context, the question of gender differences arises. For a given BMI, females are more insulin sensitive than males [71]. Moreover, studies showed that females are less prone to develop insulin resistance following WD feeding [72]. As well, WD induced less inflammatory changes in females compared to males [73]. This could partly explain gender bias in TBI outcomes in patients on WD.

4.2. KD produces an opposite effect post-TBI

As part of the adaptive metabolic response to injury, the brain shifts towards ketone body metabolism as an alternative energy source [33, 74, 75] reducing the inefficient glycolytic breakdown of glucose and increased lactate production. This can decrease oxidative damage, improve ATP production, increase ATP hydrolysis, decrease inflammation and free radical production, and increase autophagy [30, 76]. Moreover, KD feeding for 72 h post-TBI significantly reduced release of cytochrome c from brain mitochondria, leading to decreased mitochondria-induced apoptosis [77]. Importantly, KD reduced TBI-induced oxidative stress, increase protein expression of cytosolic and mitochondrial antioxidant factors such as Nrf2/ARE, induced NAD (P)H dehydrogenase quinone-1 and superoxide dismutase, and increase ATP production by promoting the activity of complex II [78]. Overall, KD can decrease the impact of brain injury by enhancing cerebral bioenergetics and metabolism.

5. Mechanisms underlying the effects of WD in TBI

5.1. WD disrupts normal neuron-glial cell communication

The increased release of glutamate following TBI could stimulate astrocytic glycolysis and lactate production [79]. Astrocytic clearance of glutamate from the synaptic cleft, which takes place through sodium coupled reuptake, induces Na^+/K^+ ATPase in astrocytes. The Na^+/K^+ ATPase then stimulates glucose uptake and its subsequent glycolysis in astrocytes. The lactate, formed as a byproduct of glycolysis in astrocytes, is then shuttled to neurons and used as an energy source [80]. Several studies support the role of lactate in cerebral metabolism following brain injury, a concept known as “lactate as energy on demand”. Yet, this metabolite can only be used in neurons receiving enough oxygen and having functional mitochondria [81]. Findings in animal models back the potential benefit of lactate metabolism in humans following TBI. For example, brain-injured rats supplied with intravenous lactate showed improved cognitive abilities [82]. Furthermore, the ability of the brain to use lactate as a fuel may be one of the key predictors of the outcome of TBI in humans [83]. Interestingly, it was shown that the expression of astrocytic glutamate transporters is reduced in hippocampi of mice on a WD, which correlated with decreased lactate levels [84]. Glutamate transporter downregulation could also lead to the accumulation of glutamate in the synaptic cleft, thus contributing to excitotoxicity [84]. In addition, WD was shown to decrease astrocytic expression of connexin-43, a protein component of gap junctions that connect neighboring astrocytes. Gap junctions are essential for the formation of the astrocyte metabolic network and for proper lactate dynamics [84]. In this context, WD could interfere with the metabolic supply, further contributing to the metabolic dysfunction post TBI.

5.2. WD induced-dysbiosis contributes to the secondary injury

The gut-brain axis constitutes a signaling link between the gastrointestinal tract and the CNS [85]. Around 3×10^{13} bacterial cells colonize the human body [86]. Of specific interest, this microbial diversity influences the gut-brain axis through a bidirectional interaction. The gut flora can contribute to the production of a range of neuroactive molecules, such as acetylcholine, histamine, melatonin, and serotonin [87]. In addition, several studies show that gut microbiota composition can impact insulin resistance, which is known to compromise cognitive functions as discussed above. Commensal gut bacteria may enhance insulin sensitivity by modulating the production of the incretin hormone glucagon-like peptide-1 [88]. Moreover, alterations in microbial diversity has been linked to microglial activation, BBB disruption, anxiety-like behavior and neurodegenerative diseases such as Parkinson’s disease, all of which may indicate a possible impact on TBI outcomes [89].

Following TBI, the gastrointestinal tract is affected possibly due to autonomic nervous system disruption [90]. Specifically, decreased contractility, mucosal atrophy, decreased tight junction proteins and increased permeability were observed [91, 92]. Concurrent with the increased intestinal permeability following TBI, more pathogenic substances such as LPS are able to penetrate the vascular system of the host causing endotoxemia. In this context, endotoxemia-induced systemic inflammation is hypothesized to influence the TBI-activated microglia, further contributing to the secondary injury. Importantly, intestinal permeability positively correlated with levels of markers of inflammation and the levels of endotoxins in the plasma post TBI [93].

The gut microbiome is altered as early as 2 h post-TBI in rodent models. Representation of the beneficial bacteria of the *Firmicutes* phylum was decreased while representation of pathogenic bacterial families of the *Proteobacteria* and *Bacteroidetes* phyla increased. Interestingly, injury lesion volume positively correlated with the increased levels of *Proteobacteria* and negatively correlated with the levels of *Firmicutes* [94].

Along the same lines, WD altered the *Firmicutes* to *Bacteroidetes* ratio and decreased the overall microbial diversity [95, 96]. Mice on WD exhibited decreased levels of *Bifidobacteria,* a group of bacteria shown to have protective functions. In addition, WD was noted to increase endotoxin production by the gut microbiota as well as plasma endotoxin concentrations [95]. Interestingly, other studies demonstrated that WD caused decreased hippocampal-related functions accompanied by alteration of gut bacteria [97]. Treatment of WD mice with *A. muciniphila* successfully reversed the cognitive deficits and improved cognitive performance [97]. In this context, it is evident that intake of WD induces an intestinal dysbiosis that can worsen the inflammation state as well as TBI outcomes (Fig. 1).

5.3. WD induces inflammation through the TLR-4 pathway

In the context of neuronal inflammation, WD has been associated with increased microglial reactivity [98]. Interestingly, microglial

Table 1.
The detrimental effects of HFD on the metabolism and cognition of the traumatically injured brain of experimental animals.

WD relative toTBI	Composition of the diet given	Species and age of experimental animals	Endpoint	Brain injury model	Outcome and results	References
Before	Diet rich in saturated and mono-unsaturated fats (~39%) and sucrose (~40%).	Male Sprague-Dawley rats (200−240 g)	High sucrose diet mimicking the western diet given for four weeks before the induction of the injury.	Mild TBI: fluid percussion injury	- WD aggravated TBI-induced defects in spatial memory - ↓ Learning performance - ↓ Levels of BDNF and its downstream effectors CREB and synapsin I	(66)
Before	High fat sucrose diet with 45% fat, 70% carbohydrate, and 20% protein.	Male Sprague-Dawley rats (14−15 week old)	High sucrose diet mimicking the western diet given for eight weeks before the induction of the injury.	Bilateral frontal cortical contusion injuries	- WD aggravated TBI-induced impairments in working memory - WD aggravated TBI-induced somatosensory dysfunctions - ↑ Loss of cortical tissue	(64)
Before	High fat diet with ~60% of total calories derived from fat; 20% of calories from carbohydrates, and 20% of calories from proteins.	Pups of female Sprague Dawley rats. Mothers were on the HFD diet	Pups born to females on HFD. Pups continued on the same diet before induction of the brain injury at P30 and/or P60.	Mild TBI using the modified weight drop technique	- Exacerbated mTBI-induced defects in motor functioning (↑ Average number of hind legs foot slips in beam-walking test), short-term working memory, and depressive symptoms - ↓ Telomere length - Alteration in genes involved in regulating dietary-dependent changes in neuroplasticity (i.e. BDNF, CREB etc.)	(69) (68)
Before	High-fat diet (D12492 from Research Diets, 60% of total calories from fat sources and enriched in refined sugars, sucrose, 10% by weight).	Male pups of female C57/BL6 mice. Mothers on the HFD	Pups born to females on HFD. Male pups continued on the same diet until receiving the brain injury at six weeks of age.	Mild TBI: 1 or 2 hits 24 h apart using the controlled cortical impact model	- Brain insulin resistance (demonstrated by the absence of insulin stimulated Akt phosphorylation) - Exacerbated TBI-induced neuroinflammation (↑ Microglial activation), learning and memory deficit, and anxiety-like behaviors	(70)
Before	High-fat diet (60% of total calories derived from fat sources).	Male and female C57 BL/6 mice (six month old)	HFD was given for four months before induction of the brain injury	Mild TBI: controlled cortical impact model	- ↓ Corticosterone levels and weight gain in obese male mice subjected to TBI compared to non-injured mice. - HFD-exacerbated TBI-induced microglia activity in male mice - HFD-exacerbated TBI-induced anxiety in male mice	(67)

HFD: high fat diet; BDNF: Brain-derived neurotrophic factor; CREB: cAMP response element-binding; βHB: β-hydroxybutyrate; CCI: controlled cortical impact.

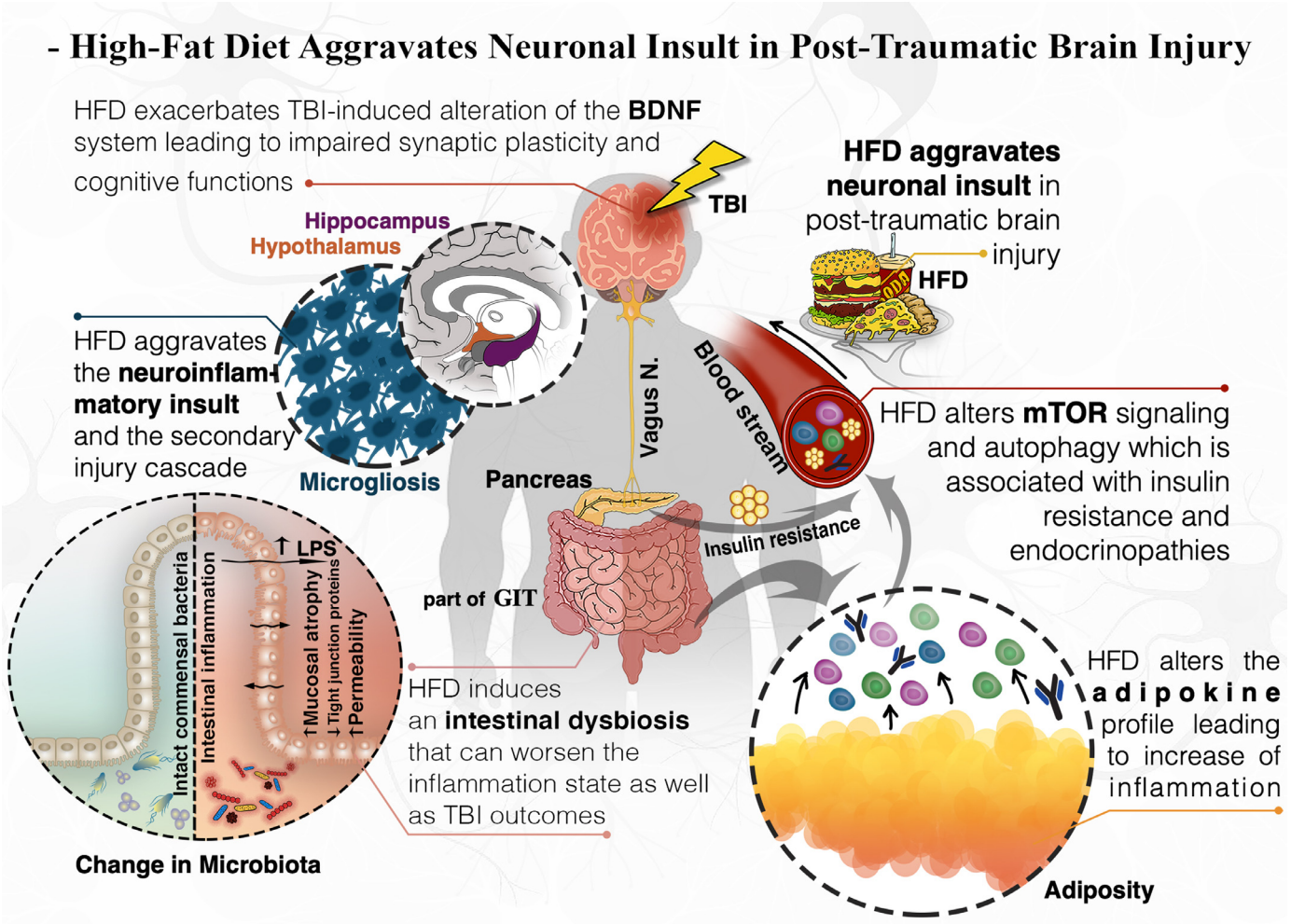

Fig. 1. *WD aggravates the neuronal insult post-TBI*: By impacting similar molecular pathways as TBI, WD can dramatically worsen the outcomes that follow TBI. For example WD can exacerbate TBI-induced energy crisis and metabolic dysfunction leading to an exacerbated neuroinflammation. Several potential pathways appear to contribute to the increased vulnerability of the brain to the outcomes of TBI in individuals who are on a WD. These contributing pathways that range from gut dysbiosis to epigenetic modulation in addition to induction of inflammatory pathways, alteration of autophagic/oxidative flux and the alteration of the adipokine profile. All of these pathways culminate in an augmented neuronal injury.

reactivity is shown to be mediated by Toll-Like Receptor 4 (TLR-4), a pattern recognition receptor that is highly expressed on brain microglia and known to bind saturated fatty acids [98, 99]. In addition, WD-fed rodents exhibited high expression of TLR-4 in the CNS, concurrently with increased microglial activation. Indeed, TAK-242, a TLR-4 antagonist, reduced hippocampal microglial inflammation in WD-fed mice while having no effect on mice fed the normal chow [98]. Downregulation of TLR-4 by TLR-4 shRNA also decreased WD-induced hypothalamic microglial inflammation and successfully restored the WD-induced alteration of glucose homeostasis [99].

In the context of TBI, TLR-4 was studied as a therapeutic target in the management of TBI outcomes. TLR-4 was found to be upregulated in hippocampal astrocytes and neurons post-injury in a manner that correlated with the extent of neuroinflammation, brain edema and neurologic deficits [100]. Silencing cerebral TLR-4 expression in rats by administering TLR-4 shRNA pre-injury successfully decreased the TBI-induced neuroinflammation. Similarly, the experimental group showed decreased brain edema and improved neurobehavioral outcomes [100]. Taken together, one can recognize that TLR-4 is a key mediator of neuroinflammation and neurobehavioral deficit both in the context of WD and TBI. We therefore hypothesize that WD exacerbates TBI outcomes by further contributing to TLR-4 activation, leading to the aggravation of the neuroinflammatory insult and the secondary injury cascade.

5.4. WD alters mTOR signaling and autophagy

The mammalian target of rapamycin (mTOR) is a highly conserved serine/threonine kinase that plays an integral role in cell growth and differentiation. It has been shown to be of specific importance in neuron physiology, where it regulates synaptic plasticity, learning and memory [101]. However, dysregulation and hyperactivation of mTOR has been associated with insulin resistance, systemic inflammation [102] and microglial activation [103]. Interestingly, WD-fed mice exhibit increased phosphorylation of mTOR in the brain coinciding with increased microglial activation and cognitive dysfunction [104]. Moreover, the increased signs of neuroinflammation post TBI, observed in high-caloric intake mice compared to normal caloric-intake mice, were accompanied by increased levels of mTOR, which demonstrates that WD contributes to the secondary brain injury in part through activation of mTOR [105]. Alternatively, mTOR acts as a potent inhibitor of autophagy. In this context, the autophagic flux was altered in the hippocampi of WD-fed mice associated with increased accumulation of amyloidogenic plaques [106]. In the context of TBI, calorie-restricted (CR) mice showed increased levels of Beclin1 and LC3B as compared to normal and high calorie-intake mice post-injury. Another study observed that administration of rapamycin (inhibitor of mTOR) post-TBI was associated with improved TBI outcomes and a decrease in apoptotic index [107]. In

conclusion, mTOR activation plays a role in the secondary injury post-TBI, a situation which can be aggravated by the intake of WD. Specific targeting of this pathway can therefore have beneficial consequences in the management of TBI, especially in obese individuals (Fig. 2).

5.5. WD increases oxidative stress parameters by impacting BDNF and anti-oxidant defense systems

Indeed, TBI is known to induce lipid peroxidation in the form of excessive accumulation of oxidized phospholipids that is almost instantaneously triggered post-injury [108]. Chronic WD feeding increased lipid peroxidation in mouse hippocampus [109]. Apart from that, the expression levels of anti-oxidant defense system proteins superoxide dismutase-2 and catalase were significantly decreased upon WD consumption [110], as well as the activation of Nrf2, the primary transcription factor responsible for regulation of phase II antioxidant response [111]. WD feeding before and after mTBI aggravated oxidative damage manifested as increased protein oxidation [112]. In the same study, WD exacerbated the effects of TBI on synaptic plasticity and cognitive functions by the enhanced suppression of BDNF, Synapsin I, and CREB expression, already attenuated by TBI. These results are in agreement with other evidence showing that TBI-induced oxidative stress can affect the injured brain by acting through the BDNF system, which modulates synapsin I and CREB to alter synaptic plasticity and cognition [113, 114]. At the same time, WD-induced oxidative stress can also suppress BDNF levels in various brain regions including the hippocampus and frontal cortex [115]. Together, it is evident that WD can exacerbate TBI-induced alteration of the BDNF system leading to impaired synaptic plasticity and cognitive functions (Fig. 1).

5.6. WD alters the adipokine profile

Adipokines are bioactive molecules, secreted by adipose tissue, that act in an autocrine, paracrine or endocrine manner and play specific roles in obesity-dependent inflammation and insulin resistance [116]. Based on their target receptors and downstream signaling, adipokines can be classified into hormones such as leptin and adiponectin, angiogenic factors such as resistin and neuregulin, or cytokines including IL-1β, IL-6, IL-10, TNF-α, and TGF-β [117]. Indeed, various adipokine receptors are present in the brain indicating that the metabolic state of the adipose tissue has the potential to modulate neuronal function [118]. Adipose tissue expands in response to excessive caloric intake [119]. This leads to aberrant secretion of adipokines including pro-inflammatory cytokines IL-1β, IL-6 and TNF-α. This adipokine imbalance appears to be involved in the mechanisms that take place in the secondary injury post-TBI. During this period of high energy demand, the expression of neuroinflammatory cytokines such as TNF-α is induced [120] mediating the metabolic changes observed following brain injury [121]. While WD feeding alters the expression levels and signaling pathways of leptin and adiponectin [122, 123] leading to inflammatory outcomes similar to these observed in Alzheimer's disease and dementia [124], little is known about the possible role of either mediator in the secondary injury post-TBI and the potential alteration of their function in the context of WD feeding (Fig. 1).

5.7. WD induces epigenetic dysregulation exacerbating secondary injury

Emerging findings have shown that dietary intake can induce changes in gene expression through alterations in the epigenetic machinery [125]. Studies of normal brains have established the vital role of epigenetic modulators in neuroplasticity, learning and memory [126]. Several epigenetic mechanisms, including DNA methylation, histones post-translational modifications, and miRNA regulation of gene expression are increasingly implicated in the pathophysiology post-TBI [127]. Interestingly, WD feeding was shown to impact neuroplasticity and behavioral changes through the modification of the *bdnf* gene methylation status in rats [128]. As mentioned previously, the BDNF system malfunction has been implicated in the pathology of TBI. Significantly, studies of the effect of different dietary patterns on *bdnf* methylation showed that WD enhanced *bdnf* methylation with a negative impact on cognitive function that was mediated by the downregulation of several cellular metabolic and mitochondrial

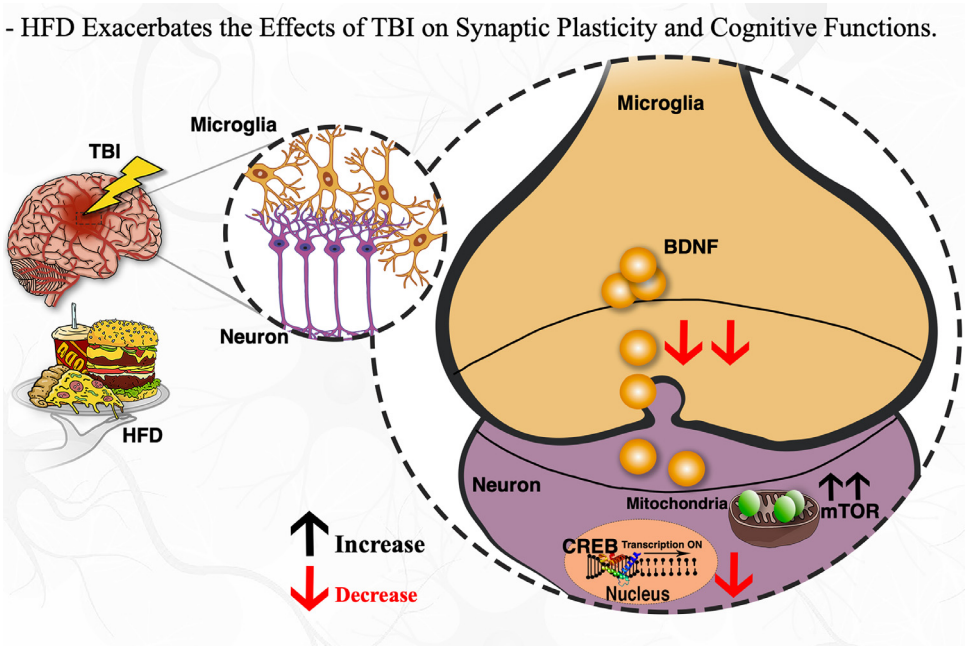

Fig. 2. *HFD exacerbates the effects of TBI on synaptic plasticity and cognitive functions*: HFD alters the molecular machinery responsible for maintaining neuronal function and homeostasis following brain injury. HFD increases oxidative stress parameters by impacting BDNF and components of the anti-oxidant defense systems. This is accompanied by pronounced decreases of CREB protein levels (a downstream transcription factor that modulates synaptic transmission). Likewise, HFD can worsen the dysregulation of mTOR which enhances the incidence of insulin resistance, systemic inflammation and microglial activation.

factors including Sirt1 and PGC-1α [128]. This adds a further layer of complexity to the effect of WD on neuronal resilience post-TBI as the ensuing epigenetic changes will not only compromise BDNF-mediated neuronal recovery, but also exacerbate the energy crisis. Of particular interest, the epigenetic neuronal impact of WD may persist for several generations. Dietary choices during the critical window of germ line development may profoundly characterize the phenotype of subsequent generations and maternal feeding on a WD can create an unfavorable intrauterine environment during pregnancy leading to long-term health outcomes after birth such as the predisposition to neurological disorders [129].

6. Exercise can ameliorate the metabolic effects of the WD and TBI

Exercise contributes to the amelioration of WD- and TBI-induced changes by affecting the molecular pathways involved in energy metabolism and synaptic plasticity [130, 131]. Its effects include being anti-oxidant, anti-inflammatory and anti-apoptotic, in addition to augmentation of neurogenesis and neuroplasticity [131, 132]. Exercise can enhance neurogenesis by increasing the levels of BDNF, IGF-1 and VEGF [133, 134]. Additionally, exercise-induced mitochondrial biogenesis can assist in repair mechanisms post-TBI [135]. A widespread mitochondrial biogenic response occurs by up-regulating PGC1α, SIRT1 and the mitochondrial enzyme citrate synthase in different regions of the brain [136]. All these mechanisms can help explain the role exercise plays in the amelioration of cognitive deficits post-TBI [137].

The beneficial effects of exercise also extend to the amelioration of the negative impacts of WD on brain function. Exercise can enhance mitochondrial performance and restore insulin sensitivity by increasing TCA cycle flux and by coupling ligand-induced PPAR activity. This pathway also includes remodeling of downstream metabolic processes mediated by PGC1 [138, 139]. Interestingly, exercise has been shown to prevent WD-induced dysbiosis. WD-fed mice that exercised exhibited decreased Firmicutes/Bacteriodetes ratio in high-fat-fed male mice [140]. In this context, it is evident that exercise can slow down or halt the metabolic changes induced by WD and as a result can alter TBI outcomes.

7. Conclusion

TBI is a debilitating brain insult associated with significant consequences, mainly due to the secondary injury. Although TBI outcomes can be silent, especially in case of mild injury, they are associated with long term impairment in brain function. Given the drastic change in eating habits in the past century, more effort towards the elucidation of mechanisms of interaction between increased caloric intake and TBI is warranted. The aim of such an effort will be to develop effective interventions to reduce the secondary injurious cascades post-TBI. By impacting similar molecular pathways as TBI, WD can dramatically worsen post-injury outcomes by exacerbating neuroinflammation (Fig. 1). Several potential pathways appear to contribute to the increased vulnerability of the brain to traumatic injury in individuals on western diet. These pathways include gut dysbiosis, epigenetic modulation, induction of inflammatory pathways, alteration of autophagic/oxidative flux, and alteration of the adipokine profile, and ultimately culminate in an augmented neuronal injury.

8. Outstanding questions

Rigorous systematic investigation of the effect of WD feeding on the progress of secondary injury in TBI patients together with the interaction with metabolic comorbidities is required. Careful experimental design with respect to the adoption of the appropriate timeframes to study different types of injury as well as the establishment of causal relationships will permit the elucidation of crucial signaling pathways with high potential for corrective outcomes after intervention. Moreover, the study of the differential effect of KD as opposed to WD is warranted. Finally, the translation of these concepts into clinical practice is prudent.

9. Search criteria

To address these questions, studies on the topic were identified by searches of MEDLINE, PubMed, Google Scholar and references from relevant articles using the search terms “High-fat diet AND Cognitive function”, “HFD AND TBI”, “Ketogenic diet AND TBI”, "Lactate AND HFD OR TBI", "HFD AND TBI AND inflammation OR oxidative stress OR insulin resistance OR oxidative stress". Additionally, searches were performed based on investigator name. Articles published between 1974 and 2019 in English and non-English languages were included.

Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

Author contributions

AS - Coordinated literature search and wrote the first draft of the manuscrpit. HH, KJH, and WF - Contributed equally to literature search and providing written summaries of search results. SA - Designed hte figures in the manuscript based on the manuscript. FA, KZ, and AHE - Contributed to literature search for manuscript revisions. AFE and FHK - conceptualized the manuscript idea, supervised the work effort, reviewed, edited and modified all versions of the manuscript. All authors reviewed and agree with the content of the manuscript.

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