



Review

# Scientific Evidences of Calorie Restriction and Intermittent Fasting for Neuroprotection in Traumatic Brain Injury Animal Models: A Review of the Literature

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**Citation:** Xu, Y.; Liu, Z.; Xu, S.; Li, C.; Li, M.; Cao, S.; Sun, Y.; Dai, H.; Guo, Y.; Chen, X.; et al. Scientific Evidences of Calorie Restriction and Intermittent Fasting for Neuroprotection in Traumatic Brain Injury Animal Models: A Review of the Literature. *Nutrients* **2022**, *14*, 1431. <https://doi.org/10.3390/nu14071431>

Academic Editor: Panteleimon Giannakopoulos

Received: 4 March 2022

Accepted: 28 March 2022

Published: 30 March 2022

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**Abstract:** It has widely been accepted that food restriction (FR) without malnutrition has multiple health benefits. Various calorie restriction (CR) and intermittent fasting (IF) regimens have recently been reported to exert neuroprotective effects in traumatic brain injury (TBI) through variable mechanisms. However, the evidence connecting CR or IF to neuroprotection in TBI as well as current issues remaining in this research field have yet to be reviewed in literature. The objective of our review was therefore to weigh the evidence that suggests the connection between CR/IF with recovery promotion following TBI. Medline, Google Scholar and Web of Science were searched from inception to 25 February 2022. An overwhelming number of results generated suggest that several types of CR/IF play a promising role in promoting post-TBI recovery. This recovery is believed to be achieved by alleviating mitochondrial dysfunction, promoting hippocampal neurogenesis, inhibiting glial cell responses, shaping neural cell plasticity, as well as targeting apoptosis and autophagy. Further, we represent our views on the current issues and provide thoughts on the future direction of this research field.

**Keywords:** traumatic brain injury; calorie restriction; intermittent fasting; mitochondrial dysfunction; hippocampal neurogenesis; glial cell responses; neural cell plasticity; apoptosis; autophagy

## 1. Introduction

Since ancient times, worldwide religions have advocated for food restriction (FR) due to its physical and psychological benefits [1–3]. However, the health benefits owing to FR have only in recent years been supported by scientific evidence. Calorie restriction (CR) is a commonly used FR strategy that restricts everyday energy intake without incurring malnutrition [4]. In experimental animal models, appropriate CR has been shown to have benefits including elongation of life span [5], promotion of weight loss [6–8], suppression of inflammation [9–11], cardiovascular disease risk reduction [12–14], and cancer prevention [2,15]. Notwithstanding these benefits, there are still concerns when applying CR, such as poor CR compliance [16]. Researchers have therefore been looking for alternative FR regimens that can provide similar benefits. One of these regimens is intermittent fasting (IF), and it has recently become a popular trend and lifestyle [17]. IF refers to

cycles of fasting and intermittent feeding window over a given time schedule [2,16,18]. There are various time-scheduled IF methods, the following three are the most common approaches: periodic fasting (PE), time-restricted feeding (TRF) and alternate-day fasting (ADF) [16]. The IF ultimately triggers a process called “the metabolic switch”, which shifts the metabolism from glycogenolysis to the mobilization of fat via fatty acid oxidation and ketogenesis, resulting in related biochemical pathway changes [1,19,20]. It is widely accepted that these changes under IF positively contributes to human health in multiple areas [21–24]. Recent studies in the field of neuroscience have found scientific evidence that IF exerts protective effects against multiple neurological diseases and disorders, including Alzheimer’s disease (AD) [25,26], Parkinson’s disease (PD) [27,28], multiple sclerosis (MS) [29,30], epilepsy [31,32], ischemic stroke [33–35], and depression [36–38].

Traumatic brain injury (TBI), a temporary or permanent disruption of normal brain function due to damage incurred by external forces [39], is a major burden on those effected [40–42]. After the initial brain trauma, the secondary injury process spreads via a complex sequence of events in the pathogenesis of TBI [43–45]. Therapeutics targeting the development of the secondary injuries play a key role in limiting disabilities incurred from TBI while achieving unsatisfactory clinical outcomes [46,47]. To improve the quality of life for patients suffering from TBI, the search for more effective interventions for TBI has to continue. Our study recently found that a 1-month IF regimen prior to TBI significantly improved cognitive function following the insult, in which Npy (Neuropeptide Y)-induced neurogenesis made a contribution [48]. In addition, several studies have shown that multiple FR regimens, mainly CR and IF, exert positive effects on the development of TBI via various mechanisms [19,49,50]. However, the scientific evidence bridging CR/IF with neuroprotection in TBI has not been systematically reviewed in previous literature. Additionally, concerns regarding this research field remain elusive. To this end, here we have retrospectively reviewed the recent studies on CR/IF in the TBI, summarized the current issues, and presented our consideration of future directions in this research field.

## 2. Neuroprotective Effects of CR and IF in TBI

### 2.1. Alleviating Mitochondrial Dysfunction

The preservation of normal mitochondrial function is critical for inhibiting the deterioration of secondary TBI injury [51–53]. Davis et al. reported that acute fasting (for a single 24 h) in adult male rats, after receiving moderate cortical control impact (CCI), significantly increased tissue-sparing postinjury [54]. The underlying mechanism is suggested to be reduced mitochondrial damage, as indicated by lower levels of mitochondrial reactive oxygen species (ROS) production, calcium loading, lipid peroxidation and protein carbonyls [55]. Additionally, administration and maintenance of serum d-bHB at a level similar to the fasting state also alleviated mitochondrial dysfunction and increased tissue sparing after moderate CCI, indicating the neuroprotective role of fasting was achieved by elevated d-bHB level. Notably, a higher dose of d-bHB did not present similar neuroprotective effects, suggesting a dose-dependent effect on the efficacy of serum ketones in TBI [54]. Studies on the effects of CR on mitochondrial protection following TBI are limited. However, since CR usually induces ketone production, the study of ketogenic diet (KD) may provide some clues. KD was recently found to reduce oxidative stress following CCI, while inducing the levels of antioxidants, superoxide dismutase (SOD1/2), and NAD(P)H dehydrogenase, thereby improving mitochondrial respiratory complex activity [56]. Whether this effect can be achieved by fasting or simply calorie restriction still needs to be explored. Additionally, several variables must be considered; for instance, current studies only involve male animal models, so whether food restriction has a similar effect on the female remains to be determined. Moreover, age should also be taken into consideration. Furthermore, although Davis et al. reported that a prolonged fasting (48 h) did not show profound neuroprotection, further investigation would be required to determine whether IF or daily calorie restriction could produce the mitochondrial protection. Finally, CR alters the level of numerous factors [57–61] besides d-bHB, but other factors

contributing to the improved mitochondrial function also requires further investigation. The screening of overlapping differentially expressed genes (DEGs) by CR-induced and brain injury-induced transcriptional changes may be valuable.

### 2.2. Promoting Hippocampal Neurogenesis

Hippocampal dysfunction is a major pathological aspect of TBI that generally affects patients' spatial learning and memory [62–65]. We recently found that a 1-month IF regimen other than acute fasting prior to CCI significantly enhanced the proliferation of neural stem cells (NSCs) in the subgranular zone (SGZ) of the hippocampus and improved cognitive function postinjury [48]. A subsequent loss of function study demonstrated that the neurogenesis-promoting effect of IF following TBI was achieved by increasing the neuronal NPY expression in the hippocampus [48]. Our study, contrary to that of Davis, suggests the health benefits of an IF regimen in TBI and its underlying mechanisms. Davis's conclusion demonstrated that a single 24 h period of fasting after moderate CCI exhibited neuroprotection postinjury [54]. The cause of this contradiction may be due to the differences in species, but this requires further investigation.

To the best of our knowledge, no other study has reported the effects of IF or other types of CR on hippocampal neurogenesis after TBI. In ischemic brain injury, a three-month IF regimen prior to injury was found to limit both the proliferation of basal cells and cell death in the subgranular region of the hippocampus and SVZ—two regions of sustained neurogenesis in the adult brain [66]. However, this regimen promoted cell proliferation in the dentate gyrus of intact mice. These results raised the following questions: (1) Does the 1-month IF regimen promote or inhibit hippocampal basal cell proliferation following TBI? (2) If the fasting regimen was prolonged to 3 months, would there be any difference in the behavior of NSCs in the SGZ as we reported [48]?

Other issues must also be addressed. For instance, in a noninjury study, IF was reported to promote neurogenesis by stimulating ketogenic effects [67]. In our TBI study, the 1-month IF regimen was also found to be ketogenic; thus, whether the increased expression of Npy and enhanced neurogenesis under IF were achieved through the ketogenic effect remains to be explored. Further, some noninjury studies found that factors such as brain-derived neurotrophic factor (BDNF) and neurotrophic molecule-3 (NT-3) also participate in the IF-induced neurogenesis or differentiation of neurons in the hippocampus [68,69]. Therefore, investigations targeting other pathways or factors in the IF-induced benefits following TBI are valuable.

### 2.3. Inhibiting Glial Cell Responses

It is generally accepted that glial cell activation following brain injury plays a critical role in the progression of secondary injury following the primary insult [70–74], such as triggering the neuroinflammatory responses [75–79]. Adult male mice on a three-month CR regimen (50% of a normal daily diet) prior to TBI were found to have significantly reduced microglia activation one month after injury. As a result, the release of proinflammatory cytokines (e.g., TNF- $\alpha$ ) was profoundly inhibited, thus reducing the neuroinflammation and ameliorating neurological damage after TBI [80]. Consistently, another non-TBI study in rats also demonstrated the anti-inflammatory properties of CR, which reduced microglia activation in the hypothalamic arcuate nucleus (ARC) [81].

For astrocytes [82], a 3-month 50% CR prior to cortical puncture has been shown to lower the number of reactive astrocytes in the injured area [83]. Consistently, in another rat model study, a 1-month CR regimen following moderate TBI demonstrated the reduction of GFAP-positive cells in the hippocampal CA3 region, and improved cognitive dysfunction [84]. Notably, a ketogenic diet following moderate TBI was also found to prevent neuroinflammation and inhibit astrocytes activation in male mice [50]. Therefore, suppression of astrocyte activation by CR may involve the production of ketone bodies. In addition, IF has been shown to reduce astrocyte activation in other types of brain injury, such as the kainic acid-induced brain injury [85]. In summary, these results suggest that the CR,

either prior to or post injury, inhibits astrocyte activation and glia scar formation following TBI. These results, in future medicine, have the potential to guide clinical intervention in the progression of secondary brain injury [86–88].

#### 2.4. *Shaping Neural Cell Plasticity*

In the pathogenesis of TBI, neural cell plasticity (including synaptogenesis, alterations of neural cell structure, and change in growth factor signaling, etc.) remodels to promote functional recovery [89–93]. Earlier, Nataša et al. reported that male rats maintained on a 3-month 50% food restriction (FR) prior to TBI exhibited quantitative changes in synaptophysin (SYP), growth-associated protein 43 (GAP-43), and glial fibrillary acidic protein (GFAP)—markers of neuronal and glial plasticity, respectively [83]. FR profoundly raised GAP-43 and SYP expression in the cortex surrounding the lesion, indicating increased axonal branching and synapses [83]. In *ad libitum* (AL) rats, reactive astrocytes have been observed without immunoactivity for GAP-43 or SYP [83]. These results suggest that the FR promotes recovery by enhancing neuronal plasticity while inhibiting reactive astrogliosis. In a noninjury study, a daily IF regimen (22 h fasting per day) for 3 weeks significantly increased mushroom dendritic spine density and hippocampal expression of BDNF, suggesting a change in the dendritic spine remodeling (2). Altogether, these data point to the conclusion that a relatively long period of FR may improve cognitive function following TBI by shaping neural cell plasticity, in which multiple pathways and factors are involved. Whether short-term or acute calorie restriction has similar benefits still remains to be determined. In addition, the effect of IF on female animal models remain elusive and need to be investigated in future studies.

#### 2.5. *Targeting Apoptosis and Autophagy*

Studies have shown that apoptosis and autophagy play detrimental roles in the pathogenesis of TBI [94–97]. By targeting apoptosis or the activity of autophagy, progression of TBI can possibly be attenuated [94,95]. Earlier, Natasa et al. demonstrated that a 50% CR regimen lasting 3 months, prior to cortical stab injury (CSI), suppressed caspase-3 expression in the ipsilateral cortex, which attenuated the secondary injury after the primary insult (3). The same group later reported that the 50% dietary restriction (DR) for 3 months before TBI affected the intrinsic apoptotic pathway [98]. The DR prevented the increase of the proapoptotic gene Bax while enhanced the expression of antiapoptotic genes Bcl-2 and Bcl-xl in the ipsilateral cortex post injury (4).

Additionally, CR has been reported to affect autophagy. In one study, rats were fed a 70% CR diet for a period of 3 months after mild TBI (mTBI) was induced, the findings revealed decreased the mammalian target of rapamycin (mTOR) activity [84], which is responsible for the inhibition of autophagy. In the same study, enhanced LC3B expression in the hippocampus [84], which promotes autophagy, was also noted. In addition, the postinjury cognitive dysfunction was ameliorated under the CR. These results suggest that the CR after mTBI improves cognition by enhancing hippocampal autophagy.

The above studies support the idea that a variable degree of calorie cut promotes neural cell survival in both the cortex and hippocampus, via different pathways. However, investigations on female animal models are still lacking. A more systematic comparative study on the effect of different ratios and durations of energy cuts in preventing cell death or promoting cell survival in different brain regions is still needed. More reputable loss-of-function studies could be helpful in bridging these mechanisms with improved cognition or tissue spares after TBI.

### 3. Current Issues and Perspectives

Although various types of CR have been shown to bring health benefits via multiple mechanisms in TBI, there are still several issues to be addressed. (1) The IF and simply CR must be clearly distinguished. In simply CR studies, as the everyday insatiety promotes cravings for food, pellets are consumed in a short time once provided. Therefore, the

experimental subjects were left without food for the time remaining, consequently allowing them to enter the IF state. In some IF studies, whether the neuroprotective effect is achieved via a specific fasting regimen or simply by energy restriction should also be determined. To clearly distinguish between these two conditions, we suggest that food pellets be provided several times per day in simply CR studies, to avoid long fasting intervals. (2) As the recovery process initiates immediately after TBI, but acute CR was not able to cause significant improvement in the recovery within a very short time, thus previous studies usually planned the long-term CR regimen before injury. This raises the question of whether the therapeutic relevance of such an approach might be zero. Investigating the neuroprotective mechanisms of long-term CR and thence screening for therapeutic targets that mimic the benefits of CR may be helpful. In future research, the post-traumatic CR regimen may need to be modified to test for a therapeutic effect. (3) Female animal models are usually not involved in previous studies. Due to the roller-coaster ride of the sex hormone in menstrual cycle, female subjects usually exhibit huge variability in response to CR. Keeping the other variables consistent and largely increasing the N number in the experiment could potentially ameliorate this issue. (4) In our study, we found that when the daily energy cut was more than 30% over a prolonged period of 10 days, the mice become thin, weak, and inactive. Thus, health conditions, especially the risk of malnutrition, should be carefully monitored and reported in CR studies. (5) Circulating metabolites, such as blood glucose,  $\beta$ -hydroxybutyric acid, and insulin, greatly change during CR; however, this has yet to be extensively studied in TBI cases. Some of them might act as the mediators connecting the CR with its neuroprotective effect. Furthermore, the levels of these metabolites can easily be changed through clinical interventions. Thus, we suggest further investigations of the role of these metabolites in future TBI studies.

**Author Contributions:** Y.X. and Z.L. searched and reviewed the literature and drafted the manuscript; S.X., C.L., M.L., S.C., Y.S., H.D. and Y.G. provided critical comments and discussed and revised the manuscript; X.C. and W.L. designed and formulated the review theme, viewed the literature, and finalized the manuscript. All authors have read and agreed to the published version of the manuscript.

**Funding:** This work was supported by the Fundamental Research Funds for the Central Universities (grant number: 20826041E4142) from Sichuan University, and the College Students' Innovative Entrepreneurial Training Plan Program (grant number: 20220966L) from Sichuan University.

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** Not applicable.

**Conflicts of Interest:** The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

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