Neuroprotective Effects of Calorie Restriction and Intermittent Fasting

Subjects: Neurosciences

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Calorie restriction (CR) is a commonly used food restriction (FR) strategy that restricts everyday energy intake without incurring malnutrition. Intermittent fasting (IF) refers to cycles of fasting and intermittent feeding window over a given time schedule. Traumatic brain injury (TBI), a temporary or permanent disruption of normal brain function due to damage incurred by external forces, is a major burden on those effected. Various CR and IF regimens have recently been reported to exert neuroprotective effects in TBI through variable mechanisms.

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][2][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][7][8], suppression of inflammation [9][10][11], cardiovascular disease risk reduction [12][13][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][22][23][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][34][35], and depression [36][37][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][41][42]. After the initial brain trauma, the secondary injury process spreads via a complex sequence of events in the pathogenesis of TBI [43][44][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.

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 [48][49][50]. 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 [51]. 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 [52]. 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 [51]. 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 [53]. 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 [54][55][56][57][58] 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 [59][60][61][62]. The researchers 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 [63]. 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 [63].

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 [64][65][66][67][68], such as triggering the neuroinflammatory responses [69][70][71][72][73]. 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-α) was profoundly inhibited, thus reducing the neuroinflammation and ameliorating neurological damage after TBI [74]. 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) [75].

For astrocytes [76], a 3-month 50% CR prior to cortical puncture has been shown to lower the number of reactive astrocytes in the injured area [77]. 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 [78]. Notably, a ketogenic diet following moderate TBI was also found to prevent neuroinflammation and inhibit astrocytes activation in male mice [79]. 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, s86uch as the kainic acid-induced brain injury [80]. 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 [81][82][83].

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 [84][85][86][87][88]. 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 [77]. FR profoundly raised GAP-43 and SYP expression in the cortex surrounding the lesion, indicating increased axonal branching and synapses [77].

2.5. Targeting Apoptosis and Autophagy

Studies have shown that apoptosis and autophagy play detrimental roles in the pathogenesis of TBI [89][90][91][92]. By targeting apoptosis or the activity of autophagy, progression of TBI can possibly be attenuated [89][90]. 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 [93].

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 [78], which is responsible for the inhibition of autophagy. In the same study, enhanced LC3B expression in the hippocampus [78], 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.

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