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Review Article

Dietary restriction in cerebral bioenergetics and redox state ☆

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ABSTRACT

The brain has a central role in the regulation of energy stability of the organism. It is the organ with the highest energetic demands, the most susceptible to energy deficits, and is responsible for coordinating behavioral and physiological responses related to food foraging and intake. Dietary interventions have been shown to be a very effective means to extend lifespan and delay the appearance of age-related pathological conditions, notably those associated with brain functional decline. The present review focuses on the effects of these interventions on brain metabolism and cerebral redox state, and summarizes the current literature dealing with dietary interventions on brain pathology.

Contents

Introduction

The brain is responsible for a large amount of energy consumption in vertebrate organisms, and especially in primates. Although it accounts for only 2% body weight, it consumes 20% of the oxygen and 25% of glucose from these organisms. This energy consumption is required to maintain ionic balance in neurons, produce action potentials, generate post-synaptic currents and recycle neurotransmitters [6]. Since metabolite diffusion from the blood is restricted by the brain–blood barrier, the brain must synthesize its own neuroactive compounds such as glutamate, aspartate, glycine or D-serine from glucose [71]. In addition, neurons are highly susceptible to oxidative damage and glucose oxidation in the pentose phosphate pathway is required to obtain NADPH and regenerate reduced glutathione, which is essential to maintain redox balance in the brain [12]. All these characteristics make the brain highly dependent on glucose and an organ extremely sensitive to energy deficits.

In addition to its high energy expenditure, the brain is also responsible for directly sensing and integrating energetic cues that are sent from peripheral tissues in the form of nutrients and

Abbreviations: AD, Alzheimer's disease; CR, caloric restriction; FR, food restriction; IF, intermittent fasting; KA, kainic acid; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NOS, nitric oxide synthase; PD, Parkinson's disease; PTZ, pentylenetetrazole; ROS, reactive oxygen species; TCA, tricarboxylic acid cycle

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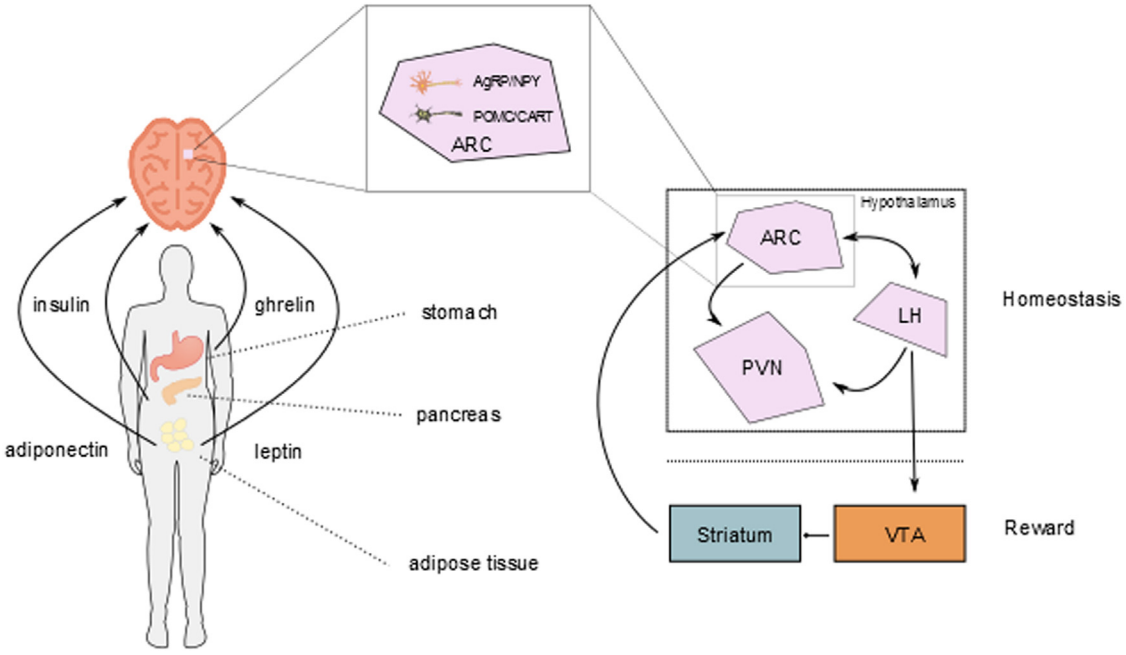

Fig. 1. The brain as a master regulator of body energy control. The figure represents a simplified scheme of how the brain receives signals from peripheral tissues in the hypothalamus. Orexigenic (AgRP/NPY) and anorexigenic (POMC/CART) neurons in the arcuate nucleus (ARC) of the hypothalamus sense these and other cues, such as circulating blood glucose levels. These signals are further integrated by interaction with other hypothalamic nuclei (LH—lateral hypothalamus; PVN—paraventricular nucleus) and finally project into the areas of the brain involved in the reward system, including the ventral tegmental area (VTA) and the nucleus accumbens in the striatum.

hormones (see Fig. 1), orchestrating physiological and behavioural responses [31]. Therefore, the brain acts as a master regulator for energy balance in the organism, determining food intake and expenditure, at the same time as it is the primary energy consumer of the body and the organ most susceptible to oxidative damage.

Dietary restriction prolongs lifespans in a wide range of organisms, spanning from yeast to rodents. More importantly, animals not only live longer, but their health is improved and the appearance of aging markers delayed [39]. Despite huge interest in the effects of dietary limitation, the causes that underlie these beneficial effects are still incompletely understood, due both to physiological and methodological reasons. Dietary restriction produces large-scale systemic effects, with predicted synergic interactions among tissues. For example, reducing total caloric intake prevents the metabolic syndrome, which in turn is a risk factor for other pathological conditions, such as stroke [41]. Therefore, discriminating between systemic and tissue-specific effects is not always straightforward, hampering the identification of molecular targets or specific pathways involved. Moreover, the relevance of each of these targets or pathways might differ between different pathological conditions. On the other hand, methodological issues hampering the understanding of the effects of restricted diets include the lack of consensus on how to perform dietary restriction. The term "caloric restriction" is often used to describe different diets, including some which don't even limit the amount of calories ingested [21]. As will be detailed below, the latest literature is beginning to unveil important differences between these diets. Interestingly, recent results show that, although the final effects of different diets can sometimes be similar, the pathways and mechanisms involved in these outcomes may not be the same [3,22,67,70]. In addition, important differences arise based on the animal model used, the duration of the diet and the age in which the diet is started.

This review will briefly discuss the effects of different dietary interventions on brain metabolism, redox balance and function, focussing on some of the most important age-related brain pathologies.

Systemic effects of different dietary interventions

Dietary restriction has pleiotropic effects that far exceed simple reduction in body weight. Reducing food intake induces a concomitant decrease in body fat, which in turn affects the levels of circulating adipokines, endocrine molecules produced by the white adipose tissue. Low levels of fat are usually correlated with decreased circulating levels of insulin and leptin, and an increase in adiponectin (see Fig. 1), all of which favour a better regulation of glucose homeostasis [89]. Keeping fat tissue at low levels also favours the production of anti-inflammatory over pro-inflammatory cytokines, with inflammation now being regarded as an important player in the pathogenesis of obesity-related insulin resistance [56]. Inflammatory signals can in turn induce oxidative imbalance and reactive oxygen species (ROS) production in many tissues. One of the means to promote oxidative stress by these signals is the stimulation of the inducible nitric oxide synthase (iNOS), which produces high levels of nitric oxide, facilitating the formation of other reactive oxygen and nitrogen species [17].

Historically, a number of different diets have been referred to under the term "calorie restriction" [21]. In recent years, there has been an increasing awareness of the particular effects of each different dietary intervention and their specific mechanisms are now beginning to be separately unravelled. In the present work, we will focus on the three most prevalent protocols in the literature: intermittent fasting (IF), food restriction (FR) and caloric restriction (CR), and will use the term 'dietary restriction' to refer generically to any of the three.

IF, also known as "every other day feeding", is a dietary protocol in which animals alternately fast and have access to food *ad libitum* every 24 h. Under these conditions, body weight usually decreases, although with 10–20% oscillations between feeding and fasting days [69]. Interestingly, although animals kept on this diet for short periods may eat less than their *ad libitum*-fed counterparts, food intake may be similar after longer periods, due to overeating on feeding days [22]. Consistently with reduced food intake, short periods of IF improve glucose tolerance. However,

after longer periods, insulin resistance is observed in abdominal adipose tissue and skeletal muscle. Redox imbalance is also present in these tissues, with high levels of hydrogen peroxide [22].

Another common way to limit caloric ingestion is to restrict the total amount of food, a protocol that will be referred to here as "food restriction" (FR). In this diet, restricted animals are given an amount of food equal to 60–80% of that eaten by *ad libitum*-fed animals. Rats and mice lose weight and fat and display many beneficial features, such as good peripheral insulin sensitivity [3,22]. However, FR can lead to malnutrition and low body growth due to low levels of micronutrients such as copper, iron, selenium or magnesium [21], which are essential for redox reactions such as oxidative phosphorylation and ROS scavenging.

When FR is complemented with micronutrients, the diet can legitimately be considered "caloric restriction" (CR), since only calories are limited. Commonly, supplementation is performed by increasing the percentage of micronutrients in the diet to an extent equivalent to the calorie restriction imposed (*i.e.* a 60% micronutrient

Fig. 2. Glucose use in the brain. Glucose is used for multiple functions in the brain. Glycolysis followed by oxidation of acetyl-CoA in the TCA cycle provides reduced equivalents that can be used by mitochondria to synthesize ATP. Alternatively, oxidation through the pentose phosphate pathway provides NADPH, required for the reduction of glutathione, a central anti-oxidant in the brain. Glucose is also required as a precursor to synthesize neurotransmitters, and can be stored to some extent in astrocytes in the form of glycogen. In the absence of glucose, ketone bodies produced in the liver can cross the blood–brain barrier and partially replace glucose as an energy source.

supplemented diet to a 40% calorie restriction). Although the phenotype is very similar to FR (especially when restriction is low or in short-term diets) some differences have been observed after long periods, such as a reduction in the nitration of the insulin receptor in skeletal muscle and adipose tissue, indicating lower oxidative damage [22].

How does dietary restriction affect brain function?

Although during fasting ketone bodies produced from fatty acids in the liver can partially replace it, glucose is still required by the brain under these conditions. First, glucose is necessary for the biosynthesis of complex carbohydrates that are components of glycoproteins and glycolipids, amino acids, one-carbon donors for methylation reactions and neurotransmitter synthesis [71]. Second, oxidation of ketone bodies requires activity of the tricarboxylic acid (TCA), since formation of acetoacetyl-CoA from β-hydroxybutyrate and acetoacetate is dependent on succinyl-CoA [25], and complete ketone body oxidation requires oxaloacetate to promote TCA cycling. Finally, a significant amount of cerebral glucose is metabolised through the pentose phosphate pathway in order to regenerate reduced cytosolic glutathione via NADPH, and maintain antioxidant activity [11]. In addition, astrocytes, but not neurons, can accumulate glucose in the form of glycogen, which acts as a short-term energetic reservoir in the brain during fasting [16] (Fig. 2).

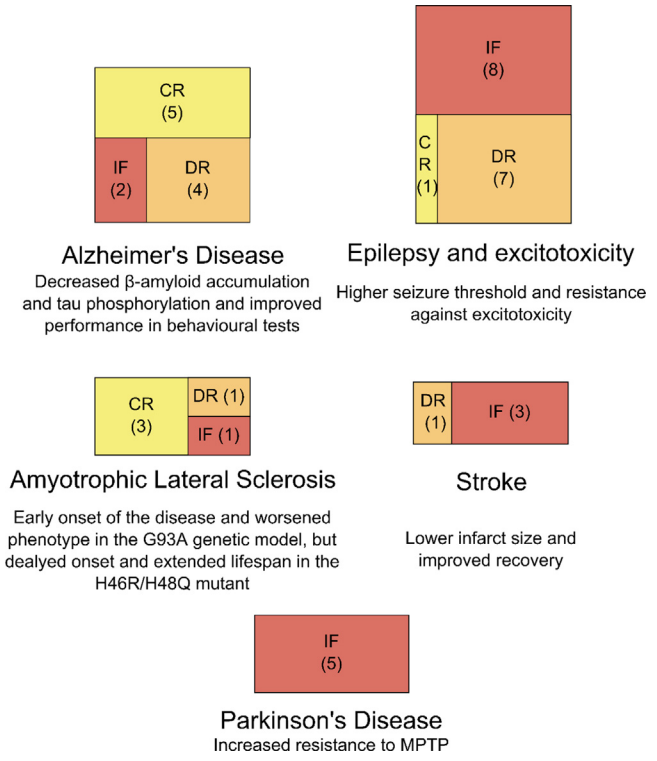

Fig. 3. Effects of CR, FR and IF on some neurodegenerative conditions. The sizes of the rectangles represent the relative number of publications for each pathology (numbers are in parenthesis), summarized from the following: Anson et al. [3], Armentero et al. [4], Arumugam et al. [5], Azarbar et al. [7], Bhattacharya et al. [10], Bough et al. [13], Bough et al. [14], Bruce-Keller et al. [18], Contestabile et al. [27], Costantini et al. [29], Dhurandar et al. [32], Duan and Mattson [34], Duan et al. [33], Eagles et al. [35], Greene et al. [45], Griffioen et al. [46], Halagappa et al. [48], Hamadeh and Tarnopolsky [49], Hamadeh et al. [50], Hartman et al. [52], Holmer et al. [53], Kumar et al. [58], Lee et al. [58], Liu et al. [62], Mantis et al. [64], Mouton et al. [74], Parinejad et al. [80], Patel et al. [81], Patel et al. [79], Pedersen and Mattson [82], Qin et al. [85], Qin et al. [86], Qiu et al. [88], Wang et al. [98], Wu et al. [99], Yoon et al. [102], Yu and Mattson [103], Zhu et al. [105].

Consistent with these specific energetic demands of the brain, dietary restriction induces a metabolic reprogramming in most peripheral tissues in order to maintain sufficient glucose blood levels. Whereas *ad libitum* diets favour oxidation of carbohydrates over other energy sources, in dietary restriction fat metabolism is increased [19]. This increase in the use of fatty acids is paralleled by an increase in $FADH_2$ use by mitochondria, since β-oxidation produces $FADH_2$ and NADH at the same proportion, while NADH production due to carbohydrate oxidation is five-fold that of $FADH_2$.

Metabolic adaptions of the brain to dietary restriction are less understood. Nisoli et al. [78] showed that IF could induce mitochondrial biogenesis in several mouse tissues, including brain, through a mechanism that requires eNOS. However, other works using different protocols and/or animal models have provided diverging results. Whereas in brains from mice subjected to CR an increase in mitochondrial proteins and citrate synthase activity has been observed [23], other studies using FR in rats have failed to observe changes in mitochondrial proteins or oxygen consumption in the brain [51,60,93]. Interestingly, an increase in mitochondrial mass has also been observed in cells cultured in the presence of serum from rats subjected to 40% CR or FR, suggesting the existence of a serological factor sufficient to induce mitochondrial biogenesis [23,63].

The idea that mitochondrial biogenesis is stimulated under conditions of low food availability may seem counterintuitive. Indeed, mitochondrial mass normally increases in response to higher metabolic demands, such as exercise in muscle or cold in brown adipose tissue [51]. Different hypotheses have been put forward to explain this apparent discrepancy. Guarente suggested that mitochondrial biogenesis could compensate for metabolic adaptations induced by dietary restriction. In peripheral tissues, more mitochondria would make up for the lower yield in ATP production per reducing equivalent, due to an increase in $FADH_2$ use relative to NADH [47]. Analogously, in brain the use of ketone bodies also increases the $FADH_2$/NADH ratio, although to a lesser extent, suggesting that a similar explanation could apply.

How is this metabolic reprogramming induced? In recent years, attention has been given to SIRT1, a protein deacetylase from the sirtuin family. In many tissues, including brain, SIRT1 expression is enhanced in response to dietary restriction, and pharmacological activation of SIRT1, using drugs such as resveratrol, can mimic some of its effects [26]. Since PGC-1α, the master regulator of mitochondrial biogenesis, is among SIRT1 targets [75], a mechanism was initially suggested whereby SIRT1-mediated deacetylation of PGC-1α would be responsible for the increase in mitochondrial mass observed in response to SIRT1 activation by resveratrol, a mechanism that could also extend to dietary restriction [59]. However, recent reports using a more specific SIRT1 agonist, SRT1720, have shown contradictory results regarding a direct role for SIRT1 in mitochondrial biogenesis [36,40,72]. Despite this, several observations support the role of SIRT1 as a stimulator of fatty acid oxidation in liver and muscle, and of lipid mobilization in white adipose tissue, indicating that its activation could indeed induce a metabolic reprogramming similar to that observed in dietary restriction [36,84,91]. Similarly, adiponectin, whose levels increase when fat tissue is low, has also been shown to promote fatty acid oxidation in skeletal muscle and liver [100]. Furthermore, adiponectin knockout mice show increased lipid retention in the liver [104], making this hormone another suitable candidate for the role of metabolic reprogramming mediator.

At the cellular level, starvation stimulates macroautophagy (which will be referred hereafter as “autophagy”) in a wide number of tissues. Although nutrient deprivation is a well-known inducer of autophagy in most tissues and cell types, until recently it was believed that the brain was an exception to this rule [73]. However, recent reports using more sensitive methods indicate that autophagy is indeed induced in primary neuronal

cultures [101] and neurons *in vivo* [2] in response to nutrient deprivation. In addition SIRT1, which is highly expressed in rodent brain in response to FR or IF [26,44,96], has been described as an important regulator of autophagy *in vivo*, and overexpression of SIRT1 in cell lines is sufficient to stimulate basal autophagy [61].

Although the classical view of autophagy was that of an unspecific catabolic pathway, it is now common knowledge that autophagy can also act in a more selective way, as in the case of the removal of damaged mitochondria, a process termed mitophagy [43]. Observations in yeast support a preeminent role for mitophagy in the effects of CR in aging [90]. In rats on a FR regimen, an increase in mitophagic markers is observed in kidneys [30] and an improved autophagic response *in vivo* is present in liver [92]. The observation that both mitophagy and mitochondrial biogenesis could be stimulated during dietary restriction suggests an increased mitochondrial turnover, which could be acting as a "quality control" mechanism to provide a healthier pool of these organelles [47].

Dietary restriction in brain pathology

Aging is the most important risk factor for several pathological conditions including cancer, cardiovascular disease and neurodegeneration [76]. By extending lifespan, dietary restriction is also able to delay the onset of these age-associated diseases. In the following paragraphs we have summarized the current literature dealing with the effects of dietary restriction on some of the most important brain pathologies (Fig. 3).

Stroke

Stroke is caused by an interruption in the blood supply to the brain which in most cases is due to a blockage of the vessels that irrigate the brain, and specifically in the middle cerebral artery. During ischemia, lack of oxygen impairs oxidative phosphorylation and maintains electron transport chain proteins in a reduced state. Upon reperfusion, oxygen is restored and by interacting with these reduced proteins promotes a burst of ROS production, which mediates injury. In addition, ROS are also generated in the cytoplasm and the plasma membrane by means of xanthine oxidase, NOS and NADPH oxidase [66].

Most systemic changes induced by IF, CR and FR, such as decreasing inflammation and improving glucose metabolism, are potentially favourable against stroke. In addition, both IF and FR have been shown to decrease blood pressure in rats [65]. Hypertensive rats, which are stroke-prone, increase their survival probabilities about 50% when subjected to a 40% FR diet [62]. IF reduces infarct size and improves recovery of both mice [5] and rats [103] subjected to middle cerebral arterial occlusion, a common animal model for human stroke.

In heart, the beneficial effects observed after 30% FR could be related to increased deacetylation of mitochondrial proteins, which in turn decrease ROS formation upon reperfusion [94]. However, the role of SIRT1 in the brain remains unclear since, although SIRT1 knockout animals show larger infarct sizes than wild type mice, these animals can still respond to a 40% FR diet by decreasing both the extent of the infarct volume and the neurological deficit [62]. In addition, NAD^+ consumption due to SIRT1 activation could be detrimental to stroke outcome [83]. Loss of NAD(H) is has been demonstrated to play a decisive role in post-ischemic neuronal loss [38].

A putative player in this scenario could be adiponectin, It has been shown that adiponectin knockout mice are more susceptible to middle cerebral arterial occlusion and that adenovirus-mediated supplementation of adiponectin is protective both in wild type and knockout animals, through a mechanism that requires eNOS [77].

Alzheimer's disease

One of the most common causes of dementia in the elderly is Alzheimer's disease (AD), a pathological condition that comprises both genetic and environmental factors. Autosomal dominant forms, which account for only a small percentage of cases, are linked to mutations in the genes of amyloid precursor protein, presinilin 1 or presenilin 2. Brains from AD patients often present senile plaques and neurofibrillary tangles formed by hyper-phosphorylated forms of the microtubule-associated protein tau, along with increased oxidative imbalance and mitochondrial dysfunction [20,97].

Mitochondria from AD patients show characteristic alterations, including reduced complex II and IV activity, and inhibition of enzymes from the TCA cycle such as α-ketoglutarate dehydrogenase, leading to impaired ATP production [24]. In addition, calcium homeostasis and permeability transition pore opening susceptibility are also affected [28].

Improvement in behavioural tests is observed in different AD mouse models subjected to either IF, CR or FR. While FR and CR also promote a decrease in the presence of beta amyloid and phosphorylated tau in the brain [29,74,81,85,86,98,99] , IF could be acting through a different mechanism, since improved outcome occurs in the absence of detectable changes in amyloid peptide deposition [48].

Evidence points to a possible role of SIRT1 in the beneficial effects of CR in AD models. In p25-CK mice, a mouse strain which displays similar features to AD, SIRT1 levels are increased and stimulation of SIRT1 by resveratrol or injection with SIRT1 lentivirus protects against neuronal death [57]. In addition, 30% FR for 3 months further increased SIRT1 concentration in the brain, delayed the onset of the disease and maintained synaptic function [44]. Increasing SIRT1 levels or activating SIRT1 pharmacologically with NAD^+ *in vitro* has also be shown to increase α-secretase activity and decrease β-amyloid deposition in primary neuronal cultures from Tg2576 mice, another AD mouse model [85].

Interestingly, a link between AD and type 2 diabetes has been recently suggested, since both situations could share a common inflammatory origin [37]. In this context, the benefits of dietary restriction would not be restricted to direct effects on the brain, but would also extend to indirect effects due to improved insulin response.

Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is the most prevalent motor neuron disease. The etiology is complex, with 5–10% of the cases related to autosomal mutations, of which 15–20% are in the superoxide dismutase 1 gene. Sporadic ALS has poorly understood environmental causes (reviewed in [42]).

Contrary to other pathologies, and despite the fact that dietary restriction reduces oxidative imbalance, which is believed to be a main cause in ALS progression, the benefits of dietary restriction in ALS are far from clear. In a study using mice that overexpress a G93A mutation in the superoxide dismutase 1 gene, a common genetic model to study ALS, long-term 40% CR hastened the onset of the disease [50,79]. Transient (13–15 days) CR followed by *ad libitum* feeding also hastened disease development in males, while females remained unaffected by the diet [49]. In the same model, IF was also ineffective in delaying the onset of the disease and detrimental for disease progression [82]. However, a delay in the appearence of pathological traits and extended lifespan has been observed following 40% FR in another ALS genetic model, mutant H46R/H48Q mice, which harbour a different mutation in

the superoxide dismutase 1 gene [10]. These results suggest that the progression of the pathology is different in these two models, and indicate that too little is known to predict what results would be expected with the use of dietary restriction in human ALS.

Epilepsy

Epilepsy is a term used to describe a variety of disorders which can arise from different causes, characterised by the appearance of spontaneous and recurrent seizures. Although the etiology is not clear, oxidative imbalance and mitochondrial dysfunction are believed to be possible mediators of epileptogenesis [1].

Epilepsy is studied in rodents using convulsive drugs such as pentylenetetrazole (PTZ) or kainic acid (KA), or by electrical stimulation, which induces seizures and damage in the CA1 and CA3 regions of the hippocampus. Early dietary treatments of epilepsy showed that a ketogenic diet, which has high fat and low carbohydrate content, was effective in reducing seizures (for a historical review see [8]). By using fat over carbohydrates, the ketogenic diet promotes the formation of ketone bodies in the liver which, unlike fatty acids, are able to cross the blood–brain barrier and used in the brain as an alternative to glucose (see Fig. 2). Thus, ketones have been identified as putative mediators of the ketogenic diet effect.

Since the ketogenic diet itself has fewer calories than a normal diet, it is plausible that some of its effects could be due to restricting the amount of calories ingested. Supporting this hypothesis, dietary restriction can partially mimic the ketogenic diet in the context of epilepsy. Both IF and FR have been shown to reduce the extent of cell death in the hippocampus following KA injection [3,18,27]. The higher efficacy of IF over FR observed in one of these works was correlated with the higher levels of β-hydroxybutyrate, specifically increased in IF.

As for seizure appearance, FR as low as 10% is sufficient to greatly increase the threshold to the toxin PTZ. Although this effect was somewhat lower than with an isocaloric ketogenic diet, it occurred in the absence of a noticeable increase in the concentration of β-hydroxybutyrate, suggesting that the increase in circulating ketone bodies could be less important in the development of seizures than originally thought [13]. More insight was obtained in a recent work in which the effects of short-term IF, FR and the ketogenic diets in response to different epileptogenic stimuli in Swiss mice was studied. When seizures were induced by 6 Hz treatment, the ketogenic diet was protective, while both IF and FR increased seizure activity. However, when seizures were induced by KA administration, IF, but not the ketogenic diet, was protective (DR was not assayed in this test). In a third test, the maximal electroshock test, where a sine wave pulse is delivered rather than the square waved pulse used in the 6 Hz test, IF showed a lower threshold than AL, and the ketogenic diet showed no effect. Finally, IF was also shown to be ineffective against PTZ. Moreover, the authors failed to see a correlation between the levels of glucose or circulating ketones with seizure susceptibility [52].

Interestingly, it has been reported that pre-treatment with adiponectin protects cultured hippocampal neurons against KA-induced excitotoxicity [87]. Protection has been also observed *in vivo* using intracerebroventricular administration of adiponectin, followed by subcutaneous injection of KA, which resulted in decreased cell death in the hippocampus [55]. Although seizures were not evaluated in this latter work, these observations pinpoint adiponectin as a possible mediator of some of the effects of dietary restriction in KA-induced neuronal damage.

Parkinson's disease

Another well-known neurodegenerative condition is Parkinson's disease (PD), which causes progressive motor dysfunction due to selective loss of dopaminergic neurons from the *substantia nigra* that project to the *striatum*. In addition, accumulation of Lewy bodies containing aggregated proteins such as α-synuclein, increased inflammation, mitochondrial dysfunction and oxidative imbalance are all common features observed [54].

Mitochondrial alterations in PD include increased mitochondrial permeability transition pore opening, loss of NAD, defective mitochondrial dynamics and impaired clearance of damaged mitochondria, leading to accumulation of mitochondrial DNA mutations and high ROS levels. PD-linked mutations in genes that codify for mitochondrial proteins include PINK1, parkin, and LRRK2 [95,24].

Several models are used to study PD, including α-synuclein mutant mice, which develop a degenerative condition similar to PD in humans, and administration of rotenone or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which induce a parkinsonian phenotype by impairing mitochondrial complex I activity [15].

Mice on an IF diet are protected against neuronal loss in the *substantia nigra* and show improved motor function after MPTP administration [34]. The same diet has shown beneficial effects even when started after MPTP administration, decreasing the extracellular levels of striatal glutamate [53]. In addition, reports indicate that IF can alleviate some of the collateral effects of PD, such as the elevated heart rate in a mouse model of α-synuclein accumulation [46] and the high levels of circulating corticosterone, which are detrimental for neuronal viability and plasticity [88]. However, the same diet was ineffective in rats against nigrostriatal degeneration induced by 6-hydroxydopamine, an alternative model for PD [4]. Interestingly, a study carried out in primates indicates that a 30% CR diet prior to MPTP administration increases the level of neurotrophic factors in the brain, improves motor activity and reduces the loss of dopamine and its related metabolites [68].

Recent evidence indicates that the gastrointestinal system could play a noted role in the development of PD and that the orexigenic signal ghrelin, which is produced in the stomach in response to fasting and whose levels are increased during dietary restriction, could be neuroprotective [9].

Conclusions

The special metabolic requirements of the brain, along with its fundamental role in managing energy homeostasis of the organism, make this organ a primary target of dietary interventions. The cellular adaptations of neurons and astrocytes under these conditions are still poorly understood, but probably involve changes in mitochondrial function and metabolic reprogramming, and take place in a coordinated manner with alterations in other organs, including a lower use of carbohydrates, mobilization of fat reservoirs and changes in levels of circulating hormones that regulate energy use and inflammation.

Despite a lack of knowledge regarding its molecular mediators, the effects of dietary restriction in the context of brain pathology are remarkable. Importantly, the effects are usually not only restricted to preventing the onset of these conditions, but they also delay development once started or promote faster recovery. In the search for the mechanisms through which dietary restriction acts, special attention must be given to situations where interventions have proven to be inefficient or even detrimental, such as ALS. The identification of singularities in these models may provide important clues as to how these diets operate. Detailed and unified protocols are also vital in this pursuit.

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