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Review

Rationale for using intermittent calorie restriction as a dietary treatment for drug resistant epilepsy

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ABSTRACT

There has been resurgence in the use of dietary treatment, principally the classical ketogenic diet and its variants, for people with epilepsy. These diets generally require significant medical and dietician support. An effective but less restrictive dietary regimen is likely to be more acceptable and more widely used. Calorie-restricted diets appear to produce a range of biochemical and metabolic changes including reduced glucose levels, reduced inflammatory markers, increased sirtuins, increased AMPK signaling, inhibition of mTOR signaling, and increase in autophagy. There are studies in animal seizure models that suggest that these biochemical and metabolic changes may decrease ictogenesis and epileptogenesis. A calorie-restricted diet might be effective in reducing seizures in people with epilepsy. Hence, there is a sufficient rationale to undertake clinical trials to assess the efficacy and safety of calorie-restricted diets in people with epilepsy.

1. Introduction

Dietary treatment for epilepsy has probably been used for over 2000 years. The modern implementation of this form of therapy started in the 1920s with the development of the ketogenic diet (KD) to mimic the metabolic changes of starvation. The classical KD was generally initiated with a 24-hour fast, the total calories were then typically restricted to 80–90% of the individual's caloric requirement, and the ratio of fat to protein plus carbohydrate ranged from 2:1 to 4:1. The use of the KD became less popular with the introduction of newer antiepileptic drugs in the 1930s. In the last 20 years, there has been a marked rise in the introduction of new antiepileptic drugs, but there has also been the realization that all the new antiepileptic drugs may not have changed the prognosis of epilepsy. Over this same period, there has been a marked resurgence in the use of the KD. The use of the classical KD is restrictive with respect to amounts and food choices for each meal; it generally requires a hospital stay for initiation and continued dietitian support and is often poorly tolerated. This led to the development of less restrictive variants such as the modified Atkins diet, the medium chained triglyceride (MCT) diet, and the low glycemic index treatment (LGIT). All the variants appear to have efficacy comparable with the classical KD, and all require significant medical and dietician support. An effective diet therapy that requires little or no dietician support and is better tolerated would allow more people with epilepsy to benefit. We propose the use of a relatively easy-to-follow calorie-restricted diet and provide the rationale as to why such a diet might reduce seizures in people with epilepsy.

2. The metabolic effects of daily calorie restriction

The study of the effects of calorie restriction probably started with the observation that severe calorie restriction led to increased lifespan in rodents [1]. Much research has been undertaken since. Daily calorie restriction (DCR) has now been shown to prolong life in a variety of animal species including yeast, flies, worms, and laboratory rodents [2]. One primate study demonstrated an effect of DCR on prolonging life [3], while a preliminary report on a study conducted by the National Institute of Aging, USA, did not. The mechanism by which calorie restriction confers benefit is not fully understood, but it is known that calorie restriction produces a range of biochemical changes which are thought to be important in mediating its benefit on general health and in increasing longevity. The main changes that are thought to be important and which are discussed in one review [4] are the following:

decrease in insulin-like growth factor 1 (IGF-1);
increase in sirtuins;
increase in adenosine monophosphate-activated protein kinase (AMPK); and
decrease in mammalian target of rapamycin (mTOR).

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Another way of looking at the potential mechanisms of calorie restriction on longevity benefits is to examine the key processes that are thought to underlie the aging process, i.e., oxidative stress and chronic inflammation. A review of the literature suggests that these processes are powerfully reduced by calorie restriction [5].

3. Intermittent calorie restriction produces similar effects to daily calorie restriction

Intermittent calorie restriction (ICR) or intermittent fasting has been studied as an alternative to DCR in an attempt to find a more acceptable diet regimen. It has also been suggested that intermittent calorie restriction is actually the way our hunter gatherer ancestors fed for nearly 2 million years; hence, our physiology probably functions optimally under such condition. A number of studies and reviews suggest that, in the main, daily calorie restriction and intermittent calorie restriction produce similar metabolic and physiological changes. There are studies showing effects of DCR not seen in ICR and vice versa.

In a clinical study, 107 overweight or obese premenopausal women were randomized to ICR (approximately 647 calories/day for 2 days/week) or DCR (approximately 1500 calories/day for 7 days/week) for a period of 6 months. Analysis showed that ICR and DCR are equally effective for weight loss. Both groups experienced comparable reductions in leptin, free androgen index, high-sensitivity C-reactive protein, total and LDL cholesterol, triglycerides, and blood pressure and increases in sex hormone-binding globulin and in IGF-binding proteins 1 and 2. Reductions in fasting insulin and insulin resistance were greater with ICR than with DCR. Hence, ICR is as effective as DCR on most measures and more effective on two markers [6]. In a transgenic mouse study, ICR and DCR appeared to have similar effects on ameliorating age-related cognitive deficit [7]. In rats, ICR and DCR had similar effects on increasing the high frequency component of heart rate variability suggesting an increase in parasympathetic tone and on decreasing the low frequency component of diastolic blood pressure variability suggesting a decrease in sympathetic tone [8].

A review of the effects of ICR and DCR suggests that the two dietary interventions can promote the health of the nervous system through their effects on fundamental metabolic and cellular signaling pathways. There are multiple interacting pathways and molecular mechanisms by which ICR and DCR benefit neurons including those involving insulin-like signaling, FoxO transcription factors, sirtuins, and peroxisome proliferator-activated receptors. These pathways stimulate the production of protein chaperones, neurotrophic factors, and antioxidant enzymes, all of which help cells cope with stress and resist disease [9].

4. Calorie restriction reduces seizures in animal models

Calorie restriction alone appears to reduce seizures in animals. In a genetic mouse model of idiopathic epilepsy, calorie-restricted diets delayed onset and reduced incidence of seizures compared with those fed ad libitum. In juvenile animals, a 15% calorie-restricted diet of regular chow had a greater antiepileptogenic effect compared with a KD fed ad libitum [10]. In epileptic EL mice, blood glucose levels remained high in the standard diet and KD groups when calories were unrestricted but were significantly reduced in the calorie-restricted groups. Plasma beta-hydroxybutyrate levels were significantly higher in the calorie-restricted groups than in the respective unrestricted groups. Seizure susceptibility was significantly reduced after three weeks in both calorie-restricted groups, while remaining high in the calorie-unrestricted groups [11]. The effects of calorie restriction, ketosis, and carbohydrate intake on pentylenetetrazole (PTZ)-induced seizures were studied in rats fed a high carbohydrate diet that was calorie-restricted to 90%, 65%, or 50% and those fed a standard KD that was calorie-restricted to 90%. Seizure threshold was elevated in proportion to calorie restriction, and animals fed a high carbohydrate diet, calorie-restricted to 50%, had thresholds similar to those fed a KD, calorie-restricted to 90%, suggesting that calorie restriction alone has an antiseizure effect. This also suggests that restricting a lower carbohydrate/higher fat diet is likely to be more effective than restricting a high carbohydrate diet [12].

In an electrophysiological study, rats were fed one of three diets: (1) ketogenic 80–90% calorie-restricted, KCR; (2) normal 80–90% calorie-restricted, NCR; and (3) normal ad libitum, NAL. Compared with the NAL group, both KCR and NCR groups showed greater paired pulse inhibition, increased resistance to electrographic seizures, and an absence of spreading depression-like events. This suggests that KCR and NCR have anticonvulsant effects, possibly through augmentation of fast inhibition. In the maximal dentate activation MDA model, both KCR and NCR groups showed increased thresholds, but only animals in the KCR group showed prolongation of electrographic seizure duration, suggesting that the KCR may have additional antiepileptogenic action [13]. There is a long-standing hypothesis that KD and calorie restriction have similar mechanisms. A carefully conducted study, however, showed that calorie restriction and KD in juvenile mice with matching weights differ in their acute seizure test profiles. Matching the weights of animals eliminated the possible confounding effect of differences in weight. This suggests that KD and calorie restriction may have different underlying anticonvulsant mechanisms [14].

5. Mechanisms by which calorie restriction might reduce seizures

Calorie restriction leads to a range of biochemical and metabolic changes which are probably closely interrelated. Some of these changes have been shown in animal studies to increase seizure thresholds and to decrease epileptogenesis. The changes that might be relevant in affecting ictogenesis include decreases in glucose levels and in systemic inflammation, increase in adenosine monophosphate kinase (AMPK), inhibition of mTOR, and increase in autophagy.

5.1. Decreased glucose levels can lead to activation of KATP channels to stabilize neuronal membranes

A calorie-restricted diet generally leads to a decrease in glucose levels (see above). A decrease in glucose levels has many physiological effects, and of particular interest is the effect on neuronal membranes. In rat and mouse hippocampal CA3 neuronal preparations, a decrease in extracellular glucose levels has been shown to open channels to release intracellular adenosine triphosphate (ATP). In the extracellular space, ATP is dephosphorylated to adenosine, which then activates the adenosine receptors. Activation of adenosine receptors opens the KATP channels, stabilizing neuronal membranes and increasing seizure thresholds [15].

5.2. A number of inflammatory markers are reduced by calorie restriction

A review of inflammatory markers in aging suggests that the age-related increases in NF-kB, IL-beta, IL-6, TNFalpha, cyclooxygenase-2, and inducible NO synthase are all reduced by calorie restriction [16]. There is considerable evidence that inflammation is involved in the process of seizure generation [17]. A recent review of the role of glial cells in epilepsy suggested that, although neurons have the main role in generation of seizures, glia can promote hyperexcitability. If glia exhibit increased inflammatory markers, the neurons become more hyperexcitable [18]. Hence, the effect of calorie restriction on reducing inflammation would be expected to reduce neuronal excitability.

5.3. AMPK signaling activates PGC-1α, increases mitochondrial ATP production, and inhibits mTOR

The AMPK signaling pathway appears to be an intracellular fuel sensor that registers elevated adenosine monophosphate (AMP):ATP and