Ketogenic diet in migraine - a new approach for treatment?

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Abstract

Migraine is a common neurological disorder greatly affecting quality of life, especially if it becomes chronically. WHO ranks migraine among the world’s most disabling medical illnesses. Since prophylactic therapies in migraine are problematic, new approaches for treatment should be considered.

This paper reviews hypothesis on the effect of a ketogenic diet in migraine. Besides epilepsy, there is increasing evidence for an effect of a ketogenic diet in other neurological disorders. The neurometabolic effect of the ketogenic diet may be very divers.

According to its pathophysiology different mechanisms due to a ketogenic diet could theoretically prevent migraine. A case report confirms this assumption. The diet could affect a suggested hyperexcitability in migraine, like it is postulated for epilepsy. Moreover it could be active by affecting a serotonergic or sympathetic dysfunction. Also an antiinflammatory effect of a ketogenic diet could prevent migraine.

Keywords

migraine disorders;
neurogenic inflammations;
prevention and control;
diet therapy;
diets, Carbohydrate-Restricted;
Peroxisome Proliferator-Activated Receptors
Introduction

Migraine is a common primary episodic headache disorder characterised by various combinations of neurological, gastrointestinal, and autonomic changes (Silberstein, 2004). Its prevalence is about 4% to 10% in men and 11% to 25% in women (Leonardi et al, 2005). WHO ranks migraine among the world’s most disabling medical illnesses. The burden is highest in patients suffering from chronic migraine. Migraine triggers discussed are very complex and difficult to manage (Kelman 2007). There are increasing economic costs because of treatment patients with chronic analgetics abuse (Neubauer 2002). That means effective prophylactic therapies are strongly needed.

Current prophylactic therapies including therapy with adrenergic and antiepileptic drugs and antidepressants are only moderately effective (Goadsby et al, 2002; Buchanan & Ramadan, 2006). A combined application of different drugs is discussed to improve efficacy (Dodick & Silberstein, 2007). Since they entail substantial side effects this is critical (Goadsby et al, 2002; Dodick & Silberstein, 2007). New preventive therapies, especially for the management of chronic intractable migraine, should be considered.

The ketogenic diet

The ketogenic diet is a high-fat diet developed in the 1920s to mimic the biochemical effects of fasting, which had been shown to be effective in epilepsy (Freeman et al, 2007). The weight ratio of fat to protein and carbohydrate traditional is 4:1. Today it is a worldwide established treatment for intractable epilepsy. There is evidence for an effectiveness of less restricted fatty diets like the Atkins diet or a low-glycemic-index diet (Pfeifer & Thiele, 2005; Kossoff et al, 2003; Kossoff et al, 2006). Though being used especially in children efficacy of a ketogenic diet was shown in adults, too (Sirven et al, 1999; Coppola et al, 2002; Mady et al, 2003).
The basic physiological change on a ketotic metabolism is prefering fat and ketone bodies respectively as substrates for energy production instead of glucose. A wide range of neurometabolic effects are discussed including effects on energy metabolism but also neuromodulatory effects, antioxidant mechanisms or a protective mechanism by carbohydrate restriction (Sankar et al, 1999; Szot et al, 2001; Yudkoff et al, 2001; Cullingford et al, 2002; Volek et al, 2002; Ziegler et al, 2003; Sullivan et al, 2004; Taha et al, 2005; Bough & Rho, 2007; Weiyuan et al, 2007). Recently, there is increasing evidence for an effect of a ketogenic diet in neurological disorders other than epilepsy, including Alzheimer’s, Parkinson’s or Huntington’s disease (Van der Auwera et al, 2005; Jabre & Bejjani, 2006; Zhao et al, 2006; Mattson et al, 2003). So the neurometabolic action may be very divers.

Migraine is a neurological disorder, too. Researchers assume a neurological dysfunction causing a pain reaction without a painful stimulus (Ebersberger 2002; Silberstein 2004; Dodick & Silberstein, 2006). The detection of mediators involved in inflammation, like prostaglandins, calcitonin-gene-related peptid (CGRP) and nitric oxide (NO) indicates a neurogenic inflammation. There is evidence that migraine, like epilepsy, is associated with a neuronal hyperexcitability (Battelli et al, 2002; Ambrosini et al, 2003; Moskowitz et al, 2004; Lang et al, 2004; Sang et al, 2004; Welch 2005).

One case report provides evidence that a ketogenic diet may have a therapeutic effect and suggests to study this diet in migraine management (Strahlman 2006). In this report, a female patient with chronic migraine was headache free after ketosis was induced. Even after returning to her regular diet, she continued to be free from migraine for more than 6 months. Different mechanisms could account for this positive effect. Each mechanism is described in detail below (Figure 1).
Preventing neurogenic inflammation

A neurogenic inflammation could be reduced because of an enhanced PPARα-activation. As it was shown in mice a fasting-induced ketosis results in an induction of PPARα dependent gene expressions. (Leone et al, 1999; Le May et al, 2000).

PPARs are a group of transcription-factors working as regulatory fatty acid receptors (Issemann & Green, 1990; Bocos et al, 1995; Escher & Wahli, 2000). Fatty acid-bound-PPARs promote transcription of different genes presenting the PPAR-response element (Juge-Aubry et al, 1997). PPARα is strongly activated by polyunsaturated fatty acids (PUFAs) (Forman et al, 1997) and a significant increase of brain PUFAs has been shown by a ketogenic diet (Taha et al, 2005). In addition there is evidence that PPARα becomes more active when insulin is reduced (Shalev et al, 1996; Latruffe et al, 2000). First, PPARα was identified in the liver. In 1998 it was found in the brain, too (Cullingford et al, 1998).

Since PPARα acts by inhibiting pro-inflammatory pathways (Chung et al, 2000; Delerive et al, 2002; Delerive et al, 2000; Sethi et al, 2002; Chen et al, 2007), a ketogenic diet-induced activation of PPARα could theoretically prevent migraine. Studies have shown that plasma levels of CGRP and NO are raised significantly in migraine patients examined interictally, suggesting these changes being responsible for a predisposition towards migraine (Fusayasu et al, 2007; Ashina et al, 2000; D'Amico et al 1998). There is evidence that PPARα inhibits NO production of microglia (Xu et al, 2005). Since NO causes CGRP synthesis and release from trigeminal neurons (Bellamy et al, 2006), PPARα activation could prevent CGRP release, too.

Compensation serotonergic dysfunction

Another mechanism of the diet could be linked to the role of serotonergic dysfunction in migraine. Drugs for treating acute migraine attacks are serotonin (5-HT_{1B/D}) receptor
agonists, which are located on pain modulating neurons (Bartsch et al, 2004; Shields & Goadsby, 2006). One recent PET study suggests a reduced cerebral serotonin synthesis interictally promoting an attack (Sakai et al, 2008). Consistently there is evidence from IAEP-studies of a significantly reduced serotoninergic neurotransmission in migraines interictally (Ambrosini et al, 2003b; Proietti-Ceccini et al, 1997).

Experiments on rats showed an enhanced brain serotonin synthesis after a fasting period (Kantak et al, 1978; Fuenmayor et al, 1984; Schweiger et al, 1989; Pirke et al, 1993). This indicates that ketosis may also improve serotoninergic transmission. An animal study on changes in amino acid metabolism in fat-fed rats also showed a significant genetic downregulation of the degradation of the serotonin-precursor tryptophan (Sheikh et al, 2007). Because this effect was also shown after applying a PPARα agonist, a fat-induced PPARα activation is suggested to be responsible.

The antiepileptic effect of a ketogenic diet may also result from serotoninergic modulation, as it has been shown for serotonin-receptor activation (Theodore, 2003).

Inhibition neuronal excitability

Glutamat and GABA. An inhibitory effect on neuronal excitation is discussed in epilepsy (Yudkoff et al, 2001; Dahlin et al, 2005) and may be relevant in migraine as well. Studies have shown a modified tricarboxylic acid cycle (TCA) affecting synthesis of the important brain neurotransmitters glutamate and GABA (De Vivo et al, 1978; Yudkoff et al, 1997; Margareta et al, 2006). A reduced excitatory glutamatergic neurotransmission and an improved inhibitory GABAergic transmission is suggested to have an antiepileptic effect. Since GABA receptors in brainstem are involved in antinociception and may inhibit trigeminal pain (Xiao et al, 2005; Storer et al, 2004), pain in migraine patients could be prevented. There is also evidence for an increased glutamatergic neurotransmission in
migraine (Sang et al, 2004). This is indicated by an genetic polymorphism of the astrocytic Na⁺/K⁺-ATPase, which is associated with familiar hemiplegic migraine, a special kind of migraine (Moskowitz et al, 2004). As activity of astrocytic Na⁺/K⁺-ATPase is essential for glutamate clearance from the synaptic cleft (Magisretti & Pellerin, 1999) an impairment may cause neuronal hyperexcitability. Correspondingly, also epilepsy is associated with a polymorphism in the Na⁺/K⁺-ATPase gene (Wolf et al, 2005).

Norepinephrine. Experiments on rats also showed a significant increase of cerebral norepinephrine and an association of an intact norepinephrine synthesis with the antiepileptic effect of the diet (Szot et al, 2001). Consistently PPARα activation has been shown to reduce gene expression of hepatic phenylalanine hydroxylase (Kersten et al, 2001). Since phenylalanine is a precursor of norepinephrine, synthesis could be promoted.

In migraine an impairment of the sympathetic nervous system has been described, which could result from a reduced noradrenergic transmission (Peroutka, 2004). Central noradrenergic projections - via the locus coeruleus - cause major inhibition of the trigeminal system (Sasa et al, 1979; Matsutani et al, 2000). Accordingly the improved noradrenergic transmission could suppress trigeminal neuralgia in migraine.

Cerebral energy. In addition, it has been suggested that the ketogenic diet leads to an increase in cerebral energy reserves (Hasselbach et al, 1994; Pan et al, 1999; Bough et al, 2006). A modified TCA or an upregulation in mitochondrial biogenesis shown in the rat may raise brain ATP production (Bough et al, 2006).

This could inhibit migraine, as energy deficiency seems to promote an attack. An association between migraine and mitochondrial diseases, as well as with hypoglycemia has been described (Marsters et al, 1986; Jacome, 2001; Sparaco et al, 2006). A low cerebral energy level and a downregulated glucose metabolism were also shown (Welch et al, 1989; Barbiroli et al, 1992; Sacquegna et al, 1992; Montagna et al, 1994; Gutschalk et al, 2002).
be based on an evidenced genetic polymorphism of the peripheral insulin receptor (McCarthy et al, 2001) which is also expressed by glia cells (Schwartz et al, 1992). An impairment of this receptor can affect neuronal activity, because astrocytes play a central role in distributing energy substrates from circulation to neurons (Magisretti & Pellerin, 1999). An impairment of the astrocytic Na⁺/K⁺-ATPase is of particular importance again, due to an energy depletion, which affects homeostasis and neuronal excitation, respectively (Silver & Erecinsyca, 1997). Again an enhanced PPAR activation could be part of the energetic upregulation, since it has been described as stimulator of mitochondrial genome transcription (Casas et al, 2000).

Conclusion

Several mechanisms could account for a positive effect of the ketogenic diet on migraine. Recent prophylactic therapies are only moderately effective and entail substantial side effects (Goadsby et al, 2002; Dodick & Silberstein, 2007). This makes a strong case for direct investigations of the ketogenic diet in migraine, especially for the management of chronic intractable migraine. Maybe a combination of effects by a ketogenic diet precisely is a potent prophylactic treatment.

With regard to its implementation it should be considered that there is evidence for an effectiveness in epilepsy of less restricted fatty diets. In addition, according to studies on epilepsy as well as to the mentioned case report about migraine and ketosis, short periods of the diet may be sufficient for a lasting improvement. A moderate form of the traditional ketogenic diet would mean an easier implementation and there a less difficult adherence.
Legende

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FFA : Free Fatty Acids

PUFA : Polyunsaturated Fatty Acids

PPAR : Peroxisome Proliferator-Activated Receptor

TCA : Tricarboxylic Acid Cycle

180 GABA: γ-Aminobutyric Acid

SNS : Sympathetic Nervous System

↓ : Down-Regulation

↑ : Up-Regulation

A → B : A affects B

A → B : A affects B strongly

A ↔ B : A inhibits B
Figure 1: Schematic overview of hypotheses for an effect of the ketogenic diet in migraine prevention.