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A pyruvate dehydrogenase complex disorder hypothesis for bipolar disorder

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ABSTRACT

Ketosis is a metabolic state in which the body uses ketones derived from breakdown of fatty acids as the primary mitochondrial fuel source instead of glucose. In recent years an accumulation of evidence for the beneficial effects of the ketotic state on the brain have heightened interest in its potential for use in neurological conditions. The ketogenic diet (KD) induces ketosis and is an effective treatment for medically resistant epilepsy. There is significant comorbidity between epilepsy and bipolar disorder (BD) and both conditions are treated by anti-convulsant drugs. In addition, reports on bipolar disease online fora have highlighted subjective mood stabilization effects associated with the KD. These KD reported effects could be explained if there was a disorder in the conversion of pyruvate into Acetyl-CoA (and subsequent impairment of oxidative phosphorylation) which was bypassed by ketones providing an alternative substrate for oxidative phosphorylation. This is consistent with growing evidence that mitochondrial dysfunction plays a causal role in BD and explains the reported TCA cycle dysfunction and elevated pyruvate levels in BD. Reduced levels of ATP affects the normal operation of the Na, K-ATPase in the brain with differing levels of reduction either leading to reduced neuronal action potential and inhibition of neurotransmitter release (consistent with the depressed state in BD) or increased neuronal resting potential and hyper-excitability (consistent with a [hypo]manic mood state). We hypothesize that the mitochondrial dysfunction is due to a disorder of the Pyruvate Dehydrogenase Complex (PDC) and/or Mitochondrial Carrier Protein (MCP) shuttle which moves intracellular pyruvate into mitochondria. The resultant reduction in ATP generation could explain mood instability and cycling in BD (through mechanisms such as those delineated by Mallakh and Peters). This proposed novel causal pathway could explain mood de-stabilization in BD and the reported positive effects of KD. If true, this hypothesis would suggest that there should be increased research attention to PDC (and in particular the E1 alpha subunit) as potential therapeutic targets and further study of a possible role of KD in BD to improve mood stability. Experimental approaches, such as through a clinical trial of KD on mood stabilization in BD, are required to further investigate this hypothesis.

Introduction

Ketosis is a metabolic state where the body uses ketones derived from breakdown of fatty acids as the primary fuel source instead of glucose. In recent years an accumulation of evidence for the beneficial effects of the ketotic state on the brain have heightened interest in its potential for use in neurological conditions. Such benefits include improvements in cerebral metabolism [1] changes in neurotransmitter levels [2,3], increase of mitochondrial glutathione levels [4], increased NADH oxidation [5], increased mitochondrial biogenesis and other significant neuroprotective effects [6].

Therapeutic use of the ketogenic diet in refractory epilepsy

Ketosis is induced primarily through fasting or adherence to the ketogenic diet (KD) which is a high fat, very low carbohydrate and adequate protein dietary program. The KD is currently used as an effective treatment for medically resistant epilepsy with its effect confirmed through meta-analysis of clinical trials. Through strict adherence to the diet long term seizure reduction can be achieved [7,8]. Several proposed mechanisms of seizure prevention are summarized by Simeone [9], however there is as yet no consensus as to the mode of action.

The most significant biological effect of the KD is the metabolic switch from glucose as the primary fuel substrate for ATP production to ketones as the primary mitochondrial fuel. The ketotic state has been shown to increase both mitochondrial ATP production and the opening of K(ATP) channels in neurons [10]. Several researchers suggest that the profound mitochondrial effects of the ketotic state lead to seizure reduction through the re-establishment of sodium-potassium pump (Na, K-ATPase) function in neurons [10]. Ketone levels have been found to be associated with the anticonvulsant effect, with this action being reversed rapidly by intravenous infusion of glucose [11]. This may indicate that an underlying mechanism such as the Na, K-ATPase which responds rapidly to changes in cellular energy is implicated in epileptic seizures. Eliminating metabolically sensitive K(ATP) channels abolishes the anti-convulsant effect of ketogenic diet [10].

Ketosis and bipolar disease (BD)

There is significant comorbidity between epilepsy and bipolar disorder (BD) and both conditions are treated by anti-convulsant drugs

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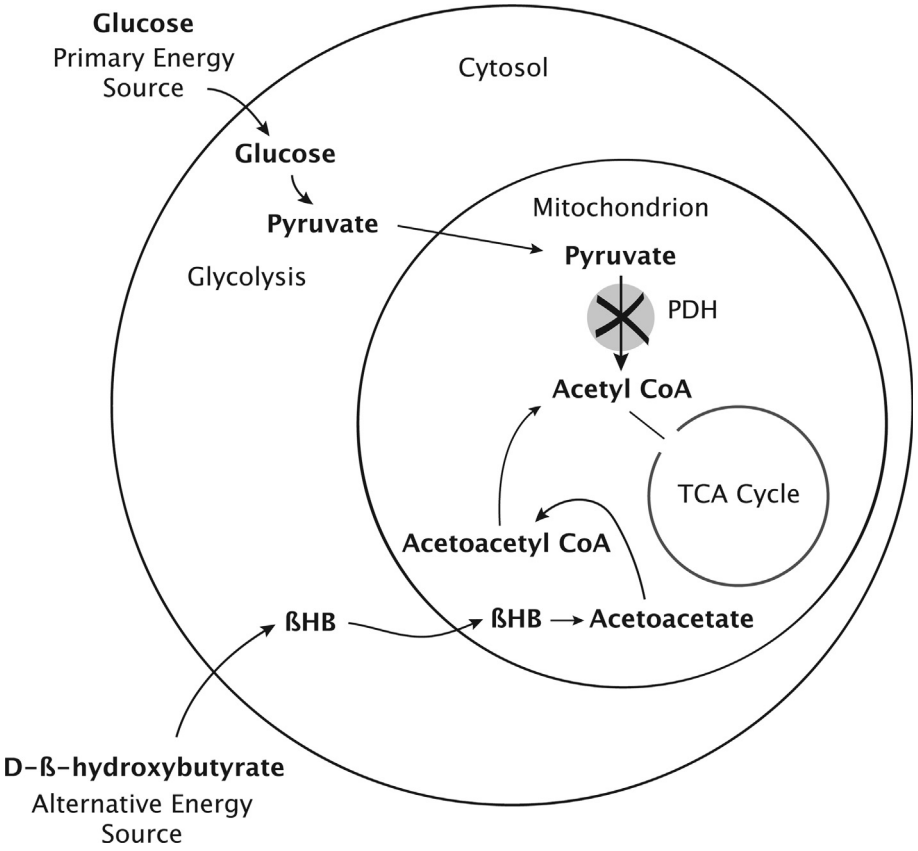

Fig. 1. Ketone body D-beta-hydroxybutyrate bypasses a block in the PDH (pyruvate to acetyl CoA) in the cytoplasm and provides acetyl CoA to the TCA Cycle.

[12,13]. Both conditions are characterized by an episodic nature, [14] altered mitochondrial energy production [15] and show evidence of functional brain abnormalities as well as altered neuronal ion gradients [14]. A review of bibliographic databases on ketosis and BD identified only two small reports [16,17]. In one report the subject failed to achieve a detectable level of ketones [16], in the other both subjects reported significant mood stabilization exceeding that achieved through medication [17]. However, a google search of online fora identified many testimonials from BD forums with dramatic reports of improvement. A controlled analysis of these reports concluded that the association between adoption of a ketogenic diet and improved mood stabilization in BD is worth further investigation and is not fully explained by selection and reporting biases in self-reported observational data [18].

The ketogenic diet and the mitochondrial dysfunction hypothesis for BD

Recent research evidence has strengthened support for the hypothesis that mitochondrial dysfunction has a causal role in BD. This has recently been elaborated in detail by Kato [19] and Kim [20] who highlight the MRI, biochemical and genetic data which support this hypothesis. It has been noted that mitochondrial dysfunction would be expected to influence neural processes which could underlie BD such as altered sodium/calcium dynamics and signaling and increased creation of reactive oxygen species with resulting oxidative stress [20]. Silver suggests that altered neuronal sodium/calcium dynamics may indicate that there is a minimum ATP requirement for full function of the neuronal Na, K-ATPase which is not met under inhibition of either glycolysis or oxidative phosphorylation [21]. The resultant loss of Na, K-ATPase function leads to large calcium influx to neurons with resultant glutamate excitotoxicity and neuronal apoptosis, both of which play a central role in neurodegeneration in BD [21].

Mitochondrial dysfunction as the cause of mania and depression in BD

As early as 1983 Mallakh et al hypothesized that Na, K-ATPase dysfunction could underlie both manic and depressed states in BD [22]. He noted that a modest reduction of Na, K-ATPase function in the brain can lead to a hyper-excitable state by bringing the resting potential of neurons closer to the threshold for activation. Elevated calcium in the neuron due to decreased rate of clearance would also increase the duration of neurotransmitter release. This state may explain both the mood state and the elevated neuronal calcium observed in mania. Further reduction in Na, K-ATPase function would bring the resting potential even closer to the threshold for activation yet decrease the amplitude of the action potential with resultant inhibition of neurotransmitter release. This state of impaired neuronal activity may contribute to the low-energy depressed state in BD. Brietzche [23] recently highlighted Peters [24] “Selfish Brain” hypothesis which describes a similar dynamic where neurons enter an excitatory state with release of glutamate under modest reduction of ATP and a refractory state under larger yet non-critical reduction in ATP levels.

Silver [21] demonstrated that the ATP threshold for normal Na, K-ATPase function can only be achieved through the combination of oxidative phosphorylation and glycolysis. In his study impairment of oxidative phosphorylation of the kind commonly observed in BD led to reduction of Na, K-ATPase function and calcium accumulation in neurons.

Mitochondrial dysfunction and pyruvate dehydrogenase

Impairment of oxidative phosphorylation is a key component of the reported mitochondrial dysfunction in BD but the source of this dysfunction is currently unknown.

Metabolomic studies have shown disruption of the TCA cycle in BD

and increased levels of pyruvate [25] We hypothesize that the increased levels of pyruvate and consequently lactate (as a product of increased glycolysis) commonly observed in BD are caused by a dysfunction in the Pyruvate Dehydrogenase Complex resulting in impaired ability to utilize pyruvate within the TCA cycle [25].

In a state of ketosis, high plasma levels of ketones such as beta-hydroxybutyrate act as an alternative energy source and can supply acetyl coA directly to the TCA cycle providing an alternative pathway to that from pyruvate (see Fig. 1). The reports of the positive effects of the ketogenic diet on mood stabilization in BD are consistent with a reduced formation of acetyl CoA from pyruvate which is bypassed by this alternative source of acetyl CoA from ketones. This, in turn, implies reduced activity of mitochondrial pyruvate dehydrogenase (PDH) or reduced carriage of intra-cellular pyruvate transport across the mitochondrial membrane by mitochondrial carrier proteins (MPC) – (see Fig. 1).

There is some support for this interpretation since the ketogenic state has been shown to restore the function of the TCA cycle. This has been well demonstrated in cases of PDH (also known as PDC) deficiency and the KD is the standard care for these conditions [26]. KD has also been reported to maintain ATP production with resultant neuroprotective effects under hypoxic, glycolytic conditions where oxidative phosphorylation is inhibited [27]. In these circumstances the pyruvate dehydrogenase complex is de-activated by pyruvate dehydrogenase kinases [28]. In PDH deficiency dysfunctional PDH kinases create an inhibition of PDH complex function which is prolonged. Most reported cases of PDC dysfunction to date have been shown to be due to the inactivation of the PDH E1 alpha subunit, which contains a sulfhydryl enzyme vulnerable to damage from reactive oxygen species [29]. This enzyme acts as a phosphorylation switch which can be affected by various factors, including trauma, ageing and genetic mutation [29,30] Ketones bypass the PDH complex to provide an alternative substrate for the TCA cycle and so mitochondrial function can be restored even under such conditions. It is worth noting that in cases of traumatic brain injury KD has been reported to show similar metabolic and neuroprotective effects [31]. Tissue specificity of these effects to the brain is likely explained by the existence of at least 4 isozymes of pyruvate dehydrogenase kinase (PDK), with PDK3 being the principal kinase regulating PDH activity in the brain in mice [32].

PDH complex dysfunction unites several lines of evidence in the etiology of BD. As a mechanism, it provides biologically plausible explanations for diverse observations of mitochondrial dysfunction, oxidative stress, altered neuronal sodium/calcium, increased pyruvate and lactate levels, excitotoxicity and the reported effectiveness of ketogenic diet which merit further study. The cascade of effects resulting from PDH dysfunction are detailed in Fig. 2.

Despite the KD being a commonly recommended intervention in online BD forums with many reports of benefit, there are currently no randomised controlled trials of the KD in BD. In addition, there are no studies, to our knowledge, directly assessing PDC function in BD patients. The available data on the association between ketogenic diet and BD are observational and very limited (and hence findings are not yet replicated). There is a need for experimental data to explore whether there is any evidence for causal associations. It is interesting to note, however, that while there is no direct research into PDC function in BD the 2 primary biomarkers of PDC dysfunction (elevated CSF lactate and pyruvate) are also 2 of the most commonly observed biomarkers noted to be increased in BD [17]. Additionally, PDC dysfunction is a mitochondrial disorder and these have been shown to be associated with a greatly increased risk of BD [33].

Most published data on PDC dysfunction describe the rare, severe form which has onset in early childhood. The features of classic PDC dysfunction would not be expected in our model which hypothesizes a gradual long-term reduction of PDC function due to genetic and/or environmental factors. Most cases of severe PDC dysfunction are due to a mutation in PDHA1 affecting a major subunit of the enzyme [33]. This occurs rarely but has a severe phenotype. However, PDC is one of the largest enzyme complexes in humans and many other genetic mutations and variants are described, leading to a wide range of phenotypes. These include late onset PDCDs [34]. The PDC is vulnerable to damage from several environmental and biological factors as it contains a sulfhydryl enzyme which is damaged by reactive oxygen species. PDC activity reduces with age due to a combination of these causes [35]. There are few studies of later onset forms of PDC dysfunction and it is unknown what nature of symptoms would be expected in such cases. This pattern of a rare severe deleterious mutation having a severe phenotype but more frequent less deleterious mutations/variants in the same gene with less severe phenotypic consequences is common in Mendelian conditions.

A recent publication describes the development of a brain-specific PDHA1 knockdown mouse model [36]. This study demonstrated that the resulting metabolic defects in brain glucose metabolism were associated with the joint presence of both “episodic neuronal hyperexcitation” [seizures] and “reduced basal cerebral electrical activity”. These defects were reversed in part by intraperitoneal injection of acetate, a downstream metabolite. These findings were in the context of a study of epilepsy but they provide support for the general mechanisms in our hypothesis for BD, including for the action of ketone bodies generated by individuals on a ketogenic diet.

Conclusion

We hypothesize that in some cases of BD dysfunction of Pyruvate Dehydrogenase and/or Mitochondrial Carrier Proteins may be an important causal pathway which could explain mood destabilisation and the reported positive effects of KD. The E1 alpha subunit dysfunction is the most common reported source of PDC dysfunction and contains a sulfhydryl group vulnerable to proton donors making it liable to damage. Inability to convert pyruvate into Acetyl-CoA leads to impairment of oxidative phosphorylation and explains the commonly observed elevated pyruvate levels in BD. In response to this dysfunctional state the body shifts primarily to glycolytic energy production to generate ATP. High levels of lactate are then generated as a byproduct of glycolysis – another key biomarker of BD. The levels of ATP generated by glycolysis-only have been shown to be incapable of sustaining normal operation of the Na, K-ATPase in neurons. Under conditions of severe but non-critical lack of ATP this leads to decreased action potential in neurons, decreased neurotransmitter release and the depressed state in BD. Under conditions of less severe lack of ATP, inhibition of Na, K-ATPase function results in an excitatory state in the brain caused by the resting potential of neurons moving closer to the threshold for activation. This under-regulated state leads to calcium flux through neurons, glutamate excitotoxicity, (hypo)manic mood state and neuronal apoptosis.

The next step forward would be to develop experimental approaches to further investigate these observational descriptive data. This could be done through the conduct of a clinical trial of the KD in BD with robust measures of mood stabilization as trial outcomes.

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Declaration of Competing Interest

None.

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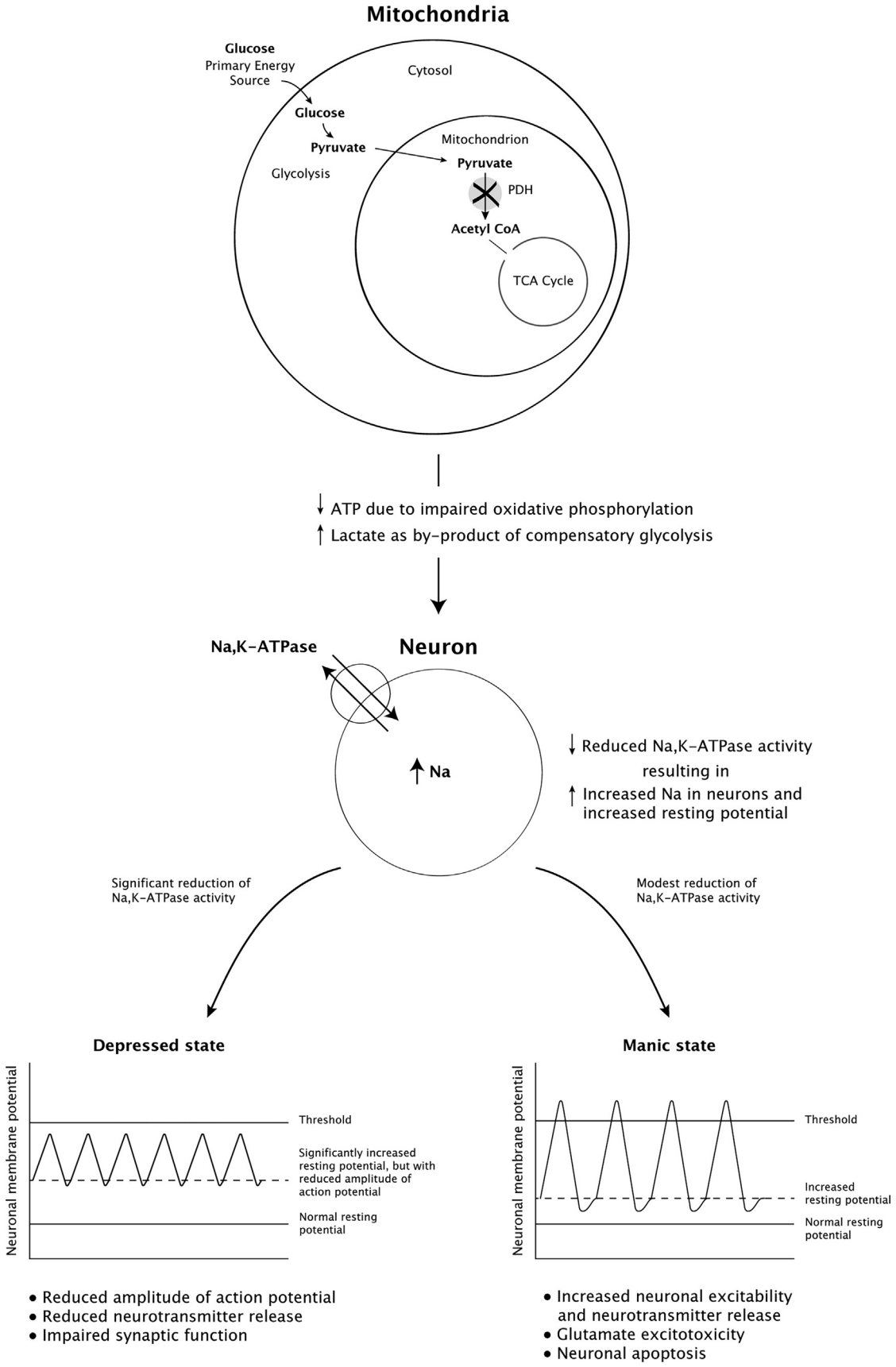

Fig. 2. PDH dysfunction leading to, impaired oxidative phosphorylation, reduced ATP production, reduced Na, K-ATPase activity and bipolar mood states.

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