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Low-carb diets, fasting and euphoria: Is there a link between ketosis and γ-hydroxybutyrate (GHB)?

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Summary Anecdotal evidence links the initial phase of fasting or a low-carbohydrate diet with feelings of well-being and mild euphoria. These feelings have often been attributed to ketosis, the production of ketone bodies which can replace glucose as an energy source for the brain. One of these ketone bodies, β-hydroxybutyrate (BHB), is an isomer of the notorious drug of abuse, GHB (γ-hydroxybutyrate). GHB is also of interest in relation to its potential as a treatment for alcohol and opiate dependence and narcolepsy-associated cataplexy. Here I hypothesize that, the mild euphoria often noted with fasting or low-carbohydrate diets may be due to shared actions of BHB and GHB on the brain. Specifically, I propose that BHB, like GHB, induces mild euphoria by being a weak partial agonist for $GABA_B$ receptors. I outline several approaches that would test the hypothesis, including receptor binding studies in cultured cells, perception studies in trained rodents, and psychometric testing and functional magnetic resonance imaging in humans. These and other studies investigating whether BHB and GHB share common effects on brain chemistry and mood are timely and warranted, especially when considering their structural similarities and the popularity of ketogenic diets and GHB as a drug of abuse.

Introduction

Since recorded time, across many cultures, fasting has been used in rituals aimed at attaining a higher state of being. Fasting for religious and spiritual reasons has been mentioned in the Bible, both Old and New Testaments, the Koran and the Mahabharata [1]. Anecdotal feelings of well-being and mild euphoria also litter the popular literature on low-carbohydrate diets. For example, one diarist wrote after 2–3 days on the Atkin's Diet: ''It is not an unpleasant feeling, a sort of mild, foggy euphoria''. [2]. From an evolutionary perspective, mild euphoria associated with short-term fasting may ease anxiety and aid the search for food. Ketosis occurs during the first few days of fasting or a low-carbohydrate diet, when breakdown of fat (β-oxidation) outstrips breakdown of carbohydrate (glycolysis). Three ketone bodies are produced by the liver: acetone, acetoacetate and β-hydroxybutyrate (BHB). Whilst BHB is usually referred to as a

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ketone body, it should be noted that it lacks a ketone group and is in fact a short-chain hydroxy fatty acid. After 2—3 days of fasting BHB reaches millimolar levels in the blood and brain [3], and together with acetoacetate provides the brain with an alternative energy source to glucose. Several biochemical explanations have been proposed for the feelings of euphoria often associated with short-term total fasting or low-carbohydrate diets. Bloom [4] postulated that accumulation of acetoacetate produces a mild intoxication similar to ethanol. Phillips [5] speculated from his studies in dairy cows that the accumulation of isopropyl alcohol (a byproduct of acetone metabolism) in neural tissue might be responsible for fasting-induced religious, mystical or hallucinatory experiences.

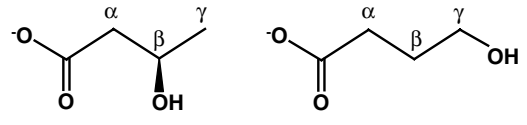
Hypothesis

Here I propose that diet-induced euphoria may involve production of BHB, and may be at least partially explained by the well-known psychological effects of its isomer, γ-hydroxybutyrate (GHB) (Fig. 1). Considering their structural similarities, it is perhaps surprising that no one has linked BHB and GHB before.

Discussion

γ-hydroxybutyrate

GHB occurs naturally in the brain where it can undergo interconversion with the inhibitory brain neurotransmitter γ-aminobutyric acid (GABA) [6,7]. However, in recent years, there has been burgeoning interest in GHB in relation to its potential as a treatment for alcohol and opiate dependence and narcolepsy-associated cataplexy. GHB has also gained notoriety as a major recreational drug of abuse and as a ''date-rape'' drug [6]. Sold illegally under a variety of names (including G, liquid ecstasy, GBH, grievous bodily harm, Georgia home boy, and fantasy), GHB attracts recreational drug-users due to the euphoria that it initially produces. The euphoria and other central nervous system-dependent effects are mostly ascribed to GHB's effects on $GABA_B$ receptors [7]. Endogenous GHB occurs at micromolar concentrations, as opposed to the millimolar concentrations believed to be obtained for exogenously administered GHB, and has been proposed to act via its own recently-cloned receptor [6,7]. Whether BHB may act via these or similar receptors to enhance mood is unknown. But it is important to note that BHB and GHB possess enough common structural features to apparently share the same carrier across the blood—brain barrier [8].



A. *D*-beta-hydroxybutyrate **B.** gamma-hydroxybutyrate

Figure 1 Chemical structures of two hydroxybutyrates. GHB differs from BHB in that its hydroxyl-group is on the last, γ-carbon whereas BHB's hydroxyl-group is on the third, β-carbon and has a right (D)-handedness.

Evidence that BHB has effects on the brain

There is a growing body of evidence that ketogenic diets have antiepileptic and neuroprotective effects. Ketogenic diets have been used to treat refractory epilepsy since the 1920s [9]. The anticonvulsant properties of this dietary intervention are not known and may not be strictly related to BHB [9]. A ketogenic diet slowed progression of the clinical and biological manifestations of a transgenic mouse model of motorneuron disease, Amyotrophic lateral sclerosis [10]. Tieu et al. [11] demonstrated that BHB protects dopaminergic neurons in a mouse model of Parkinson's disease. Cell culture studies have also shown that BHB protects neurons in models of Parkinson's and Alzheimer's disease [12] as well as hypoxia [13]. Considering that astrocytes outnumber neurons nine to one and take up the half the volume of the brain, it is noteworthy that astrocytes, like liver cells, can produce large amounts of ketone bodies. It has been proposed that astrocytes might supply neurons with ketone bodies and hence exert a neuroprotective effect [14].

Apart from acting as a putative agonist for $GABA_B$ receptors, BHB could exert GHB-like effects indirectly through enhancing the synthesis of glutamate and GABA production [15]. BHB could also be a ligand for a yet to be defined receptor in the brain. As a precedent, BHB is the first endogenous ligand identified for a G-coupled membrane protein receptor [16]. PUMA-G or its human ortholog HM74a is highly expressed in adipocytes and macrophages but only weakly-expressed in the brain. It is feasible that BHB may influence the activity of related receptors in the brain or perhaps ion channels or even act as ligands for nuclear receptors such as the peroxisome proliferator-activated receptors considering that these are activated by fatty acid derivatives [9,14].

Whereas the ketogenic diet has been studied extensively particularly as an antiepileptic therapy, direct activity of ketone bodies on neuronal electrical activity still remains little documented. Studying rat ventromedial hypothalamic (VMH) neurons, Minami and coworkers [17] found that BHB significantly facilitated the firing rate of VMH neurons in a dose-dependent manner. By contrast, Thio and colleagues [18] found that BHB did not alter synaptic transmission in rat hippocampal neurons. However, as conceded by the authors [18], these negative results could reflect weaknesses inherent in the methods, tissues and/or neurotransmitters selected.

The reported neurological effects of ketogenic diets and GHB do not completely overlap. For example, the sleep-promoting effect of administered GHB is not noted with ketogenic diets. These diets however are often associated with an initial lack of appetite, possibly related to BHB, which is not noted with administered GHB. Differences in potency and duration of action may help to explain discrepancies in the effects of GHB and BHB. It should also be noted that whereas BHB readily undergoes β-oxidation and hence is a potent energy-producing substrate, β-oxidation apparently is not a major pathway for GHB disposal and hence its metabolism is unlikely to provide much energy.

How to test the idea

Numerous approaches have been employed to determine the neurological targets of GHB [6,7]. Similar approaches could be employed for BHB. However, investigating subjective effects like euphoria and well-being can be problematic. I have selected three approaches, which specifically address the hypothesis that BHB, like GHB, induces mild euphoria by being a weak partial agonist for $GABA_B$ receptors.

1. Agonist radioligand assays for $GABA_B$ receptors could be performed for BHB in animal neuronal cells as has been done for GHB [19], in competition with GABA or GHB. Using these and comparable assays, GHB was found to be a weak partial agonist for $GABA_B$ receptors with an EC50 of ~5 mM [7]. It is likely that BHB would also have a low affinity for $GABA_B$ receptors and only exert effects at the millimolar concentrations found in response to fasting and ketogenic diets. It is unclear what effect the positioning of the hydroxyl-group on BHB versus GHB (Fig. 1) has on their relative affinities for the $GABA_B$ receptors.
2. Recently, drug discrimination studies using trained rats, showed that GHB and its metabolic precursors produce similar subjective effects that differ from those of other sedative-hypnotic drugs [20]. Similar studies could be performed to test if BHB elicits similar subjective effects to GHB.
3. BHB, GHB or placebo/vehicle-control could be administered to healthy human volunteers with psychometric assessment for feelings of euphoria/well-being. The D-isomer would need to be administered, since this is the major naturally-occurring form of this ketone body. Co-administration of a $GABA_B$ receptor antagonist should ablate any feelings of euphoria if these are exclusively mediated by the $GABA_B$ receptors. These studies ideally would include functional magnetic resonance imaging to map areas of brain activity. A possible problem with this approach is that, the millimolar brain concentrations of BHB obtained after 2–3 days fasting may not be readily attainable [3].

These and other studies investigating whether BHB and GHB share common effects on brain chemistry and mood are timely and warranted, especially when considering their structural similarities and the popularity of ketogenic diets and GHB as a drug of abuse.

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