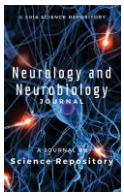

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Research Article

Neurocognitive Effects of Exogenously Administered Beta-Hydroxybutyrate In Adults: A Proof of Concept Study

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ABSTRACT

βeta-hydroxybutyrate (BHB) is a ketone body produced by the liver in a process known as ketosis, as an alternative fuel source during fasting or carbohydrate caloric restriction, and is readily used as fuel throughout the body, including in the brain. While glucose is the brain's principal energy source, when limited, ketones derived from fats become the major energy substrate. Exogenous BHB is safe to administer orally and can enhance energy and physical performance. While the literature suggests cognitive and/or behavioural performance improvement in animal models following elevation in ketones, and in clinical human samples such as those with Mild Cognitive Impairment, Alzheimer's disease, epilepsy, and severe traumatic brain injury, the literature investigating the neurocognitive effects of exogenous administration of ketones in nonclinical, healthy samples remains limited. For this proof of concept, we present twelve subjects who underwent exogenous administration of 11.7 g of BHB. After ingestion, participants performed significantly better in attentional accuracy compared to pre-intervention scores ($p < 0.05$; $d = 0.65$), demonstrating that exogenous administration of BHB may have positive effects on the attentional accuracy domain of neurocognition in neurotypical adults. Further analysis and its clinical implications are discussed.

Introduction

In a neurotypical brain, glucose is the primary source for energy. When glucose is limited during periods of fasting, starvation or carbohydrate restriction to the point of glycogen depletion, ketones become the major energy substrate through a process known as ketosis. Ketone bodies include Acetone, Acetoacetate, and β-hydroxybutyrate. β-hydroxybutyrate (BHB) is produced by the liver under normal physiological conditions but it rarely reaches blood levels above 1mM. Levels of BHB can rise above 1mM (approximately up to 6-8mM) during periods of caloric restriction, prolonged exercise, or by self-induced ketogenic diet, with nutritional ketosis being considered between 1-8mM [1]. In comparison, levels of BHB in diabetic ketoacidosis rise to 15-25mM range, and is considered dangerously elevated. However, below this threshold, BHB is a readily used fuel source throughout the body, including in the brain [2].

When used as a source of energy, ketones are rapidly taken up into the brain via monocarboxylic acid transporters [2]. Clinically, BHB is safe to orally administer to humans, and is used by the body to increase energy and is recreationally used to improve physical performance [2]. There is growing evidence from basic science literature suggesting significant neuroprotection and cognitive improvement in rodent models following the administration of exogenous ketones in clinical conditions, such as BHB in moderate to severe traumatic brain injuries (TBI) [3]. Benefits of ketogenic effects are also found in those with Mild Cognitive Impairment, Alzheimer's disease, other memory impaired individuals, and the elderly [4-8]. In addition, documentation of utilization of fasting

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mechanism (to induce ketosis) for treating epilepsy dates back to 500 BC, and diet induced ketosis for treatment of epilepsy was introduced in the 1920's [9]. In TBI, mitochondrial bioenergetics are significantly disrupted days to weeks post-injury. TBI seems to preferentially target pyruvate dehydrogenase, blocking the flow of electrons into the electron transport system, thus decreasing mitochondrial bioenergetics via NADH-linked respiration. BHB functions as a reducing agent for NADH and FADH2, thereby bypassing the blockage in the flow of electrons in the electron transport system. Other studies have demonstrated that when isolated mitochondria from the cortex were treated with BHB, this partially restored deficit in NADH-linked mitochondrial ATP synthesis (State III) and State-V (complex-I) driven respiration [2, 10, 11].

These data indicate that BHB restores mitochondrial bioenergetics in models of injury. As for this mechanism's translational effects in humans, ketone bodies as alternative biofuel, have demonstrated safety and suggested efficacy for a myriad of neurologic and non-neurologic conditions in humans, including in epilepsy and athletic performance [2, 10, 11]. However, there is limited literature to investigate the neurocognitive effects of exogenous administration of ketones in nonclinical, healthy samples. Accordingly, this pilot study aimed to establish a proof of concept, by studying any potential difference between exogenous pre- and post-BHB administration related neurocognitive performances, in a nonclinical, healthy sample.

Methods

Twelve healthy subjects (33.3% male; age M=24, SD= ±5.4) underwent exogenous administration of 11.7 g of BHB for this proof of concept pilot study. Inclusion criteria included subjects between the ages of 18 and 55, with no history of active psychiatric disorder, gallbladder disease, hypertension, or diabetes; no pregnant or nursing women, and no known allergies to dairy, soy, wheat, peanuts, fish, shellfish, tree nuts, sulphites, or corn (per manufacture's warning). All experimental protocols were approved by the Institutional Review Board at the University of Kentucky. Informed written consent was obtained from all participants. This experiment has not been previously reported in the literature.

At baseline, participants completed a computerized neurocognitive assessment (select subtests of the Automated Neurocognitive Assessment Metric-4; ANAM) [12]. ANAM consists of nine subtests designed to assess fatigue levels, current mood state, and cognitive performance in the domains of reaction time, learning, attention, and memory (for a full description of the nine subtests see Reeves *et al.*) [12]. Participants were asked to fast for at least 8 hours prior to testing, to attempt to standardize stomach absorption rates. Upon completing baseline ANAM assessment, they were asked to ingest 11.7 g of BHB dissolved in 236.59 mL of water, designed to achieve approximately 1-2mM in blood, mimicking a conservative state of nutritional ketosis. Participants then waited an hour to allow BHB to absorb, and then completed the neurocognitive assessment again.

Results and Discussion

Performance accuracy ANAM results are illustrated in (Figure 1). Baseline and post-intervention ANAM data were analysed using paired t-tests with an alpha level of 0.05 (IBM SPSS Statistics, Version 23) for each of the presented subtests. Analyses revealed significantly better attention performance accuracy (M=98.0, SD=1.95) following ingestion of BHB compared to their baseline performance (M=93.92, SD=6.53; $t(11)=2.24$, $p < 0.05$, $d = 0.65$) (Figure 1). All other results were not significant ($t \leq 1.65$, $p \geq 0.13$). Interestingly of note, mild, non-significant downward trend was noted in other subdomains of accuracy. However, especially with Memory Recall Accuracy, the measurement's primacy/recency interference was noted during the assessment, leading us to hypothesize that this confound may suggest an even more robust interpretation of the significant finding with Attention Accuracy.

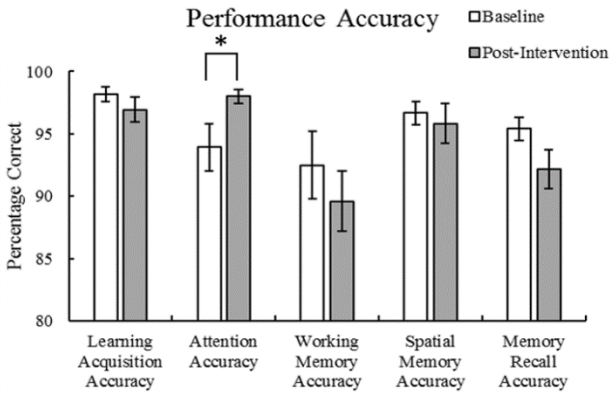

Figure 1: Performance accuracy (percent correct) on ANAM in healthy, neurotypical samples (N = 12) prior to baseline and following post-intervention exogenous administration of BHB. Error bars are SEM. *P < 0.05.

The potential benefits of ketone bodies, such as BHB, induced by nutritional ketosis via caloric restriction, exercise, or even exogenous administration, have been established in the literature in animal models and clinical samples such as epilepsy, Alzheimer's disease, and TBI [3, 4, 7]. In addition, ketone bodies reportedly boost athletic performance in nonclinical healthy samples [2]. However, ketone bodies' effects on neurocognitive performances in healthy individuals have not been formally investigated until the current proof of concept pilot study. As this pilot's initial inference is restricted to its small within group comparison, data are limited in their translation. However, with the demonstrated medium to large effect size, the hypothesis of BHB induced neurocognitive improvement warrants further investigation.

Conclusion

The current findings of attentional accuracy improvement post-BHB ingestion at 11.7 g are consistent with the clinical and animal data in the literature. Subsequently, current findings open a myriad of questions beyond clinical neurologic management, including mechanism related questions for daily performance and functioning for the general public. Of note, the current study's dosing at 11.7 g, designed to achieve approximately 1-2mM in blood, represents a conservative (lower end) state of nutritional ketosis. Given this conservative sample's favourable/medium to large effect size ($d = 0.65$), more investigation is needed to explore optimal dosing in nutritional ketosis levels and its related effects. As the current study was designed to be a proof of concept pilot, further research will be required to investigate the

mechanism of improved attentional accuracy from BHB in healthy adults. The current dataset may be useful as a reference point for more dose effect investigations, and clinical use and feasibility investigations for other conditions involving neurocognition.

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Conflicts of Interest

None.

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