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Effects of a ketogenic diet on auditory gating in DBA/2 mice: A proof-of-concept study

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Abstract

Although the ketogenic diet has shown promise in a pilot study and case report in schizophrenia, its effects in animal models of hypothesized disease mechanisms is unknown. This study examined effects of treatment with the ketogenic diet on hippocampal P20/N40 gating in DBA/2 mice, a translational endophenotype that mirrors inhibitory deficits in P50 sensory gating in schizophrenia patients. As expected, the diet increased blood ketone levels. Animals with the highest ketone levels showed the lowest P20/N40 gating ratios. These preliminary results suggest that the ketogenic diet may effectively target sensory gating deficits and is a promising area for additional research in schizophrenia.

Keywords

Gating; Ketogenic Diet; Hippocampus; P50; Schizophrenia

1. Introduction

Hippocampal inhibitory dysfunction and its associated neurophysiological abnormalities are a topic of great interest in schizophrenia, due in large part to their utility as potential targets for therapeutic intervention. Neuroimaging studies in human patients frequently have observed increased activity in the hippocampus in patients with schizophrenia, relative to comparison subjects (reviewed by Heckers and Konradi (2014); Tamminga et al. (2012); Tamminga et al. (2010); Tregellas (2014)). The magnitude of this abnormality may predict positive (Ebmeier et al., 1993; Friston et al., 1992; Gur et al., 1995; Kawasaki et al., 1996;

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Contributors

JRT, KTL and KES designed the study. JRT and KES performed statistical analyses. JRT, JS, KLTrevi and KES wrote the manuscript. All authors have contributed to and approved the final manuscript.

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Liddle et al., 1992; Molina et al., 2005; Schobel et al., 2013; Schobel et al., 2009), negative (Schobel et al., 2009; Tregellas et al., 2014), and cognitive (Tregellas et al., 2014) symptoms. It follows that treatments that can reduce hippocampal activity may confer therapeutic benefit in schizophrenia.

One strategy for targeting this phenotype is to attempt to repurpose interventions for other brain disorders associated with neuronal hyperactivity, such as epilepsy (Smucny et al., 2015). One relatively low-risk intervention is the ketogenic diet, which has been approved for treatment-resistant epilepsy (reviewed by Klein et al. (2014)). The diet typically consists of a high ratio (for example, 4:1) of fats to carbohydrates plus proteins. The ketogenic diet and related diets have shown potential efficacy in a limited number of case studies and small pilot studies in schizophrenia (Kraft and Westman, 2009; Pacheco et al., 1965). Its effects on schizophrenia patients and in animal models of disease mechanisms are, however, largely unknown.

As a first step towards preclinical evaluation of the ketogenic diet, the goal of this study was to administer the diet in the DBA/2 mouse to examine its effects on a hippocampal hyperactivity-associated physiological abnormality that mirrors the schizophrenia endophenotype (Singer et al., 2009). At present, perhaps the most well-established translational, clinically predictive physiological assay to assess hippocampal inhibitory circuitry in rodent models of schizophrenia is hippocampal auditory P20/N40 gating (reviewed by Smucny et al. (2015)). This assay, conducted using depth electrodes implanted into the mouse hippocampus, was developed to mirror P50 gating deficits in schizophrenia. P50 gating deficits refer to the phenomenon in which patients are unable to filter early (50 ms post-stimulus) neuronal response to the second of a pair of identical, repeated auditory click stimuli (Adler et al., 1982; Freedman et al., 1983; Javitt and Freedman, 2015; Miwa et al., 2011). P50 gating dysfunction is one of the most frequently studied and consistently replicated electrophysiological endophenotypes in the illness, with an established genetic basis (polymorphisms on the $\alpha 7$ nicotinic receptor gene potentially contributing to reduced receptor expression) (Olincy and Freedman, 2012; Sinkus et al., 2015) leading to $\alpha 7$ nicotinic receptor-targeted investigational therapies (Olincy et al., 2006; Winterer et al., 2013; Zhang et al., 2012). Neuroimaging and depth recording studies in humans and rodents have localized P50 gating generators to the hippocampus, among other brain areas (Bak et al., 2014; Bickford-Wimer et al., 1990; Grunwald et al., 2003; Williams et al., 2011). The neuronal basis for gating deficits is hypothesized to be due to the reduced ability of hippocampal interneurons to generate persistent inhibition to an auditory stimulus. The area is therefore less able to reduce its response to repeated stimuli, contributing to a sensory “flooding” of irrelevant information as first reported in case studies in patients in the 1960s (McGhie and Chapman, 1961; Venables, 1964). P50 gating may therefore be a translational, physiological measure of hippocampal inhibitory dysfunction in schizophrenia contributing to hyperactivity. Relative to other mouse strains, the DBA/2 mouse shows a similar deficit in hippocampal auditory gating of the mouse analogue of the P50, the P20/N40 wave (Stevens et al., 1996). The aim of this study, therefore, was to determine if the ketogenic diet can improve hippocampal auditory P20/N40 gating in the DBA/2 mouse, establishing proof-of-concept that the ketogenic diet could be repurposed to target an electrophysiological endophenotype associated with inhibitory dysfunction in schizophrenia.

2. Materials and Methods

2.1. Animals

DBA/2 male mice (Harlan SP, Indianapolis, ID) were group housed on aspen chip bedding with nestlettes, and food and water continuously available (except for an overnight fasting period prior to electrophysiological recording; see below). Lights cycled at 12 hr intervals (on at 0600). The Institutional Animal Care and Use Committee of the University of Colorado Anschutz Medical Campus approved the experimental protocols.

2.2 Ketogenic Diet

Upon arrival, mice were fed with a standard diet (60% carbohydrates, Harlan Teklad) for at least 2 weeks. Mice were then transitioned to the TD 96355 ketogenic diet (0.6% carbohydrate, Harlan Teklad), an extremely low-carbohydrate diet similar to diets used previously to cause ketosis in mice (Brownlow et al., 2013). Mice were maintained on the diet for 3 weeks, at which time they were studied, because blood ketone measurements (below) indicated that ketosis had been achieved. Animals underwent an overnight fast prior to electrophysiological recordings.

2.3 Blood Ketone Measurement

Blood (collected by tail snip) ketone levels were measured using a Nova Max Plus ketone meter (Nova Biomedical Corp., Bedford, MA). Ketones were measured immediately before animals began the ketogenic diet, weekly, and immediately before recordings. Prior to beginning the ketogenic diet, all animals showed blood ketone levels of 0.1 mmol/L or below. After completion of the diet, 6 animals showed ketone levels of 0.5 mmol/L or below ("low-ketosis" group), and 6 animals showed ketone levels greater than 0.5 mmol/L ("high ketosis" group) (Figure 1).

2.4 Hippocampal Recordings of Sensory Inhibition

Mice were fasted overnight prior to testing for sensory inhibition. *In vivo* hippocampal recordings were performed as described previously (Smucny et al., 2014). Mice (22–30 g) were anesthetized with chloral hydrate (400 mg/kg, ip) and pyrazole (400 mg/kg, ip) to retard the metabolism of the chloral hydrate. The mouse was placed into a mouse adaptor for a stereotaxic instrument and maintained at 37°C with a heating pad. The scalp was incised and retracted. A burr hole was opened over the dorsal hippocampus (1.8 mm posterior to bregma, 2.7 mm lateral to midline (Paxinos and Franklin, 2004)) for the recording electrode and a second hole opened over the contralateral cortex rostral to bregma for the reference electrode. A Teflon-coated, stainless steel wire recording electrode (127 μ M diameter) was lowered to the pyramidal cell layer of hippocampal area CA3 (–1.5–1.8 mm below dura). Final recording position was determined by the presence of complex spiking patterns typical of pyramidal cells (Miller and Freedman, 1995). An identical electrode was placed on the anterior cortex to act as reference. Miniature earphones attached to hollow ear bars, placed at the externalization of the aural canal, delivered the computer-generated auditory stimuli. EEG responses to paired click stimuli (3000 Hz, 10 ms, 70 dB SPL, presented 0.5 sec apart, with 9 sec between pairs) were amplified 1000 times with bandpass filtering at 1–500 Hz

and led to a computer for storage and analysis. Data were collected and analyzed using SciWorks data acquisition and analysis program (DataWave, Loveland CO). The responses to 16 pairs of stimuli were collected and averaged at 5-minute intervals. The maximum negativity between 20 and 60 msec after the stimulus (N40) was selected and measured relative to the preceding positivity (P20). This composite component has been shown to be less variable than either component (P20 or N40) alone (Hashimoto et al., 2005). Three parameters were measured per record: conditioning amplitude—the magnitude of the response to the first stimulus (S1), test amplitude—the magnitude of the response to the second stimulus (S2), and TC ratio—the ratio of the test amplitude/conditioning amplitude, which is a measure of the level of inhibition (Stevens et al., 1996). A TC ratio of 0.5 or less is evidence of normal sensory inhibition (Freedman et al., 1983).

Consistent with previous studies from our laboratory examining chronic effects of investigational compounds on P20/N40 gating (e.g. Stevens et al. (2008)), the 3 most similar records per mouse were selected and conditioning amplitude, test amplitude and TC ratio averaged to obtain characteristic parameters for each mouse. Ketone levels were correlated against TC ratio for each mouse ($n=12$). Data were compared between high and low ketosis groups for analysis of the 3 parameters ($n=6$ per group).

3. Results and Discussion

Representative S1 and S2 waveforms for a mouse in the low-ketosis group and a mouse in the high-ketosis group are shown in Figure 2. Overall, ANOVA for TC ratio revealed a significant difference with the high ketosis group having a significantly lower TC ratio [$F(1,10)=45.516$, $p<0.001$] (Figure 3). ANOVA for conditioning amplitude showed no significant difference between the two groups [$F(1,10)=1.468$, $p=0.253$] while that for test amplitude was significantly reduced for the high ketosis group [$F(1,10)=7.463$, $p=0.021$] (Figure 3). A Pearson's correlation between ketone level and TC ratio showed a negative correlation such that the higher the ketone level the lower the TC ratio (improved sensory inhibition) ($r=-0.679$, $p=0.008$) (Figure 4).

To our knowledge, this study is the first to show that the ketogenic diet may improve hippocampal auditory P20/N40 gating in the DBA/2 mouse. Furthermore, the diet was found to significantly enhance suppression of the second response, consistent with the hypothesis that the diet may target dysfunctional hippocampal inhibitory circuitry in these animals. Though the mechanism by which a ketogenic diet increases inhibitory function is still an area of active investigation, multiple pathways may be involved, including an alteration in glutamatergic transmission, glycolysis inhibition and/or ATP-sensitive potassium channel activation (Lutas and Yellen, 2013). Based on studies that have demonstrated that treatment effects on P20/N40 gating in the DBA/2 mouse predict effects in human subjects (reviewed by Smucny et al. (2015) as well as Olincy and Stevens (2007)), the present results suggest that the ketogenic diet may be expected to show similar effects in patients with schizophrenia.

The finding that ketosis level was strongly predictive of gating ratio suggests that the gating ratios observed in this study were due to the ketogenic diet as opposed to other factors.

Although a control diet was not included in this preliminary study, previous studies in our laboratory have found that gating ratios in untreated DBA/2 mice given a standard (Harlan Teklad) diet (60% carbohydrates, 16% fats, 24% proteins) are consistently higher than those observed in DBA/2 mice that were in ketosis (e.g. Wildeboer-Andrud and Stevens (2011)). Our baseline readings also suggest that animals were not in ketosis prior to beginning the diet, suggesting that observed effects were due to the diet's relative ability to induce ketosis. Nonetheless, future studies should examine the gating effects of other diets that vary in carbohydrate, protein and fat content to more thoroughly examine the relationships between dietary content and sensory inhibition.

The only published study on the ketogenic diet in schizophrenia was motivated by the observation that carbohydrate consumption preceded psychotic episodes (Pacheco et al., 1965). The study demonstrated potential efficacy of the diet at improving positive symptoms, although it was not placebo controlled. The ketogenic diet also reduced positive symptoms in a treatment-resistant patient in a more recent case report (Kraft and Westman, 2009). Unfortunately, to our knowledge, these findings have not been followed up in a controlled trial and/or a larger cohort of patients. The present study is the first to demonstrate that the ketogenic diet may normalize a prominent endophenotype of schizophrenia, P50 gating deficits, in an established mouse-model of the phenomenon. Based on the present and previous findings, as well the fact that the diet is well-tolerated (Schoeler et al., 2014), we suggest that future studies should examine the neuronal and behavioral effects of a ketogenic diet as a potential treatment for schizophrenia.

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Figure 1. Box plot demonstrating distribution of blood ketone levels for mice in the low ketosis group ($n=6$) and mice in the high ketosis group ($n=6$).

Figure 2.

Representative S1 and S2 waveforms for a mouse that showed low ketosis (left) and a mouse that showed high ketosis (right). The burst response at the beginning of each waveform represents the auditory stimulus. The mouse with low ketone levels (left) showed poor gating as evidenced by similar S1 and S2 amplitudes resulting in a TC ratio close to 1. The mouse with high ketone levels (right) showed robust gating as evidenced by reduced S2 amplitude (relative to S1) resulting in a smaller TC ratio (0.17).

Figure 3.

Comparison between TC ratio, S1 amplitude, and S2 amplitude between mice in the low and high ketosis groups. Significantly lower TC ratio and S2 amplitude was observed for mice in the high ketosis group.

Figure 4.
Negative correlation between blood ketone level and TC ratio.