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Ketogenic diet and olanzapine treatment alone and in combination reduce a pharmacologically-induced prepulse inhibition deficit in female mice

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ABSTRACT

We used the acute NMDA receptor hypoactivity model of schizophrenia in mice to compare the efficacy of a long-term ketogenic diet and a commonly used antipsychotic, olanzapine, and to explore the interaction between these treatments. We found that a ketogenic diet in female mice was as effective as olanzapine to diminish MK-801-induced disruption of prepulse inhibition (PPI). Furthermore, combination of the diet with olanzapine treatment resulted in a similar effect compared to either treatment alone. These results suggest that ketogenic diet can be used effectively together with antipsychotics drugs over an extended period.

1. Introduction

Clinical evidence suggests a metabolic involvement in the pathophysiology of schizophrenia (Fujimoto et al., 2007; Beasley et al., 2009; Harris et al., 2013; Sullivan et al., 2018; Sullivan et al., 2019). For example, impaired pyruvate and adenosine-triphosphate (ATP) production was found in the cortex of schizophrenia patients in vivo (Du et al., 2014) and in post-mortem samples of the medial dorsal thalamus (Martins-de-Souza et al., 2010). These changes result in decreased energy availability for the brain and may lead to impaired neuronal functioning (Arnaiz et al., 2001; Lamport et al., 2009). Post-mortem studies of the thalamus and dorsolateral prefrontal cortex of schizophrenia patients suggested that glycolysis was the main pathway impaired (Martins-de-Souza et al., 2010; Sullivan et al., 2018). We hypothesised that a ketogenic diet may provide an alternative fuel source to glucose by causing a metabolic shift to fatty acid utilisation (Paoli et al., 2013). We recently reported in an acute *N*-methyl-D-aspartate (NMDA) receptor hypofunction model in male mice, that a ketogenic diet exerts antipsychotic-like effects (Kraeuter et al., 2015; Kraeuter et al., 2019), suggesting that it may provide an adjunct therapy to commonly used antipsychotics. Indeed, recent clinical case studies have shown encouraging results with ketogenic diet being used as an adjunct therapy (Palmer, 2017; Gilbert-Jaramillo et al., 2018; Palmer et al., 2019; Sarnyai et al., 2019). However, in the clinical setting this dietary intervention would presumably be administered together with antipsychotic treatment over an extended period of time. Therefore, the interaction between long-term ketogenic diet and antipsychotic administration remains to be investigated.

Our previous studies have only investigated the effects of ketogenic diet in male mice. Recent studies in mice have shown sex differences in the behavioural and metabolic effects of ketogenic diet (Ruskin et al., 2017a, 2017b, Cochran et al., 2018). For example, in a mouse model of Autism Spectrum Disorder, ketogenic diet improved multiple measures of sociability and reduced repetitive behaviour in female mice, but there were limited effects in males (Ruskin et al., 2017a, 2017b). In contrast, in a maternal immune activation model, ketogenic diet prevented these behaviours in males, but not females (Ruskin et al., 2017a, 2017b). Therefore, to compare to our previous studies in male mice, the present study was conducted in female mice.

In this study we used acute disruption of prepulse inhibition (PPI) by the NMDA receptor antagonist, MK-801. Information

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processing deficits are a clinical manifestation of schizophrenia (Braff et al., 2001). PPI is a measure of sensorimotor gating and is highly translatable between rodents and humans (van den Buuse, 2010, Swerdlow and Light, 2018). Here, (1) we investigate the efficacy of the ketogenic diet in female mice, (2) to compare it to a commonly used antipsychotic, olanzapine, and (3) to explore the interaction between these treatments.

2. Methods

The experiments were approved by the Animal Ethics Committee of James Cook University (A2036) and were conducted according to the NHMRC/AVCC Statement and Guidelines on Research Practice (1997). Female C57/BL6 mice ($n = 52$) of 7 weeks of age were obtained from the James Cook University breeding facility and kept on a 12 h light/dark cycle with ad libitum access to food and water. All experiments were done during the light phase.

At commencement of the study, mice were randomly allocated to either ketogenic diet (carbohydrates: 9.4%, protein: 9.5%, fat: 77.6%; SF14-063 Specialty Feeds, WA, Australia) or standard diet (carbohydrates: 67.6%, protein: 17.7%, fat: 6.1%; Goldmix Stockfeeds, Norco, Lismore, NSW, Australia). After 4 months on their diet, animals were randomly allocated to four experimental groups ($n = 13$ each): standard diet - saline, ketogenic diet - saline, standard diet - olanzapine, ketogenic diet - olanzapine. From then on, mice remained on their diet but were also injected intraperitoneally (i.p.) twice daily (morning and evening) with either 2 mg/kg olanzapine (Albaugh et al., 2006; Dudek et al., 2016) or 0.9% saline. Olanzapine (Chem-Supply, Australia) was dissolved in 0.1 M HCl, which was brought to pH 5.5 with 0.1 M sodium hydroxide (Ferno et al., 2011). The first round of behavioural testing was conducted after 8 weeks of olanzapine treatment. Olanzapine treatment was continued until the end of the second behavioural testing round. Thirty minutes prior to testing, mice were injected i.p. with 0.25 mg/kg of MK-801 (dizocilpine, Sigma-Aldrich, Australia) or 0.9% saline solution. One week later the animals were tested again and mice that were treated with MK-801 received saline injection and saline-treated animals received MK-801 injection in a cross-over design.

PPI was assessed using automated startle chambers (SR-Lab; San Diego Instruments, San Diego, CA, USA). Animals were subjected to 104 trials consisting of four blocks of 8 pulse-alone trials at 115 dB white noise, 64 prepulse-pulse trials (four groups of eight at 2, 4, 8, and 16 dB over baseline with an interstimulus interval of 30 msec or 100 msec) and eight NOSTIM trials (Chavez et al., 2009; Kraeuter et al., 2019).

PPI data were analysed using analysis of variance (ANOVA) with MK-801 treatment, diet and olanzapine treatment as independent factors, followed by Bonferroni-corrected post-hoc analysis (SPSS version 25, IBM SPSS Statistics). Because not all animals completed both PPI sessions, ANOVA was not repeated measures. A p value of <0.05 was considered to be statistically significant. Data were expressed as the mean ± standard error of the mean (SEM).

3. Results

Similar to our previous results (Kraeuter et al., 2015; Kraeuter et al., 2019), there was an initial reduction of weight gain in mice on a ketogenic diet, leading to lower body weights in these animals compared to standard-diet controls for about four weeks. However, by the time behavioural testing was done, there were no differences in body weight between the groups. There were no differences in weight gain in animals treated with olanzapine alone or the combination with ketogenic diet (data not shown).

Acute MK-801 treatment significantly impaired PPI at the 100 msec ISI (main effect, $F_{(1,77)} = 31.29$, $p < 0.001$). While there were no significant main effects of diet or olanzapine treatment, there were significant interactions between diet and MK-801 ($F_{(1,77)} = 4.61$, $p = 0.035$) and olanzapine treatment and MK-801 ($F_{(1,77)} = 7.07$, $p = 0.010$), as well as a MK-801 x diet x olanzapine treatment interaction ($F_{(1,77)} = 6.29$, $p = 0.014$; Fig. 1A). Post-hoc analysis revealed that MK-801 administration reduced PPI in mice

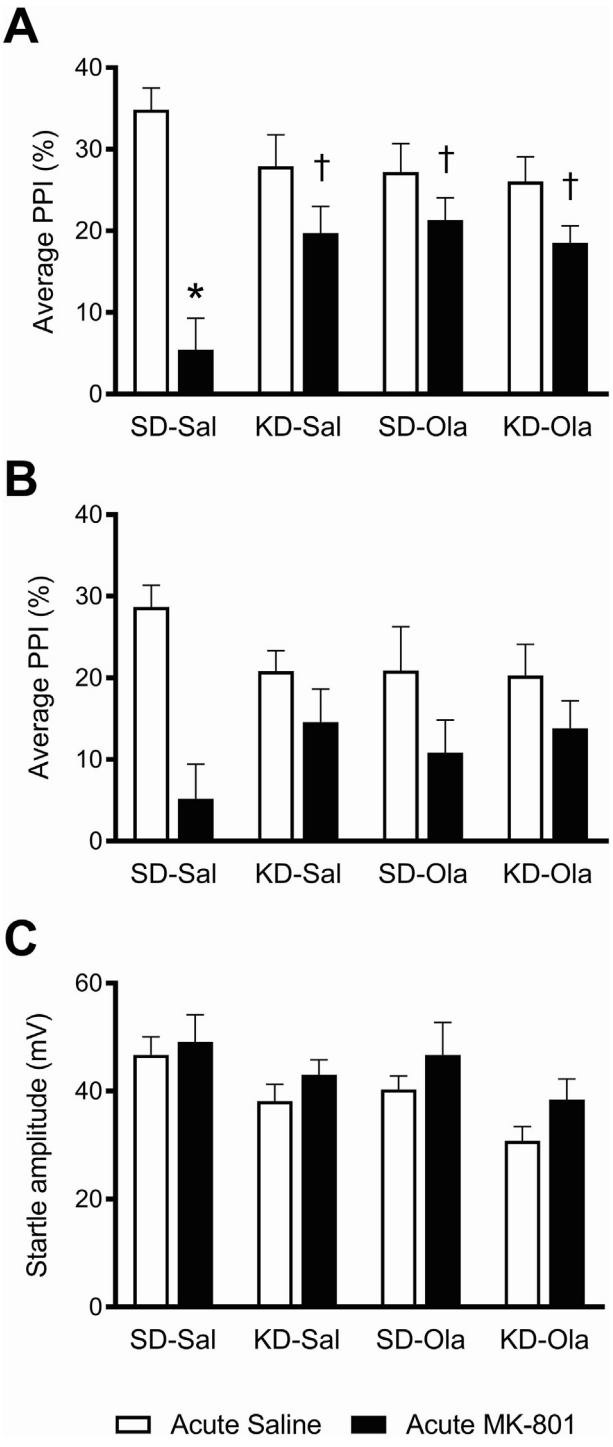

Fig. 1. (A) Average prepulse inhibition (PPI) of startle at the 100 msec interstimulus interval (ISI) was significantly reduced by acute MK-801 treatment in mice on standard diet (SD) and vehicle antipsychotic treatment (Sal). Ketogenic diet (KD), olanzapine (Ola) and both treatments combined diminished the effect of MK-801 on PPI. (B) PPI at the 30 msec ISI was significantly reduced by MK-801 (main effect) but effects of ketogenic diet or olanzapine failed to reach significance. (C) Average startle amplitude was slightly, but significantly increased by MK-801 and reduced by KD (significant main effect). *$p < 0.05$ for MK-801 effect within treatment group, † $p < 0.05$ compared to MK-801 in the SD-Sal group. There were $n = 10–13$ mice per group.

on standard diet ($p < 0.001$) but not in any of the other groups (Fig. 1A). The effect of MK-801 on PPI was significantly inhibited by the ketogenic diet ($p = 0.002$), olanzapine treatment ($p < 0.001$) and the combination of ketogenic diet and olanzapine treatment ($p = 0.016$) (Fig. 1A).

Acute MK-801 treatment significantly impaired PPI also at the 30 msec ISI (main effect, $F_{(1,79)} = 21.33$, $p < 0.001$). Although the direction of effects of ketogenic diet and olanzapine treatment was similar as those at the 100 msec ISI, PPI was generally lower and more variable at the 30 msec ISI, and only a trend toward an interaction between diet and MK-801 ($F_{(1,79)} = 3.81$, $p = 0.054$) was found (Fig. 1B).

Acute MK-801 treatment slightly, but significantly increased average startle (main effect, $F_{(1,94)} = 3.96$, $p = 0.049$). Ketogenic diet reduced startle ($F_{(1,94)} = 9.27$, $p = 0.003$) but olanzapine treatment had no effect and there were no significant interactions (Fig. 1C).

4. Discussion

We previously demonstrated in male mice the efficacy of ketogenic diet on a variety of behavioural changes by normalising hyperactivity, stereotypic behaviour, social behaviour, working memory (Kraeuter et al., 2015) and pre-pulse inhibition of startle (Kraeuter et al., 2019) in an acute NMDA receptor hypofunction model. In the present study, we found that the beneficial effects of ketogenic diet on MK-801-induced disruption of PPI could be generalised to female mice. Furthermore, comparison of the effect of ketogenic diet and a widely used antipsychotic, olanzapine, showed that these approaches are equally effective and that the combination of ketogenic diet with olanzapine treatment over an extended period was similarly effective as the treatments by themselves.

Olanzapine administration results in weight gain and other metabolic side effects (Tschoner et al., 2007). Ketogenic diet may affect the same metabolic processes (Feinman et al., 2015; Mohorko et al., 2019; Sarnyai et al., 2019). Therefore, we considered a possible interaction between olanzapine and ketogenic diet in their metabolic effects. We found no difference in weight gain in animals treated with olanzapine alone or the combination with ketogenic diet (data not shown). After an initial body weight loss, body weight change in ketogenic diet mice did not differ from standard diet animals, consistent with our previous findings (Kraeuter et al., 2015; Kraeuter et al., 2019). However, a detailed analysis of the interaction between ketogenic diet and olanzapine on metabolic processes will be required before their combined use can be introduced in clinical practice.

The finding, that the efficacy of ketogenic diet on PPI disruption in male mice (Kraeuter et al., 2015; Kraeuter et al., 2019) is similarly seen in female mice, is potentially of clinical relevance. Woman experience more antipsychotic–related side effects (Seeman, 2010) and, therefore, would benefit from alternative antipsychotic approaches devoid of metabolic side effects. Our present results are in line with recently published case studies in which female patients with schizophrenia benefitted from ketogenic diet (Palmer, 2017; Gilbert-Jaramillo et al., 2018; Palmer et al., 2019). However, future animal model studies will need to investigate the efficacy of the ketogenic diet in females in a wider battery of behavioural tests modelling a range of positive, negative and cognitive symptom domains of schizophrenia.

Disruption of PPI is a widely reported hallmark of psychosis-like state in preclinical models and patients with schizophrenia (Braff et al., 2001; van den Buuse, 2010; Swerdlow and Light, 2018). Our results, showing olanzapine treatment reversing the effects of NMDA receptor hypofunction, are in line with previous studies (Geyer et al., 2001, Anastasio and Johnson, 2008). Also other atypical antipsychotics such as clozapine and quetiapine, but not typical antipsychotics such as haloperidol, are effective in reversing NMDA receptor antagonist-mediated PPI impairments (Geyer et al., 2001; van den Buuse, 2010). Importantly, we found that the effect of the combination of ketogenic diet and olanzapine treatment resulted in an effect similar to that of ketogenic diet or olanzapine treatment alone. This finding has clinical significance if a ketogenic diet would be used as an adjunct therapy to commonly used clinical drug treatment, similar to the way it is used in epilepsy (Neal et al., 2008). However, it will be important to rule out potential interaction of the ketogenic diet with other antipsychotic drugs in the future.

The findings on PPI cannot be explained by changes in startle amplitudes. We found that MK-801 administration resulted in an increase in startle amplitudes across all treatment groups. Ketogenic diet, on the other hand, caused a minor reduction in startle responses. Our previous studies showed that neither ketogenic diet nor MK-801 altered startle response in male mice (Kraeuter et al., 2019). Other studies have demonstrated that MK-801 results in an increased startle response, which is more pronounced in female mice (Nozari et al., 2015). These results point to sex differences in the effect of NMDA receptor antagonism on startle, indicating the importance to include both sexes in such preclinical studies.

There are several beneficial effects of the ketogenic diet such as weight loss and improved metabolic functioning (Abbasi, 2018). However, previous studies assessing the practicality of the ketogenic diet stated challenges such as inability to feed patients, lack of dieticians with expertise, and the optimal ketogenic diet protocol (Farias-Moeller et al., 2017; Gilbert-Jaramillo et al., 2018). However, these same studies demonstrated that the diet was well-tolerated and feasible (Farias-Moeller et al., 2017; Gilbert-Jaramillo et al., 2018). Compliance remains a problem, with a recent meta-analysis reporting compliance rates of only 45% in adults (Ye et al., 2015). A study by Palmer (2017) demonstrated that ketogenic diet was effective in treating schizo-effective disorder, however compliance issues resulted in a lack of ketosis, which decreased symptom control. Thus, although ketogenic diet is effective in treating schizophrenia, potential initial side effects and compliance issues may result in discontinuation of the diet and worsened symptoms (Palmer, 2017; Gilbert-Jaramillo et al., 2018; Palmer et al., 2019; Sarnyai et al., 2019).

In conclusion, this study demonstrated that (1) ketogenic diet shows efficacy to prevent the MK-801-induced sensorimotor gating deficit in female mice, (2) this efficacy is similar to that of olanzapine and (3) co-administration of ketogenic diet and olanzapine is as effective as either of the treatment alone. These results raise the possibility of using ketogenic diet as an adjunct to atypical antipsychotics in female subjects.

Contributors

AKK and ZS conceived the idea and designed the study. AKK carried out the behavioural studies, analysed the data and wrote the first draft of the manuscript. Nadia Archambault (NA) assisted with data collection. ZS and MvdB analysed some of the data and edited the draft to the final version. All authors contributed to and have approved the final manuscript.

Declaration of competing interest

The authors have no conflict of interest to report.

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