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EFFECTS OF KETOGENIC DIET AND BDNF DEFICIENCY IN MOUSE CHRONIC RESTRAIN STRESS MODEL

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Major depressive disorder (MDD) is a great challenge for psychiatry with up to 40% of treatment-resistant patients. Therefore, non-pharmacological interventions such as different diets seem a promising tool. Ketogenic diet is a powerful tool for epilepsy and metabolic diseases while new clinical and animal studies show also its potential against mental disorders such as MDD, PTSD, bipolar disorder and schizophrenia [1]. Several neurobiological pathways have been suggested to mediate effect of ketogenic diet for the brain and mental health with neurotrophic and neuroplasticity factor BDNF among them. Therefore, here we estimate the effect of ketogenic diet in male and female C56Bl/6J and BDNF heterozygous mice under the chronic restrain model of depression. Mice were kept on medium-chain fat-based ketogenic diet (paste, 75% fats, 10% proteins, 3% carbohydrates) or regular chow (crushed into powder, 5% fats, 19% protein, 59% carbohydrates) during 4 weeks – 2 weeks before the restrain and then 2 weeks along with daily two-hour chronic restrain stress. Body weight was monitored once a week during the first two weeks of diet and daily during the restrain. Fecal samples were taken before start of the diet and after the end of stress for corticosterone measurement using standard ELISA kits. Mice were then tested in sucrose preference test and tail suspension test for depression-like behavior, in elevated plus maze, light-dark box and open field test for anxiety and in social interaction test for social behavior. Postmortem blood and brain samples were taken for ex vivo studies, which results are not reported here.
Male mice showed similar body weight reduction under chronic restrain stress regardless of diet and genotype, while among females BDNF deficiency resulted in greater body weight loss on both diets. Fecal corticosterone levels were much higher in females than in males but not affected by diet or genotype. Anxiety was increased by the chronic restrain stress in the open field test (measured by total travelled distance and by the time spent in the peripheral zone) but not in the elevated plus maze (time spent in the open arms) and the light-dark box (time spent in the light chamber). While BDNF deficiency has been previously shown to be a model of stress vulnerability [2], our data shown mutant mice, both males and females, to be less anxious in the open field and elevated plus maze regardless of the restrain stress. Ketogenic diet was found to slightly increase overall anxiety in the open field across male groups. Depression-like behavior in the sucrose preference test and the tail suspension test, social exploration in social interaction test remained unaffected by stress, diet and BDNF deficiency. Our results show that BDNF deficiency might not always lead to increased stress vulnerability and in the mild stress models results in the opposite effects

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EVALUATING THE EFFECTS OF CHRONIC CANNABIDIOL TREATMENT ON AUTISM-LIKE BEHAVIOURAL CHANGES IN MICE PRENATALLY EXPOSED TO MATERNAL IMMUNE ACTIVATION

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Background: Autism Spectrum Disorder (ASD) is a heterogeneous neurodevelopmental condition characterized by deficits in social communication and interaction, as well as repetitive behaviours [1]. To date, there is no medication available for treating the core symptoms of ASD. Increasing evidence suggests that altered endocannabinoid (eCB) system signaling might contribute to ASD pathogenesis [2]. Remarkably, the eCB system is increasingly acknowledged as an important modulator of emotional and social responses, as well as the immune system, both of which have been found to be altered in children with ASD [3]. Hence, there is great interest in investigating the therapeutic potential of pharmacological modulation of the eCB system in ASD. Particularly, cannabidiol (CBD), a phytocannabinoid present in the Cannabis sativa plant, emerges as a valuable therapeutic option for mitigating both the core symptoms and comorbidities of ASD.
Aim: In this study, we examined the potential therapeutic effects of chronic CBD administration on the ASD-like behavioural phenotype and eCB system in a murine model of ASD, induced by maternal immune activation (MIA) during pregnancy.
Methods: MIA model was induced by administering a single dose of polyinosinic:polycytidylic acid (Poly I:C, 20 mg/kg) or saline (for controls) to pregnant C57BL6/J female mice. Offspring of both sexes received treatment with CBD (30 mg/kg), or vehicle from post-natal day (PND) 28 to 40. Twenty-four hours after the conclusion of CBD treatment (PND 41-60), offspring underwent several behavioural tests targeting different domains impaired in ASD: the three-chamber social test and reciprocal social interaction for the social domain, marble burying and grooming test for repetitive behaviours, and open-field and elevated plus-maze for anxiety, one of the most common conditions associated with ASD. At the end of behavioural testing, brain samples were collected to analyse the expression and levels of the key components of eCB system in brain areas such as the prefrontal cortex and hippocampus, which are involved in the modulation of behavioural domains impaired in ASD. All data were analysed by applying three-way ANOVA followed by post-hoc Tukey's test.
Results: Here we present preliminary data. In the open-field test, all animals exhibited similar levels of locomotor activity, but they differed in the percentage of time spent in the center of the arena [prenatal treatment*postnatal treatment: $F(1,82 = 7.898$, $p = 0.0062]$. Specifically, CBD treatment exerted paradoxical effects on the anxiety profile in MIA and control offspring, regardless the sex. CBD treatment significantly reduced the time spent in the center of the arena in MIA offspring, whereas increasing it for control offspring ($p<0.01$). In the three-chamber social test, male mice exposed to MIA displayed deficits in social preference as they spent a similar amount of time sniffing the social stimulus compared to the object [prenatal treatment*sex*stimulus: $F(1,82) = 8.819$, $p = 0.0039$, p = ns], but CBD treatment did not ameliorate this deficit.
Conclusions: Our preliminary findings align with existing literature regarding the impact of CBD on emotional regulation, but analyses are ongoing to elucidate its effects on other behavioural domains relevant to ASD, as well as eCB components.

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EXERCISE PARADIGMS: CONTRASTING EFFECTS OF TREADMILL AND VOLUNTARY WHEEL RUNNING ON HIPPOCAMPUS-ASSOCIATED FUNCTIONS IN RATS

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Introduction and Aim: Physical exercise has been reported to enhance cognitive