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Ketogenic diet may protect against stress experienced in the womb.

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Type of research; not peer reviewed/experimental study/animals

Researchers have shown that young rats fed a ketogenic diet – a diet with high fat and low carbohydrates – are protected from the lasting experience of pre-natal stress. This work, which needs to be confirmed in humans, is presented at the ECNP conference in Amsterdam

An extensive body of research has shown that if mothers experience stress while pregnant, the offspring can suffer ongoing psychological and development-related conditions.

Now a group of Italian researchers have shown that the biological changes induced by a ketogenic diet may help them to escape from the long-lasting effects of stress experienced in the womb.

The pregnant rats were stressed in the final week before birth. The offspring were weaned at 21 days after birth, and assigned either a control diet, or a ketogenic diet. At 42 days, the young animals were then tested for a variety of stress-induced deficits, such as poor sociability, or lack of interest in their surroundings (anhedonia). The animals which had received the ketogenic diet showed some notable differences over the control group, such as exhibiting longer grooming times, and greater sociability. The researchers found that if fed a normal diet, 50% of the rats born to stressed mothers showed stress-related problems in later life. However in those rats fed a ketogenic diet only 22% of male offspring, and 12% of female offspring, developed these problems.

The ketogenic diet has been shown to induce a variety of biological changes, such as enhancing mitochondrial efficiency and changing hormone balance.

According to lead researcher Dr Alessia Marchesin (of the University of Milan):

“We discovered that feeding young rats a ketogenic diet - a high-fat, very low-carbohydrate regimen - right after weaning almost completely

protected them from the lasting effects of stress they'd experienced before birth. The diet seems to have acted like a shield for their developing brains, so preventing social and motivational problems from ever taking root.

This matters because it suggests a simple way to prevent the occurrence of mood and social disorders that often originate from childhood adversity. Rather than waiting until symptoms appear and then treating them with medications—many of which carry side effects—we might one day take advantage of the therapeutic properties of dietary interventions early in life to prevent the manifestation of full-blown pathologic condition. What's more, we found that males and females benefited via different biological routes—males by reducing inflammation, females by boosting antioxidant defences—hinting that we could personalize and refine such dietary interventions.

If these findings translate to humans, we may be able to treat the long-term burden of prenatal trauma simply by adjusting what at-risk kids eat".

She added,

"There are a couple of points to note. The animals on the ketogenic diet grew more slowly than the controls, and so it may be that the reduced calory intake is associated with the later mental health benefits. And we see sex-specific differences which need to be better understood before we can apply this to humans".

Commenting, Dr Aniko Korosi, Associate Professor at the University of Amsterdam says:

"This work nicely contributes further to the nascent field of Nutritional Psychiatry. The role of nutrition in modulating mental health is gaining attention and its potential is more and more appreciated in the field. However important questions remain in the field as to which nutrient, when and for whom are effective in modulating mental health. The

presented study interestingly shows that prenatal stress-induced risk to altered behaviour can be modulated with a ketogenic diet fed after weaning. It will be intriguing to further explore what are the biological processes involved in these beneficial effects and if such effects are sex specific".

This is an independent comment, Dr Korosi was not involved in this work.

ENDS

Notes for Editors

This work is presented at the 38th ECNP Congress, taking place in Amsterdam and online 11-14 October 2025, see https://www.ecnp.eu/congress2025/. With more than 6,500 participants the ECNP Congress is Europe's leading platform for the latest research in disease-related neuroscience.

Conference Abstract
Sex-specific neuroprotective effects of ketogenic diet in a rodent model of early-life stress

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Introduction:

Exposure to early-life stress is a well-established risk factor for the development of psychiatric disorders such as depression. These adverse experiences can induce persistent behavioural and neurobiological alterations, including social impairments and emotional dysregulation. Given the limited efficacy of current pharmacological treatments there is growing interest in alternative therapeutic strategies, including dietary interventions. The ketogenic diet (KD), a high-fat, low-carbohydrate regimen that shifts the body's metabolism toward ketone utilization, has garnered attention for its neuroprotective and anti-inflammatory properties. Emerging evidence suggests KD may improve mitochondrial function, modulate monoaminergic circuits, regulate the hypothalamic–pituitary–adrenal (HPA) axis, and reduce oxidative stress. [1]

Aim:

In this study, we examined the efficacy of KD in mitigating behavioural and molecular alterations induced by prenatal stress (PNS), and whether sex modulates these effects.

Methodology:

Pregnant Sprague Dawley rats were subjected to repeated restraint stress during the final gestational week to induce prenatal stress. Offspring were weaned at postnatal day 21 (P21) and assigned to either a control diet (CD) or KD for four weeks. Behavioural assessments, including social interaction and the splash test for anhedonia, were conducted during adolescence (P42–

P45). Statistical analyses were conducted using Two-way ANOVA and Tukey's multiple comparisons' test when needed.

Results:

KD-fed animals exhibited reduced weight gain and food intake, regardless of stress exposure or sex. Behaviourally, PNS-exposed offspring displayed impaired social interactions, consistent with prior findings [2]. However, this deficit was ameliorated in PNS animals maintained on KD from weaning, suggesting a preventive effect on stress-induced sociability impairments. While PNS did not alter grooming behaviours, KD increased total grooming time, implying improved self-care. Notably, vulnerability to PNS, defined by behavioural impairments, was observed in roughly 50% of CD-fed animals. KD significantly reduced this proportion to 22% in males and 12% in females, supporting its protective role against stress-induced emotional dysfunctions.

We further examined the prefrontal cortex to investigate molecular underpinnings, focusing on neuroinflammation and oxidative stress markers. KD reduced complement component C4 expression in both sexes, while C3 downregulation and GFAP suppression were restricted to males, indicating a broader anti-inflammatory effect in male rats. In contrast, KD enhanced antioxidant responses selectively in females, upregulating Nrf2 and its target gene Gclc1, particularly in PNS-exposed females. This occurred alongside normalization of KEAP1 levels, suggesting a restoration of redox homeostasis. Conversely, in males, KD impaired antioxidant defences by downregulating Nrf2 and Gclc1 and increasing KEAP1, potentially diminishing cellular resilience to oxidative stress despite reduced inflammation. C1q expression remained unchanged across all groups, indicating that KD does not induce global immune suppression but targets specific inflammatory pathways.

Conclusions:

Collectively, these findings highlight the therapeutic potential of KD in preventing behavioural dysfunctions linked to early life stress and underscore the importance of considering sex as a biological variable. KD appears to exert sexually dimorphic effects: males primarily benefit from anti-inflammatory mechanisms, while females exhibit enhanced antioxidant responses. These insights advocate for personalized dietary strategies in the prevention and treatment of stress-related psychopathology.

[1] González Ibáñez F, Halvorson T, Sharma K, et al. Ketogenic diet changes microglial morphology and the hippocampal lipidomic profile differently in stress susceptible versus resistant male mice upon repeated social defeat. Brain Behav Immun. 2023;114:383-406. doi:10.1016/j.bbi.2023.09.006

[2] Creutzberg KC, Begni V, Orso R, et al. Vulnerability and resilience to prenatal stress exposure: behavioral and molecular characterization in adolescent rats. Transl Psychiatry. 2023;13(1):358. Published 2023 Nov 22. doi:10.1038/s41398-023-02653-6