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Perspective

Probiotic Supplementation Modulates Sleep, Depression and Glucose Metabolism in Pubertal Mice

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DESCRIPTION

Mood disorders are a leading cause of disability and financial strain due to their disease-related consequences. Depression alone affects over 280 million people globally. Clinical depression is characterized by pervasive despair or anhedonia, significant weight changes and/or disrupted sleep. Although pharmacological treatments have advanced, the biological mechanisms underlying depression during puberty and adolescence remain complex and not fully understood. Puberty, which marks the attainment of sexual maturity, is distinct from adolescence, a broader phase involving ongoing physiological, social, emotional and cognitive development. Understanding how depression evolves during these stages may inform better treatment and prevention strategies.

Chronic stress during puberty and adolescence heightens the risk of adult depression and causes lasting alterations to the gut-brain axis. For instance, prolonged activation of the Hypothalamic-Pituitary-Adrenal (HPA) axis due to chronic stress can lead to gut dysbiosis and increased intestinal permeability, which are linked to higher neuroinflammation and depression. Chronic sleep disruption for seven days, either during adolescence (postnatal day 42) or adulthood (postnatal day 70), increased corticosterone levels following restraint stress in both adolescent and adult females compared to their non-sleep disrupted counterparts. However, it only induced depression-like behavior in pubertal male and female mice.

Certain brain metabolites are associated with depression pathophysiology. For example, tryptophan, an essential amino acid and serotonin precursor, is typically low in individuals with major depressive disorder but increases with antidepressant treatment. Improved availability of energy-providing molecules may also have antidepressant effects. L-lactate, a by-product of glucose metabolism, can be synthesized by astrocytes to produce Adenosine Tri Phosphate (ATP), a key energy source for neurons and stimulate neuroplasticity by increasing Brain-Derived Neurotrophic Factor (BDNF) expression. Chronic intraperitoneal L-lactate injections in adult male mice reduce depression-like behavior with efficacy comparable to Desipramine and both treatments increase hippocampal L-lactate and astrocyte activity. Improving metabolite concentrations associated with antidepressant effects may help alleviate depression during puberty and adolescence.

Probiotic treatment involves the oral supplementation of gut microbiota with beneficial bacterial strains. The gut microbiota produces biomolecules such as tryptophan, serotonin and L-lactate, among over 150 other metabolites, which can influence brain function and disease. Consumption of foods fermented with Lactic Acid Bacteria (LABs) has been linked to temporary increases in blood lactate levels. Probiotic LAB supplementation may improve access to these beneficial biomolecules and offer a palatable, gastric distress-free alternative to existing methods for manipulating physiological levels of blood and brain lactate.

This project aims to evaluate the antidepressant effects of probiotic LABs in a pubertal mouse model of sleep disruption-induced depression. We seek to replicate our previous findings that chronic sleep disruption during puberty increases depression-like behavior. We hypothesize that chronic sleep disruption will reduce hippocampal glucose, L-lactate, tryptophan and serotonin levels, as well as BDNF expression in the brain. Additionally, we anticipate that sleep disruption will delay sleep onset and termination, resulting in decreased Non-Rapid Eye Movement (NREM) duration during the light phase and increased NREM duration in the early dark phase. Finally, we hypothesize that probiotic treatment will prevent depression-like behaviors associated with sleep disruption and normalize serotonin, tryptophan, glucose and L-lactate levels in affected mice. Despite these promising findings, the precise mechanisms through which probiotic LABs alleviate depression-related symptoms are not yet fully understood and warrant further research before considering them as adjunct treatments for pubertal depression.

CONCLUSION

Depressive disorders are challenging to treat due to their diverse range of symptoms. Probiotic LABs could offer a unique approach for addressing the multifaceted nature of pubertal and adolescent depression, particularly when induced by chronic sleep disruption. Probiotic mixtures such as Cerebiome and

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Lacidofil have been shown to reduce depressive behaviors in pubertal mice affected by chronic sleep disruption. Sleep disruption typically lowers concentrations of antidepressant-associated biomolecules like tryptophan in the prefrontal cortex and L-lactate in the hippocampus. However, mice experiencing sleep disruption but treated with probiotic LABs maintain normal levels of these biomolecules. Additionally, Cerebiome and Lacidofil can mitigate the impact of sleep disruption on sleep architecture: Cerebiome increases Rapid Eye Movement (REM) sleep per bout, while Lacidofil extends NREM duration during the light phase.