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PROJECT TITLE
Evaluation of PEA effect in CNS disease: role of the gut microbiota as pharmacological target.

Project description
Palmitoylethanolamide (PEA) is an endogenous N-acylethanolamine with anti-inflammatory, analgesic, and neuroprotective properties. Naturally produced in response to cellular stress and found in foods such as egg yolk and soy, PEA has emerged as a safe and effective dietary supplement for several CNS disorders (1). Preclinical studies have highlighted its therapeutic potential in neurodevelopmental and neurodegenerative disorders, including autism spectrum disorders (ASD) and Parkinson's disease (PD) (2,3). While several mechanisms have been proposed, mainly involving immune and neuroinflammatory pathways, the role of the gut microbiota in mediating PEA's effects remains largely unexplored.
Recent findings point to microbiota-derived extracellular vesicles (mEVs) as key players in gut-brain communication (4-6). Once thought to be inert waste carriers, mEVs are now known to influence brain function and gene expression, suggesting a potential role in ASD pathogenesis and therapy.
The first aim of this project is to investigate mEVs as novel mediators of gut-brain interaction in ASD, using a maternal immune activation (MIA) mouse model triggered by prenatal exposure to poly(I:C) (7-14). The study will assess whether PEA's protective effects are mediated through changes in mEV distribution, with a focus on their impact on gut and brain function and autistic-like behaviors.
The second aim addresses PEA's antidyskinetic potential in PD, using a 6-OHDA-lesioned mouse model with L-DOPA-induced dyskinesia. Although L-DOPA remains the gold standard for PD treatment, its long-term use leads to motor complications (15). The project will explore how PEA may influence gut microbiota composition and metabolites, thereby improving L-DOPA absorption and reducing dyskinesia severity.
Overall, this project aims to uncover novel microbiota-mediated mechanisms underlying PEA's therapeutic effects and support the development of innovative, gut-brain-targeted strategies for ASD and PD.

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