University of Naples Federico II

Department of Pharmacy

International PhD course in

Nutraceuticals, Functional Foods and Human Health

Investigation of gut-brain axis in autism spectrum disorders: potential pathogenic role and pharmacological control of gut microbiota-derived extracellular vesicles in MIA offspring

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Project description

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental condition characterized by impaired social communication and repetitive behaviors. Traditionally seen as a psychiatric disorder, ASD is now also associated with physical comorbidities, particularly gastrointestinal issues, suggesting a dysfunctional gut-brain connection. Alongside neural, hormonal, and immune pathways, microbe-derived metabolic products and microbiota-derived extracellular vesicles (mEVs) have emerged as key players in this communication. Once considered cellular waste carriers, mEVs are now recognized as potential mediators influencing brain function and gene expression, possibly contributing to neurodevelopmental disorders (1-3). Being cargo messengers, they may also have physiological and/or therapeutic properties, representing a double-edged sword within gut-brain axis.

This PhD project aims to investigate the involvement of mEVs, as novel players of gut-brain axis, in the prenatal and postnatal phases of the pathogenesis of ASDs and to study the effect of palmitoylethanolamide (PEA) or *Lactobacillus rhamnosus*-derived mEVs on autistic-like phenotype in maternal immune activation (MIA) mouse model, where pregnant mice are exposed to poly(I:C) to mimic viral infection. MIA offspring showed diverse behavioral impairments (i.e. autism-like behaviors and cognitive deficits) (4-11). Apart from maternal inflammation during pregnancy, other maternal factors have been recognized to promote MIA-associated traits. Kim et al. (12) have demonstrated that poly(I:C)-induced MIA requires maternal intestinal bacteria to induce an alteration of behavioral phenotypes in offspring.

This study will explore the relationship between the blood and brain mEVs distribution in MIA offspring and the development of ASDs, focusing on brain and gut function, and behavior. It will also evaluate the therapeutic potential of PEA and L. rhamnosus-derived mEVs in MIA offspring for tackling autistic traits and the associated brain and gastrointestinal alterations. It will also examine mEVs' role in PEA's protective mechanisms and their use as a novel postbiotic therapy to complement existing ASD treatments.

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