Lactobacillus caséi restores dysbiosis-induced gut inflammation and sickness behaviors associated with biochemical and electrophysiological alterations in the hippocampus

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The intestinal microbiota importantly contributes to the bidirectional interaction between the Central and Enteric Nervous Systems. In particular, the so-called microbiota-gut-brain axis (MGBA) represents the major substrate of pathophysiological mechanisms in chronic inflammatory bowel disorders and psychiatric comorbidities (Grenham et al., 2011).
Besides the gastrointestinal functions, microbiota and its metabolites are likely to be involved in modulating different brain processes, including emotional behaviors, stress-related responsiveness (Dinan and Cryan, 2012), pain modulation (Bercik et al., 2012) and food intake regulation (Alcock et al., 2014). A number of studies have indicated that alterations in the normal microbiota, referred as dysbiosis, are responsible for functional and behavioral changes in animals and humans (Fond et al., 2015). Interestingly, the recent characterization of the human microbiome broke new ground for investigate potential epigenetic mechanisms of neurodevelopmental disorders with gastrointestinal comorbidities, including autism spectrum disorders (ASDs) or attention-deficit hypersensitivity disorder (ADHD) (Fond et al., 2015). Indeed, epidemiological studies revealed a link between alterations in the gut microbiota and the risk of later neuropsychiatric disorders in childhood, suggesting the early probiotic treatment as a successful intervention (Frye et al., 2015; Petra et al., 2015). Based on current evidence, in this study we have investigated the behavior, as well as, the biochemical, and electrophysiological alterations in an antibiotic-induced experimental dysbiosis. Mice were exposed to a mixture of antimicrobials (ampicilline, streptomicin and clyndamicin) for 2 weeks. Afterwards, they received *Lactobacillus casèi* or vehicle up to 7 days via gavage. Microbiota perturbation induced an overall gut inflammatory state, accompanied by sickness behaviors, including increased immobility and reduced social interaction. Altered behavior was associated with neuronal firing activity in the hyppocampus. Moreover, morphological rearrangements of non-neuronal cells in brain areas controlling depression-like behavior were observed. Lactobacillus casèi treatment counteracted the gut inflammation and restored the behavioural phenotype as compared with vehicle-treated animals. The biochemical and functional changes occurring in the brain of dysbiotic mice resulted also normalized. Our findings identify the supraspinal biomolecular modifications responsible for behavioural alterations associated with gut dysbiosis. Indeed, probiotic treatment normalized mice behaviour by restoring intestinal immune environment. This study encourages that intestinal microbiota perturbation might contribute to the psychiatric comorbidity in patients with inflammatory bowel disorders.

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