TARGETING SPHINGOSINE 1-PHOSPHATE RECEPTORS IN AUTISM SPECTRUM DISORDERS: FOCUS ON GUT AND BRAIN

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Autism Spectrum Disorders (ASD) are neurodevelopmental disorders characterized by social communication deficits and repetitive/stereotyped behaviors. Gastrointestinal disorders are often present as comorbidities.
Etiopathogenesis for the majority of cases is currently unknown however, neuroinflammatory and immune changes are recognized as pivotal mechanisms in ASD: activation of microglial cells, the resident immune cells of the central nervous system, and increased levels of pro-inflammatory cytokines has been reported in ASD children and animal models. Imbalance of intestinal gut mucosal barrier components (mucosal immune-system, epithelial barrier and microbiota) has been also involved.
Fingolimod (FING), a non-selective S1P receptor (S1PR) modulator, is the first oral approved therapy for multiple sclerosis; the phosphorylated FING, the active form of the drug, causes internalization of S1PR thus acting as a functional antagonist. After systemic administration, FING readily accesses the CNS where it limits the inflammatory response while promoting the neuroprotective effects of microglia.
Converging literature data support a potential role of S1P pathway in the pathogenesis of ASD; indeed, changes S1P levels were found in both patients and animal model of ASD and the chronic administration of FING was found able to improve cognitive deficit in animal models of neurodevelopment disorders.
Moreover, as for GI diseases, FING ameliorates both Th-1and Th-2experimental colitis as well as reduces inflammatory signalling in a model of colitis-associated colonic cancer.
The present study was designed to verify whether S1PRs represent a reliable therapeutic target in ASD; we evaluated the effects of subchronic FING administration on behavioral, inflammatory and the gut to immune response in BTBR mice, the most widely used mouse model of ASD.
Fingolimod (Sigma-Aldrich) or vehicle were administered intraperitoneally in two-month-old BTBR male subjects for 4weeks; after the last administration, BTBR male were tested in a Male-Female social interaction (with sexually receptive female partners) and grooming test; the trials were videorecorded and subsequently analysed. After behavioral tests, mice were sacrificed and tissues collected for biochemical and molecular analyses carried out to evaluate brain and gut inflammatory states. Furthermore resident peritoneal macrophages were isolated from saline and FING treated mice, cultured and stimulated with LPS to test their inflammatory response.
Behavioural analysis demonstrated an increase of social investigation with a concomitant decrease in explorative and stereotyped responses in FING treated mice which also displayed an enhanced hippocampal expression of BDNF and Neuregulin 1, two trophic factors significantly reduced in BTBR mice vs the control strain C57BL6/j. Furthermore a reduction of inflammatory markers (IL1b, iNOS and MnSOD) were founded in cortical and hippocampal tissues.
After LPS stimulation, macrophages from saline treated BTBR accumulated higher levels of NO in the culture medium than FING treated animals, suggesting that FING modulated the altered inflammatory profile of BTBR mice. Moreover colonic and MLN IL-6and IL13mRNA content increased in FING treated BTBR mice that become comparable to C57mice values.
Our data showed that 4-week FING treatment is able to normalize some BTBR autistic-like behavioral alterations and to normalize the expression of BDNF and Neuregulin1in the hippocampus of BTBR mice; furthermore, FING administration reduces the inflammatory response in these mice both at central and peripheral level and reverses their altered gut immune profile.
These results provided information on FING effects in BTBR mice as well as on relationships among sphingosine metabolism, behavioral dysfunction, brain and gut inflammation supporting S1P receptors as potential therapeutic target for Autism spectrum disorders.