POTENTIAL EFFECTS OF A NOVEL FORMYL PEPTIDE RECEPTOR 2 AGONIST IN TWO MOUSE MODELS OF AUTISM SPECTRUM DISORDER

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Introduction: Autism spectrum disorder is a neurodevelopmental disorder characterized by abnormal social interactions and repetitive behaviors. Among environmental factors associated with the risk of autism, one of the most common is the presence of ongoing neuroinflammation. A growing number of studies has demonstrated the potential beneficial effects of lipids in inflammatory processes. Lipoxins (LXs) are a group of endogenous lipid mediators, which have the potential to contribute to the control of the inflammation and able to reduce neuro-inflammatory effects. In particular, lipoxin A4 (LXA4) is one of the most important arachidonic acid metabolites and has potent anti-inflammatory properties mediated by its receptor formyl peptide receptor 2 (FPR2). Interestingly, decreased plasma levels of LXA4 were recently found in children with autism spectrum disorders. However, there has been a paucity of studies investigating the role of LXA4 and FPR2 in animal models of autism. In the present work, we examined for the first time the effect of a novel ureidopropanamide based N-formyl peptide receptor 2 (FPR2) agonist, named MR-39, on neuro-inflammatory state and on behavioural phenotype in two mouse models of autism spectrum disorder.

Materials and methods: We used two mouse models of autism: the inbred strain BTBR T + tf/J (BTBR) mice and the murine model of ASD induced by prenatal exposure to valproic acid (VPA). C57BL/6 mice were used as control. FPR2 agonist (MR-39) was intraperitoneally administered to mice, using either acute or sub-chronic regimens (8 consecutive days) at different doses (1-50 mg/kg) by intraperitoneal administration. To assess behavioural phenotype, mice were tested in the marble burying, self-grooming, three-chambered social test and in the reciprocal social interactions test. We also performed biochemical analyses in whole brain to analyse FPR2 level using ELISA kits and RT-PCR to evaluate the expression of various inflammatory markers in both mouse strains and their possible modulation by MR-39.

Results: Our data showed that chronic systemic administration of MR-39 at the dose of 10mg/kg for 8 consecutive days was able to attenuate the deficit in social behavior in the three-chambered social test and in the reciprocal social interactions test, without altering exploratory behavior. Moreover, ELISA analysis revealed the activation of FPR2 by MR-39 in mouse brain. Finally, to further define the possible neuroprotective effect of MR-39, we found that MR-39 was able to decrease some pro-inflammatory cytokines as interleukin-1β and tumor necrosis factor-α in mouse brain.

Discussion and conclusion: These findings suggest for the first time that the novel FPR2 agonist (MR-39) was able to reduce neuro-inflammation and to increase social behavioral in murine models of autism, supporting an important role for FPR2 in the disease. Our results are very promising and open a new scenario in the treatment of autism spectrum disorder.