Endocannabinoid system dysregulation drives inflammatory state and human immune system cell alterations in autism spectrum disorders

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Autism is now considered as multifactorial disorder associated with complex genetic and environmental interactions contributing to various risk factors. The newest dramatic increased prevalence of its rates recall the urgent needed for finding a definitive cure, as well as the finding for a specific biomarker for early diagnosis. Recently, several studies highlight a key involvement of endocannabinoid (EC) system in autism pathophysiology. EC system is a complex network of lipid signalling pathways comprised by arachidonic acid-derived compounds (anandamide, AEA) and 2-arachidonoyl glycerol (2-AG), their G-protein-coupled receptors (cannabinoid receptors CB1 and CB2) and the associated enzymes. Beyond autism, EC system is also involved in several other psychiatric disorders (i.e. anxiety, major depression, bipolar disorder and schizophrenia). This system is also a key regulator of other metabolic and cellular pathways involved in autism, such as food intake, energy metabolism and immune system controlling. Early studies in autism animal models demonstrated alterations in the brain's endocannabinoid system. Autism is characterized by immune system dysregulation. This alteration includes differential monocyte and macrophage responses, abnormal cytokine and T cell levels. Endocannabinoid system dysfunction in monocyte cellular model of autism has been demonstrated by showing that the mRNA and protein for CB2 were significantly increased, whereas mRNA for the gene that synthesizes anandamide, N-acylphosphatidyl-ethanolamine-hydrolyzing phospholipase D (NAPE-PLD), was significantly decreased. This dysfunction could result from insufficient endocannabinoid system tone. More interesting, monocyte-derived macrophagic cells also reveal EC system dysregulation, further indicating the involvement of the EC system in autism associated immunological disruptions. Taken together, all these new findings are offering novel perspectives in autism research and indicate that the EC system could represent a novel target option for autism pharmacotherapy. Potential future drugs could target CB2 receptor, in order to design new personalized strategies in the pharmacotherapeutical management of autism.

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