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CANSHANK

Involvement of the insula in the Autism neurodevelopmental disorder

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We will explore the pathophysiological mechanisms underlying autism spectrum disorder (ASD). ASD is a multifactorial complex disorder involving multiple genes, environmental factors, and the interaction among these factors. We will focus our attention on the involvement of a neuromodulatory system, the endogenous cannabinoid system, in specific cell types of a crucial brain region that represents a hub of communications, the insular cortex. We will use a well-recognized genetic mouse model of ASD, the deletion of the Shank3 gene, and several complementary experimental approaches: additional genetic mouse models, behavioral and electrophysiological techniques, viral vector strategies to express and delete some genes in specific cell types in the brain, strategies to investigate the use and the transformation of energy at the cellular level and human cerebral organoids. These techniques will provide important information to clarify the specific mechanisms underlying ASD. We hypothesize that the genetic deletion of Shank3 makes an imbalance of the insular endocannabinoid system signaling in specific cell types in a vulnerable period during neurodevelopment. These alterations seem responsible for the onset of neurodevelopmental alterations leading to ASD and the different symptoms of this disorder. We are a consortium with all the tools and expertise to successfully achieve our proposed objectives. Our research will have uniqueness and will result in a deeper understanding of the brain mechanisms involved in the onset and development of ASD. The inclusion of human organoids mimicking this neurodevelopmental disorder and the interaction with a SHANK3 haploinsufficiency/ Phelan McDermid patient organization will provide high translational value to our proposal. Our elucidation of novel mechanisms will deliver novel insights to shed light on innovative therapeutical approaches.