Amygdala synaptic neuromodulatory mechanisms and role of mGlu4 in Autism Spectrum Disorders (MAGNOLIA)

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Autism spectrum disorders (ASD) refers to a range of developmental disorders of the brain. Affected persons show repetitive stereotyped behaviors and are challenged in their social abilities, emotional states and in how they perceive things in the world. Drug treatments for ASD are currently very limited, and those available are poor at improving social abilities, so there is a need to identify new drugs that would help alleviate these symptoms. Therefore, a more complete understanding of the underlying mechanisms of ADS in the brain is indispensible. As for many neurodevelopmental disorders, there is evidence for a dysfunction of synapses, the communication points between neurons. Their activity can be controlled my modulatory receptors, among them the glutamate receptor type 4 (mGlu4) which could be an intervention point for several brain-related diseases. Indeed, we recently demonstrated that facilitating the activity of mGlu4 relieves autistic-like behavior in mouse models of ASD. The purpose of this research project is to further explore the therapeutic potential of mGlu4. We will focus on a brain region called the amygdala and its connections with other brain structures that together form a network regulating social, cognitive, emotional and sensory behavior. Our hypothesis is that mGlu4 controls the function of specific aspects of this network, which is dysfunctional in ASD but can be rescued when mGu4 is activated by drugs. We will test this hypothesis using two mouse models that show ASD-like deficits and working with an interdisciplinary team of researchers which are experts in animal behavior, synaptic communication and development of new classes of light-sensitive drugs that can switch mGlu4 receptors on and off by light. The latter is of particular importance as it allows for the precise investigation of the role of mGlu4 in space and time. Findings from our project will expand our knowledge about the molecular, synaptic and network mechanisms in the brain that underlie ASD and the beneficial effects of mGlu4 activation on autistic symptoms, and hopefully pave the way for the development of new classes of drugs that can provide more effectively treatment.