

Unlike brain diseases caused by sudden lesions, the clinical symptoms of neurodevelopmental disorders result from complex interactions among many brain regions, networks, and proteins. Using genetic mice models of ASDs we show here that the maintenance of a proper balance between excitation and inhibition in a neural network is a delicate process that starts early in development.

I have analysed three mice models in which genes that cause special forms of Autistic Spectrum Disorders (MeCP2, the mutated gene in Rett Syndrome patients), belong to a family responsible for many cases of ASDs (Neurologin-1) or their mutations induce cases of idiopathic ASD (Neurobeachin) have been knocked-out. Autistic spectrum disorders (ASDs) have been proposed to result from an excitatory/inhibitory network imbalance caused by synaptic impairments. Since all of these proteins are presumably involved in synaptic formation and maturation, we investigated the functional and structural synaptic and subsequent network changes caused by their absence in the first postnatal week. We used the brainstem respiratory network as an experimental model, since this network is functional immediately after birth and we employed patch-clamp methods doubled by immunocytochemistry and Western Blotting.

Our results show that the deletion of these proteins in mice leads to specific alterations in the function and the maturation of the synapses starting from an early developmental stage. The deletion of MeCP2 results in a decreased density of both inhibitory and excitatory synapses and in the reduced expression of developmentally important GABA and NMDA postsynaptic receptor subunits. The absence of Neurologin-1 leads to reduced function of NMDAergic synapses, while the Nbea KO mice present severe alterations in the formation and function of both excitatory and inhibitory synapses. These synaptic impairments are translated in imbalance in the overall network inhibition and excitation, and the severity of this imbalance is correlated with the ability of the neural network to perform its output function, in our case respiration. To resume, my study supported the idea of autism and its related disorders as synaptopathies and moreover showed that synaptic impairments appear in mice models of ASDs early in development, conclusive with the neurodevelopmental aspect of these disorders.

