ATM INHIBITION AS INNOVATIVE STRATEGY TO ENHANCE KCC2 EXPRESSION AND PROMOTE GABAERGIC DEVELOPMENT.

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The establishment of the right equilibrium between the inhibitory and excitatory synaptic transmission (I/E balance) is emerging as a fundamental principle underlying a variety of neuropsychiatric and neurodevelopmental disorders. The I/E imbalance can be responsible for the generation of pathological states such as epilepsy, schizophrenia, bipolar disorder, fragile X syndrome and Rett syndrome (for review, see Levitt et al., 2004; Lewis et al., 2012). Recently, we found that the large protein kinase Ataxia Telangiectasia mutated (ATM) plays an important role in the development of GABAergic inhibition by controlling levels of the potassium/chloride co-transporter KCC2. Taking advantages of plated neurons we found in ATM heterozygous cultures, a significant excitatory/inhibitory unbalance toward inhibition as indicated by: the higher frequency of mIPSCs, the increased number of GABAergic synapses and the more precocious development of the inhibitory system (i.e. excitatory to inhibitory GABA switch). In vivo, the enhanced inhibition still persists as well as a reduced neuronal excitability (Pizzamiglio et al, 2016). Thus, starting by these evidences, we are now exploiting the pharmacological blockade of the ATM kinase in order to increase GABAergic function and restore the proper excitatory/inhibitory balance in such pathological circuits characterized by a poor inhibition. Administration of KU55933, the selective inhibitor of ATM kinase is responsible, in neurons prepared by wt mice, for an higher inhibitory events and synaptic puncta as evaluated by electrophysiological and immunocytochemical experiments. Thus, since in literature it has been described that Mecp2 knockout (KO) mice for Rett syndrome present as key feature a reduced GABAergic signalling in several brain areas demonstrated by an impaired synaptic inhibition and stronger excitatory synapses in the hippocampus (Gaston Calfa etal, 2015; Li W et al, 2016), we are now investigating if the KU treatment could be beneficial for the rescue of these cognitive alterations described in animal model and clinic. Preliminary data display that Mecp2 KO hippocampi present a reduced KCC2 expression and an increased ATM levels thus suggesting that our approach with the ATM inhibitor could be potentially effective in the restoration of pathological features described in Rett disease. These data unveil an unexpected role of ATM in the maintenance of an appropriate GABAergic development and transmission in hippocampal formation, laying the basis for a new pharmacological approach in psychiatric and neurodevelopmental disorders.

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