INSIDE THE MULTIMODAL EFFECTS OF MATERNAL SEPARATION IN C57BL6J MICE: EARLY LIFE STRESS AND CHANGES IN NEURONAL FUNCTIONS, COGNITIVE AND MOTIVATED BEHAVIORS

Giuseppe Talani[1], Eleonora Saolini[2], Daniele Colombo[2], Gian Marco Calandra[2], Francesca Biggio[2], Giovanni Biggio[2], Enrico Sanna[2]

[1]National Research Council, Istitute of Neuroscience, Cagliari - Italy, [2]University of Cagliari, Cagliari - Italy

Introduction: Traumatic events occurring early in life may be a predictive factor, in both humans and rodents, for a higher prevalence of neuropsychiatric disorders in adulthood. A number of studies documented that repeated maternal separation (RMS) in newborn rodents represents a useful experimental model for investigating the long-term effects of neonatal stress on brain function later in life including an enhanced vulnerability to ethanol (EtOH) abuse. Since previous work suggested that some effects of RMS appears to be dependent on gender, we here extended our recent findings about the potential mechanisms involved in the long-term effects of RMS in C57BL/6J adult mice by evaluating the changes in neuronal plasticity at both GABAergic and glutamatergic synapses in the hippocampus (hip) and nucleus accumbens (nacc), areas involved in learning and memory function and drug reward, respectively.

Materials and methods: Newborn animals were separated from the dams for 360 min daily, for 15days starting from PND 2, and at PND 60, electrophysiological and behavioral tests were conducted in order to examine, *ex vivo*, the effect of RMS on GABAergic and GLUergic synaptic plasticity, and *in vivo*, cognitive and addictive behavior.

Results: Patch-clamp experiments performed in the dentate granule neurons revealed that RMS causes a significant enhancement in the tonic component of the GABAergic inhibition in male, but not females, mice. RMS is also accompanied in males by a marked increase in the frequency of GABAergic IPSCs recorded in the same neurons. Interestingly, all these changes induced by RMS were paralleled by an impairment in LTD formation in the CA1subregion in male but not in female mice, an effect that may involve an increased function of the endocannabinoid system and which was accompanied by an impaired cognitive performance in the Barnes maze test. RMS is also associated in males with a marked increase of EtOH intake and preference in the two-bottle free choice paradigm, while in females a similar result is not detected. In addition, we observed a significant RMS-induced changes in synaptic plasticity with a reduction of LTD formation in the nacc neurons, an effect accompanied by an impairment of the AMPA/NMDA ratio. Interestingly, these functional and behavioral changes were no longer appreciable in RMS male mice when treated with a single injection of beta-ethinylestradiol at PND3, suggesting that alteration in the neonatal hormonal asset may strongly influences the neuronal and behavioral impact produced by RMS.

Discussion/Conclusions: The present work shows that stress occurring during early life, associated to the repeated separation from the dams, is able to change certain physiological aspects of hip and nacc circuitry, including modification of long term synaptic plasticity in C57BL/6J male but not in female mice. These impairments are mirrored by a profound alteration in specific ehavioral responses, such as propensity for novelty and spatial learning, and EtOH consumption, that are controlled by hip formation and nacc play a crucial role respectively. Taken together, these findings demonstrate that RMS is associated with long-lasting effects on synaptic plasticity in both hip and nacc of C57BL/6J male mice, alteration of learning and memory as well as goal directed behavior. In line with previous findings, our data may support a gender-dependent effect of neonatal RMS on brain development and function. Supported by CNR-DISVA-Sardegna Ricerche