LONG-TERM IMPACT OF PRENATAL STRESS EXPOSURE ON ACUTE RESPONSIVENESS IN ADULT MICE: FOCUS ON INFLAMMATION AND OXIDATIVE BALANCE

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Background and aim: Although everyone experiences stress, it is difficult to define what stress is, given its nature of a highly subjective phenomenon. The difficulty in finding a satisfactory definition of stress relies on the fact that it may have a different impact on each of us depending on several variables, which are associated to the intrinsic traits of the stressed subject- who may be more vulnerable due to genetic background- and to the nature of the stressful event. In fact, the severity and the persistence of the stress can favor a harmful trajectory leading to pathological consequences. Indeed, it is well established that stress represents the main environmental risk factor for the development of psychiatric diseases such as major depression disorder and schizophrenia. Given the high prevalence of these mental disorders and the unmet needs associated to their pharmacological treatment, it is crucial to identify the molecular mechanisms through which stress might exert an etiological role. Another critical variable that may influence the detrimental impact of stress is time. Specifically, it is well known that early-life stress, occurring in specific perinatal periods during which the brain is developing, may induce long-lasting changes in physiological, emotional and behavioral functions that might enhance the susceptibility to mental disorders in adulthood. On these bases, the aim of this study was to evaluate the long-term impact of the exposure to an early-life stress on molecular targets known to be altered in psychiatric disorders, such as mediators of the inflammatory and oxidative systems.

Methods: By using real time RT-PCR and western blot, we analyzed the gene and/protein expression of pro- and anti-inflammatory cytokines, microglial markers and mediators of pro- and anti-oxidant activity in the brain of adult mice prenatal exposed to stress. Moreover, in order to assess the potential influence of prenatal stress on the acute responsiveness in adulthood, we used a "second hit model" approach. Specifically, the analyses were performed in adult prenatally stressed animals in both basal conditions as well as after an acute stress, which represents a challenge that can be adequately addressed only if the molecular mechanisms required have not been altered by the previous events. For the prenatal stress, pregnant dams were exposed to an immobilization paradigm lasting 45minutes during the last three days of gestation. The male offspring born from control and stressed mothers were left undisturbed until adulthood and then subjected to an acute forced swim stress for 6min. Molecular analyses were performed 5min or 2h after the end of the acute stress.

Results: We found that prenatal stress has not only long-term effects on the inflammatory and oxidative balance in the brain of adult mice under basal conditions, but it is also able to interfere with the acute responsiveness. Specifically, we observed increased expression of the pro-inflammatory cytokine IL-1b paralleled by a reduction of the anti-inflammatory cytokine IL-10 in the hippocampus of adult mice prenatally stressed. In the same animals, we found an impairment of redox balance after the acute stress, as suggested by the up-regulation of the transcription factor NRF-2, the anti-oxidant enzyme sulfiredoxin, and the hyper-oxidized protein PRX-SO3, a modulation not observed in control mice.

Conclusions: Based on the etiological role that early-life stressful experiences may have in the development of psychiatric disorders, our results support the idea that this may occur through the impairment of specific molecular systems crucial for a proper coping with challenging situations.