LONG-LASTING EFFECTS OF STRESS IN ADOLESCENCE: ANALYSES OF BEHAVIOURAL AND MOLECULAR ALTERATIONS IN AN ANIMAL MODEL OF SOCIAL ISOLATION

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The exposure to adverse events early in life is associated with long-lasting neurochemical, structural and behavioural changes that may enhance the vulnerability to mental disorders, such as major depression and schizophrenia. The pathologic outcome may depend upon the timing and duration of the adverse experience due to the differential impact on specific brain regions and circuits. Previous studies from our laboratory have shown that exposure to stress during gestation produces long-lasting alterations in the function of the HPA axis as well as defects of neural plasticity, which may be sustained by epigenetic mechanisms.

In the present study we investigated the effects of stress exposure during adolescence, a critical developmental period that, being characterized by intensive neural and behavioural changes, may be highly vulnerable to adverse events. We used social isolation, a well-established paradigm of stress for adolescent rats, in order to investigate the long lasting functional and molecular effects of this manipulation. We used 12 experimental litters of 10 pups each, comprising 5 males and 5 females. All pups were weaned at PND21 and housed either in group or individually until PND49, followed by re-socialization in groups of 3 rats per cage until adulthood. Animals underwent behavioural tests from PND70-80 and they were killed two weeks later.

In the sucrose preference test, aimed to investigate the presence of a depressive like phenotype, we observed a significant effect of both housing and gender ($p<0.001$). Isolated rats, both males and females, show a reduction of sucrose preference, as compared to their group-housed counterpart ($p<0.05$). However the cognitive performance of isolated rats was not different from control rats, as revealed in the novel object recognition test ($p>0.05$).

The preliminary results of the molecular analyses performed in the prefrontal cortex revealed that isolation in female rats caused a reduction of total Bdnf mRNA levels, as compared to group housed female animals ($p<0.05$). A similar effect was also found with respect to the pool of Bdnf transcripts with the long 3' UTR, which are preferentially targeted to dendrites.

In order to investigate if the stressful experience during adolescence may alter the ability to cope under a challenging condition, a group of rats (control or isolated) were exposed to a 1h-session of acute immobilization stress immediately before killing. We found that acute stress produced a significant up-regulation of the mRNA encoding for the activity regulated genes Arc and Zif 268 ($p<0.05$), an effect that was similar between group housed and isolated rats, suggesting that isolation rearing during adolescence does not impair the responsiveness of the prefrontal cortex under a challenging situation.

In summary, our results demonstrate that social isolation experienced during adolescence produce a depressive like phenotype, which is associated with a reduction in the expression of the

neuroplastic marker BDNF. Future and on-going analyses will try to establish the pattern of genetic changes that may sustain the behavioural impairment, including the possibility to delineate sex and anatomical specificity as a consequence of the adverse experience early in life.