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Prenatal Stress as a Risk Factor for Major Depression: an Investigation On Therapeutic Intervention with Antipsychotics and the Role of Social Stimuli During Periadolescence

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Introduction. Children exposed to adverse psychosocial experiences, or early parental loss, are at an increased risk for later depression. Preclinical data indicate that epigenetic regulation of gene expression mediates the effects of early life stress (ELS) on adult behavior and health. In addition to stress-responsive systems (glucocorticoids), the expression of neurotrophic factors in the brain may be regulated epigenetically in the context of ELS contributing to mental health, or systemic disease at adulthood. **Objectives**. In order to investigate epigenetic changes in target genes involved in the long-term effects of early adversity on psychopathology, we have set up an animal model (rat) of prenatal stress. **Results** show that ELS leads to a long-term down-regulation in the expression of target genes, such as the receptor for glucocorticoids and Brain derived neurotrophic factor (BDNF), thus mimicking adult conditions characterizing increased risk for psychopathology. Behavioral and neuroendocrine changes accompanying these differences in gene expression suggest increased stress responsivity, as well as impaired social behavior. Chronic treatment with the antipsychotic lurasidone during adolescence was able to counteract the changes in BDNF expression produced by ELS, preventing the down-regulation of long 3'-UTR BDNF levels that occurred from late adolescence into young adulthood. Furthermore, interaction with a non-stressed rat conspecific ameliorated behavioural dysfunction. **Overall** data indicate potential therapeutic targets to counteract prenatal stress and suggest that the perinatal environment can act as a potential buffer for stressful conditions occurring around birth. Support: ERA net-NEURON 'Poseidon" and Fondazione Cariplo 2012.

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