Nurturing nature : testing the three-hit hypothesis of schizophrenia

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Preface

Schizophrenia is a devastating mental disorder characterized by a hyperactive dopamine system and deregulated stress system. Human studies have suggested that the schizophrenia symptoms precipitate if a hyperactive dopaminergic genotype interacts with adverse life experiences that activate the stress system. To examine this gene-by-environment interaction, we exposed rats genetically-selected for enhanced apomorphine susceptibility to two stress-provoking life events, poor maternal care early-in-life, and isolation rearing later-in-life. This promoted the development of schizophrenia endophenotypes.

Our experiments involved two complementary steps:

First, we focused on the immediate endocrine adaptations to maternal separation in common rats. It is known that a single episode of prolonged maternal separation slowly increases corticosterone levels in the neonate rat. We discovered that if the pups had been previously exposed to maternal separation, this rise in corticosterone was abolished, suggesting that the pups had learned to predict the return of the dam. While readily adapting to repeated maternal absence, the pups, surprisingly, stayed alert and displayed a rapid response to an acute stressor. We then investigated whether pup's stress responsiveness was influenced by the context of maternal separation. It appeared that the experience of being kept in isolation in a novel environment during repeated maternal separation, rather than the maternal absence *per se*, caused priming of the amygdala fear pathway, with lasting consequences for the responsiveness of the neuroendocrine and behavioral stress system. These endocrine and behavioral alterations, caused by early-life stress experience, consisted of schizophrenia-like phenotypes.

Second, we sought to investigate the interplay of such early-life stress experience with schizophrenia genetic predisposition and/or later-life social stress experience. Thus, we were able to test the *three-hit* (*cumulative stress*) and the developmental *mismatch hypotheses*. The former states that exposure to early-life adversity and later-life psychosocial stressors, superimposed on genetic susceptibility, result in a severe schizophrenia-like phenotype. The latter proposes that experiences early-in-life program the developing brain in preparation for the future. In the case of genetically-predisposed apomorphine susceptible rats (*schizophrenia-susceptible*), we provide strong evidence for the *three-hit hypothesis*. In the case of the non-genetically selected Wistar rats, the *mismatch hypothesis* is supported since the outcome of early-life stress often negatively interacted with the pre-puberty social context.

In agreement with the *three-hit hypothesis* of schizophrenia, we conclude from the current experiments that early-life stress experience in interaction with highly reactive dopaminergic alleles, leads to amygdala priming that, together with additional stressors, precipitate schizophrenia.