Schizophrenia endophenotypes and stress hyper-reactivity co-precipitate following adverse life events in genetically susceptible rats.

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Introduction

- Schizophrenia is a mental disorder, with complex symptomatology, driven by genetic and environmental risk factors.
- The purpose of this study is to test the “three-hit hypothesis” of schizophrenia by examining the interaction between predisposing genes, early-life experience, and later-life environment.

Hypothesis

We test if, in genetically predisposed rats, neuroendocrine programming of the stress system by adverse early-life experience and later psycho-social stressors is necessary for precipitation of schizophrenia endophenotypes.

Approach

- Genetic predisposition (G): We have used rats of the pharmaco-genetically selected apomorphine-susceptible line (APOSUS), which are characterized by schizophrenia-like phenotypes. These animals display enhanced dopamine receptor reactivity and show resistance to glucocorticoids (i.e. corticosterone; CORT).
- Early-life experience (EE): Poor mother-pup interaction (i.e. % licking & grooming) was used as a marker of an adverse early-life experience causing epigenetically programmed enhanced stress responsiveness.
- Later-life environment (LE): Isolation rearing starting from adolescence was used as an unfavourable environment for late brain maturation, a condition known to produce sensorimotor gating deficits.

Conclusions

- Our data support the three-hit hypothesis of psychopathology: early-life adversity enhances vulnerability of the genetically predisposed APOSUS animals to a later psycho-social stressor resulting in a severe schizophrenia-like phenotype, provided central and peripheral stress reactivity is enhanced by stressful life events in the face of glucocorticoid feedback resistance.
- It is expected therefore that the analysis of aberrant glucocorticoid responsive genes in this model will reveal a novel susceptibility pathway and hence deliver possible novel targets for therapeutic intervention.