

TIME-DEPENDENT EFFECTS OF RISPERIDONE ON HIPPOCAMPAL NEUROGENESIS IN THE POLY I:C MODEL OF SCHIZOPHRENIA

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Introduction

Maternal infection during pregnancy enhances the risk of the offspring for schizophrenia. With the rat Poly I:C model it was successfully attempted to mimic this association in animals. In utero exposure to maternal infection leads in the offspring to postpubertal emergence of numerous behavioural (sensorimotor gating, attention deficit (disruption latent inhibition and rapid reversal learning), abnormal prepulse inhibition, hypersensitivity to amphetamine) and structural (enlarged ventricles, smaller hippocampi) abnormalities associated with schizophrenia (for review see ref. 1 and 2). These abnormalities were prevented when the offspring treated with neuroleptics in adolescence¹. We were interested in elucidating, if the observed reduction of offspring's hippocampal volumes might in part be due to a disturbed hippocampal neurogenesis, and if the administration of neuroleptics may be helpful in normalizing the putatively disrupted cell proliferation.

Material and methods

On gestational day 15 pregnant dams received Poly I:C (4mg/kg) or saline under isoflurane anesthesia. Between postnatal days 34 and 47 offspring of Poly I:C or saline dams received daily injections with risperidone (0.045mg/kg) or saline. BrdU was administered daily either between postnatal days 49 and 51 (group A) or considerably later (between postnatal days 77 and 79, group B). An additional group of off-

spring of poly I:C or saline treated dams were treated with BrdU prior to the preventive treatment, between postnatal days 34 and 36 and were decapitated 21 days thereafter (group C). All rats were sacrificed 21 days after the last BrdU application.

Results

Group C: In comparison to the offspring of saline treated rat dams, rat pups born to Poly I:C mothers showed a significantly reduced hippocampal neurogenesis. Group A and B: There was no statistically significant difference of BrdU labeled hippocampal cells between the offspring of Poly I:C and saline rat dams. Administration of risperidone increased the proliferation rate in the offspring of both saline and Poly I:C mothers. The effect of risperidone was stronger immediately after the treatment (group A) comparing with the effect seen a month after treatment cessation (group B).

Discussion

We found that Poly I:C treatment of pregnant rat dams reduces the hippocampal neurogenesis in juvenile rats. This is in accordance to findings of others³ and might in part explain the reduced hippocampal sizes of the offspring. Since neuroleptic treatment has been reported to increase cell proliferation/cell survival⁴ we had expected that risperidone treatment would show a beneficial effect and normalize the reduced neurogenesis in Poly I:C offspring. As expected, risperidone

administration increase neurogenesis in both groups. However, the effect of risperidone was less efficient a month after treatment cessation.

Our data show again that poly I:C induce a decrease in increase neurogenesis in juvenile and not adult rats. Increase neurogenesis during adolescence period can be one part of the mechanism by which risperidone prevents the postpubertal emergence of both behavioral and brain schizophrenia-like abnormalities.

References

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