Maternal immune activation leads to age-related behavioral and immunological changes in male rat offspring – the effect of antipsychotic drugs

Agnieszka Basta-Kaim¹, Ewa Szczêsny¹, Monika Leœkiewicz¹, Katarzyna Głombik¹, Joanna Ślusarczyk¹, Bogus³awa Budziszewska¹, Magdalena Regulska¹, Marta Kubera¹, Wojciech Nowak², Krzysztof Wêdzony³, W³adys³aw Lasoñ¹

¹Department of Experimental Neuroendocrinology, Institute of Pharmacology, Polish Academy of Sciences, Smępna 12, PL 31-343 Kraków, Poland
²Faculty of Medicine, Jagiellonian University, Medical College, Św. Anny 12, PL 31-008 Kraków, Poland
³Laboratory of Pharmacology and Brain Biology, Institute of Pharmacology, Polish Academy of Sciences, Smępna 12, PL 31-343 Kraków, Poland

Correspondence: Agnieszka Basta-Kaim, e-mail: basta@ii-pan.krakow.pl

Abstract:
Background: Prenatal immune system disturbances have been postulated to play an important role in pathogenesis of schizophrenia and related disorders. In the present study, we sought to answer the question whether behavioral changes in the neurodevelopmental model of schizophrenia in rats are accompanied by alterations in proliferative activity of splenocytes and pro- and anti-inflammatory cytokine levels. Furthermore, the effects of two antipsychotic drugs on these parameters were determined.

Methods: Lipopolysaccharide (LPS) was administered subcutaneously to pregnant dams at a dose of 1 mg/kg every second day from the 7th day of pregnancy till delivery. Age-dependent behavioral and immunological changes were studied when control and prenatally LPS-pretreated offspring male rats were 30 and 90 days old. Chlorpromazine (10 mg/kg ip) or clozapine (10 mg/kg ip) was administered chronically (21 days) after behavioral verification to 3 months old offspring males. Changes in sensorimotor gating (prepulse inhibition, PPI), mitogen-induced proliferative activity of splenocytes ([³H]-thymidine incorporation) and cytokine levels (ELISA) were measured.

Results: Prenatally LPS-pretreated rats showed PPI deficit only at 90 but not at 30 days of age, whereas an enhancement of mitogen-stimulated proliferative activity of splenocytes was observed in both time points. Additionally, the level of proinflammatory cytokines (IL-1β, IL-2, IL-6, TNF-α) in prenatally LPS-pretreated rats was enhanced when they were 30 days old and remained elevated in 90 days old offspring. No changes in IL-10 level were observed. Chronic administration of chlorpromazine or clozapine reduced the deficit in PPI deficit in prenatally LPS-treated rats. In the used model, chlorpromazine normalized both T and B lymphocyte proliferation, whereas clozapine B lymphocyte activity only. Moreover, both antipsychotics modulated the enhanced levels of IL-1β, IL-2 and TNF-α in the offspring of LPS-treated mothers.

Conclusions: This study indicates that in LPS-evoked model of schizophrenia, peripheral immunological changes are long-lasting and precede behavioral deficit. The disturbances in T cell-mediated immunity as well as cytokine production were attenuated by antipsychotic drug administration.

Key words: schizophrenia, chlorpromazine, clozapine, proliferative activity of splenocytes, cytokines