DISSECTING THE CONTRIBUTION OF PRENATAL FEVER AND HYPOFERREMIA INDUCED BY TURPENTINE IN THE DEVELOPMENT OF SCHIZOPHRENIA-LIKE BEHAVIOURS

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**Background.** Maternal infection or inflammation during the first 2 trimesters of human pregnancy is associated with greater incidence of schizophrenia (SCZ) in the adult offspring. Interleukin-6 (IL-6), a pro-inflammatory cytokine released during infection/inflammation, is thought to play a central role. IL-6 is fundamental in the induction of fever and of a decrease in the circulating levels of non-heme iron (hypoferrremia) in the mother, which is the source of iron for the fetus. Both fever and hypoferrremia may result in alterations in neurodevelopment, leading to increased risk of SCZ. We investigated the role these two factors on the effects of a prenatal aseptic inflammatory insult with turpentine oil (TURP) in an animal model. **Procedure.** To elicit an inflammatory response in pregnant rats at gestational day (GD) 15, we injected i.m. 100 µL of TURP or saline (SAL) as control. Body temperature (BT) was recorded 0, 8, 10 and 24 h after. One batch of dams was sacrificed 11 h after injection and blood was collected for circulating IL-6 and iron determination. Another batch of dams was allowed to give birth and the adult (60 days old) offspring were analyzed for pre-pulse inhibition (PPI) of acoustic startle and acute amphetamine (AMPH)-induced locomotion [2 mg/kg of body weight (BW)]. In a third batch of dams, SAL and TURP were co-administered with iron-dextran (1 daily i.p. injection of 20 mg/kg of BW from GD 15 to 18), in order to test the effect of hypoferrremia. Behavioral responses of the offspring were correlated with maternal fever to investigate whether a link exists between these variables. **Results.** TURP treatment induced a significant febrile response in the GD 15 mothers, with a peak of 38.03 °C at 10 h, which receded within 24 h. This response was accompanied with a 6-fold rise in circulating IL-6 levels and a decrease in serum iron levels (from 246±30 in SAL to 82± 11 µg/dL in TURP). In the adult offspring, those animals whose mothers were treated with TURP presented a deficit in PPI but no changes in the response to a single injection of AMPH. Interestingly, maternal BT at the peak of fever significantly correlated with PPI ($r^2=0.39$, $p<0.05$) and locomotion after AMPH ($r^2=0.7$, $p<0.01$). Finally, PPI deficits induced by TURP were reversed by prenatal iron co-treatment. **Conclusions.** Our correlation analyses suggest that maternal fever may contribute to the development of behavioral alterations in the adult offspring, as well as reduced iron supply.