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A Link Between Preeclampsia and Psychiatric Disorders: a Behavioral Analysis in an Animal Model of Intrauterine Hypoxia

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Introduction: The association between preeclampsia (PE), known as a disorder of pregnancy characterized by the onset of systemic arterial hypertension, and the promotion of neurodevelopmental disorders has been hypothesized by several studies. Indeed, it is believed that multifactorial psychiatric conditions may arise after a compromised anatomical and functional brain development due to low oxygen levels. However, a solid relation between intrauterine hypoxia and potential subsequent neurodevelopmental deficits remains unknown. Therefore, studies in animal models of PE become essential for understanding this specific cause and effect from a behavioral perspective. The aim of this study was to evaluate behavioral alterations in 2-month-old (P60) male rats from females Wistars treated with L-NAME, a hypertensive agent that inhibits nitric oxide synthase (NOS). In addition, we sought to identify a possible protective effect of Sildenafil Citrate (CS), a potent vasodilator, against PE.

Methodology: Firstly, pregnant female Wistar rats were treated by gavage, daily, from the 1st to the 18th day of pregnancy (DP) with L-NAME (50 mg/kg) and with CS (10 mg/kg) from the 7th to the 18th DP. Control animals were treated with similar volumes of pure water. The pups were then divided accordingly: 1) Control; 2) L-NAME; 3) CS; 4) L-NAME+CS. The behavioral tests were performed in P60 animals; the male rats were subjected to open field, social interaction, sucrose preference and contextual fear conditioning tests. The results were analyzed by *One Way* ANOVA with Bonferroni's *post-hoc.* Data are presented as mean ± SD (in % of Control group).

Results: As expected, the SBP (Systolic Blood Pressure) was significantly elevated in L-NAME treated rats than in controls (149.40 ± 15.45 *versus* 100.40 ± 2.37, $p<0.0001$). Still, it was possible to notice a reduction in SBP after the concomitant administration of L-NAME and CS in comparison to L-NAME group (117.00 ± 17.79 *versus* 149.40 ± 15.45, $p<0.0001$). No significant differences were verified among all groups evaluated in the open field or social interaction tests ($p>0.05$). However, the L-NAME group showed a decrease in sucrose preference test (64.12 ± 10.98, $p<0.05$). Lastly, the results of contextual fear conditioning test pointed towards a reduction in freezing time in L-NAME animals in comparison to the Control group (33.89 ± 33.96 *versus* 193.00 ± 122.00, $p<0.01$).

Discussion: L-NAME administration induces an increase in SBP that possibly can lead to intrauterine hypoxia and may explain anhedonia and cognitive impairments observed in preeclampsia-like rats. Curiously, such phenotypes are important features of several neurodevelopmental disorders, like Intellectual Disability, Autism Spectrum Disorder and Attention Deficit Hyperactivity Disorder, as well as the prodromal phase of Schizophrenia. Our study also indicates that CS administration reverses part of the behavioral alterations observed after PE.

Conclusion: Increased SBP during pregnancy promotes intrauterine hypoxia, which seems to be a crucial factor in triggering behavioral alterations that are consistent with neurodevelopmental disorders.

Keywords: L-NAME; Preeclampsia; Psychiatric disorders.