STRESS REGULATES GLUCOCORTICOID-RESPONSIVE GENES EXPRESSION IN PREFRONTAL CORTEX BY ALTERING DNA METHYLATION: IMPLICATION FOR LURASIDONE TREATMENT

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Introduction: Stress represents one of the main factors that contribute to the development of mental illness. Recently, epigenetics has been hypothesized as a potential mechanism by which environmental factors can contribute to psychiatric disorders, including major depression. In particular, DNA methylation can result in long-lasting changes that may modulate neurobiological processes, as well as the neuroendocrine systems. Hence, the purpose of our study was to investigate the effect of chronic stress exposure on the functional activity of the hypothalamic pituitary adrenal (HPA) axis, by focusing on the DNA methylation of genes containing the glucocorticoid responsive element (GRE), namely Gadd45b, Sgk1and Gilz. Furthermore, we evaluated the long-lasting effect of prolonged stress after a period of recovery. In this scenario, we assessed the possible role of the pharmacological intervention with the multimodal antipsychotic lurasidone (LUR) in modulating the epigenetic alterations induced by stress.

Material and methods: Adult male rats were exposed to 7weeks of chronic mild stress (CMS) and treated with lurasidone (3mg/kg/day) starting from the second week of stress for the five subsequent weeks. Another batch of animals was exposed to 4weeks of chronic restraint stress (CRS), treated with LUR starting from the second week of stress while continuing the CRS procedure and then left undisturbed in the homecage for other 3weeks. Gene expression and DNA methylation analyses were conducted in rat prefrontal cortex, a brain area mainly involved in stress response.

Results: CMS produced a downregulation of the expression of Gadd45b and Gilz, whereas Sgk1mRNA levels were not altered by stress exposure. LUR normalized the stress-induced alteration of Gadd45b. The reduction of Gadd45b at transcriptional level was sustained by alterations at epigenetic level. Indeed, chronic stress induced an increased DNA methylation specifically in the GRE, effect that was reversed by chronic LUR treatment. By contrast, Gilz and Sgk1methylation was not altered either by CMS or by the pharmacological treatment.
Furthermore, stress has long-lasting consequences on the expression of these genes. Indeed, after a period of washout from stress, Gadd45b and Gilz were still downregulated, while no changes were observed for Sgk1. LUR was able to normalize only the reduction observed on Gilz expression. According to the persistent effect of the stress on the mRNA levels, after the washout, the CGs in the GRE of Gadd45b and Sgk1were hypermethylated in stressed rats in comparison to control animals. Interestingly, lurasidone treatment was not able to counteract the modulations induced by stress at methylation level.

Discussion and conclusion: Our results indicate that chronic stress mainly affects the expression and the methylation status of Gadd45b, effects that are prolonged over time. In conclusion, these data highlight that stress exposure leads to persistent changes in DNA methylation of specific genes related with glucocorticoids signaling, even after a period of washout, and that lurasidone acts as a modifier of such mechanisms, pointing out its potential properties as "epigenetic modulator".