INFLUENCE OF CHRONIC STRESS EXPOSURE ON COGNITIVE PERFORMANCE: A ROLE FOR GLUCOCORTICOID RECEPTORS

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Psychiatric diseases are characterized by an altered function of the HPA axis. Moreover, the activation of this system is also involved in learning and memory processes and its deregulation may underline the development of cognitive deficits. Corticosteroids, in the brain, activate two types of receptors: the glucocorticoid receptors (GR) and the mineralocorticoid receptors (MR) through different ways. The nuclear receptors modulate genes transcription while membrane-associated receptors are involved in the release of neurotransmitters such as glutamate.

On these bases, this study focused on the effects of chronic mild stress (CMS) exposure on the genomic vs non genomic activity of GR and MR in the dorsal hippocampus, a brain area involved in cognitive functions. We also investigated the influence of CMS on the cognitive performance thought the exposure to the novel object recognition (NOR) test.

Wistar rats were exposed to CMS for 7 weeks and the sucrose consumption test was performed at weekly intervals. At the end of the CMS, all the animals were exposed to NOR. All the molecular analysis was performed in the dorsal hippocampus. The analysis of mRNA levels of GR responsive genes was carried out by Real-Time PCR, whereas Western blot was used to conduct protein analyses of MR, GR, FKBP5 and SYNAPSIN-Ia/b.

Animals exposed to CMS develop an anhedonic phenotype, as indicated by the reduction of sucrose intake ($p<0,001$ vs No stress, Student's t test) as well as an impairment in the cognitive performance assessed in the NOR test ($p<0,01$ vs No stress, Student's t test). At molecular level, CMS per sè increased the protein levels of GR (+70%, $p<0,01$ vs No stress; Student's test) in the membrane compartment, effect that was paralleled by an up-regulation of the phosphorylation in Ser603 of the SINAPSYN Ia/b (+130%, $p<0,05$ vs No stress/Naive, two way ANOVA with Fisher PLSD). Differently, NOR test exposure induced a significant increase of GR protein levels (+87%, $p<0,01$ vs No stress/Naive, two way ANOVA with Fisher PLSD) in the nucleus, specifically in no stress rats. Accordingly, this increase mirrored an upregulation of the transcriptional activity of GR as demonstrated by the effect observed on Gadd45 and SGK-1 mRNA levels (+41%, $p<0,001$; +47%, $P<0,001$ vs No stress/Naïve, two way ANOVA with Fisher PLSD). No significant effects were observed in the cytosol for GR and in all the cellular fractions investigated for MR.

These findings suggest that the activation of the genomic pathway mediated by GR is fundamental for the correct cognitive performance, while chronic stress exposure induces a behavioral deficit probably interfering with this mechanism. This failure to activate GR in stressed rats might be indicative of the so-called "glucocorticoid resistant" a key feature of depressed patients. Moreover, CMS, increasing the availability of GR at membrane levels, seems to direct preferentially the action of hormones more towards the non-genomic pathways.