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MULTIOMIC PROFILING OF RAPID ANTIDEPRESSANT MECHANISMS IN A RAT MODEL OF DEPRESSION

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Background: The stress response is a physiological event finely orchestrated by the brain and aimed at restoring the homeostasis lost in case of environmental changes perceived as dangerous for survival. Most subjects successfully activate an adaptive stress response however, when the exposure to stressful stimuli is prolonged over time or overwhelming, some individuals may fail in activating coping strategies. This condition refers to stress vulnerability and increases the risk of developing systemic diseases, particularly psychiatric disorders. Accordingly, stress is considered a key risk factor in the onset of depression, and most preclinical models of psychopathologies are based on the exposure of animals to validated stress protocols [1]. Chronic Mild Stress (CMS) is one of the most widely used animal models of depression to study both etiopathogenetic and antidepressant mechanisms. Recently, the NMDA receptor antagonist ketamine has emerged as the first rapid-acting antidepressant drug effective in patients with treatment resistant depression (TRD) [2]. The study of the mechanisms underlying ketamine antidepressant response are crucial to identify the molecular underpinnings of the rapid antidepressant effect, thus making a step forward in the development of novel antidepressants.

Aims & Objectives: The aim of the study was to draw a multiomic picture of rapid antidepressant mechanisms in the hippocampus of an animal model of depression.

Methods: Male rats were exposed to CMS for 5 weeks, sucrose preference test was used to measure the anhedonic phenotype and acute subanesthetic ketamine (10 mg/kg) was intraperitoneally injected 24 h before sacrifice [3]. Sucrose preference test was used to classify the rats stress resilient and vulnerable and ketamine responder/non-responder. The hippocampi were collected to obtain DNA, RNA, and protein extracts (both total extract and synaptic terminals). Genome-Wide DNA methylation was assessed by RBBS, transcriptional changes were evaluated by RNA-seq analysis, and DIA-PASEF label free analysis was used for proteomics. Bioinformatic enrichment analysis was performed with WebGestaltR v.4.0.3 and the Gene Set Enrichment Analysis (GSEA) method.

Results: Starting from 3 weeks of CMS, stress vulnerable rats developed depressive-like behavior. Acute ketamine induced antidepressant-like behavior in most of the animals but some of them (about 30%) were non-responders remaining anhedonic. Our omic analyses revealed several effectors differentially regulated among the groups (FDR<0.05). Enrichment analysis showed differences between control and vulnerable rats and between ketamine responders and non-responders particularly in pathways involved in synaptic plasticity.

Discussion & Conclusion: Overall, our results highlighted several pathways affected by stress and potentially involved in the rapid antidepressant effect of ketamine. Future studies will better elucidate how these changes may contribute to ketamine antidepressant mechanism of action and resistance.

References

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