S164. GABAergic Dysfunction in the Chronic Mild Stress Model: Modulation by Lurasidone Treatment

Andrea Carlo Rossetti[1], Maria Serena Paladini[1], Paola Brivio[1], Giulia Sbrini[1], Mariusz Papp[2], Francesca Calabrese[1], Raffaella Molteni[1], and Marco Riva[1]

[1]University of Milan, [2]Institute of Pharmacology, Polish Academy of Sciences

Background: Exposure of rats to chronic stress is able to produce functional alterations that are associated with different psychiatric disorders, which may be target of pharmacological intervention. The aim of the present study was to investigate the ability of a chronic treatment with lurasidone in normalizing the behavioral and molecular changes produced by chronic mild stress (CMS) in rats.
Methods: Adult male Wistar rats were exposed to CMS for 2 weeks and sucrose consumption was used to identify rats that were susceptible to the manipulation. Control and CMS-susceptible rats were then randomized to receive chronic vehicle or lurasidone (3 mg/kg/day) for 5 more weeks, while continuing the stress procedure (n¼10/experimental group). Animals were tested for anhedonia and for cognitive impairment before being sacrificed for the dissection of brain regions to be used for the molecular analyses.
Results: CMS produced a significant reduction of sucrose intake (-49%, $p<0.001$) as well as cognitive impairment, which were normalized by chronic lurasidone treatment. Rats exposed to CMS also display a significant reduction of parvalbumin expression in dorsal hippocampus (-58%, $p<0.001$), an effect that was associated with a dysregulation of redox mechanisms. Interestingly these abnormalities were counteracted by chronic lurasidone administration.
Conclusions: Our results demonstrate that exposure to CMS produces functional and molecular alterations, which are relevant for different 'domains' of psychiatric disorders. We show that lurasidone treatment is capable of normalizing such changes and may therefore promote resilience toward adverse environmental conditions, such as stress, which represents a major vulnerability element in the etiology of mental illness.

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