Regulation of clock gene expression in the chronic mild stress model: modulatory activity of the novel drug lurasidone

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Disruptions in biological rhythms are known to be associated with mood disorders. This has led to hypothesize that abnormalities in the molecular clock may contribute to the development of these disorders and normalization of these changes may be important for therapeutic efficacy. The cellular clock is a transcriptional-translational feedback loop involving a number of different genes that may possess separate functions in circadian rhythms and mood regulation. While this machinery has been extensively characterized in the suprachiasmatic nucleus, little is know on the role exerted by individual clock genes in other brain structures, such as hippocampus and prefrontal cortex, which are important for mood disturbances. In the present study we have employed the chronic mild stress (CMS) model of depression in order to establish if possible alterations in the expression of clock gene machinery in hippocampus and prefrontal cortex.

Male Wistar rats were exposed to CMS for 2 weeks and sucrose consumption was used to distinguish between susceptible and non-susceptible animals. Control and CMS-susceptible rats were then randomized to receive chronic vehicle or the novel multi receptor drug lurasidone (3 mg/kg/day) for 5 more weeks, while continuing the stress procedure, in order to evaluate the ability of chronic drug treatment to normalize the phenotype associated with CMS.

Our data show that the mRNA levels for Per1 and Per2 are significantly down-regulated in the prefrontal cortex of CMS rats, and this is associated with a slight up-regulation of Bmal1 expression. No changes were found for Clock mRNA levels, whereas a small reduction was found for Cry2 expression. Interestingly, chronic treatment with lurasidone, which per se produced limited changes on clock gene mRNA levels, was able to normalize the molecular changes induced by stress exposure. The modifications of Per1 and Per2 expression after exposure to CMS appear to be anatomically selective, since we did observe similar changes in dorsal or ventral hippocampus.

We believe that changes in clock gene expression as a consequence of CMS exposure may contribute to the disturbances associated with mood disorders and may bridge circadian abnormalities with neuronal function in critical brain regions. With this respect, the ability of chronic lurasidone to modulate clock gene expression in association with its ability to normalize the anhedonic phenotype in CMS rats provide further support to its therapeutic properties in ameliorating functions that are deteriorated in patients with major depression and stress-related disorders.