Genome-wide analysis of LPS-induced inflammatory response in the rat ventral hippocampus: modulatory activity of chronic treatment with the antidepressant agomelatine

A.C. Rossetti[1], M.S. Paladini[1], G. Racagni[1], M.A. Riva[1], A. Cattaneo[2,3], R. Molteni[1]

[1]Dept. of Pharmacological and Biomolecular Sciences, University of Milan, Milan (Italy)
[2]IRCCS Centro San Giovanni di Dio, Fatebenefratelli, Brescia (Italy)
[3]Dept. of Psychological Medicine, Institute of Psychiatry, King's College London, London (UK)

Given the large body of clinical and preclinical evidence suggesting that the activation of the immune/inflammatory system may contribute to depression pathogenesis [Dantzer et al. 2008], several studies mainly focused on pro-inflammatory cytokines reported that antidepressant drugs have immunoregulatory effects in humans as well as in animals [Janssen et al. 2010]. In this context, we have previously demonstrated that the antidepressant agomelatine attenuated the inflammatory response induced by a systemic injection of lipolysaccharide (LPS) in the rat by acting on specific components of the immune/inflammatory system [Molteni et al. (2013)]. However, it is important to consider the complexity of the inflammatory response, which implies the integration of different mechanisms triggered by various systems. Accordingly, the aim of the present work was to assess the anti-inflammatory properties of chronic agomelatine treatment with an unbiased genome-wide approach by using the well-established microarray technique.

Adult male Sprague-Dawley rats received agomelatine (40 mg/kg, p.o.) or vehicle for 21 days before being challenged with an acute injection of LPS (250 µg/kg; i.p.) or saline 16 h after the last drug administration. Animals were sacrificed 2 h after the immune challenge and the ventral hippocampus was dissected and processed for RNA extraction. Transcriptomic analysis was performed using Affymetrix® Rat Gene 2.1 ST Array and the results were analyzed with Partek Genomics Suite for data visualization and statistical testing and with Ingenuity Pathway Analyses (IPA) software to identify the associated canonical pathways.

We found that the administration of LPS induced the transcription of 284 genes mainly associated with pathways related to the inflammatory system such as those involved in the interferon signaling, acute response phase to infections and IL-6 pathway. Conversely, chronic treatment with agomelatine modulated 105 transcripts belonging to different signaling pathways in saline-treated rats. Among them, the pathway of the phospholipase C (PLC) that is also activated by other antidepressants, and the pathway of the chemokine receptor CXCR4, which may contribute to potential neuroprotective and anti-inflammatory effects of this drug. Moreover, from the total 296 transcripts found significantly modulated in the animals treated with agomelatine and challenged with LPS, the antidepressant was able to prevent the LPS-induced modulation of 91 genes with respect to the control group and of 52 genes with respect to animals treated only with LPS. An intersection analysis between these two lists of genes led to the identification of some transcripts induced by LPS on which the pharmacological pre-treatment with agomelatine has the larger effect of normalization.

In summary, by using a genome-wide approach, we have highlighted the transcriptional profile of a chronic treatment with agomelatine in the rat ventral hippocampus both in basal condition -identifying genes and pathways related to its antidepressant effect- and in condition of acute inflammation -identifying genes and pathways associated to its anti-inflammatory properties. These genes might represent attractive candidates for studies aimed to establish their potential role as new targets for pharmacological intervention of depression associated to inflammation.

Dantzer et al. (2008) *Nat. Rev. Neurosci*. 9 46-56.
Janssen et al. (2010) *Hum. Psychopharmacol*. 25, 201-215.
Molteni et al. (2013) *Eur Neuropsychopharmacol,* 23**,** 1645-55.