

**Title:** Effect of the antidepressant agomelatine on the inflammatory response induced by lipopolysaccharide: a genome-wide study in the rat ventral hippocampus

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**Abstract:** Growing evidence suggests that the activation of the immune/inflammatory system may be associated with depression pathogenesis and, in line with this observation, several studies mainly focused on pro-inflammatory cytokines reported that antidepressant drugs have immunoregulatory effects. However, given the complexity of the inflammatory response, which implies the integration of different mechanisms triggered by various systems, the aim of the present work was to assess the anti-inflammatory properties of the antidepressant agomelatine with an unbiased genome-wide approach by using the microarray technique. Specifically, we analyzed the gene expression profile of the ventral hippocampus, a cerebral area relevant for depression, of adult rats chronically treated with the antidepressant before to receive a systemic injection of lipopolysaccharide (LPS) in comparison with animals treated with saline. To this aim, adult male Sprague-Dawley rats received agomelatine or vehicle for 21 days before being challenged with an acute injection of LPS 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® Array and the results were analyzed with Partek Genomics Suite and with Ingenuity Pathway Analyses software. We found that LPS administration induced the transcription of 284 genes mainly associated with pathways related to inflammation. Conversely, chronic treatment with agomelatine alone modulated 105 transcripts belonging to different pathways in saline-treated rats, like the phospholipase C and the CXCR4 pathways. Moreover, the drug 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 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 both at basal state - identifying genes and pathways related to the basal effects of the antidepressant- and in condition of acute inflammation - identifying genes and pathways associated to its anti-inflammatory properties. These genes/pathways might represent potential new targets for pharmacological intervention of depression associated to inflammation.

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