Chronic agomelatine reverses corticolimbic transcriptome changes induced by corticosterone in a neuroendocrine model of depression

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INTRODUCTION

Agomelatine, is an antidepressant with agonistic action of melatoninergic receptors 5-HT1~7 and antioxidative properties at 5-HT1~7 receptor (de Bodinat et al., 2007). It has demonstrated efficacy in major depressive disorders in several clinical trials (Goodwin, 2009). Furthermore, numerous preclinical studies indicated that agomelatine showed antidepressant and anxiolytic-like effects on animal behavior in various animal models (Papp et al., 2001). El-Fouad et al. (2011) notably in a neuroendocrine model of depression, because chronic corticosterone administration, we observed that antidepressant and anxiolytic-like effects were associated with normalization of dark/light ratio of home-cage activity and reversal of hippocampal neurogenesis deficits induced by corticosterone in adult mice (Rainer et al., 2011). Here, in a similar manner to the study of Surget et al. (2009) looking at chronic corticoid stress and reversal effects of chronic antidepressants treatment on gene expression in corticolimbic regions of the mouse brain, we investigated at transcriptome effects of chronic corticosterone administration in brain regions involved in mood regulation (dorsal & ventral hippocampus, amygdala, cingulate cortex), and the reversal effects of chronic agomelatine administration in these regions.

Here, we show that corticosterone induces gene expression changes that are brain region-specific and that agomelatine reverses the CORT-induced transcriptome profile in a region-specific and state-dependent manner.

MATERIALS AND METHODS

Animals: Male C57BL/6J mice from Janvier Labs (Dominot), 9-10 weeks old, were used in these experiments.

Drugs and treatment: Corticosterone (5mg COR/T g body wt.) or saline (0.9% NaCl) were injected intraperitoneally (IP) at time 0, 1.5 and 48h. The mice were sacrificed at the end of 72h. The mice were housed in cages with access to food and water ad libitum. The animals were handled according to the guidelines for animal care and use of the Institutional Animal Care and Use Committee. The experimental procedures were conducted in accordance with the National Institutes of Health guidelines for the care and use of laboratory animals.

Behavior analysis: Four commonly used behavior tests: Open Field Test, Novelty Suppressed Feeding (NF), Forced Swim test (FST) and Tail suspension test performed as previously described (Rainer et al., 2011) were used to measure components of animal emotionality. Z-score methodology was used to investigate the potential of combining results within and across the different behavioral tests for discriminative-like behaviors and investigate the treatment effects on the CORT model (Guilloux et al., 2011).

Tissue collection: At sacrifice, total RNA was isolated from frozen tissue samples using the TRIzol reagent (Invitrogen, USA). RNA quality was assessed using a Bioanalyzer and only samples with a RNA Integrity Number (RIN) > 7.0 were used in the analysis.

Microarray experiment: Gene expression profiling analysis was performed using three Mouse GeneChip Nigro Microarray (G4124A) Agilent Technologies, USA. The comparison between samples was performed in a direct way. 1 ul of RNA was labeled using the LSI Profiler kit, Cy3-Cy5 for all samples and internal standards came from RNA Spike-in kit Agilent Technologies, USA. All samples were run in duplicates and evenly distributed on slides to avoid any batch effect. After washing, slides were scanned with a DNA Array Scanner Agilent Technologies, USA.

Data analysis: Gene expression in each corticolimbic brain area and the concordance across brain regions were analyzed by identifying CORT and antidepressant effects, unpaired T-student test was performed to investigate the CORT and antidepressant reversal effects within each brain area and to assess the concordance among treatments. To identify effects, the comparison between pairs of groups and genes were significantly differentially expressed with the following criteria: p-value < 0.05 and absolute changes > 1.0.

REFERENCES


BEHAVIORAL STUDY

Corticosterone-induced high emotionality is decreased by chronic agomelatine treatment

Here we show that corticosterone induces high emotionality, as evidenced by increased time spent in boundary zones, and reduced time spent in the center of the open field paradigm. Agomelatine significantly reduced the time spent in boundary zones, and increased the time spent in the center, compared to vehicle-treated mice. In the novel suppressed feeding paradigm, corticosterone administration significantly increased the latency to feed induced by corticosterone treatment, with no effect on vehicle-treated mice. Chronic agomelatine administration reversed this corticosterone-induced increase in latency to feed, and the effect was evident in vehicle-treated mice. In the forced swim test, corticosterone administration increased the immobility duration in both vehicle and corticosterone-treated mice. Agomelatine significantly decreased immobility compared to vehicle-treated mice. Additionally, in all tests, agomelatine significantly reversed the corticosterone-induced increase in immobility duration in both vehicle and corticosterone-treated mice.

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