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CHRONIC AGOMELATINE ADMINISTRATION MODULATES NEURONAL PLASTICITY MARKERS IN THE RAT PREFRONTAL CORTEX, HIPPOCAMPUS AND AMYGDALA

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Neuronal plasticity alterations including cytoskeletal dynamics and synaptic markers have been recently associated with the treatment of major depression. Here we investigated the effects of agomelatine, a novel antidepressant with melatonergic (MT_1/MT_2) agonist and 5-HT_{2C} receptor antagonist properties, on cytoskeletal microtubular proteins and synaptic markers in the rat hippocampus, prefrontal cortex (PFC) and amygdala.

Adult male Sprague Dawley rats received daily i.p. administration of hydroxyethylcellulose 1% (vehicle) or agomelatine (40mg/kg) for 22 days. The rats were then sacrificed and hippocampi, PFC and amygdala dissected for analyses of microtubule dynamics markers (Tyr/Glu-Tub, Delta2-Tub and Acet-Tub) and synaptic markers (synaptophysin, PSD-95 and spinophilin) by Western blot.

In the PFC, agomelatine decreased Tyr/Glu-Tub and the neuronal-specific Delta2-Tub, suggesting decreased microtubule dynamics. In contrast, in the hippocampus Tyr/Glu-Tub and Delta2-Tub were increased, indicative of enhanced microtubule dynamics. A similar pattern to those seen in the hippocampus, but of higher magnitude, was observed in the amygdala where an important increase of Tyr/Glu-Tub accompanied by a decrease of the stable form Acet-Tub was observed. These findings were paralleled by decreased hippocampal spinophilin (dendritic spines marker), increased synaptophysin (pre-synaptic marker) and spinophilin in the PFC and amygdala and increased PSD-95 (post-synaptic marker) in the amygdala, all consistent with synaptic remodelling phenomena.

Taken together, these data shown that chronic agomelatine induces a differential modulation of microtubule dynamics and synaptic markers in the rat hippocampus, PFC and amygdala. These findings may have a particular relevance considering the fundamental role of these three brain areas in depression.

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