Fluoxetine counteracts the opposite effects of stress and enrichment on the inflammatory response and microglial status

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Accumulating evidence demonstrated that the quality of the living environment is among the most relevant factors in determining the onset of major depression. In addition, clinical and preclinical studies have shown that the outcome of an antidepressant treatment with SSRI is also influenced by environmental factors [1]. Microglia, the resident immune cells of the brain, have recently attracted a lot of interest in the field of biological psychiatry. The immune system, and microglia cells, are exquisitely sensitive to environmental changes. These cells being equipped with receptors for a plethora of molecules can sense environmental changes and adjust brain function accordingly [2- 3].

Although the role of molecular and cellular components of the immune system in the etiology and treatment of depression is now well recognized, data on the effects of antidepressants treatment on markers of inflammation are somewhat contradictory.

Based on the assumption that this may depend on environmental variables, we treated adult C57BL/6 mice previously exposed to chronic unpredictable stress with fluoxetine or vehicle (21 days) while being exposed to either an enriched or a stressful condition.

We measured the effects of fluoxetine on the expression of pro- and anti-inflammatory-related genes in the whole hippocampus and in isolated microglia from stressed or enriched mice

receiving either vehicle or fluoxetine. In the same experimental conditions we determined microglial density, distribution, and morphology to investigate their surveillance state.

We already showed that mice treated with fluoxetine in an enriched condition overall improved their depression-like phenotype compared with controls, whereas those treated in a stressful condition showed a distinct worsening. Here we demonstrate that the effects of fluoxetine treatment on inflammation and microglial function, as compared to vehicle, were dependent on the quality of the living environment. Specifically, fluoxetine administered in the enriched condition increased the expression of pro-inflammatory markers compared to vehicle, while treatment in a stressful condition produced anti-inflammatory effects.

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