

## **Beneficial and adverse consequences of increased brain plasticity: the interplay between the serotonergic system and quality of the environment**

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Selective serotonin reuptake inhibitors (SSRI), whose mechanism of action consists in blocking the serotonin transporter and increasing extracellular serotonin levels, are the most commonly used treatment for major depression. However, their efficacy is variable and incomplete. A recent hypothesis posits that the increase in serotonin levels induced by SSRI may not affect mood per se, but enhances neural plasticity and, consequently, renders the individual more susceptible to the influence of the environment. Thus, SSRI administration in a favorable environment would lead to a reduction of symptoms, while in a stressful environment might lead to a worse prognosis. To test this hypothesis, we chronically treated C57BL/6 adult male mice with fluoxetine while exposing them to either (i) an enriched or (ii) a stressful condition. Anhedonia, brain BDNF and corticosterone levels, considered endophenotypes of depression, were investigated. In an enriched environment, treated mice improved their depression-like phenotype compared to controls while, in a stressful environment, treated mice showed a more distinct worsening. Our findings suggest that the effect of SSRI on depression-like phenotypes in mice is not determined by the drug per se but is induced by the drug and driven by the environment.

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