

Beneficial and Adverse Consequences of Increased Brain Plasticity: the Interplay Among Serotonin, Susceptibility to the Environment and Depression

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Antidepressants represent the standard treatment for major depression. However, their efficacy is variable and incomplete. A growing number of studies suggest that the environment plays a major role in determining the efficacy of these drugs, specifically of selective serotonin reuptake inhibitors (SSRI). We recently hypothesized that the increase in serotonin levels induced by SSRI may not affect mood *per se*, but enhance neural plasticity and, consequently, renders the individual more susceptible to 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 treated C57BL/6 adult male mice with chronic fluoxetine while exposing them to either (i) an enriched environment, after exposure to a chronic stress period aimed at inducing a depression-like phenotype, or (ii) a stressful environment. A wide number of molecular, cellular and behavioral endpoints considered endophenotypes of depression were investigated. These include long-term potentiation, BDNF levels, hypothalamic-pituitary-axis activity, neurogenesis, anhedonia and optimistic attitude (cognitive bias). Mice treated with fluoxetine in an enriched condition improved their depression-like phenotype compared to controls, displaying an overall reduction of all endophenotypes of depression investigated. By contrast, when chronic fluoxetine administration occurred in a stressful condition, mice showed a more distinct worsening of the depression-like profile. 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. These findings may be helpful to explain variable effects of SSRI found in clinical practice and to devise strategies aimed at enhancing their efficacy by means of controlling environmental conditions.