Antidepressant treatment during stress:
the adverse consequences of increased brain plasticity

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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). 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 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. Anhedonia, brain BDNF and circulating corticosterone levels, considered endophenotypes of depression, were investigated. Mice treated with fluoxetine in an enriched condition improved their depression-like phenotype compared to controls, displaying higher saccharin preference, higher brain BDNF levels and reduced corticosterone levels. By contrast, when chronic fluoxetine administration occurred in a stressful condition, mice showed a more distinct worsening of the depression-like profile, displaying a faster decrease of saccharin preference, lower brain BDNF levels and increased corticosterone levels. 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 device strategies aimed at enhancing their efficacy by means of controlling environmental conditions.

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