Most antidepressants that are currently available take several weeks to exert their effects, and clinical evidence has suggested co-administration of an antagonist of α₂-adrenoceptors as a potential strategy to overcome this drawback. However, the mechanisms by which blockade of these receptors accelerates the improvements in mood are still largely unknown. Now, Yanpallewar et al. provide compelling evidence that this effect is mediated by an increase in adult neurogenesis and in the production of neurotrophic factors in the hippocampus.

Both acute and chronic administration of α₂-adrenoceptor agonists to adult rats caused a decline in the proliferation of hippocampal progenitors, and this was prevented by pretreatment with the α₂-adrenoceptor antagonist yohimbine. When the authors tested a combined treatment of yohimbine and the antidepressant imipramine, they observed an increase in the proliferation of hippocampal progenitors by day 7, whereas imipramine alone had the same effect only after 21 days of treatment. Remarkably, the combined treatment showed the expected reduction in the latency to feed by day 7, whereas those treated with the antidepressant alone only exhibited this effect by day 21.

Taken together, these findings provide additional support for the hypothesis that slow-onset adaptive changes in neurogenesis and in the expression of trophic factors in the hippocampus are responsible for the delayed action of antidepressants. In addition, they suggest that pharmacological blockade of α₂-adrenoceptors could become a valuable strategy to accelerate the speed of response to antidepressant treatment. This effect seems paradoxical considering that noradrenaline is known to stimulate progenitor proliferation in the hippocampus. The explanation probably relates to the specific adrenoceptor subtypes that are being activated in this case. Future studies could provide a more detailed characterization of the receptor populations involved, so that they can be specifically targeted by novel therapeutic agents to be used in combination with current antidepressants, maximizing their speed of action.

Cristian Bodo

A faster way to happiness

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