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PSYCHIATRIC DISORDERS

Run for your MIF

Exercise can have antidepressant effects in humans and in animal models, but questions remain about the underlying mechanisms. A study by Moon *et al.* now shows that in rodents, the pleiotropic cytokine microphage migration inhibitory factor (MIF) mediates these effects by increasing hippocampal brain-derived neurotrophic factor (*Bdnf*) transcription and serotonin synthesis.

The authors subjected rats to 28 days of voluntary wheel running (VWR) and found that this treatment increased *Mif* mRNA and protein levels in the hippocampus.

Hippocampal neurogenesis has been implicated in the antidepressant effects of exercise. The authors showed that MIF treatment upregulated the expression of the neurogenesis-related gene *Bdnf in vitro* and that intracerebroventricular (ICV) MIF injections increased hippocampal *Bdnf* expression in rats. Furthermore, VWR increased hippocampal levels of *Bdnf* and doublecortin mRNA (a marker for new neurons) in wild-type mice but not in *Mif*-deficient ($Mif^{-/-}$) mice.

Increases in serotonin levels have also been implicated in the effects of exercise. MIF administration increased the expression of the gene encoding tryptophan hydroxylase 2 (*Tph2*) — the rate-limiting enzyme in serotonin biosynthesis — *in vitro* and *in vivo*, and MIF treatment increased intracellular serotonin levels *in vitro* in a dose- and time-dependent manner. Importantly, VWR increased hippocampal *Tph2* expression in rats and wild-type mice but not in $Mif^{-/-}$ mice.

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The authors next showed that inhibition of the MIF-binding protein CD74 or its effector GTPase RHOA (which activates the extracellular signal-regulated kinase 1/2 (ERK1/2) signalling pathway) reduced the induction of *Bdnf* and *Tph2* and the increase in serotonin levels by MIF treatment in a neuronal cell line.

ICV administration of MIF in rats reduced immobility in a forced swim test, providing direct evidence for an antidepressant role for the cytokine. Furthermore, in this test, $Mif^{-/-}$ mice were more immobile than wild-type mice and, unlike in wild-type mice, VWR did not increase mobility in $Mif^{-/-}$ mice.

Together, these findings suggest that VWR-induced MIF expression may — through ERK1/2 signalling — underlie both the increased hippocampal *Bdnf* expression and the activation of the serotonin system associated with VWR and its antidepressant effects.

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ORIGINAL RESEARCH PAPER Moon, H. Y. *et al.* Macrophage migration inhibitory factor mediates the antidepressant actions of voluntary exercise. *Proc. Natl Acad. Sci. USA* **109**, 13094–13099 (2012)