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Gym rats

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A neurotrophic factor mediates the mood-elevating effects of exercise.

A runner's high might help if you are feeling low. In addition to its cardiovascular benefits, exercise elevates mood. What is the mechanism of its antidepressant actions? Hunsberger *et al*. report that exercise-induced expression of the neurotrophic factor VGF decreases depressive behaviors in a recent article in *Nature Medicine*.

Traditional antidepressant drugs take several weeks to several months to take effect. Researchers think that this delay is due to the induction of antidepressant-induced neural plasticity or adaptation. Both traditional antidepressants and exercise upregulate neurotrophic factors, including brain-derived neurotrophic factor (BDNF). To identify new factors that combat depression, the authors examined exercise-induced changes in neurotrophic and growth factors and their associated signaling cascades in the hippocampus, which is affected by stress and depression.

Mice housed with running wheels ran approximately 10 km each night. Microarray analysis showed 33 hippocampal genes differentially regulated by exercise in these mice relative to sedentary mice that did not have access to running wheels. Exercise-regulated hippocampal genes included BDNF and genes involved in BDNF signaling, such as mitogen-activated protein kinase kinase-2 (*Mek2*) and extracellular signal-regulated kinase (*Erk2*). Exercise regulated neuritin (*Nrn1*), which is involved in neurite extension, in both the hippocampus and the cortex. In the hippocampus, exercise strongly induced the expression of the secreted neuropeptide precursor *Vgf*. Sedentary and exercised mice showed low and high levels of VGF immunoreactivity, respectively.

Electroconvulsive shock alleviates depression. Researchers previously showed that electroconvulsive shock induced *Vgf* expression, so exercise-induced VGF expression may be involved in the antidepressant effect of exercise. Normally, mice and rats try to escape threatening situations. However, when placed in water or suspended by their tails for long periods, they become immobile for some of the time. Antidepressant treatment reduces immobility time, so researchers use immobility in forced-swim and tail suspension tests as a measure of depressive behavior. In both rats and mice, VGF treatment decreased immobility in forced-swim and tail-suspension tests. However, VGF treatment did not affect behavior in tests of anxiety, including the elevated-plus maze, which evaluates fear of heights, and open-field test, which evaluates fear of open spaces, in mice.

Vgf knockout mice have low survival rates, so the authors tested *Vgf* null heterozygous ($Vgf^{+/-}$) mice. Although they showed

normal behavior in the elevated-plus maze and open field, *Vgf*$^{+/-}$ mice showed increased immobility in the forced-swim and tail-suspension tests relative to wild-type mice. Unlike wild-type mice, sedentary and exercised *Vgf*$^{+/-}$ mice showed similar immobility, suggesting that VGF deficiency blocks the antidepressant effects of exercise.

Together, these data suggest that VGF is important in generating exercise's mood-elevating effects. If this mechanism is also found in people, VGF might be a valuable target for fast-acting antidepressants.

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1. Hunsberger, J. G. *et al.* Antidepressant actions of the exercise-regulated gene VGF. *Nature Medicine* **13**, 1476–1482 (2007). | Article | PubMed | ChemPort |