CLINICAL IMPLICATIONS OF BASIC RESEARCH

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Muscling In on Depression

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The mental health benefits of physical exercise are well established, and yet the way in which exercise influences the brain to alter mood is not clearly understood. A recent study by Agudelo and colleagues[1] suggests that kynurenine metabolism in skeletal muscle mediates resilience to stress-induced behavior associated with psychiatric illnesses such as major depression. The

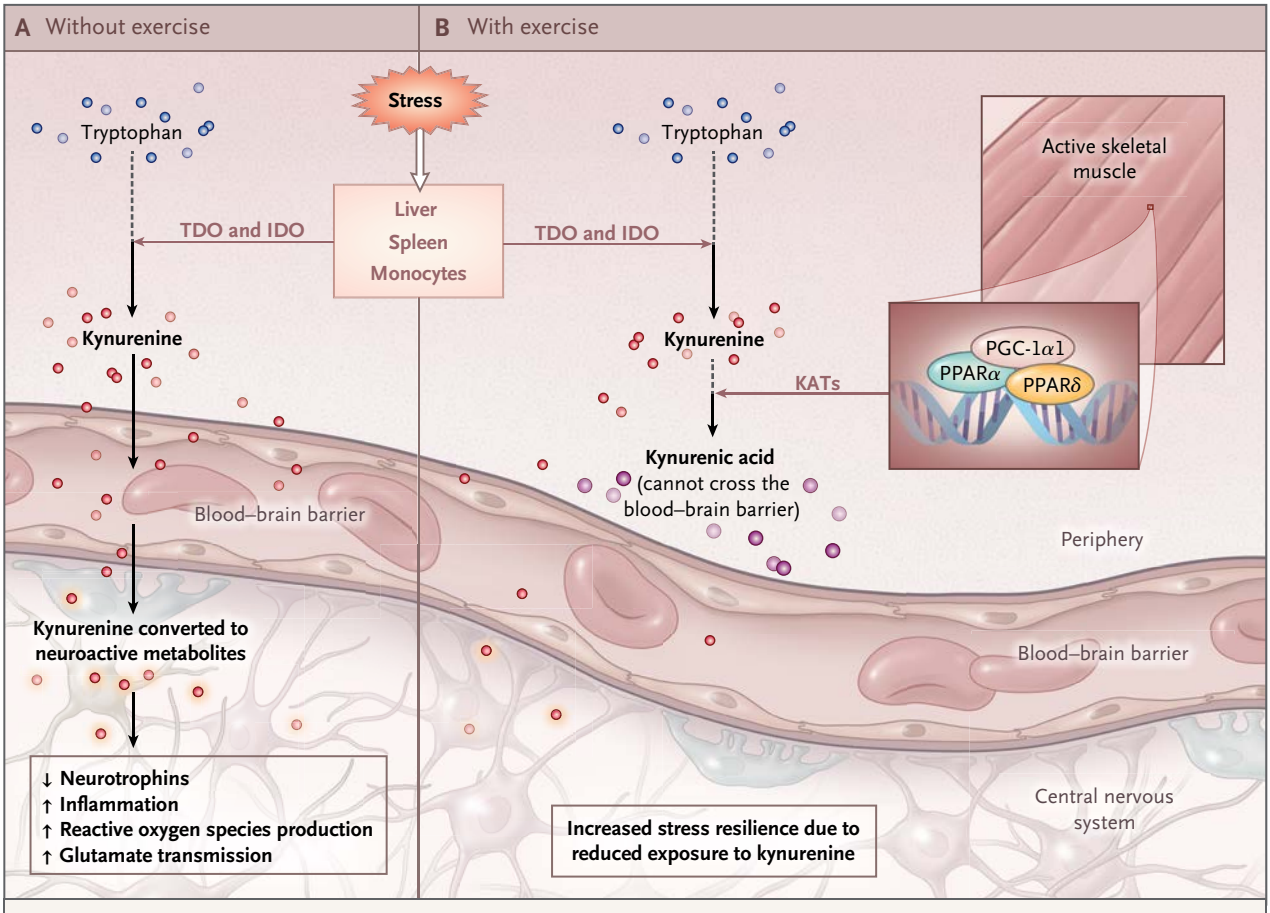

Figure 1. The Role of Exercise and KAT Expression in the Response to Stress.

Panel A shows the effects of stress in the absence of exercise. Stress activates the kynurenine pathway through the induction of indoleamine 2,3-dioxygenase (IDO) (monocytes) or hepatic tryptophan 2,3-dioxygenase (TDO), culminating in proportionate and sometimes excessive increases in circulating kynurenine. On entering the brain, kynurenine is converted into neuroactive metabolites that promote cellular stress and alter glutamate neurotransmission; these factors influence neurotrophy and behavior. Panel B shows the effects of stress accompanied by exercise. Exercise promotes an increase in the expression of the transcriptional coactivator PGC-1α1, which, through PPARα and PPARδ, leads to an increase in the expression of kynurenine aminotransferases (KATs) in skeletal muscle. KATs metabolize kynurenine to form kynurenic acid, which is incapable of crossing the blood–brain barrier, thereby reducing the exposure of the brain to kynurenine and promoting resilience to stress.

kynurenine pathway is the principal pathway by which the amino acid tryptophan is metabolized in peripheral body tissues, including skeletal muscle, liver, and white cells, leading to the production of brain-penetrating kynurenine. Kynurenine, in turn, may be converted into metabolites, some of which have been implicated in pathophysiological aspects of a number of brain disorders, including depression.[2]

Stress hormones, such as cortisol, or inflammatory mediators, such as interferon-γ, can activate the kynurenine pathway by inducing the expression of enzymes responsible for kynurenine synthesis and thus leading to increases in the levels of circulating kynurenine available to the brain. The conversion of kynurenine to kynurenic acid by kynurenine aminotransferases (KATs) in the periphery, however, limits kynurenine levels and therefore the availability of kynurenine to the brain, because kynurenic acid is incapable of crossing the blood–brain barrier.

Agudelo and colleagues have shown through their experiments with mice that increasing the activity of the transcriptional coactivator PGC-1α1 in skeletal muscle (which accrues normally during exercise) mediates resilience against stress-induced depression-related behaviors and deficits in the expression of a range of molecular markers of neurotrophy. Together with PGC-1α1, the transcription factors PPARα and PPARδ induce the expression of KATs, which reduces the amount of kynurenine that reaches the brain and therefore reduces the generation of metabolites in the brain that are associated with altered neurotransmission and behavior (Fig. 1). The link between peripheral kynurenine metabolism and stress resilience is further supported by the induction of PGC-1α1 and up-regulation of KATs in skeletal muscle and the increase in circulating kynurenic acid concentrations in response to freewheel running in mice. Moreover, the authors observed that aerobic exercise was associated with increases in PGC-1α1 and KAT enzyme expression in biopsied muscle tissue from humans. Exercise may thus act as a key adjunct therapy in the treatment of stress-related disorders, such as depression, by limiting the amount of kynurenine that reaches the brain. The effect of exercise on PGC-1α1 activity is likely to be of greatest clinical significance when expression of the transcriptional coactivator is reduced. PGC-1α1 expression in skeletal muscle is known to decline with age and in persons with type 2 diabetes, and increased kynurenine accumulation in the brain may be a contributor to coexisting depression. This proposed mechanism also provides a platform from which experimental new treatments — possibly mediators of the skeletal-muscle pathway — may be tested for their ability to bring about exercise-like responses and stress resiliency. In the meantime, further assays of circulating kynurenine and kynurenic acid — in addition to assays of other serum biomarkers — after exercise training in humans is warranted.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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