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NANO-REVIEWS

High-Intensity Functional Training: Molecular Mechanisms and Benefits

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Abstract

High-intensity interval training (HIIT) and strength exercise are known to improve health markers, such as cardiovascular health, metabolic health, and cognitive function, as well as to reduce all-cause mortality. High-Intensity Functional Training (HIFT) is a training paradigm derived from both HIIT and strength exercise to elicit greater muscle recruitment than repetitive aerobic exercises, thereby improving both cardiovascular fitness and strength parameters. Herein, we provide a focused review of the known molecular mechanisms that underlie the beneficial effects of HIFT on cardiovascular, metabolic, and cognitive functions.

Keywords HIFT · HIIT · mTOR · Mechanical tension · Resistance training · Crossfit®

High-intensity functional training (HIFT), which also includes the Crossfit® training concept, is a training paradigm derived from the well-studied high-intensity interval training (HIIT) and strength training paradigms. HIFT incorporates a variety of functional movements, performed at high-intensity, and designed to improve parameters of general physical fitness and performance (Feito et al. 2018). HIFT can be adapted to various fitness levels and can elicit greater muscle recruitment than aerobic exercises, improving both cardiovascular endurance and strength (Feito et al. 2018).

Functionally, while HIFT was shown to improve body composition markers, such as lean and fat mass, body fat percentage, and glucose regulation (Feito et al. 2018), it was also shown to enhance several cognitive domains. For example, a 3-month training paradigm in middle-school adolescents was shown to enhance short-term spatial learning, visual pattern separation, and inhibitory control (Ben-Zeev et al. 2020), and when compared with low-intensity aerobic training, HIFT was shown to improve working memory (Wilke 2020).

The HIIT component in HIFT was shown to induce secretion of the pro-angiogenic vascular endothelial growth factor (VEGF) (Morland et al. 2017), a growth factor that promotes angiogenesis, the formation of new blood vessels. The underlying mechanism for this effect involves lactate accumulation and subsequent secretion from muscle cells (Morland et al. 2017). Circulating lactate, in turn, activates the lactate receptor, Hydroxycarboxylic Acid Receptor 1 (HCAR1), expressed on endothelial cells. This results in increased availability of oxygen and nutrients within the neural tissue. Exercise-induced secretion of VEGF and angiogenesis was also shown to promote vasodilation of blood vessels via nitric oxide (NO), known for its roles in vascular remodeling (Calverley et al. 2020). HIIT also promotes the production of free radicals and associated reactive oxygen/nitrogen species (ROS/RNS), which at physiological concentrations play a role in maintaining cerebrovascular O_2 homeostasis and upregulate the expression of antioxidant enzymes, VEGF, brain-derived neurotrophic factor (BDNF), and Insulin-growth factor-1 (IGF-1) (Calverley et al. 2020).

HIFT increases muscle mass due to the full range of motion strength exercises (Wackerhage et al. 2019). When muscles generate force against an external resistance, distinct molecular pathways sense the mechanical tension and transfer it to molecular signals. One of the proteins most sensitive to mechanical signals is α7β1 integrin, which spans

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the cellular membrane, connecting the extracellular matrix (ECM) to the cytoskeleton. Upon interaction of α7β1 integrin with the ECM, focal adhesion kinase (FAK) is recruited to the cytoplasmic tail of the α7β1 integrin, causing inhibition of the tuberous sclerosis complexes 1 and 2 (TSC1/2) and activation of PI3K/AKT signaling cascade. This, in turn, increases the activation of the mTORC1 complex, a nutrient sensor that activates protein translation (Klossner et al. 2009) (Fig. 1a).

In addition, HIFT induces activation of stretch-activated ion channel (SAC), which spans the cell membrane and activates upon muscle fiber contraction. SAC activation decreases the membrane resting potential and, as a result, elevates intracellular calcium (Stary and Hogan 2016). This, in turn, activates the c-Jun N-terminal kinase (JNK). JNK increases its activity when increments in mechanical load are applied. JNK can also be activated by increases in muscle contraction, especially eccentric contraction (Gehlert et al. 2015). Thus, JNK leads to increased protein synthesis via p70s6k phosphorylation (Gehlert et al. 2015) (Fig. 1a). The increase in protein synthesis following HIFT results in an increase in muscle size. When mechanical tension/load is applied to muscles, cytoskeletal tension increases, and, as a result, yes-associated protein (YAP) enters the nucleus and activates transcription of the leucine transporter Lat1 (Hansen et al. 2015). Leucine is an anabolic branched-chain amino acid, and an increase in leucine levels activates mTORC1 and increases protein synthesis. (Wackerhage et al. 2019) (Fig. 1a).

The skeletal muscle secretes myokines that systemically affect different organs. Three important myokines secreted during both HIIT and strength exercise are BDNF, Fibronectin-Type III Domain Containing 5 (FNDC5, also known as IRISIN), and Insulin-growth factor-1 (IGF)-1 (Pedersen and Febbraio 2012). These pleiotropic factors promote neurogenesis, neuronal survival, neuroplasticity, and cognitive abilities (Tari et al. 2019). Increasing muscle size as a result of HIFT results in increased production of the BDNF, IRISIN, and IGF-1 myokines (Wackerhage et al. 2019). BDNF is particularly central for the beneficial effects of exercise on cognitive abilities. When elevated, BDNF binds to tyrosine-related kinase B (TrkB), which activates transcription factor cAMP response element-binding protein (CREB) (Vaynman et al. 2003). CREB activity results in the transcription of immediate early genes such as c-Fos and JunD, which help to form the

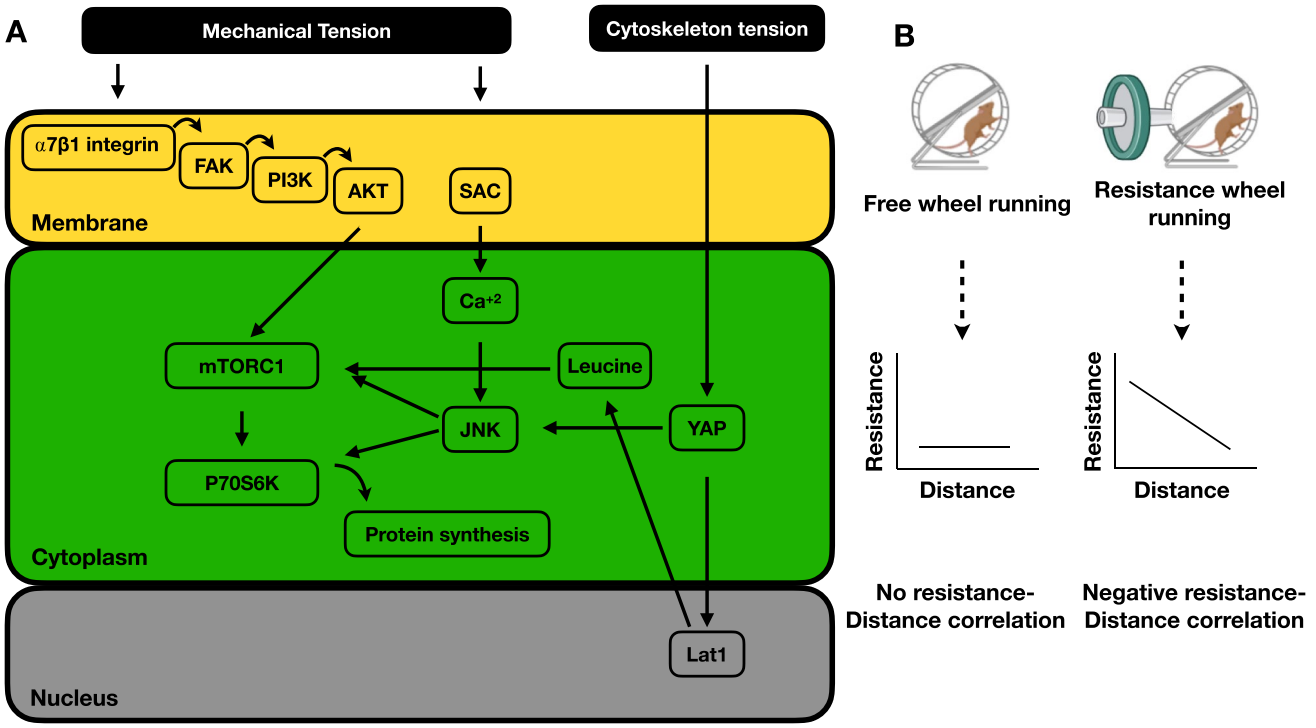

Fig. 1 HIFT promotes mTOR-mediated protein synthesis. **a** Engaging in resistance exercise applies mechanical tension to skeletal muscles. This, in turn, activates 3 signaling pathways in parallel: (I) α7β1 integrin integrates with FAK, which activates AKT, which, in turn, activates the mTORC1 complex. (II) SAC activation increases intracellular calcium levels and JNK, which in turn phosphorylates p70s6k. (III) Cytoskeleton tension translocates YAP to the nucleus and activates Lat1 transcription, resulting in increased leucine content and elevated protein synthesis. **b** In free weight wheel running, there is no correlation between running distance and wheel resistance. In RWR, there is a negative correlation between running distance and wheel resistance

transcription factor AP-1 that promotes neurogenesis and neuronal survival, which underlies the benefits of physical exercise in learning and memory (Impey et al. 2004; Finkbeiner et al. 1997; Barak et al. 2015). Some of the cognitive benefits attributed to HIFT could be the result of these pleiotropic myokine factors that have been shown to improve cognitive abilities (Tari et al. 2019).

Skeletal muscle contraction during HIFT is mechanistically involved in modulation of the immune system. In rodents, an increase in muscle mass is correlated with an increase in interleukin (IL)-15. IL-15 is an important factor for immune T cell proliferation, the formation of $CD8^+$ memory T cells, and for lowering the levels of inhibitory receptors, which suppress T cell activation (Wu et al. 2020). IL-15 also boosts cytokine secretion, such as interferon (IFN)-γ and tumor necrosis factor (TNF)-α following viral infection, promoting a stronger immune response to viral infection (Wu et al. 2020). Indeed, muscle mass has been attributed to reduced all-cause mortality (McLeod et al. 2016), possibly via pleiotropic immune effectors such as IL-15.

HIFT is a relatively new training paradigm that was developed in order to enhance both cardiovascular fitness parameters as well as skeletal muscle strength parameters. Additional research is needed in order to thoroughly assess its underlying molecular mechanisms that contribute to the improvement in cardiovascular fitness and cognitive functions. As most of the evidence of the efficacy and underlying mechanisms of HIFT was obtained from studies on human volunteers, there is a need to develop mouse models that enable further mechanistic studies of HIFT. One potential way to induce HIFT in mice is to use resistance wheel running (RWR). RWR induces a greater hypertrophic response, enhances spatial learning, and elevates BDNF levels when compared with free weight wheel running (Lee et al. 2012). The increase in wheel resistance increases muscular mechanical tension in the mice as opposed to freewheel running in which resistance remains minimal and constant (Fig. 1b). In RWR, when wheel resistance increases, running distance decreases, resulting in a negative correlation between wheel resistance and running distance, whereas no such correlation is present in freewheel running (Fig. 1b). Since RWR involves, to a large degree, both the cardiovascular and skeletal muscle systems, we propose that RWR can be used as a reliable intervention to model HIFT in mice, allowing a more in-depth future mechanistic study.

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Compliance with Ethical Standards

Conflict of interest The authors declare no competing interests.

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