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LETTER TO THE EDITOR

Attenuation of exercise conditioning by metformin—a consequence of HSF1 inhibition

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To the Editor: Metformin is the most widely prescribed medication for the prevention and treatment of type 2 diabetes. Exercise and weight loss are the most effective lifestyle interventions for type 2 diabetes therapy. Recently, a number of diverse studies have discovered that metformin impairs exercise conditioning and limits exercise-induced mitochondrial genesis and function (Konopka et al. 2019; Walton et al. 2019). Additionally, metformin attenuates exercise-induced insulin sensitivity (Sharoff et al. 2010). Explanations for the non-beneficial effects of metformin on exercise are being explored but have not yielded clear answers. We propose that metformin's well-documented activation of AMPK (AMP-activated protein kinase) leads to phosphorylation of HSF1 (heat shock factor 1) at serine 121, thereby partially inactivating HSF1 and diminishing the cellular stress response (Dai et al. 2015). Exercise normally activates HSF1 and the cellular stress response. Indeed, Hsp72 transgenic mice endure exhaustive exercise four times longer than their wild counterpart. The Hsp72 transgenic skeletal muscle has robust mitochondria—both in number and in activity (Henstridge et al. 2014). Furthermore, HSF1 improves insulin sensitivity and glycemic control (Hooper et al. 2014). Combining two effective therapies can lead to unintended loss of therapeutic efficacy. Understanding the complex interactions of cellular stress pathways can be essential in arriving at viable answers.

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