Effects of sildenafil on the gastrocnemius and cardiac muscles of rats in a model of prolonged moderate exercise training

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Moderate exercise training improves energetic metabolism, tissue perfusion and induces cardiac and skeletal muscle remodelling (Gielen et al., 2010). In fact, a large body of evidence suggests that regular physical activity induces marked vascular remodeling in skeletal muscle and myocardium by increasing angiogenesis and arteriogenesis, myocardial perfusion, energetic metabolism, oxygen uptake, substrate oxidation and resistance to fatigue (Timmons , 2011). These effects are mediated by the activation of several signalling pathways involved in the maintenance of energy homeostasis and mitochondrial biogenesis (Stepto et al., 2012).
Sildenafil, a potent phosphodiesterase-5 inhibitor used to treat erectile dysfunction, reduces infarct size and increases tissue oxygenation in experimental models of cardiovascular disease (Kukreja et al., 2005). Moreover, sildenafil has been shown to ameliorate exercise capacity both in subjects affected by cardiopulmonary diseases in normoxia (Kloner, 2004), and in healthy subjects in hypoxia (Hsu et al., 2006). Interestingly, although sildenafil does not have an indication for use in equine veterinary medicine, in 2000 it was the eighth most frequent drug found in urine samples from racing horses, which suggests its use in doping (Colahan et al., 2010).
We have evaluated the effects of prolonged moderate exercise training and a repeat administration of sildenafil on the rat gastrocnemius and cardiac muscles.
Animals were divided into two groups: sedentary and trained. Each group was subdivided into animals treated with vehicle or with two doses of sildenafil (10 or 15 mg/kg/day) during the last week of training. Physical exercise did not induce cardiac hypertrophy, whereas it increased mRNA and protein levels of the PGC-1α, HIF-1α and VEGF genes in gastrocnemius and in the heart, which are involved in mitochondrial biogenesis and angiogenesis. Physical exercise also reduced the atrophy genes such as FoxO3a, MuRF-1 and Atrogin-1 in gastrocnemius and cardiac muscle. A repeat administration of sildenafil reduced significantly in a dose-dependent manner the effective time of running. Sildenafil dose-dependently promoted both angiogenesis, shown by increased capillary density, and muscle atrophy, as shown by muscle fibre size. These effects were more pronounced in trained animals. Haemodynamic and echocardiography measurements revealed that exercise training did not affect mean arterial pressure (MAP) but on the other hand significantly reduced heart rate (HR). Treatment with sildenafil dose-dependently reduced MAP in both sedentary and trained rats and reduced HR only in trained rats. Finally, training and treatment with sildenafil significantly increased EF.
Our data confirmed the beneficial effects of a moderate and prolonged training on cardiovascular and skeletal system and for the first time described the positive and negative effects of sildenafil on skeletal and cardiac muscle. This report may impact on its use as a sports performance-enhancing substance.

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