Long-term cardiac programming by short-term juvenile exercise training

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Exercise exerts its beneficial effects in the cardiovascular system not just through reducing the burden of cardiovascular risk factors, but also by directly affecting the cellular and molecular structure and function of the heart (Waring *et al.,* 2014). An elevation in workload imposed on the heart can occur either by exercise training, which is transient and non-pathological or, by hypertension or cardiac valve disease, which is persistent and pathological (Kemi & Wisloff, 2010). Cardiomyocytes are the muscle cells that make up the cardiac muscle and have a high mitochondrial density (Torrent-Guasp *et al.,* 2005). As the heart grows and approaches maturity, the cardiomyocytes progressively lose their mitotic activity, and hypertrophy of myocytes becomes the principal process of cardiac enlargement. However, recent evidence is suggesting that cardiomyocyte proliferation may play an unrecognized role during the period of developmental heart growth between birth and adolescence (Mollova *et al.,* 2013).

The objective of this study was to investigate the impact of short-term endurance training during juvenile life on the structure and function of the left ventricle in adulthood. Male rats (Wistar Kyoto) were trained on a motorized treadmill at 20m/min (1h/day), 5 days/week for 4 weeks. Training was conducted in either juvenile (5-9 weeks old) or adult (20-24 weeks old) rats, and compared to sedentary rats. Cardiac structure and function were assessed at 9 and 24 weeks of age using transthoracic echocardiography. At 9 or 24 weeks of age rats were anaesthetized with intraperitoneal Ilium Xylazil-20 (30 mg/kg) and Ketamine (100mg/kg) (Gallo *et al.,* 2012), perfusion-fixed and the hearts excised. The total number of cardiomyocytes was stereologically measured, and the proportion of mononucleated and binucleated cardiomyocytes, longitudinal and cross-sectional cardiomyocyte area and levels of myocardial fibrosis determined using confocal microscopy and image analysis.

When compared to adult sedentary rats, exercise training during the juvenile and adult periods significantly increased posterior wall thickness ($P<0.0001$), interventricular septum thickness ($P<0.001$) and left ventricle mass (28%; $P=0.0003$), indicative of left ventricle hypertrophy. Juvenile exercise training, but not adult exercise training increased cardiomyocyte number (36%; $P=0.0037$), doubled the proportion of mononucleated cardiomyocytes (14%; $P<0.0001$), and increased the cross-sectional and longitudinal areas of binucleated cardiomyocytes ($P<0.0001$). This study is the first to unveil the regenerative potential of juvenile exercise training for the adult heart, with novel findings of cardiomyocyte proliferation without increased levels of fibrosis, in the hypertrophied left ventricle. These findings demonstrate that the physiological cardiac adaptation produced by 4 weeks of juvenile exercise training persist into adulthood, and may protect against cardiovascular disease in later life.

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