Mechanisms involved in the crosstalk between leptin and mineralocorticoid receptor in the cardiac fibrosis associated with obesity

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We have investigated the potential role of mineralocorticoid receptor (MR) on the profibrotic effects of leptin in cardiac myofibroblasts, as well as the mechanisms involved. The presence of the MR antagonist eplerenone reduced the leptin-induced increase in protein levels of collagen I, transforming growth factor β, connective tissue growth factor and galectin-3 and the levels of both total and mitochondrial of superoxide anion in cardiac myofibroblasts from adult rats. Likewise, the MEK/ERK inhibitor, PD98059, and the PI3/Akt inhibitor, LY294002, showed a similar pattern. Additionally, leptin stimulates aldosterone production in a dose- and time-dependent manner in cardiac myofibroblasts. This production was not affected by either PD98059 or LY294002, but was reduced by the antioxidant melatonin. Mitochondrial reactive oxygen species (ROS) scavenger (MitoTempo) attenuated the increase in body weight, interstitial fibrosis and superoxide anion levels observed in rats fed a high fat diet (35% of fat; HFD) as compared with control group (fed 3.5% fat). MitoTempo also prevented the increased circulating leptin and aldosterone levels in HFD fed animals. This study supports a role of mineralocorticoid receptor in the cardiac fibrosis induced by leptin in the context of obesity and highlights the role of the mitochondrial ROS in this process.