If channel inhibitor. Ivabradine is a selective antagonist of funny channels with anti-anginal and anti-ischaemic properties that provides pure heart rate reduction, reducing the diastolic depolarization slope, without altering other cardiac and haemodynamic parameters. There is consistent evidence that ivabradine is effective in reducing angina pectoris symptoms and myocardial ischemia. At approved doses ivabradine is safe, improves exercise performance and reduces heart rate has a positive effect on heart rate. Available literature supports its use in the management of patients with stable CAD and chronic HF. Recent studies have casted doubts on the safety of non approved high doses of ivabradine for the treatment of patients with CAD and without clinical HF, but have shown no concerns on the doses approved for clinical use.

Gene therapy. Therapeutic angiogenesis has been focused on the administration of the vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF). At present, VEGF and FGF have been the most extensively studied angiogenic agents. Growth factor proteins may be given directly or through gene-based approaches using naked plasmid deoxyribonucleic acid or a viral vector that encodes the gene so that it can be taken up by the recipient endothelial cells. These agents may be administered directly to the myocardium by epicardial, endocardial, or intracoronary injection. The studies using these agents have so far achieved inconclusive results.

Enhanced external counterpulsation. EECP is a novel treatment for patients with ischemic heart disease and refractory angina. EECP is performed by encircling the legs with compression devices that inflate during diastole to 300 mm Hg and deflate them during systole. This counterpulsation unloads the left ventricle during ventricular systole and improves coronary blood flow during diastole. In a randomised clinical trial 139 patients clinical symptoms and treadmill exercise times improved and a variable effect on myocardial perfusion was found. However, the absence of proper blinding during this study makes the results uncertain.

Spinal cord stimulation. Spinal cord stimulation, is an effective method for pain relief in patients with refractory angina not amenable to revascularisation. The treatment involves placing a stimulating electrode in the dorsal epidural space at the C7–T1 level. It has been suggested that spinal cord stimulation exerts beneficial effects by decreasing pain and sympathetic tone. Early study with spinal cord stimulators suggested an improvement in total exercise time and time to angina. However, in another trial the anginal symptoms decreased even after discontinuation of therapy suggesting a most likely primary analgesic effect of this treatment.

Despite significant advances in the percutaneous treatment of coronary artery disease medical management represents the treatment of choice in most patients. Newer therapeutic agents have been shown to be safe and effective when used in monotherapy or in association with the existing classical antianginals.

doi:10.1016/j.ijcme.2015.05.011

MR blockade protects against diet induced obesity, adipocyte dysfunction and cardiac inflammation in mice, through browning of the adipose organ and modulation of autophagy

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Abstract

Obesity is a key factor in the development of insulin resistance (IR), cardiovascular disease, hypertension, type 2 diabetes etc. Given the near epidemic incidence of obesity in western society there is a clear need for effective treatment options. Mineralocorticoid receptor (MR) blockade has shown significant promise in transgenic mouse models of obesity in limiting IR and adipocyte dysfunction, a disease that is independent of classical MR actions (renal). Female 10-week-old C57bl6 mice were fed with normal chow or a high fat (HF) diet for 12 weeks. Mice fed HF diet were concomitantly treated for 12 weeks with drospirenone (DRSP, 6 mg/kg/day), a potent MR antagonist with antiadipogenic activity, or spironolactone (SPIRO, 20 mg/kg/day). Mice fed HF diet showed a significant increase in total body weight, fat mass, mean adipocyte size, expression of white adipose tissue (WAT) marker genes and showed impaired glucose tolerance after intraperitoneal plasma glucose tolerance test. DRSP and SPIRO prevented weight gain and white fat mass expansion induced by HF diet in parametrial, perivescical, and inguinal depots without affecting interscapular fat pad weight. Magnetic Resonance Imaging (MRI) confirmed that MR antagonists blocked the HF diet-driven expansion of abdomino-pelvic (parametrial and perivescical) fat volume. High levels of MR mRNA were detected in all depots of adipose tissue. HF fed mice showed no increase in heart or kidney weight and tissue fibrosis. Cardiac macrophage recruitment and osteopontin staining was increased in hearts of HF fed mice and reversed by both MR antagonists. Moreover, both DRSP and SPIRO prevented the impaired glucose tolerance in mice fed HF diet, and countered HF diet-induced up-regulation of WAT markers transcripts and adipocyte hypertrophy. Importantly, MR antagonists increased uncoupling protein 1 (UCP-1) positive brown-like adipocyte content in WAT, and improved metabolic activity of adipose tissue, as indicated by PET/CT imaging. In keeping with this, MR antagonism significantly increased expression of brown-like adipocyte marker genes such PRDM16, CIDEA, beta-3 adrenergic receptor (ADRB3) and UCP-1 in all WAT depots analysed. In exploring the mechanism, we demonstrated that MR antagonism induced brown adipose tissue (BAT) markers, and reduced the autophagic rate, a key remodelling process in adipocyte differentiation, in WAT depots in vivo as well as in primary cultured adipocytes. We conclude that adipocyte MR regulates BAT-like remodeling of WAT through modulation of autophagy. MR blockade therefore has promise as a novel therapeutic option for the prevention of metabolic dysfunctions and the cardiac consequences of obesity.

doi:10.1016/j.ijcme.2015.05.012

Transcriptional control of ICAM-1 in human coronary artery endothelial cells by Mineralocorticoid Receptor (MR): Implications for the protective effects of MR antagonists in cardiovascular diseases

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In clinical trials, mineralocorticoid receptor (MR) antagonists decrease cardiovascular ischemia and mortality suggesting a beneficial role of MR inhibition in the vasculature. We have shown that human coronary and umbilical endothelial cells (HUVEC) express functional MR. In endothelial cells MR activation by aldosterone promoted transcription of ICAM-1. Most importantly cell adhesion assays demonstrated that aldosterone promotes leukocyte adhesion to ECs, an effect that was inhibited by spironolactone and ICAM-1