

MARTÍN DONATO ^{MTSAC}

What is the role of mineralocorticoids in vascular dysfunction?

Victorio JA, Clerici SP, Palacios R, Alonso MJ, Vassallo DV, Jaffe IZ, et al. Spironolactone prevents endothelial nitric oxide synthase uncoupling and vascular dysfunction induced by β -adrenergic overstimulation: Role of perivascular adipose tissue. **Hypertension** 2016;68:726-35.

Sympathetic hyperactivity with increased levels of catecholamines and adrenergic receptor expression is a common feature of many cardiovascular disorders such as hypertension, myocardial infarction and congestive heart failure. Although the importance of β -adrenoceptor (β -AR) overstimulation in the pathogenesis of left ventricular dysfunction has been extensively studied, its effect on vascular function is less well known.

β -AR stimulation generates abnormal vasoconstrictor response in the aorta, coronary and cerebral arteries, with increased vasoconstrictor response to isoproterenol and generation of reactive oxygen species (ROS), and uncoupling of the endothelial nitric oxide synthase (eNOS) enzyme. Thus, it is clear that β -AR overstimulation leads to vascular dysfunction; however, the molecular mechanisms underlying this disorder have not yet been elucidated.

In this study, Victorio et al. aimed to investigate the possible role of AT1 angiotensin receptors (AT1R), mineralocorticoid receptors (MR) and perivascular adipose tissue (PVAT) in vascular dysfunction induced by in vivo administration of isoproterenol. These authors hypothesized that MR activation induces eNOS enzyme uncoupling, increases oxidative stress and reduces the anti-contractile effect of PVAT following β -AR overstimulation.

To test this hypothesis aorta rings from rats treated for 7 days with isoproterenol increased their vasoconstrictor response when they were incubated with phenylephrine. This contractile effect was not altered when treated with losartan, but was blunted when the animals were treated with spironolactone. In addition, vascular relaxation stimulated with acetylcholine or sodium nitroprusside did not change with either treatment. Then, the authors evaluated the effect of eNOS enzyme inhibition on the contractile response to phenylephrine and antioxidant treatment

with superoxide dismutase, demonstrating that MR activation is responsible for the increased production of superoxide anion and for the lower NO production associated with β -AR overstimulation.

Mineralocorticoid receptor functions are achieved through translocation to the nucleus to regulate gene transcription (genomic mechanisms) or by activation of cytoplasmic signaling pathways (nongenomic mechanisms). Isoproterenol treatment increased the nuclear/cytoplasmic MR ratio in the aorta and enhanced the expression of the target gene for MR in smooth muscle cells. Since MR can be activated by aldosterone and also by some corticosteroids, the authors studied whether isoproterenol activates MR by modulating the levels of endogenous ligands. Consequently, plasma and PVAT levels of aldosterone and corticosterone were measured. Aldosterone plasma and PVAT levels increased with spironolactone treatment, consistent with a feedback mechanism associated with MR blockade. None of the treatments (isoproterenol and spironolactone) affected corticosterone plasma levels. However, corticosterone content increased in PVAT after isoproterenol treatment, while spironolactone did not alter this effect.

This study demonstrated that spironolactone, an MR antagonist, but not losartan (AT1 blocker), abrogated the increased vasoconstrictor response to phenylephrine induced by β -AR overstimulation. Spironolactone vascular effect was associated with increased eNOS enzyme dimerization, HSP90 expression and NO production. Moreover, spironolactone reduced superoxide production derived from eNOS and inhibited MR genomic and nongenomic pathways. In addition, the authors found elevated corticosterone levels in PVAT after β -AR stimulation. These results support a model in which chronic β -AR stimulation promotes activation of vascular MR, resulting in eNOS uncoupling and increased oxidative stress.

This study suggests a new relationship between β -adrenergic receptor signaling and vascular MR activation as vascular dysfunction mechanism. Thus, this model provides a new mechanism by which MR antagonists can exert protective effects in patients with cardiovascular disease, preventing vascular dysfunction associated with a hyperadrenergic state, such as heart failure, myocardial infarction and essential hypertension.