# Aldosterone–adrenomedullin: a new feedback regulation in blood vessels?

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Adrenomedullin is a 52-amino-acid, potent hypotensive peptide, which was originally isolated from extracts of human pheochromocytomas [1]. Adrenomedullin is produced by the proteolytic cleavage of preproadrenomedullin, which contains in its $NH_2$ terminus a unique 20 amino acid residue sequence with a transient hypotensive action, named proadrenomedullin *N*-terminal 20 peptide (PAMP). Adrenomedullin and PAMP are synthesized in a variety of tissues and organs, including the adrenal cortex, kidney, lung, spleen, small intestine, brain, heart and blood vessels. The most abundant production has been observed in endothelial cells, and vascular smooth muscle cells (VSMCs) have been used for transcriptional regulation studies. Factors known to stimulate the production of adrenomedullin and PAMP are volume overload and rapid ventricular pacing, as well as cytokines and growth factors. Other stimulators of adrenomedullin gene transcription include retinoic acid, adrenal steroids and thyroid hormones. Transcription of the adrenomedullin gene is inhibited in cultured VSMCs by cAMP and transforming growth factor-β. Over the last few years, evidence has accumulated that adrenomedullin and PAMP play an important role in the paracrine regulation of the hypothalamic–pituitary–adrenal axis [2], as well as of vascular tone, acting on fluid and electrolyte homeostasis and cardiovascular function with apparent physiological relevance [3,4]. In particular, adrenomedullin and PAMP inhibit adrenocorticotropin release in the anterior pituitary gland, and potassium and angiotensin II-stimulated aldosterone secretion in the adrenal gland, suggesting their involvement in pathophysiological conditions where the function of the hypothalamic–pituitary–adrenal axis has to be reset. In blood vessels, the vasodilatory effect of adrenomedullin is largely due to paracrine interaction with other vasoactive compounds, such as endothelin-1 and nitric oxide, which are also produced by the endothelium, whereas PAMP acts presynaptically to inhibit adrenergic nerves that innervate blood vessels. Both adrenomedullin and PAMP also circulate in plasma, and intravenous administration of these peptides in man causes significant pharmacological effects [5].

In this issue of the journal Uemura *et al.* [6] raise new questions concerning the regulation of proadrenomedullin-derived peptides in VSMCs by aldosterone, and their potential role in modulating the vascular effects of this hormone. In this regard, it was recently shown that an aldosterone excess in plasma leads to cardiovascular damage and remodeling, inducing fibrosis of the myocardium and proliferation and/or hypertrophy of VSMCs, both in animal and human models [7]. A production of this steroid was also demonstrated in blood vessels [8] and in the failing human heart, with the potential relevance for paracrine aldosterone production in the pathogenesis of congestive heart failure [9]. Uemura *et al.* show that supraphysiological concentrations of aldosterone stimulate preproadrenomedullin gene expression and adrenomedullin production from cultured human aortic VSMCs, and that adrenomedullin secretion is reduced by the aldosterone antagonist spironolactone. Although aldosterone levels of patients with congestive heart failure or primary aldosteronism are clearly below those employed in the experiments of Uemura *et al.*, it cannot be ruled out that aldosterone, locally produced in human pathologic vessels or the myocardium, reaches concentrations similar to those used experimentally to obtain a significant adrenomedullin stimulation. However, as the authors point out, experiments designed to assess aldosterone production, in parallel with adrenomedullin, inside the intracellular or extracellular compartments of the vascular wall would be required to support this hypothesis. Increased adrenomedullin secretion from the peripheral vasculature in response to paracrine aldosterone may comprise an in-vivo vasodilatory mechanism counteracting the

systemic vasoconstrictive effect of this mineralocorticoid. This might occur under situations of pathological aldosterone excess, either primary or secondary, such as acute myocardial infarction, severe grades of heart failure, chronic renal impairment, hypertension and primary aldosteronism. Moreover, adrenomedullin and PAMP have an inhibitory effect on aldosterone production from the adrenal cortex, with a possible increase of diuresis and natriuresis *in vivo*. Inhibition of aldosterone within the adrenal by paracrine [2] or circulating adrenomedullin might represent an additional feedback defense mechanism against blood pressure elevation and fluid-volume retention in patients with aldosterone overproduction. The absence of PAMP secretion from VSMCs observed by Uemura *et al*. in response to aldosterone remains to be explained, but it appears to exclude the contribution of this peptide to a counteracting aldosterone effect.

Another issue raised by the experiments of Uemura *et al*. is the potential effect of aldosterone-stimulated adrenomedullin on vascular and cardiac cell growth. In addition to influencing blood vessels contractility, adrenomedullin and PAMP may have a role in preventing pathologic vascular remodeling, acting directly as growth regulators [10]. In-vitro studies show that the release of adrenomedullin in response to oxidative and shear stress mediates inhibition of endothelial cell growth. In cultured human coronary artery cells, angiotensin II-stimulated cell migration is inhibited by adrenomedullin. Transcription of the adrenomedullin gene in the heart is enhanced by hormonal, genetic and physical factors, and adrenomedullin has been found to inhibit cell proliferation and hypertrophy. Although adrenomedullin is antimitogenic in most cells, proliferative effects have been also described. In fact, adrenomedullin stimulates DNA synthesis and cell proliferation in quiescent rat VSMCs and suppresses apoptosis in endothelial cells. These effects appear to be partially mediated by calcitonin-gene related peptide receptors. The experiments of Uemura *et al*. do not directly address this issue as they did not test the effect of aldosterone, and subsequent adrenomedullin and PAMP increase, on the growth rate of cultured VSMCs. The development of selective antagonists of proadrenomedullin-derived petides will be very useful to clarify whether adrenomedullin and/or PAMP may control vascular damage and remodeling induced by aldosterone. Future studies using in-vitro and in-vivo models are required to better define this issue, which may have important clinical implications.

## References


1 Kitamura K, Kangawa K, Kuwasako M, Ichiki Y, Nakamura S, Matsuo H, Eto T. Adrenomedullin: a novel hypotensive peptide isolated from human pheochromocytoma. *Biochem Biophys Res Commun* 1993; **194**: 720–725.

2 Nussdorfer GG. Proadrenomedullin-derived peptides in the paracrine control of the hypothalamo-pituitary-adrenal axis. *Int Rev Cytol* 2001; **206**:249–284.

3 Samson WK. Adrenomedullin and the control of fluid and electrolyte homeostasis. *Ann Rev Physiol* 1999; **61**:363–389.

4 Eto T. A review of the biological properties and clinical implications of adrenomedullin and proadrenomedullin *n*-terminal 20 peptide (PAMP), hypotensive and vasodilating peptides. *Peptides* 2001; **22**:1693–1711.

5 Nicholls MG, Lainchbury JG, Lewis LK, McGregor DO, Richards AM, Troughton RW, Yandle TG. Bioactivity of adrenomedullin and proadrenomedullin N-terminal 20 peptide in man. *Peptides* 2001; **22**:1745–1752.

6 Uemura T, Kato J, Kuwasako K, Kitamura K, Kangawa K, Eto T. Aldosterone augments adrenomedullin production without stimulating proadrenomedullin N-terminal 20 petide secretion in vascular smoooth muscle cells. *J Hypertens* 2002; **20**:000–000.

7 Rocha R, Stier CT. Pathophysiological effects of aldosterone in cardiovascular tissues. *Trends Endocrinol Metab* 2001; **12**:308–314.

8 Slight SH, Joseph J, Ganjam VK, Weber KY. Extra-adrenal mineralocorticoids and cardiovascular tissue. *J Mol Cell Cardiol* 1999; **31**: 1175–1184.

9 Young MJ, Clyne CD, Cole TJ, Funder JW. Cardiac steroidogenesis in the normal and failing heart. *J Clin Endocrinol Metab* 2001; **86**: 5121–5126.

10 Hinson JP, Kapa S, Smith DM. Adrenomedullin, a multifunctional regulatory peptide. *Endocr Rev* 2000; **21**:138–167.