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Editorial

Intracellular Angiotensin II is Involved on the Regulation of Vascular Tone in Resistance Vessels. Implications for Hypertension.

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EDITORIAL

The role of potassium current on the regulation of resting potential and tone of vascular resistance vessels was discussed. The finding that intracellular administration of angiotensin II (Ang II) into arterial myocytes from mesenteric arteries increases the potassium current and hyperpolarizes the cell, indicates that the internalization or local synthesis of the peptide counteracts the effect of extracellular Ang II on the regulation of vascular tone and peripheral resistance. Implications for hypertension are discussed.

The activation of the classical renin–angiotensin aldosterone system (RAAS) is known to be involved in the regulation of blood volume and blood pressure and plays an important role in cardiovascular diseases including hypertension, heart failure and myocardial ischemia [1]. Independently of the classical RAAS, local renin angiotensin systems have been identified in different organs including the heart and vessels [1].Furthermore, several RAAS components expressed in different cells [2] are able to change important physiological properties like cell communication, excitability and cell volume when applied locally [3,4,5]. Recently,angiotensin II and renin have been found in the nucleus and mitochondria [6–7] suggesting an important role on the regulation of cellular function and oxidative stress. The functional significance of the intracrine renin and Ang II was described in cardiac cells when both compounds were dialyzed intracellularly resulting in the impairment of cell communication or a change ofthe inward calcium [4,8,18]. Other studies revealed that aldosterone modulates the intracrine effect of AngII in cardiac cells of rats.Chronic treatment with eplerenone, which is an inhibitor of aldosterone, for instance,inhibited the intracrine effect of AngII in cardiac muscle indicating an important role of the mineralocorticoid receptorson the modulation of the intracrine renin angiotensin component of the local RAAS [9].

The activation of the renin angiotensin system is known to be involved in vascular remodelingincluding inflammation, fibrosis, hypertrophy,apoptosis, endothelial dysfunction and pressure action [10]. Moreover, Ang II is an important regulator of vascular tone through different mechanisms includingRhoA/Rho kinase, transient receptor potential (TRP) channels, reactive oxygen species, and arachidonic acid metabolites [11]. It is also known that the potassium current plays an important role on the regulation of resting potential and state of contractility of vascular smooth muscle cells [12].The vascular tone is controlled by the intracellular concentration of Ca^{2+} by way of Ca^{2+}–calmodulin regulation of myosin light-chain kinase [13]while potassium channels affect vascular tone through their effects on membrane potential [12].The increment of the potassium current in vascular smooth muscle cells elicited by beta-adrenergic agonists,is related to the intracellular levels of cAMP while activation of PKC inhibit the potassium current and depolarize the cell membrane [14]. In coronary arterial myocytesextracellular Ang II inhibits BKCachannels through a PKC-independent mechanism [15].

Recently,it was found that intracellular Ang II has an effect opposite to that of extracellular Ang II on arterial potassium currentin vascular resistance vessels [16] suggesting an important intracrine effect of the peptide on the regulation of peripheral resistance.Indeed,the increment of potassium current elicited by intracellular Ang II and related to the activation of protein kinase C (PKC), counteracts the reduction of the potassium current and depolarization caused by extracellular Ang II thereby relaxing the vascular smooth muscle. Valsartan administered inside the cytosol,inhibited the effect of intracellular AngII on potassium current supporting the view that an intracellular AT1 receptor was involved in the effect of the peptide [16].This is particularly important because previous studies indicated the presence of intracellular AT1 receptors in vascular smooth cells [17].

It is then conceivable that enhanced intracellular levels of Ang II in vascular resistance vessels caused by its synthesis or internalization, be an important factor on the regulation of blood pressure especially during pathological conditions in which the vascular tone and the peripheral resistance are enhanced by the elevated plasma levels of Ang II as is the case of hypertension.

Further studies will help to understand the pathophysiological implications of this finding.

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