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COMMENT

New insight into increased angiotensin II type 1 receptor expression in Snx1$^{-/-}$ mice

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The renin–angiotensin system (RAS) consists of angiotensinogen, renin, angiotensin-converting enzyme, angiotensin II (Ang II) and the Ang II type 1 (AT_1) and type 2 (AT_2) receptors [1]. RAS activities regulate blood pressure (BP), blood volume, cell proliferation and differentiation, metastasis, and tissue remodeling. Several new findings focused on topics including Ang 1–7, AT_2/Mas, and AT_4 insulin-regulated membrane aminopeptidase, several Ang II-generating enzymes, and AT_1/AT_2 heterodimerization have been reported over the past few decades.

The sorting nexin 1 (SNX) family is composed of a diverse group of cytoplasmic and membrane-associated proteins that are involved in various aspects of receptor endocytosis and trafficking through endosomes [2–4]. Endocytosis and trafficking are also important functions of G protein-coupling receptors (GPCRs), including the AT_1 and AT_2 receptors. For example, while SNX1 binds two dopamine receptors (D_1 and D_5 receptors), which are GPCRs, it binds only the D_5 receptor strongly [5, 6]. Recently, Snx1$^{-/-}$ mice were shown to have high BP associated with increased renal expression of the AT_1 receptor, nicotinamide adenine dinucleotide phosphate oxidase subunits, D_5 receptor, and sodium chloride cotransporter [7]. Acute renal-restricted depletion of SNX1 resulted in a blunted natriuretic response and high BP in mice due to impaired D_5 receptor activity. In addition, several SNX1 SNPs were shown to be associated with an antihypertensive response to hydrochlorothiazide monotherapy among hypertensive African Americans in the Pharmacogenomic Evaluation of Antihypertensive Responses study. More recently, providing greater mechanistic precision, in this issue of *Hypertension Research*, Liu et al. successfully report that Ang II-induced contraction of mesenteric arteries was much greater in Snx1$^{-/-}$ mice than in WT mice, whereas there was no obvious difference in phenylephrine-induced contraction between the mice [8]. Interestingly, AT_1 receptor protein levels in the aorta were significantly elevated in the Snx1$^{-/-}$ mice. In addition, the authors found that AT_1 receptor protein levels, but not AT_1 receptor mRNA levels, were elevated after SNX1 knockdown, probably independent of the D_5 receptor, which indicated that SNX1 may be involved in the process of AT_1 receptor protein degradation. This may represent a novel mechanism for the regulation of BP.

Proteasomes and lysosomes are the two most important proteolytic machines in cells [9]. In this study, proteasomal inhibition, rather than lysosomal inhibition, increased AT1R expression in embryonic thoracic aortic smooth muscle cells [8]. Systemic administration of proteasome inhibitors suppressed pressure-overload cardiac hypertrophy and benefitted long-term cardiac remodeling in animal models [10]. On the other hand, a proteasome inhibitor promoted maladaptive remodeling in surviving mice with transverse aortic constriction and activated the calcineurin-nuclear factor of activated T cells pathway in cardiomyocytes in vitro and in vivo [11]. Thus, the cause of this conflict in the data is unclear at this time. Notably, there has been a wealth of discussion on the effects of proteasome inhibition on vascular function and remodeling, which reduce high BP [12]. Proteasomal functional insufficiency is a major pathogenic factor in the cardiovascular system. Finally, this study provides useful information due to the finding that SNX1-mediated AT_1 receptor degradation occurs mainly through the proteasomal pathway [8].

The Fig. 1 shows possible mechanisms for the interaction between the AT_1 receptor and SNX1. Functional SNX1 initiates Ang II-mediated AT_1 receptor activation at the plasma membrane, which results in dissociation of the G protein from the receptor and activates signal transduction (high blood pressure signaling), subsequently inducing receptor internalization and trafficking (Fig. 1A). Thus,

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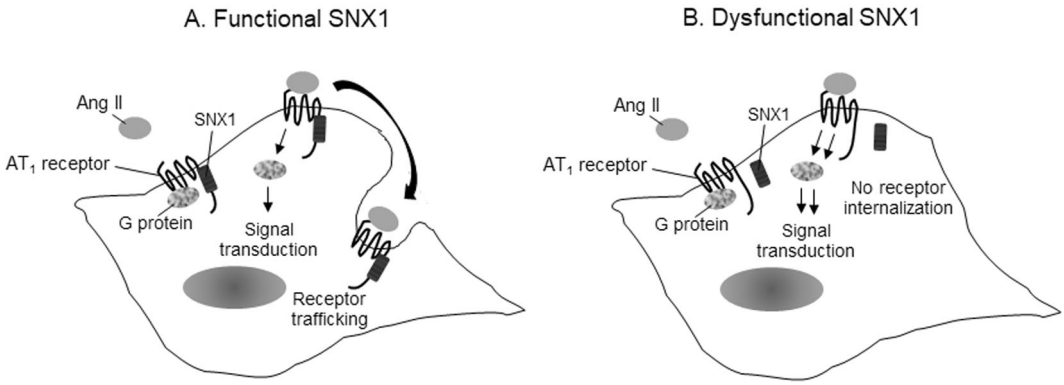

Fig. 1 Possible mechanisms for the interaction between the AT_1 receptor and functional (**A**) or dysfunctional (**B**) SNX1

functional SNX1 optimally regulates AT_1 receptor degradation. On the other hand, dysfunctional SNX1 results in failed agonist-activated receptor internalization and the continued presence of indices of high BP signaling and does not regulate AT_1 receptor degradation or increase receptor expression Fig. 1B.

In conclusion, this new model of the development of hypertension implies that the trafficking protein SNX1 may be a crucial target of hypertension and antihypertensive therapy.

Compliance with ethical standards

Conflict of interest The author declares no competing.

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