During the past 40 years, most of the new developed and effective antihypertensive drugs target the classic renin-angiotensin–aldosterone system (RAAS) by blocking receptors (such as the mineralocorticoid receptor or the angiotensin II type 1 receptor) and also by inhibiting enzymes within the angiotensin II (Ang II) formation pathway, such as the angiotensin-converting enzyme I (ACE I) and renin as well. More recently, a different group of targets within the RAAS has been explored as antihypertensive molecules. This parallel RAAS has been described as the natural vasodilatory and counterregulatory pathway of the RAAS. By year 2000, this pathway was discovered consisting of ACE2, angiotensin 1–9 (Ang1–9), Ang(1–7) and recently, alamandine. These endogenous molecules display biological effects opposed to Ang II; thus, their activation induces vasodilation, blood pressure reduction, antihypertrophy, and antihyperplasia, suggesting a plausible antihypertensive role of this axis. In this issue of Hypertension, the role of dipeptidyl peptidase III (DPP III) as a new antihypertensive agent has been characterized in the mice.1

As a direct enzymatic product of ACE2, Ang (1–7) has been studied profusely, and it has shown to activate the G-protein–coupled Mas receptor, which triggers a signaling cascade that results in vasodilation, oxidative stress reduction, and antihypertrophic and antifibrotic effects. A cyclic Ang (1–7) analog containing a thioether bridge that makes it resistant to enzymatic digestion and also a formulation of Ang (1–7) incorporated to hydroxypropyl-β-cyclodextrin/Ang (1–7) β-cyclodextrin has revived prospects for exploring the therapeutic antihypertensive potential of Ang (1–7)–related peptides.2

Most research about the DPP family has been focused on DPP IV and its family members (Table) in several biological paths and different pathologies, such as glucose homeostasis and diabetes mellitus, the immune system and inflammation, and atherosclerosis.3 Within this group, there is a significant connection between their members about substrate specificity, inhibitors, and functions.4 In Dahl salt-sensitive rats, high-salt diet for 7 days increases blood pressure, and treatment with the DPP IV inhibitor vildagliptin reduces circulating DPP–4 activity, increases plasma glucagon–like peptide 1, and reduces the development of salt-induced hypertension, which is associated to increased urine sodium excretion.9

Together with ACE2 and the abovementioned vasoactive peptides Ang (1–7), Ang (1–9), and alamandine, DPP III is...
a multifaceted cytosolic oligopeptide N-end cutter that regulates, among others, the Ang II and Ang IV turnover (Figure). Thereby, this enzyme can regulate several physiological and pathological processes associated with these peptides. DPP III is an ubiquitous peptidase, and its activity has also been detected in extracellular fluids, such as retroplacental serum, seminal plasma, and cerebrospinal fluid. The mechanism of entry of this peptidase into these fluids is not clear (it could be the result of its release as a consequence of injury or death of the cell of its origin or by secretion via prostasome-like membranous bodies). Tetrapeptides to octapeptides have proved to be their best substrates, and any modification of the C-terminal carboxyl group does not affect the catalytic efficacy of the peptidase.

In this issue Pang et al, an elegant proof of concept study in mice, have shown that DPP III administered during 4 weeks (3× per week by intravenous injection), through catalytic reduction of Ang II levels, significantly diminished systolic blood pressure, cardiac hypertrophy, and myocardial fibrosis induced by Ang II in an extent at least similar to the effect of the angiotensin receptor blocker candesartan in effective antihypertensive doses. In the same experiments, they observed that DPP III diminished urine albumin excretion, kidney damage, and the renal protein levels of the proinflammatory molecule monocyte chemoattractant protein-1 and the procoagulant platelet activator inhibitor-1. The focus of this study was on the capability of DPP III to hydrolize Ang II, the main effector of the RAAS. In addition, this enzyme is able to hydrolize Ang IV implicated in hypertrophy, the nuclear factor kappa-light-chain-enhancer of activated B cells activation and also in increased levels of platelet activator inhibitor-1, monocyte chemoattractant protein-1, interleukin-6, and tumor necrosis factor-α. Moreover, Ang IV does regulate cell growth in cardiac fibroblasts, endothelial cells, and vascular smooth muscle cells as well.

Future aspects to be answered to precise the antihypertensive role of DPP III starting from this study are reproducibility, efficacy, and safety in different experimental models of hypertension; its effect on hypertension independent of Ang II—in this study, no antihypertensive effect was observed in noradrenaline-induced hypertension; DPP III delivery and bioavailability; and also the simultaneous measurements of levels of other vasodilatory peptides from the RAAS, such as Ang (1–7), Ang (1–9), and bradykinins. Another interesting issue, which has been preliminary explored in this study, is the possible synergistic effect by combining DPP III with an angiotensin II receptor blocker (or with an ACE inhibitor) in terms of reversing residual hypertensive cardiovascular and renal damage.

Besides, as the in vitro findings here on the kinetics of its hydrolytic activity show that Ang II is cleaved by DPP III with a Km=3.7 µmol/L, a higher value compared with ACE2 (with a Km=2 µmol/L), these data could indicate a lesser catalytic efficiency of DPP III with respect to ACE2. Furthermore, it is well known that ACE2 activity can be regulated by ACE inhibitors and angiotensin II receptor blockers. Therefore, it seems relevant to determine whether conventional hypertension treatment could regulate the activity of DPP III.

This study using DPP III was aimed to effectively reduce Ang II levels by enzymatic cleavage to Ang IV and to C-terminal tetrapeptide sequence. This peptidase belongs to
a rather new concept to treat hypertension based on increasing endogenous Ang II antagonists, the beneficial molecules, by different mechanisms. ACE2, Ang (1–7), alamandine, and Ang (1–9) now belong to this group of new endogenous angiotensin II antagonism. Although further research is necessary to establish the antihypertensive role of DPP III, this study¹ has shown that DPP III possesses many attributes to become a next musketeer.

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References
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