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Is angiotensin-(3–4) (Val-Tyr), the shortest angiotensin II-derived peptide, opening new vistas on the renin–angiotensin system?

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Abstract

Angiotensin-(3−4) (Ang-(3−4) or Val-Tyr) is the shorter angiotensin (Ang) II-derived peptide, formed through successive hydrolysis that culminates with the release of Val-Tyr as a dipeptide. It is formed both in plasma and in kidney from Ang II and Ang III, and can be considered a component of the systemic and organ-based renin–angiotensin system. It is potently antihypertensive in humans and rats, and its concerted actions on proximal tubule cells culminate in the inhibition of fluid reabsorption, hyperosmotic urinary excretion of Na^+. At the renal cell signaling level, Ang-(3−4) counteracts Ang II-type 1 receptor-mediated responses by acting as an allosteric enhancer in Ang II-type 2 receptor populations that target adenosine triphosphate-dependent Ca^{2+} and Na^+ transporters through a cyclic adenosine monophosphate-activated protein kinase pathway.

Keywords

Ang-(3–4), local renal RAS, AT_1R/AT_2R heterodimer dissociation, cyclic adenosine monophosphate-dependent protein kinase, Na^+-ATPase, hyperosmotic urinary Na^+ excretion, antihypertensive action

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Introduction

During the past three decades research has progressively shown a new and fascinating world behind the century-old history of the pressoric renin–angiotensin system (RAS), discovered in several seminal steps between 1898[1] and 1941.[2–7] The new world is that of shorter peptides originating from both the decapeptide angiotensin I (Ang I) and the octapeptide angiotensin II (Ang II),[8] with Ang-(1−7) being the best known in terms of physiological effects and intracellular signaling pathways (reviewed in Alenina and Santos).[9] Interestingly, this early representative of the Ang I/Ang II-derived peptides soon emerged as a potent counterbalance to the vasoconstrictive actions of RAS.

In parallel with the discovery of the structure and actions of the shorter Ang I/Ang II-derived peptides, the simple and earlier view of RAS as a classic endocrine system shifted to a dual concept involving the coexistence of the systemic RAS – mainly regarding cardiovascular actions – with the so-called organ-based RAS.[10] In this system described in heart,[11] kidney,[12] brain[13] and liver,[14] among other organs, the main event is the local formation of Ang II.[15] Interestingly, crosstalk between different local RAS systems has physiological and pathological relevance for heart and kidney.[16] Even though the 'organ uptake theory' dominated this new view of RAS because it could explain the significant amounts of Ang II found in several organs/tissues,[17] the concept was soon expanded to include genes involved in the synthesis of renin,[18,19] precursors such as

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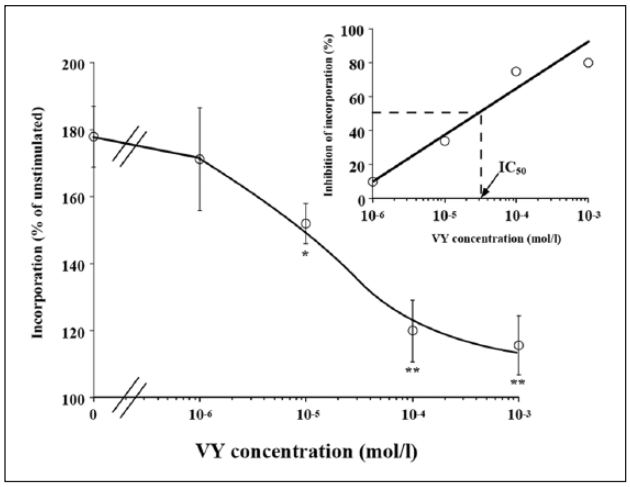

Figure 1. Proliferation of angiotensin II (Ang II)-stimulated vascular smooth muscle cells is inhibited by angiotensin-(3−4) (Ang-(3–4)) (represented by VY) in a dose-dependent manner. This figure shows WST-8 reduction by nicotinamide adenine dinucleotide (NADH) in the presence of 1 μmol/L Ang II and increasing concentrations of Ang-(3–4). The inset shows that antiproliferative action of Ang-(3–4) has a 50% inhibitory concentration (IC_{50}) in the micromolar range. Reproduced from Matsui et al.,[28] with permission.

angiotensinogen[11,20] and enzymes (from renin to the angiotensin II-converting enzymes, ACE and ACE2).[8,21,22] These components were encountered in many different organs, together with local Ang II concentrations significantly higher than those of the circulating peptide.[23]

Angiotensin-(3−4)

Moving on beyond Ang-(1–7) to the myriad of very short Ang I/Ang II-derived peptides, their formation and their potential functional role were first described in animal and plant tissues and their effects were demonstrated using extracts of these tissues.[24,25] One of the shorter peptides that was soon identified for its important physiological relevance was the dipeptide angiotensin-(3–4) (Ang-(3–4) or Val-Tyr). Ang-(3−4) was first purified from rice extracts (sake)[25] and promptly assayed for cardiovascular actions.[26,27] Earlier work on isolated luminal proximal tubule membranes and Ang II provided evidence that Ang-(3−4) was a metabolite of local renal RAS.[8] In plasma, Ang-(3−4) can be formed from angiotensin III (Ang III),[27] thus making it a component of both the local and systemic RAS.

A few reports indicated that Ang-(3−4) had significant physiological effects in cardiovascular homeostasis. As well as its clear inhibitory effect of ACE *in vitro*,[27] Ang-(3–4) was antiproliferative in cultured smooth muscle cells[28] (Figure 1), and had vasodilatory effects on the aorta in hypertensive and non-hypertensive rats.[29,30] These vascular antagonistic actions with Ang II could also be helped by its free radical reducing and scavenging ability,[30] which can be related to the very hydrophobic nature of its molecular moiety.[31] Interestingly, Ang-(3−4) is effective when administered orally,[26,32,33] a property associated with its resistance to hydrolysis and its high capacity to permeate intestinal cells.[34] One mechanism proposed to explain these effects involves L-type Ca^{2+} channels, independently of Ang II receptors.[28] In phase 1 clinical trials, Ang-(3–4) purified from sardine extracts administered orally depressed Ang II and aldosterone plasma levels (Figure 2(a)) and had clear antihypertensive effects in mildly hypertensive adults (Figure 2(b)).[32] Increased Ang I plasma levels indicated that the inhibition of ACE *in vivo* also occurred.[32] Interestingly, the plasma levels of Ang-(3–4) are markedly lower in hypertensive than in healthy individuals, levels negatively correlated with systolic pressure.[35]

Basal renal levels of Ang-(3–4) are higher than in other tissues and plasma, and renal accumulation was also observed after a single oral administration (Figure 3).[36] This raises the question as to whether this renal accumulation of Ang-(3–4) was the result of uptake from the circulating plasma or arose from local synthesis, thus being a component of the renal local RAS? From combined use of fluorescent substrates for proteolytic enzymes, specific inhibitors, high performance chromatographic analyses and a family of synthetic peptides derived from Ang I and Ang II, it was found that successive conversion, i.e. of Ang II → Ang-(1–7) → Ang-(1–5) → Ang-(1–4) → Ang-(3–4), is the main route for the formation of Ang-(3–4) in basolateral membranes of proximal kidney tubule cells (Figure 4).[21] This compartmentalisation of synthesis in basolateral membranes was indicative of a role in the important and varied transport processes − some mediated by ATPases − that carry ions across these membranes towards the renal interstitium. These processes are mostly linked to the homeostasis of body fluid compartments and the regulation of arterial blood pressure.[37,38]

Ang-(3−4) and Ca^{2+} and Na^{+} transporters in kidney: interaction with Ang II receptors?

Plasma membrane Ca^{2+}-ATPase (PMCA) is considered to be the primary active transporter responsible for fine-tuning of Ca^{2+} extrusion from the cytosol.[39] In kidney proximal tubule cells, Ca^{2+} stimulates the Ang II-regulated reabsorption of fluid[38] and, therefore, small fluctuations of the cation within the cells are significant in homeostasis in body fluid compartments. Ang-(3–4), with a very high affinity, is a potent counteracting agent ($A_{1/2}$ in the femtomolar range) inhibiting PMCA exerted by Ang II in physiological concentrations in tissues (Figure 5(a)).[40] Mechanistically, Ang-(3–4) acts through a signaling pathway that starts with Ang II-type 2 receptors (AT_2R) and includes regulatory phosphorylation mediated by cAMP-activated protein kinase (PKA), which is upregulated by Ang-(3–4)-induced dissociation of

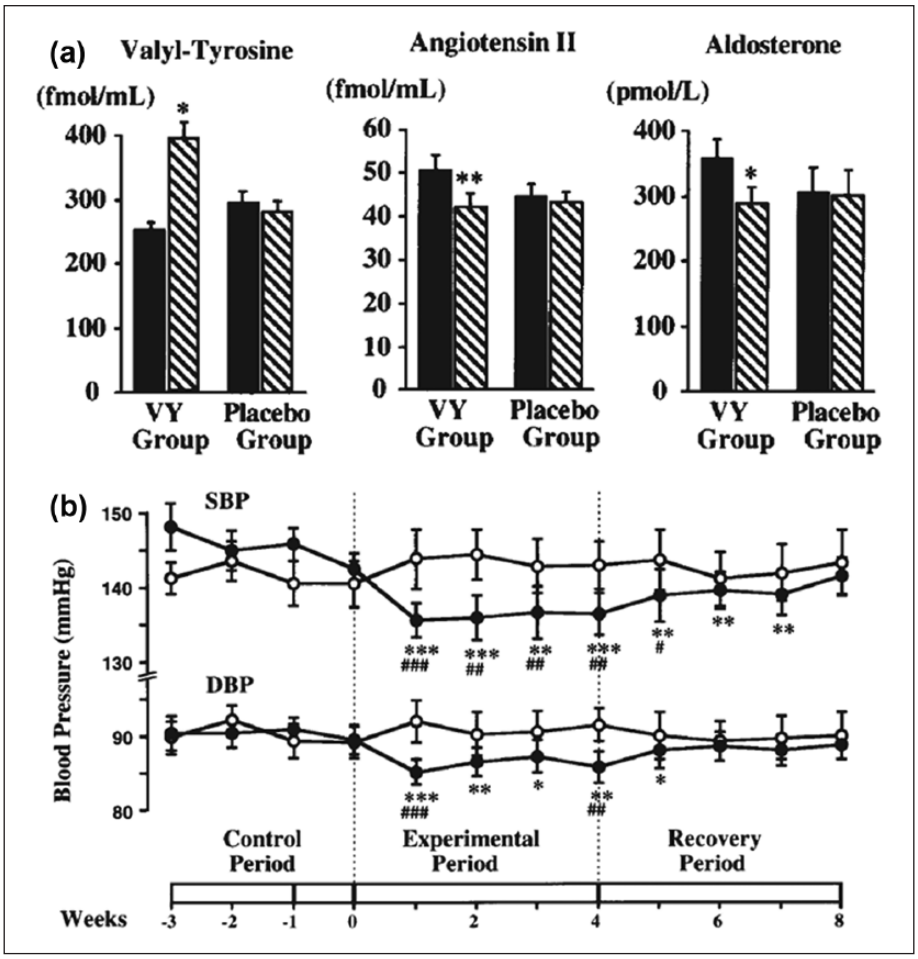

Figure 2. Oral treatment of mild hypertensive individuals with 3 mg angiotensin-(3−4) (Ang-(3–4)) (represented by VY), twice daily. (a) Plasma concentration of Ang-(3–4), angiotensin II (Ang II) and aldosterone before and after a 4-week experimental period. Increased levels of circulating Ang-(3–4) are seen in parallel with reduced plasma Ang II and aldosterone, supporting the idea that the dipeptide acts as a systemic angiotensin-converting enzyme inhibitor. (b) Systolic and diastolic blood pressure of hypertensive individuals were reduced during treatment with Ang-(3–4), which persisted for up to 7 weeks after the treatment was interrupted. Modified from Kawasaki et al.,[32] with permission.

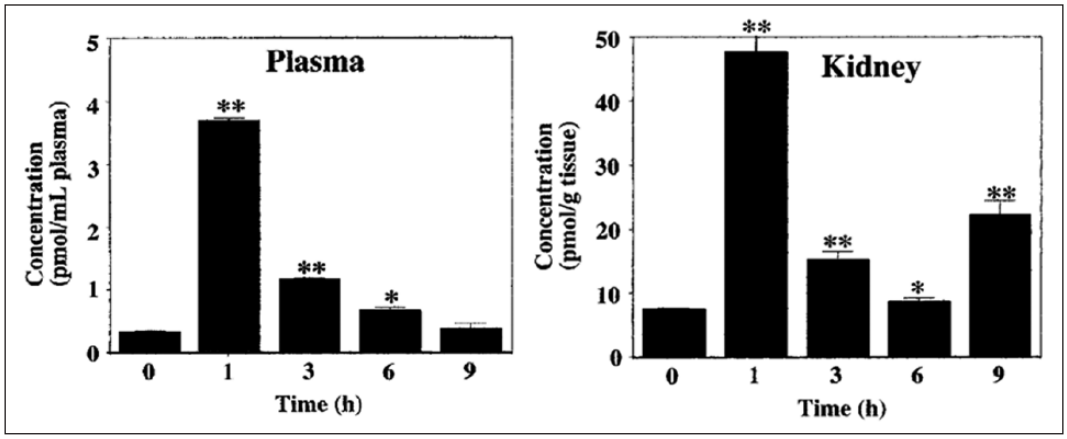

Figure 3. Plasma and kidney levels of angiotensin-(3−4) (Ang-(3–4)) after a single oral dose (10 mg/kg) in 18-week old spontaneously hypertensive rats. Although circulating concentrations of the dipeptide return to base levels 6 hours after administration, its level remains higher in the kidney, indicating the existence of a mechanism of tissue concentration or local production of Ang-(3–4). Modified from Matsui et al.,[36] with permission.

AT_1R/AT_2R heterodimers.[40,41] Using a transfected renal cell line overexpressing AT_2R, Ang-(3–4) acts as an 'allosteric enhancer' and generates very high-affinity Ang II binding sites in this family of receptors (Figure 5(b)).[41] This seems to be the first step by which Ang-(3–4) switches on an AT_2R-mediated signaling pathway that counteracts the inhibition of PMCA through the AT_1R-mediated pathway.

The antihypertensive effects of Ang-(3–4) in spontaneously hypertensive rats (SHRs)[26,27] can also be explained by the specific targeting of Ang-(3–4) on Na^+ transport in renal proximal tubules, in a local tissular environment pathologically modified due to hypertension. Ang-(3–4) strongly inhibits basolateral ouabain-resistant Na^+-ATPase of SHRs, without any effect on the ouabain-sensitive (Na^++K^+)ATPase or the ouabain-resistant Na^+-ATPase of healthy rats.[33] Orally administrated, it promotes a hypertonic natriuresis only in SHRs. Again, and probably as an indicator of the common mechanism exerted in the basolateral membranes: (a) the physiological effects of Ang-(3−4) requires dissociation of AT_1R/AT_2R heterodimers in normal rats (Figure 6(a)); and (b) inhibition of SHR Na^+-ATPase is due to AT_2R upregulating PKA (Figure 6(b)).[33] The idea of a common cell signaling mechanism receives further support because the counteracting effects of Ang-(3−4) are exerted against AT_1R-mediated protein kinase C (PKC), one of the most important Ang II-stimulated modulators of transepithelial Na^+ fluxes in the kidney.[10,37,38,42,43] Although the actions of Ang-(3−4) in renal ion-transporting ATPases are significant when intrarenal Ang II levels are high, we should note the hierarchy in these effects: at very low (femtomolar) concentrations range, Ang-(3−4) reactivates the basolateral plasma membrane Ca^{2+}-ATPase (Figure 5(a)), whereas nanomolar concentrations can inhibit Ang II-stimulated Na^+-ATPase.[33] The resulting effect, requiring a continuous increase in Ang-(3−4) levels (formed from Ang II; Figure 4), would first lead *in vivo* to depressed intracellular Ca^{2+}, diminished Ca^{2+}-dependent PKC activity, recovery of lower basal Na^+-pumping activity, and depressed active Na^+ flux towards the peritubular space. Further inhibition of the Na^+ pump itself – also by downregulating PKC activity and upregulating PKA[41–43] will occur as Ang-(3−4) increases in concentration.

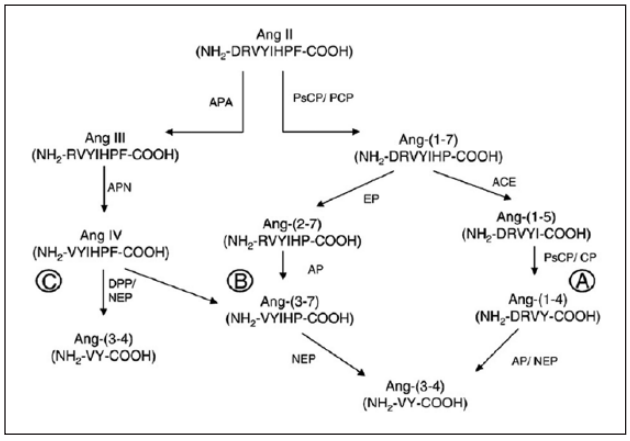

Figure 4. Enzymes and pathways responsible for angiotensin-(3−4) (Ang-(3–4)) formation in basolateral membranes from sheep kidney proximal tubule cells. Aminopeptidases and neprilysin are key enzymes required for at least one step of each pathway. AP: aminopeptidase; NEP: neprilysin; EP: endopeptidase; APA: aminopeptidase A; PsCP: Plummer's sensitive carboxypeptidase; PCP: prolylcarboxypeptidase; ACE: angiotensin-converting enzyme; APN: aminopeptidase N; DPP: dipeptidylpeptidase. Reproduced from Axelband et al.,[21] with permission.

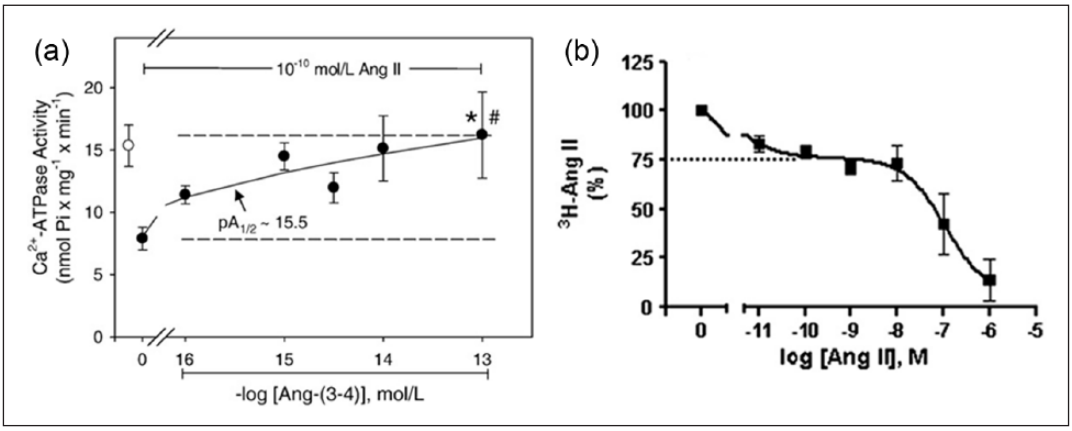

Figure 5. (a) Angiotensin-(3−4) (Ang-(3–4)) reactivates, with a very high affinity ($pA_{1/2}$ ~15.5), the angiotensin II (Ang II)-inhibited basolateral plasma membrane Ca^{2+}-ATPase. Ca^{2+} pump activity was assayed with 10^{-10} mol/L Ang II and increasing concentrations of Ang-(3–4). Modified from Axelband et al.,[40] with permission. (b) Ang-(3−4) creates a probable high affinity site for Ang II at Ang II-type 2 receptors at ~10^{-12} mol/L, i.e. with an affinity ~5 orders of magnitude higher than in the absence of Ang-(3−4) (10^{-7} mol/L). The competition binding assay was carried out in HEK 293T cells overexpressing AT_2R in 10^{-10} mol/L Ang-(3–4). Modified from Axelband et al.,[41] with permission.

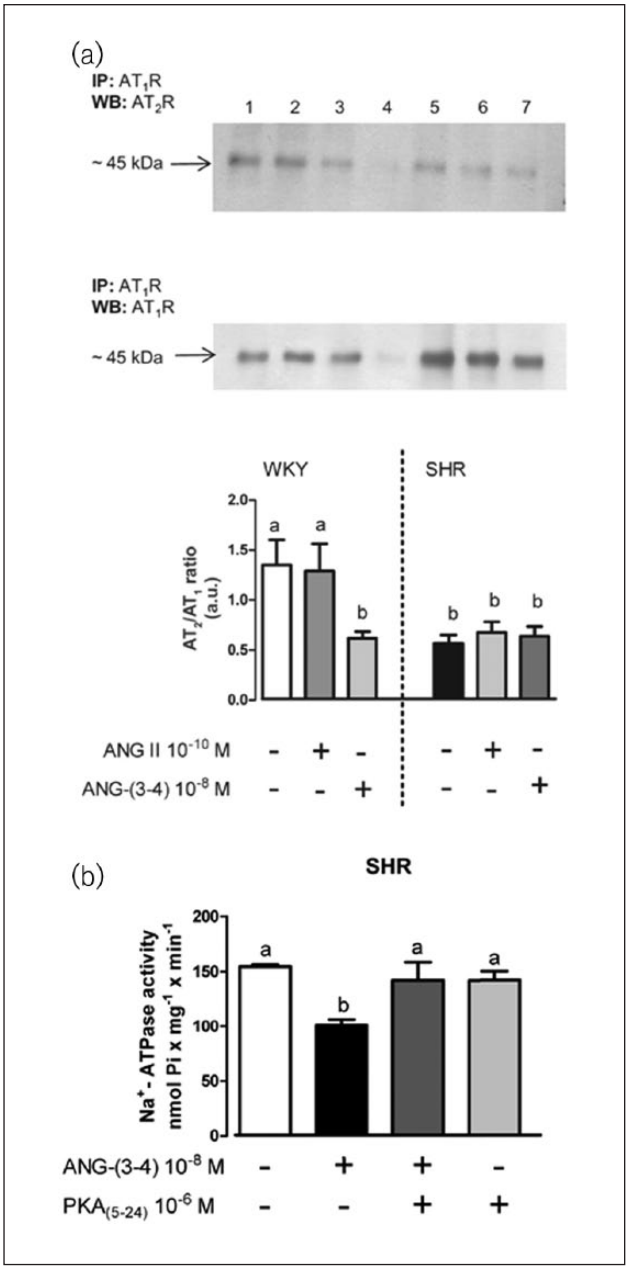

Figure 6. (a) Angiotensin-(3−4) (Ang-(3–4)) induces dissociation of Ang II-type 1 receptor (AT_1R)/Ang II-type 2 receptor(AT_2R) heterodimers in normotensive rats, but not in spontaneously hypertensive rats (SHRs). SHRs have a constitutively lower content of heterodimers. Immunoprecipitation assays were carried out using specific AT_1R antibody, followed by western blotting using specific AT_2R antibody. The specificity of the antibodies was confirmed by preadsorption of the antibodies onto the recombinant immunogenic peptide.[48] (b) Inhibition of SHR hyperactive Na^+ pump by Ang-(3–4) is mediated by protein kinase A (PKA), downstream AT_2R activation. Na^+-ATPase activity was assayed without any peptide, or in 10^{-8} mol/L Ang-(3–4) and 10^{-6} mol/L PKA inhibitor peptide $PKA_{(5-24)}$ in the combinations shown on the abscissae. Reproduced from Dias et al.,[33] with permission.

Even though interaction with AT_2R seems to play a pivotal role in Ang-(3−4) actions in renal tissue, little is known about its effects and related signaling mechanisms in other organs and tissues. As AT_2Rs are associated with a myriad of physiological actions in many different organs, and seem to be a common target of small peptides derived from natural proteins,[44] Ang-(3−4) actions might have much broader targets than initially thought. Thus it can be speculated that the AT_2R-mediated effects of Ang-(3−4) might include – beyond blood pressure control, natriuresis and vasorelaxation – neural and gastrointestinal actions, as demonstrated for other small peptides that bind to AT_2R.[44–47] Furthermore, AT_2R-independent mechanisms might also mediate Ang-(3−4) actions in other tissues. The antiproliferative actions of this dipeptide in rat aorta were demonstrated to be independent of angiotensin receptors, but influenced by Ca^{2+}-mediated pathways.[28] As the Ang-(3−4) influence on Ca^{2+} homeostasis seems to be a critical event in kidney cells,[21,40,41] Ca^{2+} would be a signaling intermediate of the dipeptide actions in different tissues.

Conclusion

In summary, Ang-(3–4) can be considered one of the most potent counter-regulators of systemic and local RAS, with an important impact on body-fluid homeostasis through common mechanisms that target renal active transporters of Ca^{2+} and Na^+, showing natriuretic and antihypertensive effects. As Ang-(3–4) permeates intestinal cells[34] and is effective when given orally,[26,32,33] it is a potential antagonist of local and systemic Ang II effects for therapeutic purposes.

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