Mini Review

# Angiotensin-(1-7): A Novel Peptide to Treat Hypertension and Nephropathy in Diabetes?

**Ranjit Singh Padda, Yixuan Shi, Chao-Sheng Lo, Shao-Ling Zhang#\* and John SD Chan#\***

*Université de Montréal, Centre de recherche du Centre hospitalier de l'Université de Montréal (CRCHUM), Tour Viger, 900 Saint Denis Street, Montreal, Quebec, H2X 0A9, Canada*

*#These two authors contributed equally to this work*

**\*Corresponding author:** John SD Chan or Shao-Ling Zhang, Université de Montréal, Centre de recherche du Centre hospitalier de l'Université de Montréal (CRCHUM), Tour Viger, 900 Saint Denis Street, Montreal, Quebec, H2X 0A9, Canada, Tel: 514-890-8000; E-mail: john.chan@umontreal.ca; shao.ling.zhang@umontreal.ca

## Abstract

The renin-angiotensin system (RAS) plays a pivotal role in mammalian homeostasis physiology. The RAS can be delineated into a classical RAS (the pressor arm) including angiotensinogen (Agt), renin, angiotensin-converting enzyme (ACE), angiotensin II (Ang II) and angiotensin type 1 receptor (AT1R), and a counterbalancing novel RAS (the depressor arm) including Agt, renin, angiotensin-converting enzyme-2 (ACE-2), angiotensin-(1-7) (Ang 1-7) and Ang 1-7 receptor (or Mas receptor (MasR)). Hyperglycemia (diabetes) induces severe tissue oxidative stress, which stimulates the pressor arm of the renal RAS axis and leads to an increase in ACE/ACE-2 ratio, with excessive formation of Ang II. There is a growing body of evidence for beneficial effects of the depressor arm of RAS (ACE-2/Ang 1-7/MasR) axis in diabetes, hypertension and several other diseased conditions. Evidence from *in-vitro*, in vivo and clinical studies reflects anti-oxidant, anti-fibrotic, and anti-inflammatory properties of Ang 1-7. Most of the currently available therapies only target suppression of the pressor arm of RAS with angiotensin receptor blockers (ARBs) and ACE inhibitors (ACEi). However, it is time to consider simultaneous activation of the depressor arm for more effective outcomes. This review summarizes the recent updates on the protective role of Ang 1-7 in hypertension and kidney injury in diabetes, as well as the possible underlying mechanism(s) of Ang 1-7 action, suggesting that the ACE-2/Ang 1-7/MasR axis can be developed as a therapeutic target for the treatment of diabetes-induced hypertension and renal damage.

**Keywords:** Angiotensin 1-7; Angiotensin converting enzyme-2; Mas receptor; Hypertension; Diabetic nephropathy

## Abbreviations:

ACE: Angiotensin Converting Enzyme; ACE-2: Angiotensin Converting Enzyme-2; Agt: Angiotensinogen; ACR: Albumin to Creatinine Ratio; Ang 1-7: Angiotensin-(1-7); Ang I: Angiotensin-(1-10); Ang II: Angiotensin-(1-8); AT1R: Ang II type 1 receptor; ARB: Angiotensin Receptor Blocker; DHE: Dihydroethidium: ERK: Extracellular-signal-Regulated Kinase; GFR: Glomerular Filtration Rate; HO-1: Heme oxygenase-1; MAPK: Mitogen-Activated Protein Kinase; NF-κB: Nuclear Factor κB; NADPH: Nicotinamide Adenine Dinucleotide Phosphate; NOX: NADPH oxidase; NHE-3: Sodium/hydrogen exchanger-3; PPAR: Peroxisome Proliferator-Activated Receptor; PKC: Protein Kinase C; RAS: Renin Angiotensin System; ROS: Reactive Oxygen Species; RPTCs: Renal Proximal Tubule Cells; SBP: Systolic Blood Pressure; STAT3: Signal Transducer and Activator of Transcription 3; STZ: streptozotocin; TACE: TNF-Alpha Converting Enzyme; TNF: Tumor Necrosis Factor; TGF-β1: Transforming Growth Factor beta1; VEGF: Vascular Endothelial Growth Factor; JNK: c-Jun N-terminal Kinase.

## Introduction

Diabetes Mellitus is becoming an endemic illness of developed countries and a major burden on healthcare services [1]. It is well established that the renin-angiotensin system (RAS) plays a key role in the pathogenesis of diabetic nephropathy (DN), leading to end stage renal disease (ESRD). The RAS regulates systolic blood pressure (SBP) and renal function through two distinct opposing arms, the pressor arm: angiotensin converting enzyme (ACE)/angiotensin II (Ang II)/Ang II type 1 receptor (AT1R) and the depressor arm: angiotensin converting enzyme-2 (ACE-2)/angiotensin 1-7 (Ang 1-7)/Ang 1-7 receptor (MasR). Under normal healthy conditions, both opposing arms work together in a balanced manner. The ACE/Ang II/AT1R axis is crucial for the reabsorption of sodium, vasoconstriction and therefore, for the increase of SBP and renal injury. On the other hand, the ACE-2/Ang 1-7/MasR axis counteracts the effects of Ang II by triggering natriuretic and diuretic effects, vasodilation for maintenance of SBP and attenuation of renal injury. Most of the therapeutic drugs target the ACE/Ang II/ATIR pathway to retard or delay the progression of renal injury in diabetes, but could not reverse the nephropathy progression. Therefore, there is a need to develop additional drug targets for the prevention of nephropathy progression in diabetes. There is emerging evidence for the benefits of ACE-2/Ang 1-7/MasR axis, which could be developed as a therapeutic target for future clinical use [2].

ACE-2, discovered in 2000, is a type 1 integral membrane protein and is widely distributed in various tissues mainly kidneys, intestines, heart and testis. ACE-2 acts as a negative regulator of Ang II and it efficiently metabolizes Ang II to Ang 1-7 for maintenance of blood pressure homeostasis. ACE-2 has a 400-fold greater catalaytic efficiency to convert Ang II than Ang I toward the formation of Ang 1-7 and Ang 1-9, respectively. The Ang II/Ang 1-7 ratio increases

markedly in chronic conditions like DN and cardiovascular disorders. It results in the accumulation of Ang II and hyperactivation of the pressor arm (ACE/Ang II/AT1R) of the RAS [3,4].

Ang II and Ang 1-7 show their antagonistic biological responses after binding to G protein-coupled receptors, AT1R and MasR, respectively [5]. Biochemically, these peptides differ only in a single amino acid at the C-terminal which gives them opposite functions. The main physiological role of Ang II is to maintain normal blood pressure. However, uncontrolled excessive formation of Ang II happens in various diseased conditions, which triggers renal injury and systemic hypertension by up-regulating fibrogenic, pro-inflammatory and apoptotic pathways.

Ang 1-7 is a heptapeptide found in the heart and kidneys. Ang 1-7 concentrations are six times higher in the kidney than in plasma, highlighting an intrarenal production of the peptide and its role in renal homeostasis [6]. Ang 1-7 is a specific ligand for MasR and, in the absence of MasR-specific binding, the biological responses of the peptide are lost [5]. Diabetic conditions cause the suppression of the protective arm of the RAS by diminishing the expression of Ace2 and MasR at both gene and protein levels. Our laboratory reported that Ang 1-7 normalizes the expression of renal Ace2 and MasR in diabetes [7].

Several beneficial roles of Ang 1-7 have been reported in various cell lines and diabetic murine models. Currently available therapies for the treatment of sHTN (ARBs, ACEi) are not effective in all of the cases and it is requisite to investigate other novel therapeutic targets. Considering that, we postulate an ideal combination therapy of two drugs, with one drug for de-activating the pressor arm of the RAS (ACE/Ang II/AT1R) and another one for activating the depressor arm of the RAS (ACE2/Ang 1-7/Mas) at the same time. In this regard, this review will provide recent updates on the importance of the ACE2/Ang 1-7/Mas axis, specifically under diabetic conditions. Nevertheless, readers are also encouraged to refer to other excellent reviews available on this topic [8-16].

## Ang 1-7 reduces systemic hypertension (sHTN)

Diabetes and HTN frequently occur together, along with other co-morbidities like obesity, inflammation, oxidative stress and insulin resistance. Ang 1-7 exerts its effects on blood pressure via three important organ systems: the brain, vascular system and the kidney. The essential role of Ang 1-7 in hypertension is to modulate renal flow by prompting vasodilation and counterbalancing Ang II-induced vasoconstriction. Several clinical and epidemiological studies have shown that men are more prone to hypertension than women. It can be linked to Ang 1-7, as females have higher plasma levels of Ang 1-7 [17] and, comparatively, renal blood flow in females is more regulated through MasR [18]. Moreover, Xu et al. showed that female sex hormones can upregulate the brain anti-hypertensive axis involving Ace2/Ang 1-7/MasR to provide a protective role against aldosterone/NaCl-induced hypertension [19]. Other studies demonstrated that an exogenous supply of Ang 1-7, especially in CNS, can reduce the pressor effect of deoxycorticosterone acetate (DOCA)-salt hypertensive male rats [20].

Nitric oxide (NO) is an important factor for lowering blood pressure by favoring relaxation of blood vessels, vasodilation, and inhibition of platelet aggregation. Ang 1-7 binds to MasR to trigger eNOS and Akt phosphorylation [21], and stimulate the release of NO and prostaglandins. Our group previously reported that overexpression of

catalase or administration of Ang1-7 normalises oxidative stress and sHTN in Akita diabetic mice (a mouse model of type 1 diabetes) and that the effect of Ang 1-7 can be reversed after treatment with MasR antagonist A-779, indicating the anti-hypertensive effect of Ang 1-7 is mediated, at least in part, via suppression of oxidative stress in diabetes [7,22].

The Ang 1-7 peptide also has natriuretic and diuretic actions [23], which help to significantly decrease blood pressure via excretion of more sodium in urine. Those effects can be reversed with A-779 treatment [24]. Our group demonstrated an up-regulation of the expression of TACE (TNF-alpha converting enzyme) and NHE-3 (sodium-hydrogen exchanger-3) proteins in renal proximal tubule cells (RPTCs) of Akita diabetic mice, which were normalised with Ang 1-7 treatment [7]. NHE-3 is a key transporter for reabsorption of sodium in RPTCs and TACE is an enzyme responsible for ACE-2 shedding. Those findings suggest that lowering of SBP by Ang 1-7 may be partly mediated through its inhibitory effect on expression of TACE and NHE-3 proteins in renal tubules, thereby preventing sodium reabsorption in RPTCs.

An additional mechanism by which Ang 1-7 may counterbalance high blood pressure in diabetes is through activation of peroxisome proliferator activator receptors or PPARs. Dhaunsi et al. showed that PPARs can show beneficial effects on blood pressure by promoting the avilability of NO [25].

## Ang 1-7 relieves renal injury by attenuating fibrogenic and pro-inflammatory pathways

Ang II is a key component of RAS for augmenting hypertension and renal injury. During diabetic conditions, renal angiotensinogen (Agt, the sole precursor of all angiotensins) gene expression is stimulated by hyperglycemia, ROS and TGF-β1 (26-28). The overexpression of renal Agt/Ang II itself leads to severe physiological and structural damage to the kidney [29,30]. However, the adverse effects of Agt/Ang II overexpression can be minimised by inhibiting the pressor arm (ACE/Ang II/AT1R) of the renal RAS system via RAS blockade [31,32]. Furthermore, Ang 1-7 treatment ameliorates the diabetes-induced damage to the renal architecture. Indeed, there was significant improvement in glomerular tuft volume, RPTC volume, tubular luminal area and tubular apoptosis in Akita mice upon Ang 1-7 administration [7]. Physiological parameters including GFR and ACR were also normalised in the Ang 1-7 treatment group [7]. The involvement of MasR signalling can be further validated by administration of MasR agonist, AVE 0991, a nonpeptide mimetic of Ang 1-7, having renoprotective effects in non-diabetic experimental acute renal injury [11].

Evidence from *in-vitro* and *in-vivo* research also supported Ang 1-7 as an anti-fibrotic peptide (33). TGF-β1 is considered as a key mediator involved in fibrogenesis and that both Ang II and high glucose upregulate TGF-β1 expression [23]. Ang 1-7 blocks TGF-β1 expression and henceforth suppresses its downstream signalling as TGF-β1/Smad complex [34,35]. Our lab also found that Ang 1-7 normalises the expression of fibrogenic molecules such as collagen type IV and TGF-β1, which was reversed with the Ang 1-7 antagonist, A-779 [7].

## Ang 1-7 normalises protein kinases signalling

Mitogen-activated protein kinases (MAPKs) are a group of complex protein kinases involved in several rudimentary cellular processes. The

most common MAPKs are extracellular signal-related kinases (ERK)-1/2, Jun amino-terminal kinases (JNK1/2/3), p38 proteins (p38 α/β /γ/δ) and ERK5. It has been shown that Ang 1-7 inhibits high glucose or Ang II induced phosphorylation of p38, ERK1/2 and JNK, which can be reversed by Ang 1-7 antagonist A779 [23], suggesting that Ang 1-7 has anti-hypertrophic effects through normalisation of MAPKs activity.

### Anti-inflammatory actions of Ang 1-7

RAS blockers including ARBs such as telmisartan, olmesartan, losartan and ACE-inhibitors (ACEi) like captopril are commonly recommended for the treatment of hypertension. It has been shown that those drugs also ultimately stimulate the ACE-2/Ang 1-7/MasR axis with higher levels of Ang 1-7 in urine [32,36], which might reflect an intrarenal formation of this heptapeptide. ARBs treatment diminishes the up-regulation of inflammatory cytokines like TNF-α, IFN-γ, IL-1β, IL-6 and pro-inflammatory markers e.g. NF-kB, iNOS. In addition, ARBs enhance the anti-inflammatory cytokines [37, 38]. Ang 1-7 directly blunts the Ang II-induced activation of pro-inflammatory signalling in kidney cells. Ang 1-7 modulates the induction of MAPKs (p38, ERK1/2 and JNK) [23,39,40] and NF-kB signalling [39,41]. It would be tempting to speculate the major role of the ACE2/Ang 1-7/MasR axis is triggering anti-inflammatory mechanisms in diabetes and other metabolic complications. Recent studies have shown that oral administration of Ang 1-7 can significantly diminish the levels of inflammation and adipogenesis related markers [42,43]. Under diabetic conditions, multiple cytokines and growth factors activate renal STAT3 (phosphorylated form), which plays a critical role in renal injury and fibrosis. Mori et al. showed that Ang 1-7 treatment prevented the phosphorylation of STAT3 in db/db mice [44].

### Ang 1-7 limits ROS generation and normalises antioxidant pathways

Reactive oxygen species (ROS) contribute to several pathologies like liver damage, kidney injury, diabetes, hypertension, cancer etc. NADPH oxidase is a membrane-bound enzyme complex, which triggers ROS production through generation of superoxide radicals. Our lab found that administration of Ang 1-7 limits the activation of NADPH oxidase by attenuating the mRNA and protein expressions of NOX4, a crucial component of the NADPH oxidase complex in diabetic RPTs [7]. Furthermore, Ang 1-7 also normalises the expression of antioxidant enzymes catalase and HO-1, and oxidative stress inducible proteins Nrf2 and HO-1 in diabetic RPTs [7,15]. The normalisation of oxidative stress with Ang 1-7 treatment can be visualised as a reduction in dihydroethidium (DHE) and 6-carboxy-2', 7'-dichlorodihydrofluorescein diacetate (carboxy-H2DCFDA) staining of kidney cells [7]. Although Nrf2 is a critical factor for the activation of antioxidant pathways, however, over-activation of Nrf2 itself by chronic hyperglycemia can trigger the expression of the renal Agt gene in diabetes [45]. Our most recent data revealed that the administration of Ang 1-7 suppresses renal Nrf2 and Agt expression and up-regulates ACE-2 expression which can be reversed by A779 (Figure 1), indicating that the beneficial effect of Ang 1-7 is mediated, at least in part, via suppression of Nrf2-activation of renal Agt expression and up-regulation of ACE-2 expression in diabetes.
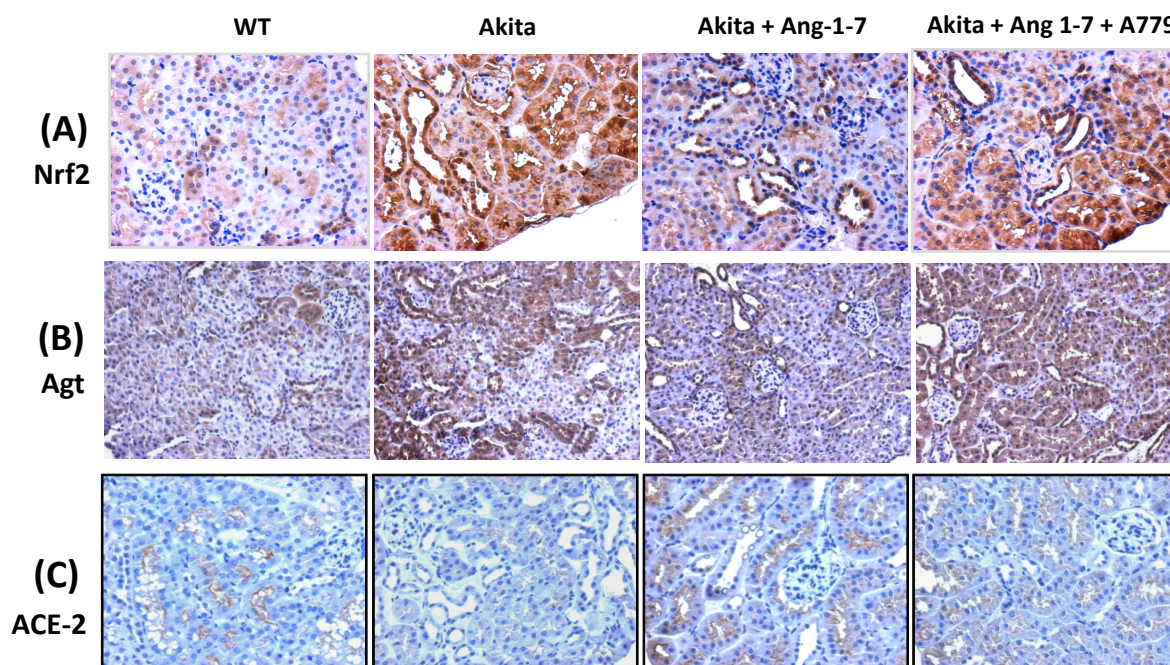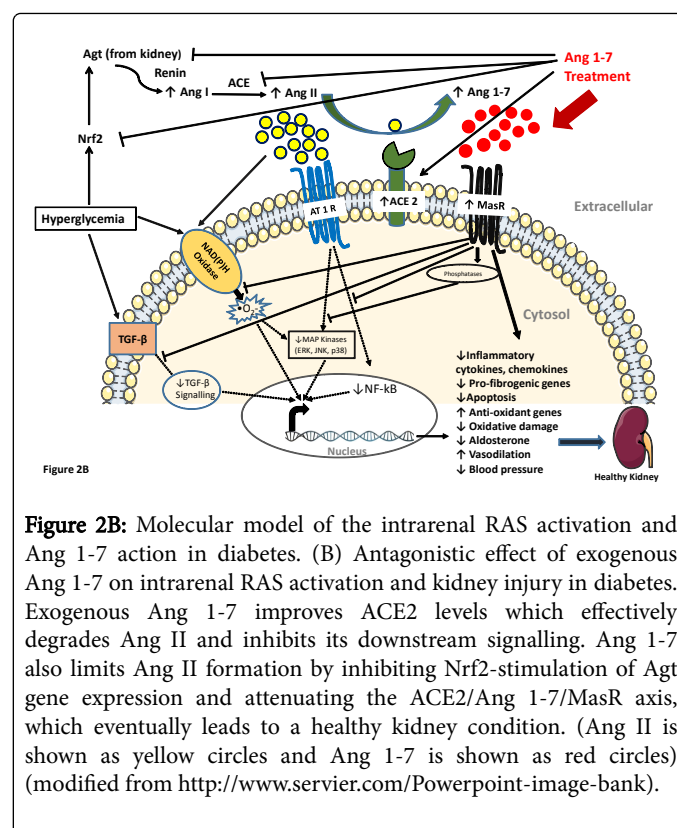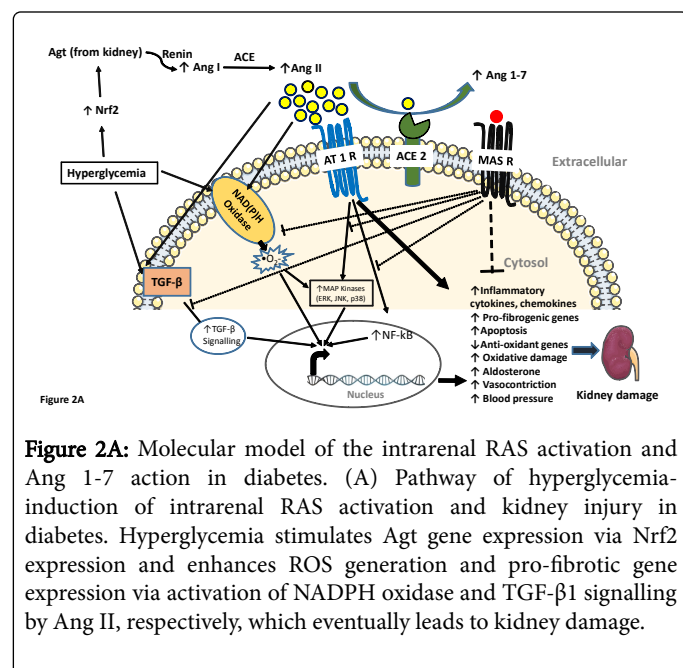


**Figure 1:** Nrf2, Agt and ACE-2 expression in diabetic Akita mice kidneys at 20 weeks of age with Ang 1-7 treatment in the absence or presence of A779 co-administration. Nrf2 (A) Agt (B) and ACE-2 (C) immunostaining (From Shi Y, Lo CS, Padda R et al. (2015) Clin Sci (London) 128:649-663)

## Ang 1-7 in clinical studies

Considering the protective role of Ang 1-7 in several diseased conditions, the ACE-2/Ang 1-7/MasR axis could have future therapeutic prospects. The Ang 1-7 peptide is already undergoing clinical trials as a chemotherapeutic agent. Ang 1-7 inhibits cellular growth and the biological response of Ang 1-7 in the tumor microenvironment is concomitant with its anti-proliferative, anti-angiogenic, anti-inflammatory properties [46,47]. Furthermore, Ang 1-7 is found to be safe in clinical trials, with limited toxic side effects [47]. The main challenge in usage of Ang 1-7 for clinical studies is its short half-life in plasma. To circumvent the quick degradation, different formulations of Ang 1-7 are being developed e.g. HPβCD/Ang 1-7 [48], NorLeu³-A(1-7) [9,49], AVE-0991 [50], cyclic angiotensin 1-7 (http://www.tarixpharma.com, accessed March 06, 2015), CGEN-856 [51]. So far, the direct beneficial effects of Ang 1-7 itself are seen in animal models. The first clinical trial is still underway and will eventually give concrete evidence for protective effects of this peptide in diabetes.

## Concluding remarks

Since the last decade, our understanding of the role of Ang 1-7 in physiological and pathophysiological conditions has advanced rapidly. In general, Ang 1-7 effectively counteracts the deleterious effects of Ang II. This novel heptapeptide is therefore appearing as a key player in modulation of RAS for maintenance of balance between heath and disease. The potential mechanism by which Ang 1-7 exerts beneficial effects appears to be mediated, at least in part, via attenuation of oxidative stress and suppression of Nrf2-stimulation of renal Agt expression which counterbalances Ang II actions including enhancing vascular relaxation and attenuating sodium reabsorption (Figure 2A and 2B).



**Figure 2A:** Molecular model of the intrarenal RAS activation and Ang 1-7 action in diabetes. (A) Pathway of hyperglycemia-induction of intrarenal RAS activation and kidney injury in diabetes. Hyperglycemia stimulates Agt gene expression via Nrf2 expression and enhances ROS generation and pro-fibrotic gene expression via activation of NADPH oxidase and TGF-β1 signalling by Ang II, respectively, which eventually leads to kidney damage.



**Figure 2B:** Molecular model of the intrarenal RAS activation and Ang 1-7 action in diabetes. (B) Antagonistic effect of exogenous Ang 1-7 on intrarenal RAS activation and kidney injury in diabetes. Exogenous Ang 1-7 improves ACE2 levels which effectively degrades Ang II and inhibits its downstream signalling. Ang 1-7 also limits Ang II formation by inhibiting Nrf2-stimulation of Agt gene expression and attenuating the ACE2/Ang 1-7/MasR axis, which eventually leads to a healthy kidney condition. (Ang II is shown as yellow circles and Ang 1-7 is shown as red circles) (modified from http://www.servier.com/Powerpoint-image-bank).

Despite available treatments for the regulation of hypertension and diabetes, a substantial population is still suffering from higher blood pressure, renal injury and other associated comorbidities. In diabetes, the suppression of the pressor arm of the RAS with ARBs, ACEi is not effective for all cases and in such conditions, there is need for therapies to activate the depressor arm. Thus, the Ang 1-7 peptide and its analogues, as new therapeutic targets in the ACE-2/Ang 1-7/Mas axis, may provide additional alternatives for the treatment of diabetes pathophysiology, and new developments using the Ang 1-7 and its analogs are on the horizon.

## Funding and acknowlegement

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