International Journal of Biochemistry Research & Review
4(3): 204-223, 2014

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The Importance of the RAS Interacting with the HGF/C-Met Receptor System in Hypertensive Type 2 Diabetes Mellitus

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

Review Article

Received 26th August 2013
Accepted 29th November 2013
Published 18th January 2014

ABSTRACT

The classic renin-angiotensin system (RAS) is described as a circulating hormone system with primary roles in the regulation of blood pressure, body water balance and thirst and control over vasopressin and aldosterone release. Recently local tissue RASs have been identified with regulatory physiological functions and also with pathophysiological processes including fibrosis, inflammation and dysfunctional cell proliferation. There is a strong correlation between organs vulnerable to diabetic–induced hyperglycemic injury (eg. kidney and retina) and the over activation of local RASs. Increased angiotensin II concentrations in these tissues promotes hypertension and end-organ damage in at least two ways: 1) By activating AT_1 receptor proteins thus inducing changes in local blood flow and tissue hydration and 2) Exacerbating hyperglycemic-induced oxidative stress, elevated polyol and hexosamine pathway variability and facilitating glycation end-products. Thus, inhibition of the RAS has become an important treatment approach to control diabetic related hypertension, nephropathy and to a lesser extent retinopathy. The present review emphasizes the recently established importance of the hepatocyte growth factor (HGF)/c-Met receptor system interacting with the RAS in Type 2 diabetes and their likely contribution to end-organ damage. A hypothesis is offered concerning how the pancreatic RAS may affect dimerization of HGF and in turn activation of the c-Met receptor to promote β cell proliferation and insulin synthesis. We conclude with details concerning the

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development of an AngIV-based small molecule HGF mimetic designed to act as an insulinotropic factor.

Keywords: Hypertension; Type 2 diabetes; Renin-angiotensin system; Angiotensin II; Angiotensin IV; Hepatocyte growth factor; AT_1 receptor subtype; AT_4 receptor subtype; c-Met receptor.

1. INTRODUCTION

1.1 Background Information

The worldwide incidence of diabetes mellitus presently numbers 250 to 350 million adults, and is predicted to reach 380-430 million by 2025 if new treatment strategies are not introduced [1,2]. Diabetes is accompanied by a significant increase in the risk of hypertension, heart attack, stroke, atherosclerosis, renal failure and end-organ damage [3-5]. Thus, the control of blood pressure is an especially important goal in preventing cardiovascular and renal dysfunctions in Type 2 diabetic patients with hypertension. Although discussion continues over the optimal target, several reports recommend maintaining blood pressure at, or below, 130/80 mm Hg (reviewed in [6,7]). In the overall population the risk of cardiovascular events doubles with each 20 mm Hg elevation in systolic blood pressure above 115 mm Hg and each 10 mm Hg elevation above 75 mm Hg diastolic pressure [8]. Diabetic patients with hypertension suffer twice the risk of cardiovascular dysfunction as nondiabetic individuals with hypertension, accompanied by an increased likelihood of diabetes specific complications such as retinopathy [9-11] and nephropathy [12]. Patients with Type 2 diabetes and hypertension have a sevenfold increased risk of progression to end-stage renal disease as compared with normotensive Type 2 diabetic patients [13]. The association of Type 2 diabetes with hypertension, cardiovascular disease, retinopathy and nephropathy portends over activation of the renin-angiotensin system (RAS) as an important predisposing factor [14-16]. The relationship between diabetes and the RAS is further supported in that increased local tissue angiotensin II (AngII) levels can result in insulin resistance by impacting insulin-stimulated elevations in insulin receptor substrate1-associated P13K activity [17], thus promoting nephropathy [18].

1.2 The Renin-Angiotensin System

The classic RAS is known for its roles in the regulation of blood pressure, body water balance and thirst and influences on vasopressin and aldosterone release [19-26]. This system has been implicated in diabetes [14,21,27-29], particularly as evidenced by the ameliorating effects of angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs, designed to block the angiotensin AT_1 receptor subtype) in treating Type 2 diabetes (see below). This review focuses on the role of the RAS in the development and sustaining of Type 2 diabetes. We discuss the recently discovered relationship among the renin-angiotensin system (RAS), the hepatocyte growth factor (HGF)/c-Met receptor system and diabetes. Next, we discuss the negative impact of elevated prorenin levels on the pancreatic RAS and how this may promote end-organ damage. A working hypothesis is presented concerning how HGF and the angiotensin IV (AngIV) peptide is facilitated during treatment with an ACE inhibitor or ARB, thus activating the c-Met receptor and promoting β cell proliferation while attenuating cellular insulin resistance. We conclude with a description

of the development of a small molecule HGF mimetic that may act as an insulinotropic factor.

2. FORMATION OF ANGIOTENSIN LIGANDS

Components of the RAS have been localized in the brain and a number of peripheral tissues including heart, kidney, skeletal muscle, adipose tissue and pancreas [25,26,30]. All angiotensin ligands are derived from the precursor protein angiotensinogen which is synthesized and secreted from the liver, as well as adipose tissue in obese individuals [31]. Angiotensin ligands are formed via several enzymatic conversion pathways Fig. 1 [32-34]. Briefly, the decapeptide angiotensin I (AngI) is derived by renin (EC 3.4.23.15) acting upon the amino terminal of angiotensinogen [35]. AngI serves as a substrate for ACE (EC 3.4.15.1) to form the octapeptide AngII [32,36]. This conversion can also be accomplished by the chymotrypsin-like serine protease, chymase [37]. AngII is converted to the heptapeptide angiotensin III (AngIII) by aminopeptidase A (APA: EC 3.4.11.7) cleavage of aspartate [38-40]. Aminopeptidase N (APN: EC 3.4.11.2) cleaves arginine at the N-terminal of AngIII to form the hexapeptide angiotensin IV (AngIV) [41]. AngIV can be further converted to Ang(3-7) by carboxypeptidase P (Carb-P) and propyl oligopeptidase (PO) cleavage of phenylalanine. Endopeptidases such as chymotrypsin, along with dipeptidyl carboxypeptidase, reduce AngIV and Ang(3-7) to inactive peptide fragments and amino acid constituents [32,42-46].

AngI is biologically inactive; while AngII and AngIII are full agonists at the AT_1 and AT_2 receptor subtypes Table 1 [25,47]. AngIV and Ang(3-7) bind with low affinity at the AT_1 receptor subtype but with high affinity and specificity at the AT_4 receptor subtype [48-53]. AngII and AngIII mediate pressor and dipsogenic effects via the AT_1 and AT_2 receptor subtypes [19]. AngIV exerts a much reduced pressor response by acting with low affinity as an agonist at the AT_1 receptor subtype [54-58].

Table 1. Binding affinity values (M) for native angiotensins, Candisartan and Telmisartan at three angiotensin receptor subtypes

Ligands	AT_1	AT_2	AT_4
Angiotensin II	7.92×10^{-9} M	5.22×10^{-10} M	1.00×10^{-6} M
Angiotensin III	2.11×10^{-8}	6.48×10^{-10}	1.60×10^{-7}
Angiotensin IV	1.00×10^{-5}	4.86×10^{-8}	1.29×10^{-9}
Candisartan	1.56×10^{-9}	1.00×10^{-5}	NA
Telmisartan	10.90×10^{-9}	10.00×10^{-6}	NA

The ligand binding affinities for the AT_1 and AT_2 receptor subtypes are from Bosnyak et al. [59] and Kukuta et al. [60]. Binding affinities for the AT_4 receptor subtype are from Harding et al. [50]. NA=not available.

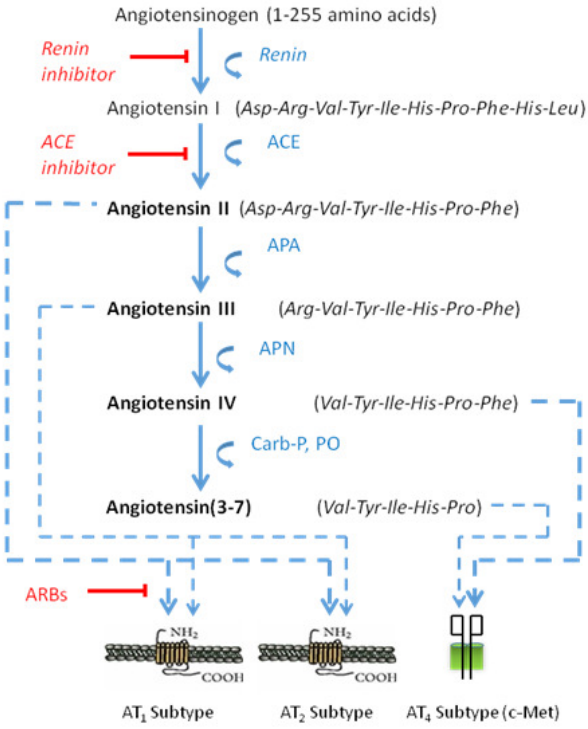

Fig. 1. RAS synthetic pathway

The renin-angiotensin pathway, including active ligands (bold), enzymes and receptors, is presented. The location of action for clinically available inhibitors designed to control angiotensin mediated hypertension are indicated in red. Abbreviations: ACE=angiotensin converting enzyme; APA=aminopeptidase A; APN=aminopeptidase N; ARBs=angiotensin receptor blockers. Carb-P=carboxypeptidases, PO=propyl oligopeptidase.

3. CHARACTERIZATION OF THE AT_1 AND AT_2 RECEPTOR SUBTYPES

The AT_1 receptor subtype is a G-protein coupled receptor with signaling via phospholipase-C and calcium. Thus, the angiotensin ligand binds to the AT_1 receptor and induces a conformational change in the receptor protein that activates G proteins, which in turn, mediates signal transduction. This transduction involves several plasma membrane mechanisms including phospholipase-C, -A_2 and –D-adenylate cyclase, plus L-type and T-type voltage sensitive calcium channels [19,61,62]. The AT_1 receptor (now designated AT_{1A}) is also coupled to intracellular signaling cascades that regulate gene transcription and the expression of proteins that mediate cellular proliferation and growth in many target tissues. Subsequently, a second AT_1 subtype was discovered and designated AT_{1B} that was also cloned in the rat [63,64], mouse [65] and human [66]. This subtype is approximately 92-95% homologous with the amino acid sequence of the AT_{1A} subtype [67,68]. Of these two isoforms the AT_{1A} subtype appears to be primarily responsible for the classic functions associated with the brain angiotensin system [69,70].

The AT_2 receptor subtype has been cloned and sequenced using a rat fetus expression library [71,72] and also evidences a 7-transmembrane domain characteristic of G-protein

coupled receptors; however it shows only about 32-34% amino acid sequence identity with - the rat AT_1 receptor. Even though this AT_2 receptor possesses structural features in common with members of the 7-transmembrane family of receptors, it displays few if any functional similarities with this group, although it does appear to be G-protein coupled [19,71,72]. While the AT_1 receptor subtype is maximally sensitive to AngII, it is also responsive to AngIII. The AT_2 receptor subtype appears to be maximally sensitive to AngIII but AngII also serves as a ligand at this receptor subtype. The functions associated with the activation of each of these receptors are presented in Table 2.

Table 2. Ligand activation of the AT_1, AT_2 and AT_4 receptor subtypes

AT_1 receptor subtype	AT_2 receptor subtype	AT_4 receptor subtype
Vasoconstriction	Vasodilation	Dendritic arborization
Aldosterone release	Antifibrotic	Changes in blood flow
Vasopressin release	Antiproliferative	Memory facilitation
Cardiac hypertrophy	Antihypertrophic	Protection against seizures
Fibrosis	Antithrombotic	Facilitates wound healing
Proliferation		
Inflammation		
Platelet aggregation		
Oxidative stress		
Endothelial disruption		

4. CHARACTERIZATION OF THE AT_4 RECEPTOR SUBTYPE

During our attempt to purify and sequence the AT_1 receptor subtype we noticed that heat-denatured purified receptor from the bovine adrenal gland lost binding to [^{125}I]-Sar^1,Ile^8-AngII, whereas [^{125}I]-AngIII binding persisted. It was initially suspected that an angiotensin receptor specific to AngIII had been isolated. However, with sufficient peptidase inhibitors added to prevent the conversion of AngIII to shorter fragments, this binding activity was also lost. These results were puzzling given that the two known receptor types at that time, AT_1 and AT_2, each accepted AngII and AngIII as ligands, albeit with different affinities. A fragment of Ang III was suspected to be acting at this new site because Sar^1-AngII, Sar^1,Ile^8-AngII (Sarile), Sar^1,Ala^8-Ang II (Saralasin), DuP753 (Losartan), PD123177, CGP42112A, AngII(1-7) and AngIII did not act as ligands [50,52]. In fact [^{125}I]-AngIV did bind at this site reversibly, saturably and with high affinity (K_d = 1 nM) [73,74]. Thus, we determined the binding profile of this protein to be distinct from the AT_1 and AT_2 receptor subtypes given that [^{125}I]-AngIV binding could not be displaced by AT_1 or AT_2 receptor antagonists.

We next set about determining the ligand requirements of this site. Using competitive assays against [^{125}I]-AngIV it was soon discovered that the three N-terminal amino acids of AngIV (valine-tyrosine-isoleucine) were necessary for binding [74-76]. Substituting a straight-chain aliphatic moiety with a carbon atom (norleucine) for valine produced the AT_4 receptor agonist, Nle^1-AngIV. This substitution resulted in an analogue with higher receptor affinity than native Ang IV, and greater resistance to enzymatic degradation. Further modification of Nle^1-AngIV by placing a reduced peptide bond (CH_2-NH_2) between norleucine and tyrosine yielded Norleucinal^1-AngIV and resulted in even greater resistance to degradation accompanied by nanomolar affinity at the receptor.

The AT_4 receptor is distributed within a number of brain structures [25] and in several peripheral tissues including heart, kidney, spleen, colon, prostate, bladder, adrenal gland and pancreas [54,77].

5. A ROLE FOR THE RAS IN TYPE 2 DIABETES MELLITUS

There is no evidence of increased plasma AngII levels associated with diabetes. In fact, circulating AngII levels have been reported to be suppressed in diabetic patients [78]. However, increased plasma levels of the renin-precursor prorenin have been measured in diabetic patients and are suggested to serve as a predictor of the onset of retinopathy and nephropathy [79,80]. Since these increases in prorenin do not appear to result in elevated plasma AngII levels, it is proposed that they act at the renin-prorenin receptor to induce tissue injury [81,82]. Along these lines, the retina and kidney have been reported to have over-active local RASs during episodes of hyperglycemia [83,84]. Elevated prorenin levels have been measured in the vitreous of the eye in diabetic patients with proliferative retinopathy [85]. Some older patients with this disorder evidence increases in vitreous AngII levels [86]. Further, there is evidence that vitreous AngII levels are positively correlated with degree of retinopathy [87].

Considerable experimental work has focused on understanding how hyperglycemia and activation of local tissue RASs, lead to cellular damage. It has been known for some time that hyperglycemia induces oxidative stress; however elevated AngII tissue levels have also been shown to act as an oxidative stress inducer [88,89]. In this way elevated AngII concentrations in diabetic tissues may exacerbate hyperglycemia-induced oxidative stress damage [90,91]. As a result oxidative stress appears to both underlie, and be the result of, pathobiochemical mechanisms of diabetic-induced tissue damage [92]. The inhibition of the RAS with ACE inhibitors or ARBs in diabetic nephropathy rats reduced oxidative stress [93]. Recent clinical trials have been conducted with young Type 1 diabetic patients evidencing vascular superoxide overproduction (and early signs of angiopathy) due to hyperglycemia-related dysfunctional intracellular antioxidant enzyme production [94]. This dysfunction was reversed by treatment with the ARB Irbesartan. Further, the ARBs Candesartan and R-147176 (a sartan with low affinity for the AT_1 receptor subtype) appear to exert direct antioxidant influences apparently independent of AT_1 receptor blockade [95]. Thus, these drugs show promise with regard to protection against diabetic-induced end-organ damage.

Several clinical trials have focused on the efficacy of RAS blockade in diabetic patients. The Renin-Angiotensin System Study (RASS) monitored the efficacy of treatment with Losartan and Enalapril to Type 1 diabetic patients over a 5 year period [96]. The DIabetic REtinopathy Candesartan Trials (DIRECT) study tested the ARB Candesartan with Type 1 and 2 diabetic patients [97]. A report on An evaluation of telMisartan and losArtan in hypertensive Type 2 DiabEtic patients with Overt nephropathy (AMADEO) was recently published [98]. Specific details concerning the results of each of these trials follow.

The RASS study monitored 2007 normotensive, normoalbuminuric Type 1 patients and focused on retinopathy. Both ACE inhibitors and ARB treatment attenuated the progression of retinopathy by 65 and 70%, respectively. However, since the majority of these patients (74%) had no evidence, or minimal evidence, of non-proliferative retinopathy at the outset of the study these results indicate the attenuation of new onset retinopathy.

The DIRECT study consisted of 5000 Type 1 and 2 diabetic patients who for the most part were normotensive and normoalbuminuric. Three substudies were conducted. In one, DIRECT-Prevent, Type 1 patients showed no evidence of retinopathy. Candesartan reduced the incidence of retinopathy. In the second, DIRECT-Protect 1, Type 1 patients with existing retinopathy treated with Candesartan showed no effect on progression [97]. The third study, DIRECT-Protect 2, monitored normotensive and treated hypertensive Type 2 diabetic patients and found that Candesartan slowed the progression of retinopathy [99].

The AMEDEO study randomly assigned Type 2 patients with hypertension to treatment with Telmisartan (final dose = 8l0 mg) or Losartan (final dose = 100 mg) over the duration of one year. Telmisartan was found to provide an effective anti-proteinuric effect in these hypertensive and overt nephropathy Type 2 patients. This effect was greater than that achieved with Losartan and blood pressure was maintained equivalently in the two groups [98].

Taken together these animal and clinical trials results indicate that inhibiting the action of the RAS with ACE inhibitors or ARBs offers significant clinical advantage in both Type 1 and 2 diabetic-induced retinopathy. These studies also illustrate the importance of gaining a better understanding of the underlying relationship between local RASs and diabetes.

6. THE HGF/C-MET RECEPTOR SYSTEM

Several years ago our laboratory began searching for a molecular target with structural homology to AngIV and physiological functions in agreement with those identified for the AngIV/AT_4 receptor system. This yielded a partial match with the anti-angiogenic protein angiostatin and the related plasminogen family member HGF. HGF is a mesenchyme-derived protein recognized as a potent mitogenic, morphogenic, and motogenic growth factor that acts via the Type 1 tyrosine kinase receptor c-Met [100]. HGF is intimately involved in cell survival, proliferation, migration and differentiation [101-103]. c-Met has been shown to play a role in multiple types of cancer [104,105], blunt neurodegenerative changes [106], facilitate long-term potentiation (LTP) [107], contribute to learning and memory consolidation [106,108-111] and c-Met has been implicated in Alzheimer's disease [112,113]. Also, inactivation of c-Met in the embryonic proliferative zones of mice results in an increase in parvalbumin-expressing cells in the dentate gyrus of the brain, accompanied by a loss of these cells in the CA3 field, with an overall loss of calretinin-expressing cells throughout the hippocampus [114]. These results suggest that c-Met is required for appropriate hippocampal development. The above functions associated with the HGF/c-Met system overlap with those mediated by the AngIV/AT_4 system including facilitated hippocampal LTP and memory consolidation, augmented neurite outgrowth, calcium signaling, dendritic arborization, facilitation of cerebral blood flow and cerebroprotection, seizure protection and facilitated wound healing [25].

These observations prompted the hypothesis that AngIV analogues may exert their activity via the HGF/c-Met system. Investigations conducted in our laboratory demonstrated that the AT_4 receptor antagonist Norleual-AngIV inhibited HGF binding to c-Met and HGF-dependent cell signaling, proliferation, invasion and scattering [115]. Additional studies indicated that Norleual-AngIV bound directly to HGF blocking the ability of HGF to dimerize, a process required for HGF activation and binding to the c-Met receptor [116]. Taken together these results suggest that the biological effects of AngIV and AngIV analogues are likely mediated through the HGF/c-Met system.

7. A ROLE FOR THE HGF/C-MET SYSTEM IN TYPE 2 DIABETES MELLITUS

The HGF/c-Met signaling pathway is involved in multiple functions including cellular proliferation, regeneration and branching morphogenesis [117]. As mentioned above, HGF must dimerize in order to bind and activate the transmembrane tyrosine kinase c-Met receptor [118]. The HGF/c-Met system is expressed in the pancreas where HGF is localized to endothelial islet and mesenchymal cells; while the c-Met receptor is present in islet, ductal and pancreatic progenitor cells [119-121]. Both HGF and c-Met are highly expressed during pancreatic development and HGF functions as an insulinotropic factor promoting β cell proliferation and regeneration [122-124]. Pancreas specific c-Met knockout mice are susceptible to low dose streptozotocin-induced diabetes [125]. These mice evidence elevated blood glucose levels accompanied by decreased glucose tolerance, hypoinsulinemia and significantly decreased β cell mass when compared with wild type litter mates. Overall this HGF/c-Met knockout mouse evidences a pattern of β cell functioning and glucose metabolism very similar to what is seen in early phase β cell failure in Type 2 diabetic patients [120]. Thus, HGF/c-Met signaling appears to be essential for appropriate glucose-dependent insulin secretion and utilization.

The HGF/c-Met system is also necessary for optimizing hepatic insulin responsiveness by interacting with the insulin receptor to form a hybrid complex of c-Met-insulin receptor [126]. These researchers reported that activation of the HGF/c-Met system facilitated insulin responsiveness in the ob/ob mouse model of Type 2 diabetes. The importance of this system is further emphasized in that HGF gene delivery slowed the progression of diabetic nephropathy in db/db mice by promoting antifibrotic and antiapoptotic actions [127]. In addition, HGF gene delivery in streptozotocin-induced diabetic mice triggered pro-survival Akt kinase activity as well as Bcl-xL expression in pancreatic islet cells thus preserving β cells [128,129].

8. HYPOTHESIS CONCERNING THE RAS AND HGF/C-MET SYSTEMS IN TYPE 2 DIABETES

Several findings are relevant in designing a model to explain how small molecule HGF mimetics may be efficacious in the treatment of Type 2 diabetes. 1) It has been determined that prorenin levels associated with local RASs are elevated in the retina and kidney during hyperglycemia [79,85,130,131]. 2) There is ample angiotensinogen available in local tissues to act as a substrate for elevated renin levels, along with the necessary ACE to convert AngI to AngII [132]. 3) Local tissue elevations in AngII have been linked with tissue injury [133,134]. 4) Severity of retinopathy has been positively correlated with the level of vitreous AngII [135].

The above findings encourage the following hypothesis concerning the relationship between the pancreatic RAS and cellular damage. Elevated prorenin levels in local tissues result in renin acting on angiotensinogen to produce increases in AngI (Fig. 2). This elevated AngI is converted to the biologically active peptide, AngII. Increased AngII levels facilitate hyperglycemic-induced oxidative stress and elevate glycation end-products resulting in β cell damage. As β cells die off progressive reductions in insulin synthesis and release follow.

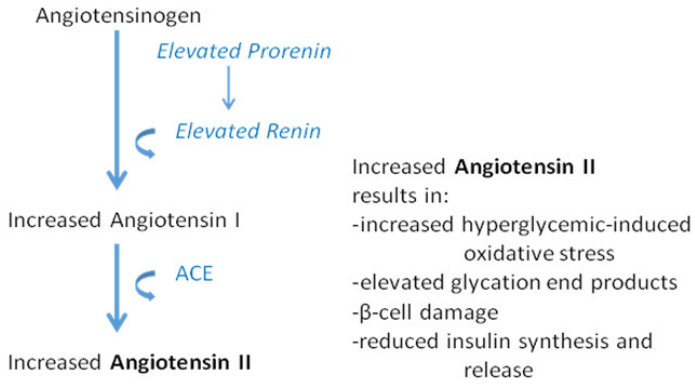

Fig. 2. Renin Angiotensin System and elevated Prorenin

Changes in the pancreas renin-angiotensin system as a result of elevated prorenin levels. Angiotensin II (bold) is biologically active.

From this prediction it is proposed that the treatment of Type 2 diabetic patients with an ACE inhibitor or ARB reduces activation of the RAS with resulting reductions in hypertension and oxidative stress (Fig. 3). Decreased RAS activity also impacts the local HGF/c-Met systems. Specifically, treatment with an ACE inhibitor would be expected to reduce the formation of AngII and result in compensatory increases in the nonapeptide, D-Asp[1], AngI. Cleavage of aspartate by APA, histidine and leucine via carboxypeptidases would convert this nonapeptide to AngIII and then to AngIV via APN cleavage of arginine Fig. 4; [47]. This elevation in AngIV causes dimerization of HGF followed by increased activation of the c-Met receptor thus optimizing hepatic insulin responsiveness accompanied by the facilitation of cellular insulin receptivity. A similar outcome would be anticipated with ARB treatment of Type 2 diabetic patients. Specifically, the positive response of Type 2 diabetic patients treated with an ARB [136-138] is accompanied by an excess of AngII that is prevented from binding at the AT_1 receptor subtype. This excess AngII may be converted to AngIII and then to AngIV and Ang(3-7) (Figs. 1 and 3). These latter angiotensins are capable of facilitating dimerization of HGF which then activates c-Met receptors in the pancreas and elsewhere. Activation of c-Met receptors in turn increments insulin production and facilitate cellular insulin responsiveness, with accompanying reductions in hyperglycemia-induced oxidative stress and end-organ damage.

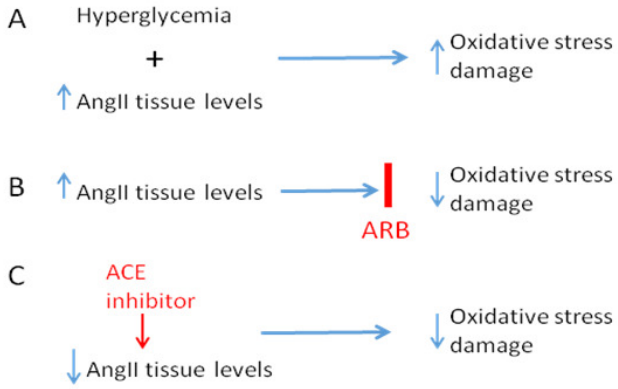

Fig. 3. Hyperglycemia and β Cell Damage: Treatment with and Angiotensin Receptor Blocker (ARB)

A) The contribution of hyperglycemia and increased tissue AngII levels results in facilitated hyperglycemic-induced oxidative stress leading to β cell damage. B) Treatment with an ACE inhibitor reduces the conversion of AngI to AngII resulting in decreased oxidative stress-induced β cell damage. C) Treatment with an ARB prevents AngII binding with the AT_1 receptor subtype resulting in decreased oxidative stress-induced β cell damage.

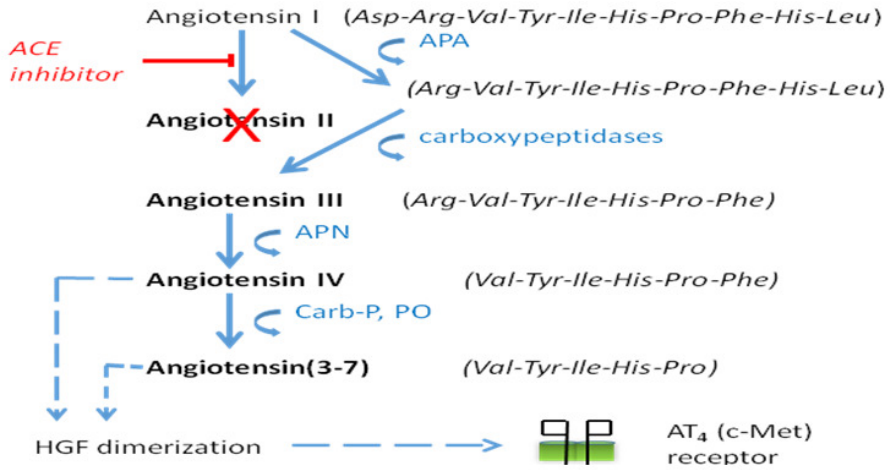

Fig. 4. Influence of ACE Inhibition on AngIV and Ang (3-7) Formation: Treatment with an Angiotensin Converting Enzyme (ACE) Inhibitor

Proposed changes in the synthesis pathway with ACE inhibitor treatment. This inhibitor reduces the formation of angiotensin II resulting in the increased formation of nonapeptide Ang(2-10). Carboxypeptidases then form angiotensin III which is converted to angiotensin IV by APN and angiotensin (3-7) by Carb-P and PO. Both AngIV and Ang(3-7) are capable of dimerizing HGF which then binds at the AT_4 (c-Met) receptor.

9. Development of a Small Molecule AngIV Analogue

During the development of AngIV analogues we determined the minimum structural features of Nle^1-AngIV capable of promoting biological activity [139]. Previous studies indicated that critical structural information resides at the N-terminal of AngIV [140,141]. Thus, we sequentially removed amino acids from the C-terminal of Nle^1-AngIV, while monitoring pro-cognitive activity. This approach suggested that memory facilitation was achievable with peptides as small as tetra- and tripeptides. Next, we modified these peptides in several ways to enhance stability and hydrophobicity. Modifications included the addition of a D-amino acid or non-α-amino acid in the #1 position, acylation of the N-terminal amino acid and conversion of the 1-2 peptide bond to a reduced-peptide bond. Several resulting molecules offered the desired stability while maintaining the required biological activity [139,142]. Included in this group were analogues protected at both the N- and C-terminals by nonmetabolizable constituents and in particular a tripeptide-sized small molecule with the ability to reverse scopolamine-induced amnesia when delivered peripherally. We are currently testing this compound for its ability to act as an insulinotropic factor in Type 2 diabetic animal models.

10. CONCLUSION

The number of individuals diagnosed with Type 2 diabetes is reaching epidemic proportions. It is essential that new and novel treatments be considered [143-145]. The deleterious contribution of local RASs has been documented in diabetic patients with hypertension. In these patients AngII promotes end-organ damage by: 1) Promoting local vasoconstriction accompanied by tissue ischemia and altered fluid electrolyte imbalance. 2) Exacerbating hyperglycemic-induced oxidation stress and deleterious glycation end-products. Recently the HGF/c-Met system has been implicated in diabetes [146,147]. This growth factor system appears to be essential for the appropriate development and maintenance of pancreatic β cells [148,149] and thus may hold the key to new treatment strategies. The presently described approach concerns the use of a small molecule HGF mimetic to increase HGF dimerization and binding to the c-Met receptor. Increased activation of c-Met receptors has been shown to facilitate proliferation and optimization of pancreatic β cells. It appears that appropriate insulin response is dependent upon engaging the insulin receptor to form a hybrid complex with the c-Met receptor [148]. Insulin refractoriness is significantly reduced when this complex is restored in Type 2 diabetic animal models. These research findings, coupled with our discovery that a small molecule AngIV analogue induces HGF dimerization (a prerequisite to c-Met binding), offer a unique potential treatment. The availability of a small molecule may offer a significant advantage over the use of HGF or large HGF analogues, to accomplish this treatment goal. It remains to be seen whether long-term treatment of Type 2 diabetes with small molecule HGF mimetics is efficacious.

ACKNOWLEDGEMENTS

The preparation of this review was supported by the Edward E. and Lucille I. Lainge Endowment for Alzheimer's Research, and funds provided for medical and biological research by the State of Washington Initiative Measure No. 171.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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