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The Renin-Angiotensin System in the Endocrine Pancreas

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Summary

Experimental data suggest that a tissue renin-angiotensin system is present in the pancreatic islets of several species, including man. However, the physiological role for this local renin-angiotensin system remains largely unknown. In vitro findings argue against a direct effect of angiotensin II on alpha- and beta-cells. In contrast, when the influence of angiotensin II on the pancreatic islets has been evaluated in the presence of an intact vascular system either in vivo or in the perfused pancreas, a suppression of insulin release has been observed, also in man. These discrepancies may be explained by the profound effects of the renin-angiotensin system on pancreatic islet blood perfusion. Alterations in the systemic renin-angiotensin system and an increased vascular sensitivity for its components have been observed in diabetes mellitus and hypertension.
Whether changes occur also in the pancreatic islet renin-angiotensin system during these conditions remains unknown. Future research may help to provide an answer to this question, and to elucidate to what extent the renin-angiotensin system may contribute to beta-cell dysfunction in these diseases.

Introduction

The systemic renin-angiotensin system (RAS) is known to be of major importance for the regulation of blood pressure [1, 2]. In recent years, the existence of a local RAS in various organs has also been demonstrated [3, 4, 5].
This implies that locally produced angiotensin II (AT II) exerts local effects, a fact which has been corroborated in several organs, e.g. gonads [6], heart [7] and adrenals [8]. An intrinsic RAS has also been demonstrated both in the endocrine and exocrine pancreas [9, 10, 11, 12]. Although much progress has recently been made, the physiological significance of the RAS in the endocrine pancreas remains conjectural. Of interest in this context is the accumulating data which suggests a crucial role of hyperexpression of angiotensinogen in essential hypertension (for a review see [13]). The close relationship between essential hypertension and type 2 diabetes [14, 15], and the beneficial effects of ACE-inhibition for insulin release in many hypertensive patients [16, 17, 18], underlines the importance of increasing our understanding of the physiological role of the RAS in the pancreatic islets.
This review will focus on the RAS in the endocrine pancreas. The morphological basis and the current knowledge of physiological functions in islets will be discussed. In addition, the potential role of disturbances in the islet RAS in diabetes mellitus and hypertension will be addressed.

Current Basic Evidence of the Importance of RAS

Presence of RAS-components in the pancreas

Angiotensinogen mRNA, angiotensinogen protein, AT II and high affinity binding sites for AT II have all been described in the canine pancreas [9]. In dogs, AT II was the most abundant RAS peptide, whereas angiotensin III and angiotensin-(1-7) were present in concentrations less than 20% of that of AT II. The concentrations of these three peptides in the canine pancreas were

several times higher than those measured in the blood. However, in the study by Chappell *et al.* [9] neither angiotensin I nor renin activity was detected in the pancreas. These findings thereby question the existence of the common processing pathway described in the blood compartment and in other tissues [4]. Thereafter, mRNA expression of angiotensinogen, renin and the AT II receptor subtypes, AT_{1a}, AT_{1b} and AT_2 were determined in the rat pancreas using reverse-transcription PCR [11]. The presence of angiotensinogen protein, a compulsory component of an intrinsic RAS, was demonstrated by Western blotting, and localized by immunohistochemistry to the epithelium of pancreatic ducts and endothelium of blood vessels [11].

However, the concentration of angiotensinogen in the pancreas of both rats and dogs was low, and constituted only approximately 2.5% of circulating angiotensinogen concentrations [9, 11]. Using the Northern blot technique, Campbell and Habener were unable to detect angiotensinogen mRNA in the rat pancreas in an earlier study [3]. This discrepancy may be explained by the lower sensitivity of Northern blots. Interestingly, when using the Northern blot technique, angiotensinogen mRNA could be detected in all tumors and cell lines derived from the radiation-induced rat pancreatic islet cell line RIN-r [19, 20]. This suggests that islets have a higher expression of angiotensinogen than the exocrine pancreas. However, it cannot be excluded that it merely reflects the undifferentiated state of these tumor cells [21]. The cellular co-existence of the components of the RAS in the exocrine and endocrine pancreas strongly suggests the existence of a local RAS generating intracellular AT II, which exerts autocrine and paracrine functions. However, it remains possible that intracellularly generated AT II is synthesized through a renin-independent pathway. For example, a study by Hojima *et al.* [22] reported that both the dog and rat pancreas contain kallikrein, i.e. an enzyme capable of forming AT II directly from its precursor angiotensinogen [23]. Since then, a number of serine proteases, all of which are capable of generating AT II from angiotensin I and angiotensinogen have been described [24]. Some of these have also been shown to be present in the pancreas [25]. In addition, it is possible that locally formed angiotensinogen is secreted and then processed extracellularly to AT II by circulating plasma renin [26]. Internalization of the peptide ligand-receptor complex by the high affinity binding sites present in the pancreatic tissue would also be consistent with the presence of AT II and the absence of angiotensin I in the pancreas.

AT II immunoreactivity in the mouse pancreas has been localized predominantly to endothelial cells and epithelial cells of ducts [27]. Less pronounced immunoreactivity for AT II could, in that study, be discerned in acinar cells and smooth muscle, whereas no AT II immunoreactivity was detected in islet cells [27]. In the canine pancreas, receptors for AT II are found on endocrine, exocrine, and vascular cells [9]. In the rat pancreas, receptors for AT II are mainly located in islets, and preferentially to the surface of alpha- and delta-cells [10]. The majority of binding sites in the canine pancreas are AT_2 receptors, although AT_1 receptors can also be seen [28]. In rodents similar numbers of AT_1 and AT_2 receptors are found in the pancreas [29]. In the human pancreas, the presence of both AT_1 receptors and (pro)renin have been demonstrated in islets [12]. AT_1 receptors are located on beta-cells and endothelial cells, whereas (pro)renin mRNA is confined to blood vessels and reticular fibers within the islets [12].

Physiological role of RAS in the endocrine pancreas

Binding sites for AT II in the rat pancreas have been demonstrated, as mentioned above, mainly on the surface of alpha- and delta-cells, i.e. in the periphery of the islets [10].

Interestingly, it has been shown that AT II receptors influence prostaglandin synthesis [30, 31], which in turn may modulate the secretion of insulin and glucagon. [32]. However, in isolated rat islet cells, AT II affects neither insulin nor glucagon release [33]. It should be kept in mind that studies on

isolated cells may not accurately reflect complex hormonal interactions seen in vivo. It is possible that AT II modulates the secretion of other regulatory pancreatic hormones such as cholecystokinin, pancreatic polypeptide or somatostatin, which then influence alpha- or beta-cell function. Moreover, the possible effects of the vascular system on islet function is not evaluated in such an in vitro system. To address the latter question, enalaprilate, an inhibitor of ACE, and saralasin, a non-selective AT II receptor antagonist, were administered in vivo to rats, and the effects on whole pancreatic and islet blood flow were then determined. Both drugs preferentially increased islet blood flow [34]. This finding suggests that islet microvessels produce higher levels of AT II than those in the exocrine pancreas, and therefore may be more sensitive to ACE- or AT II receptor inhibition. Moreover, islet blood flow seems, under normal conditions, to be suppressed by this locally produced AT II. Interestingly, in support of these in vivo findings, recent studies from me and my co-workers have shown that islet capillary endothelial cells express high amounts of ACE (unpublished observation).

Experimental studies on the effects of the angiotensin-system on insulin release were made in a pancreas with an intact vascular system by measuring insulin concentrations in the effluents from isolated perfused rat pancreata. In these preparations, enalaprilate affected neither basal nor glucose-stimulated insulin release, whereas AT II delayed the first phase of insulin release in response to glucose (Figure 1) [34]. The effect of AT II was shown to be due to vasoconstriction, and suggests a crucial role of intact islet blood perfusion for maintenance of an adequate insulin release.

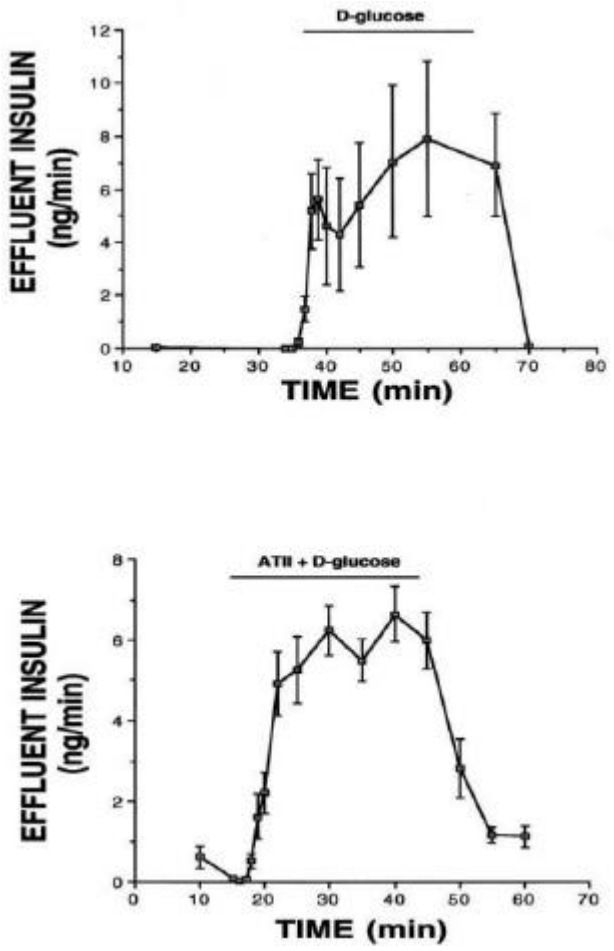

Figure 1. Insulin concentrations in effluent medium collected from perfused pancreata of male Sprague-Dawley rats. The upper panel shows insulin secretion in response to a 30-min period with 16.7 mmol/L D-glucose (bar) added to the perfusion medium. The lower panel shows insulin secretion in response to a 30-min period with 16.7 mmol/L D-glucose + 10 ng/mL angiotensin II (bar). Values represent means ± SEM for 6-7 experiments.
Modified from [34].

The effects of ACE-inhibition on splanchnic blood flow in humans is similar to that observed in rats [35, 36]. Although no studies in man have focused on the blood perfusion of the pancreatic islets, it seems possible, in view of the findings referred to above, that AT II may be involved in the control of the pancreatic vasculature in humans. Interestingly, intravenous infusion of angiotensin II in pressor doses (5.0 ng AT II x kg^{-1} x min^{-1}) suppressed both basal and pulsatile insulin secretion in humans [37]. A subpressor dose (1.0 ng AT II x kg^{-1} x min^{-1}) also tended to suppress insulin secretion.

After an oral glucose load, the insulinemic response was significantly lower and the plasma glucose concentration was significantly higher when AT II was infused as compared to a placebo. Unfortunately, the study design did not allow differentiating as to whether the actions of AT II on insulin secretion were a result of decreased blood flow to the islets or if they were mediated via AT II receptors on beta-cells.

Very scarce information exists on the occurrence of RAS in transplanted pancreatic islets. However, in recent experiments, infusion of AT II in a dose that caused no change in islet blood flow or vascular conductance in native pancreatic rat islets, caused a marked decrease in both blood flow and vascular conductance in transplanted rat islets [38]. This suggests that the blood flow response to AT II in islet grafts differs from that of native islets. In transplanted islets, a chronic marked decrease in tissue oxygen tension is seen after transplantation [39, 40]. Interestingly, it has also recently been shown that chronic hypoxia causes a marked increase in angiotensinogen, both at the gene and protein levels, in the rat pancreas [41]. Increased expression of AT_2- and AT_{1b}-receptors was also demonstrated, whereas no changes in expression of mRNA expression for AT_{1a} occurred [41]. So far, no studies have been conducted specifically on the RAS in islets during hypoxia. Whether upregulation of the RAS occurs secondary to low oxygen tension levels in the grafted islets, or merely is an effect of the implantation organ (kidney), remains to be determined.

Future Basic Perspectives

Current knowledge on RAS in the endocrine and exocrine pancreas has been obtained mainly from morphological studies. Few studies have addressed the functional role of the RAS in the pancreas. In the future, it is therefore important to expand the knowledge on this in in-vivo systems, in view of the marked vascular activity of the different RAS components. Moreover, the regulation of the RAS during different conditions and the influence of disease, e.g. diabetes and hypertension, are important to investigate. The RAS in islets seems to be affected by transplantion and the consequences of this for graft function should be evaluated.

Knowledge of Actual Importance of RAS in the Clinical Setting

The pancreatic islet RAS in diabetes mellitus

In patients treated with the ACE-inhibitor ramipril due to a high risk of cardiovascular events, a marked reduction in the incidence of diabetes and development of diabetes complications has been observed [42]. A decreased diabetes incidence after treatment with an ACE-inhibitor was also noted in the Captopril Prevention Project (CAPP) randomized trial [43]. It is well known that type 2 diabetes often occurs together with essential hypertension [14]. Moreover, hypertension is a risk factor for the subsequent development of type 2 diabetes [15]. It has therefore been hypothesized that some factor(s) common to hypertension and diabetes may underlie the strong association between these diseases. Peripheral insulin resistance is commonly found in patients with essential hypertension and type 2 diabetes [44]. However, it seems that type 2 diabetes does not develop as long as the pancreatic beta-cells can secrete sufficient quantities of insulin to maintain normal glucose homeostasis [45]. Interestingly, several studies in hypertensive patients receiving long-term treatment with ACE-inhibitors, have described an increased initial phase insulin peak in response to intravenous glucose administration [16, 17] or oral glucose [18]. Whether this improved insulin secretion response reflects vascular effects in the islets, or is mediated via AT II receptors on beta-cells remains to be determined. However, so far no studies have described the presence of AT II receptors on the surface of beta-cells, nor have any effects of AT II on isolated beta-cells or islets been found (cf. above). By comparison, profound effects of AT II on insulin release, secondary to impaired islet blood flow, has been observed in an experimental study conducted in rats [38]. It may be speculated that hyperactivity

of the angiotensin system in islet vasculature impairs insulin release. Indeed, in the diabetic state, increased ACE-concentrations occur in the mesenteric vasculature, at least in animals [46]. An increased vasopressor responsiveness to AT II in diabetic patients has also been observed [47, 48]. In addition, changes in vascular ACE seem to occur in various models of hypertension [49]. In spontaneously hypertensive rats (SHR), the renin-angiotensin system exerts a tonic vasoconstrictor action on the mesenteric vasculature [50].

Future Clinical Perspective

Even though ACE-inhibition has shown beneficial effects on islet function in several clinical studies, the mechanism behind this remains to be elucidated. The involvement of the islet RAS for the close correlation that exists between hypertension and type 2 diabetes in the clinical setting, emerges as a potential link. In the future, it will therefore be important to investigate more closely the role of the islet RAS in human diabetes and hypertension, especially with regard to potential circulatory effects.

Key words Islets of Langerhans; Angiotensin II, Insulin (secretion); Microcirculation

Abbreviations AT II: angiotensin II

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