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Possible Involvement of the Local Renin-Angiotensin System in Exocrine Pancreas Responses to Food Components

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Summary

The functioning of the exocrine and endocrine pancreas is strictly co-ordinated through an interdependent array of neural and endocrine, paracrine and autocrine hormonal factors. The responses of the exocrine pancreas to food are primarily initiated via hormones secreted by neuroendocrine cells in the gut. No role for the pancreatic renin-angiotensin system in these mechanisms has so far been established. However, because of its distribution throughout the pancreas, the renin-angiotensin system could have a function in fine-tuning of secretory responses or in integrating some of the actions of the endocrine and exocrine pancreas.

In the normal diet, we are exposed to an array of bioactive (lectins, protease inhibitors, hormone-mimics, tannins, etc). Some can profoundly alter pancreas metabolism both in a beneficial or detrimental manner. Others could have beneficial effects on the pancreas renin-angiotensin system. The effects of these compounds need to be evaluated.

General Regulation of the Exocrine Pancreas

The pancreas fulfils an array of roles in the body from production and controlled release of pro-enzymes or enzymes needed for digestion of food into the gut lumen to synthesis and secretion of hormones required to facilitate and regulate utilisation of nutrients by tissues of the body. Despite this diversity, these functions are interdependent and require to be strictly regulated to ensure proper responses to ingestion and absorption of nutrients. Functioning of the exocrine and endocrine pancreas is therefore controlled and co-ordinated through an array of neural and hormonal regulators that can upregulate or downregulate key aspects of pancreas metabolism depending on the nutritional state of the host [1, 2, 3]. This may include paracrine and autocrine links in the endocrine and exocrine pancreas [4, 5].

The primary responses of the exocrine pancreas to food are mediated via gastrointestinal hormones, such as cholecystokinin (CCK), secretin, gastric inhibitory peptide, peptide YY, somatostatin, etc that are synthesised and secreted by neuroendocrine cells in the gastrointestinal tract [1, 2, 6]. These hormones bind to pancreatic or neural receptors and modulate pancreas responses. Some, such as CCK, induce pancreas secretion whereas others, such as somatostatin, appear to inhibit secretion.

The role of CCK in the responses to dietary protein has been extensively studied [7]. This hormone is produced in neuroendocrine (I) cells of the small intestine and its release is regulated by CCK-releasing (monitor) peptides [8, 9]. These trypsin-sensitive peptides are secreted directly into the intestinal lumen or are components of pancreatic juice. When high amounts of undigested protein are present, the releasing peptides escape digestion by trypsin, bind to receptors on I cells and trigger release of CCK. The hormone binds to neural- [10] or pancreatic-receptors [11] and initiates secretion of digestive pro-enzymes or enzymes into the gut lumen. As the protein in the gut is digested, a proportion of the releasing-peptide is

degraded by trypsin. This reduces the stimulus on I cells and thereby lowers CCK and pancreatic digestive enzyme secretion. Hormones, such as secretin or insulin, may have a secondary role in potentiating this exocrine secretory response whilst others, such as somatostatin or peptide YY, may have roles in rapid attenuation of the response as lumenal protein is degraded.

The regulation of some other gut hormones may also be mediated through specific hormone-releasing peptides. [12]. Furthermore, there are indications of a further level of regulatory control over gut hormone- and pancreatic exocrine secretion since output of CCK-releasing peptides could be inhibited or reduced by somatostatin [12].

Synthesis and secretion of gut hormones and the effectiveness with which they regulate pancreas exocrine function is progressively impaired with age and this can lead to pancreatic dysfunction [13, 14, 15]. This may be due to alterations in the numbers of particular neuroendocrine cells in the gut and changes in the sensitivity of the neuroendocrine cells or pancreas acini to releasing-factors or hormones.

Renin-Angiotensin System

The circulating renin-angiotensin system (RAS) has been extensively studied and been shown to have a critical role in control of blood pressure and electrolyte balance [16, 17]. Recently, attention has focused much more on tissue specific RAS and their potential roles. These have been identified in a range of tissues including, the adrenals, pituitary, brain, kidneys, heart, epididymis and gonads [18, 19, 20].

RAS and the Pancreas

The presence of a renin-angiotensin system or components of it have been observed in pancreas from dogs [21], rats [22, 23] and humans [19]. In general, elements of the local RAS appear to be concentrated on the islets, the endothelia of the vasculature and epithelia of the ductal system [19, 23].

The local RAS has been shown to have a possible role in regulation of the endocrine pancreas [24]. In rats, blockade of the action of angiotensin by administration of an inhibitor of angiotensin-converting enzyme or an antagonist for angiotensin II receptor led to an increase in islet blood flow. Conversely, infusion with angiotensin II greatly reduced blood flow in the islets and delayed insulin responses to a glucose load [24].

Upregulation of pancreatic RAS was evident during development of acute pancreatitis and as a result of hypoxia [25, 26]. In both cases mRNA for angiotensinogen and angiotensin II receptor subtypes were greatly increased. Nonetheless, it is not yet clear whether the responses observed are a cause or an effect. It may be that triggering of the RAS severely impairs blood flow to the cells and promotes ischemia. However, the changes in RAS could also be an attempt to limit damage throughout the organ after tissue dysfunction has been initiated by another mechanism. It is also possible that RAS response, whilst initially protective, may be harmful in the long-term by exacerbating deleterious changes already initiated in the tissue. These options require extensive study. If it can be established that the changes in the local RAS, however they are initiated, are a primary or secondary cause of ischemia in the pancreas, this would certainly facilitate development of therapies to counteract or prevent tissue dysfunction.

RAS and the Exocrine Pancreas

Histochemical studies with specific-antibodies against angiotensin receptor types AT_1 and AT_2 revealed that these receptors were expressed primarily in the endothelia of the blood vessels and the epithelia of the ductal system [27]. Immuno-staining, albeit much less intense, was also observed in the acinar regions [27]. No definite role for RAS in the exocrine pancreas has been established. However, administration of angiotensin II did reduce blood flow through the whole pancreas, as well as through the islets [24]. This suggests that the local RAS does affect exocrine pancreas function.

Distribution of angiotensin II receptors throughout most regions of the pancreas coupled with the ability to produce angiotensin locally may suggest a role for the local RAS in integrating or fine-tuning the responses of the endocrine and exocrine pancreas (Figure 1). For example, if insulin secretion was delayed or limited through the action of angiotensin II on the islets, there would be little point in the exocrine pancreas releasing material into the gut lumen to facilitate digestion of food components that could not effectively be utilised once absorbed. Thus, angiotensin II might act on both the endocrine and exocrine pancreas in tandem to reduce or delay insulin release and fluid including enzyme secretion into the gut lumen. This might be consistent with slight pulsatility in release of both insulin [28] and digestive enzymes [29].

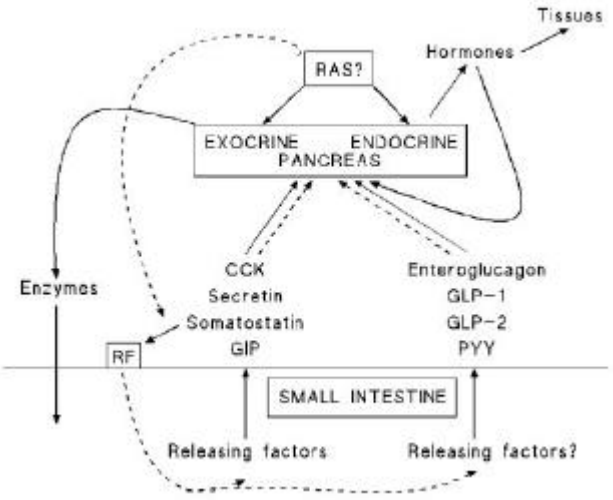

Figure 1. Possible sites of interaction of pancreas renin-angiotensin system with regulatory pathways controlling exocrine secretion of digestive enzymes or proenzymes.
RF: hormone-releasing factors.

Lowered digestive enzyme output due to the action of angiotensin II would in the short-term reduce digestion and thus absorption of nutrients. However, if significant amounts of food were present in the gut, it would also initiate secretion of gastrointestinal hormones, such as CCK, to try to increase the output of the exocrine pancreas and overcome the shortfall in digestive enzymes [29, 30]. Nevertheless, this in itself could be part of the normal counter-regulatory mechanisms controlling and fine-tuning pancreatic function.
If the local RAS is activated at the onset of pancreatitis and blood flow though and fluid excretion from the pancreas is attenuated, this in itself is likely to lead to hypersecretion of CCK and possibly other gastrointestinal hormones [29, 30]. The already damaged pancreas may thus be continually stimulated to synthesis and secrete digestive enzymes. This is likely to accelerate the deterioration in the pancreas.
It has been suggested that tissue-specific RAS may have effects that are quite distinct from those normally associated with circulating RAS [31]. A number of hormones known to be inhibitory to pancreatic secretion, such as somatostatin and pancreatic polypeptide, are found in the pancreas [1, 2, 6]. It is possible that angiotensin II might affect release of these hormones. If blood flow through and fluid secretion from the pancreas were reduced, it would seem reasonable that synthesis and secretion of digestive enzymes would also be lowered. Changes in the local levels of these hormones might also indirectly alter gut hormone secretion and hence pancreatic function through inhibitory affects on the output of hormone-releasing (monitor) peptides [12, 32]. This at present is purely speculative but is a possible mechanism that requires investigation.

Bioactive Dietary Factors

Plant material, particularly legume seeds, contain significant levels of bioactive substances (enzyme inhibitors, lectins, hormone-mimics, tannins, etc.) which can alter hormone balance and body metabolism [33,

34]. Some of these factors may alter the pancreatic RAS and thus merit study.

Dietary lectins and protease inhibitors have pronounced affects on exocrine pancreas function [35, 36]. In rats, these factors trigger prolonged release of CCK from I cells in the gut [15, 29, 37, 38]. In addition, lectins may stimulate the pancreas through other pathways [15, 39]. The net effect of lectin or protease inhibitors is to induce to long-term hypersecretion of pancreatic digestive enzymes and to cause enlargement of the pancreas by hypertrophy and hyperplasia [15, 35, 36].

In addition to CCK, dietary lectins induce sustained release of a number of gastrointestinal hormones [39, 40, 41]. These include secretin, enteroglucagon and glucagon-like peptide 1 and they can have stimulatory or inhibitory effects on pancreatic function.

A number of lectins have insulin-mimicking properties *in vitro*. Furthermore, dietary kidney bean lectins interfere with insulin synthesis and secretion *in vivo* [36, 42]. The mechanisms are unknown but may involve the lectin-mediated release of inhibitory gastrointestinal hormones [40, 41]. Alternatively, since lectins can be taken up systemically in a functional form, they may act directly on pancreatic cells [15, 39].

Soybeans and a number of other plant materials contain significant amounts of oestrogen-like substances [34, 43, 44]. Estrogens trigger the release of angiotensin [7] but may also down-regulate other aspects of RAS, particularly angiotensin-converting enzyme levels [45]. Overall, estrogens are considered to be protective against hypertension [45, 46, 47] and soy-based diets seem to have beneficial effects [48].

Long-term consumption of tannins by stroke-prone spontaneously hypertensive rats reduced the incidence of stroke and increased life span [49]. The mechanisms are unclear but may involve free radical scavenging [49].

Lectins and enzyme inhibitors in seeds are generally inactivated by cooking or processing whilst the tannins and oestrogen-like substances tend to be more heat-stable [50, 51]. In most cases, people are therefore exposed to legume-based foods that have little or no lectins and protease inhibitors but which still contain significant amounts of tannins and oestrogen-like substances. This may be beneficial against hypertension and would be likely to have protective effects against possible RAS-linked damage in the pancreas and other tissues.

It is unclear if such protective effects of tannins or oestrogen-like substances would occur should the diet also contained significant amounts of factors, such as lectin and trypsin inhibitors, that could interfere with pancreas secretory function. This could arise if raw products were consumed or a product containing high levels of lectin or enzyme inhibitors was consumed in conjunction with a cooked legume-based food. Long-term exposure of rats to raw soybean-based diets had adverse affects on pancreas metabolism [52, 53, 54].

Conclusion

Pancreas function is co-ordinated through an interdependent array of neural and hormonal factors that can attune the pancreas to respond to changes in the nutritional state of the host. Because of the distribution of its elements throughout the pancreas, the renin-angiotensin system may have a role in this regulatory control, possibly in fine-tuning of responses or integrating some of the actions of the endocrine and exocrine pancreas. In the normal diet, we are exposed to a number of bioactive factors. Some can profoundly affect pancreatic metabolism. Others may have beneficial effects on the pancreatic renin-angiotensin system. This needs to be investigated.

Key words Enzyme Inhibitors; Estrogens; Gastrointestinal Hormones; Gastrointestinal System; Lectins; Pancreatic Hormones; Pancreatic Juice

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