Hypothesis

Exocrine secretion of pancreatic hormones: possible mechanisms

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In an attempt to define secretory markers for early diagnosis of pancreatic cancer induced in Syrian hamsters, we identified insulin-like and growth hormone-like substances in the pancreatic juice of the animals, following secretin or CCK-OP administration, independent of the effect of the carcinogen [1]. The concentration of immunoreactive insulin was similar between secretin- and CCK-treated hamsters (around 30 μU/ml). A literature survey revealed that our finding was not unique and that pancreatic hormones, including insulin, glucagon and somatostatin, have been demonstrated in the pancreatic juice of several species, including man [2–9].

Since it is known that many blood-borne substances are excreted via pancreatic juice as they are by other body fluids, such as the saliva [10], the presence of these hormones in the pancreatic juice should not be surprising. However, the higher concentration of these hormones in pancreatic juice, compared to that found in the serum [7], refutes the possibility that the circulating hormones are simply diffused through acinar and/or ductal cells into ductal lumen, as is the case in the salivary gland [10]. Consequently, 3 possibilities were considered: (1) The substances identified by radioimmunoassay represent artifactual hormone immunoreactivity, as pancreatic juice contains high concentrations of proteolytic enzymes, that can damage the labeled antigen or antibody used in radioimmunoassay. (2) The excretion of hormones from serum into pancreatic juice occurs by an active transport system. (3) These hormones may come directly from the islets and be released in the juice; in such case
there will be a basal rate of secretion which can be increased depending on the stimulation or the physiologic state of the pancreas when studied.

The first possibility was ruled out following isolation and characterization of the immunoreactive components of the islet cell hormones in pancreatic juice by gel filtration technique. Immunoreactive insulin and somatostatin were detected following secretin [3,9] and CCK stimulation [4,9]. The predominant molecular forms of immunoreactive insulin and somatostatin found in canine pancreatic juice were indistinguishable from the corresponding components in pancreatic tissue with respect to molecular size, charge and immunometric properties [3,9].

The second possibility, i.e., that islet cell hormones enter the ductal lumen by an active process, could also be argued by the observation that after i.v. injection of $^{131}$I-insulin to hamsters, no radiolabeled insulin could be detected in either CCK- or secretin-stimulated pancreatic secretion which was collected at hourly intervals up to 6 h, but was detectable in serum (Pour et al., unpublished). There was free $^{131}$I and free insulin, but no radiolabeled insulin in pancreatic juice and the concentration of the free insulin was, again, much higher than that found in the serum. The results, however, cannot stand the critique that deiodination may have taken place in the blood or/and by pancreatic enzymes. However, since CCK is a powerful stimulus for the release of insulin and somatostatin [11], the greater effect of CCK infusion in eliciting a higher concentration of immunoreactive insulin and somatostatin in the pancreatic juice [3] could indicate that the hormones in the juice derive directly from the islets to the ductules [3]. However, evidence for this is lacking.

The intimate physiological and structural relationship between the exocrine and endocrine pancreas has been shown by numerous physiological, embryological, anatomic-histological and pathological studies [for review see 12–15]. Bensley [16] was the first to demonstrate intimate connections between ductal/ductular cell and islets by virtue of the presence of tiny ductular structures within the islets of guinea pigs. These intra-insular ductules were also demonstrated by us in the Syrian hamster by specific techniques [17] as was the presence of peri-insular ductules routing around some islets and showing contact with the endocrine cells [17]. These histologically inconspicuous intra- and peri-insular ductules became apparent during the ductal/ductular cell carcinogenesis in this species [17,18]. On the other hand, in many species, including man, single islet cells or groups of islet cells are found scattered between the ductal/ductular epithelium and some of these endocrine cells were found to be of ‘open form’; i.e., they reach the ductal lumen by a narrow cytoplasmic portion, which luminal surface is equipped with microvilli [13,15,17] and, thus, resemble some gut endocrine cells which are assumed to have a dual endocrine and exocrine function [19]. Moreover, a close association (attachments) between centroacinar, ductular and insular cells has been well documented [13,17,18]. This particular structural and intercellular relationship could facilitate the discharge of islet cell hormones into the ductal system. However, based on the amount of islet cell hormones found in the pancreatic juice of all the species examined, the exocrine activity of such a limited