Progress report

Is secretin secreted?[1]

In 1902, Bayliss and Starling elicited a pancreatic secretory response by introducing hydrochloric acid into a denervated loop of jejunum and concluded that a chemical substance had been carried by the blood stream from the jejunum to the pancreatic cells[1]. So the concept of 'hormone' was born and the vehicle for the concept was 'secretin'. The existence and functional significance of secretin was readily and rapidly accepted by physiologists, quite unlike the long-continued rejection of gastrin[2] and the neglect of cholecystokinin[3] and of pancreozymin[4].

The acceptance of secretin can be explained, in part, by the dramatic nature of its discovery but also owes a great deal to the demonstration of the very striking and apparently unique potency in stimulating pancreatic secretion of bicarbonate. As a result, secretin began to be used in the clinical investigation of pancreatic disease[5,6], particularly when purification, analysis,[7,8] and synthesis[9,10] made the hormone readily available.

So that secretin is a chemical substance which is very potent, is available in large quantities, and has been used to introduce a concept of genius and an important new field of physiological knowledge—a very powerful combination of attributes, which has almost completely obscured the need to evaluate the evidence for the very existence of secretin as a functional hormone, particularly in man.

Where is Secretin Found in the Body?

Bayliss and Starling reported that the pancreatic stimulant hormone could only be extracted from the mucosa of the duodenum and jejunum[1]. Subsesequent studies have confirmed the localization of secretin, although there has been controversy about the relative amounts of secretin present in the duodenum and the jejunum. Some reports noted that secretin content was maximal in the canine duodenum and decreased progressively down the jejunum[11,12] while Mellanby and Huggett[13] recorded approximately equal content of secretin throughout the upper two-thirds of the goat small intestine.

Apparent confirmation of both the two contradictory conclusions has been provided by two different investigational techniques. Direct localization of secretin in the mucosal S cells of the canine[14,15] and human[16] upper small intestine has been achieved by means of immunofluorescence. The secretin-containing cells appear to be scanty in the jejunum, in keeping with the studies showing less extractable secretin in the canine jejunum than in the duodenum. However, the content of extractable secretin cannot automatically be related to the function of different parts of the small intestine, since a high mucosal content may indicate either relatively high capacity for release of the secretin, or, conversely, that the extractable secretin represents stores from which secretin is released less readily than from mucosa in which stores of secretin are not so easily demonstrable. Similarly, before the immunohistological

demonstration of secretin can be accepted as defining the density of the secretin-producing cells, it will be necessary to demonstrate correlation between secretin content and secretin production in the cells. In other words, paucity of demonstrable secretin-containing cells may be due to absence of the appropriate cells or may be apparent, rather than real, and due to lack of specifically staining granules, because the cells are functionally active and continually secreting the hormone (at least, during the period preceding microscopic examination).

Confirmation of more uniform distribution of secretin in the jejunum and duodenum is based on physiological evidence. In man, it has been shown that the pancreatic bicarbonate response to jejunal acidification is much greater than the response to acid perfused through the duodenum[17]. Similarly, the pancreatic bicarbonate responses to acid perfusion of the proximal jejunum and duodenum are equal in the dog[18]. Such functional evidence is clearly not compatible with virtual absence of secretin-secreting cells from the jejunum, unless there is no connexion between secretin and the pancreatic response to acid. Reassessment of the assumptions underlying both the immunohistological and the physiological demonstration of secretin is therefore required.

Is Secretin Released from the Mucosal Cells and, If So, what Are the Mechanisms which Determine the Release of Secretin?

No direct evidence is yet available that secretin is secreted. Indirect evidence is based on the suggestion by Bayliss and Starling[1] that secretin is liberated into the blood stream and that it may be possible to obtain information about the factors which govern the release of secretin by measuring the levels of secretin in the blood under appropriate physiological and experimental circumstances.

Immunologically detectable increase in the levels of secretin in blood has been reported following the introduction of acid into the small intestine[19,19a] but detailed confirmation is not yet available. Immunoassay of secretin has therefore not yet helped to define the mechanisms which underlie the release of secretin from the small intestinal mucosa. Indeed, it has not even been shown that release of secretin is physiologically significant or necessary for normal gastrointestinal function in man.

Bioassay has also been used to detect the presence of circulating secretin. The technique involved comparison of the response of a target organ—specifically, the bicarbonate secretory response of the pancreas—to blood containing the presumed secretin and to known doses of pure secretin, using conscious[20] and anaesthetized dogs[21,22], anaesthetized cats[23,24,21,25] or rats[26,25,27] or an isolated perfused pancreas[28]. Quantitative interpretation of pancreatic secretory response in terms of secretin, from data provided by bioassay is, of course, only permissible if secretin is the only hormonal stimulant of pancreatic bicarbonate secretion. To put it another way, Bayliss and Starling found evidence for a hormonal mechanism controlling pancreatic secretion, but they did not prove that only one hormone was released and that the hormone, if single, was secretin (as isolated by Jorpes and Mutt).

Are There Any Other Mechanisms for Evoking Pancreatic Secretion?

Neural influences had been considered responsible for the control of pancreatic secretion[29] until Bayliss and Starling[1] demonstrated the importance

of hormonal mechanisms. However, neural control retained a residual role in the regulation of pancreatic secretion when Mellanby[30] suggested that secretin was responsible for the control of bicarbonate secretion, while the vagus regulated the secretion of pancreatic enzymes. The functional importance of the vagus was soon overshadowed by the description of an intestinal extract which stimulated the secretion of pancreatic enzymes[4]. When Jorpes and Mutt[8] determined the structure of cholecystokinin-pancreozymin (CCK-PZ) and made the partially purified hormone readily available for experimental studies in animals and man, CCK-PZ virtually completely superseded the vagus in the postulated control of the secretion of pancreatic enzymes.

Is it Possible to Distinguish Sufficiently Well between the Actions of Secretin and CCK-PZ to Determine which Hormone is Released under Experimental Circumstances?

Evidence for increase in blood levels of CCK-PZ in response to small intestinal stimuli is as incomplete as for secretin[31]. Bioassay involving measurement of pancreatic secretory response cannot satisfactorily be used to differentiate between the two hormones, particularly if they are secreted together. However, it has been suggested that CCK-PZ has a rather specific action on the muscle of the gallbladder[32]. Using the contraction of strips of gallbladder muscle as an index of the (assumedly specific) hormonal action of CCK-PZ, it has recently been suggested that CCK-PZ-like activity is released into the blood stream by acid in the small intestine[33] and that acid is the strongest stimulus of the release of the CCK-PZ. In order to determine whether secretin, or CCK-PZ, or both mediate the response to small intestinal stimulation, an attempt has been made to distinguish between the action of the two hormones by comparing the 'patterns of reaction' which make up the coordinated physiological response to the parenterally administered exogenous hormones with the response to stimuli within the lumen of the intestine.

The intravenous administration of secretin to human subjects elicits the secretion of a mixture of electrolytes, pancreatic enzymes, and (under some circumstances) bile into the duodenum. If the response to intestinal acidification is mediated by secretin, the pattern of the secretory response to acid must resemble the response pattern to some dose rate of secretin. The comparison has been made in man and it has been shown that the output of bicarbonate into the duodenum in response to acid perfusion of the jejunum resembles the bicarbonate secretory responses to large (near-maximal) dose rates of secretin[17]. However, at an equivalent level of stimulation of bicarbonate secretion, the secretory patterns in response to secretin and to acid do not match, since jejunal acidification evokes much greater secretion of pancreatic enzymes and much more marked cholecystokinesis than secretin, while much more sodium chloride is secreted into the duodenum in response to secretin than to jejunal acidification. Therefore secretin alone cannot be responsible for mediating the reaction to intestinal acidification and some other secretory stimulant, or combination of stimulant and inhibitor, must be involved.

The response, in man, to parenteral CCK-PZ alone does not resemble the response to small intestinal acidification at all, since CCK-PZ elicits secretion of only small amounts of bicarbonate and water, despite satisfactory stimulation of the secretion of pancreatic enzymes and of cholecystokinesis. However,

if a small dose of secretin is added to the CCK-PZ, potentiation of the bicarbonate and enzyme secretory responses and of gallbladder contraction occurs[34] and quite a different secretory pattern results, which more closely resembles the secretory response to jejunal acidification. It might be inferred, therefore, that small intestinal acidification released mainly CCK-PZ, with a little secretin. A little secretin, because a high dose rate of secretin changes the pattern of response to CCK-PZ[35] so that the consequent reaction pattern (with inhibition of pancreatic enzyme secretion and of cholecystokinesis) no longer resembles the response to intestinal acidification.

Experiments in animals have demonstrated that the pancreatic response to intestinal perfusion with amino acids resembles a purely CCK-PZ-like pattern, with very little pancreatic secretion of bicarbonate[36], while perfusion of the small intestine with fatty acid results in the secretion of more bicarbonate, relative to pancreatic enzymes, than is secreted in response to CCK-PZ alone [37,38]. On the other hand, the pattern of response to small intestinal perfusion with increasingly large amounts of acid resembles the response to increasing doses of secretin, since the pancreas responds to intestinal acidification by secreting increasingly large amounts of bicarbonate relative to enzymes[39,40]. Indeed, it has been suggested that the factor which limits the pancreatic secretory response to intestinal acid is the maximal capacity of the intestine to release secretin[41].

Interpretation of the response to intestinal acid in animals in terms of release of secretin depends on the assumption that the secretory pattern—high pancreatic bicarbonate output with relatively low enzyme output—is specifically characteristic of the response to secretin. However, the assumption has never been tested directly. It is known that in dogs, as in man, secretin markedly potentiates the pancreatic bicarbonate-secretory response to CCK-PZ[36] or vice versa (since it is not known which pancreatic cells secrete bicarbonate and how the pancreatic hormones actually evoke secretion) so that secretion of large amounts of bicarbonate can be stimulated by a combination of hormones and not only by secretin alone. It is not even clear that secretin is necessary for potentiating the effect of CCK-PZ since gastrin stimulates bicarbonate secretion, at least in dogs[41a], if not significantly in man[41b], and since it has recently been shown that 'vasoactive intestinal peptide' (VIP) has a secretin-like action of pancreatic bicarbonate secretion[42,43] Study of the interaction of VIP and CCK-PZ has not yet been reported but it seems possible that the pattern of reaction to the combination will resemble the response to CCK-PZ combined with secretin. There remains the problem that in animals the output of pancreatic enzymes in response to the combination of the two principal small intestinal hormones is relatively much greater than in response to intestinal acidification, a finding which may become explicable when more is known about the relative rates of hormonal release (and neural interaction) but which may also denote selective inhibition of pancreatic secretion of enzymes. Pancreatic secretory inhibitors have not been studied in detail although it has been shown that localized perfusion of the duodenum with acid may inhibit the pancreatic response to hormones, both in man[17] and dogs[44], while individual hormones, such as glucagon[44a] and calcitonin, have been shown to inhibit pancreatic exocrine secretion, at least under experimental circumstances. Nothing is known about the characteristics of the inhibitory process, so that it is not possible to comment at present on the relevance to the pattern of response to experimental acidification of the

intestine. However, it is worth emphasizing that the processes mediating the reactions to small intestinal stimuli are complex, and, although not yet understood, almost certainly involve the release of combinations of hormones.

In man, combinations of CCK-PZ and secretin do not elicit patterns of response which reproduce all the manifestations of the reaction to small intestinal stimulation. For example, if secretin alone or a low dose of secretin and a high dose of CCK-PZ are infused intravenously, the contents of the duodenum can be aspirated without difficulty in most individuals[44c]. On the other hand, if acid is perfused through the jejunum at the same time as the hormones are infused intravenously, most of the duodenal contents are regurgitated into the stomach (Thjodleifsson and Wormsley, unpublished). The mechanisms underlying the very marked retroperistaltic motor response is not clear, but may be due to release of a hormone with specific stimulant effects on the muscle of the small intestine. The rapidity of onset of the effect indicates, alternatively, that the motor response represents interaction between the effect of hormones and neural reflexes. The latter possibility raises the interesting problem that if there is neuro-hormonal interaction, the interaction may not be restricted to the muscle of the intestine but may also be involved in mediating the pancreatic secretory response and the cholecystokinetic response to small intestinal stimuli. Sufficient information is not available to permit decision, but it is worth emphasizing that when physiological reactions are recorded in terms of response to single or multiple hormones, a sort of short-hand is being used, because if a neural component is involved then a response attributed to a little secretin plus a lot of CCK-PZ may represent the stimulant effect of a little secretin plus a little CCK-PZ plus a little neural activity. Very little quantitative information is available about the hormonal equivalence of neural activity, but it has been demonstrated, for example, that satisfactory canine gastric secretion results from the potentiation of subthreshold levels of gastrin by threshold vagal stimulation[45,46].

It is necessary to have precise information about the mechanisms whereby small intestinal stimuli evoke pancreatic secretion in order to be able to interpret the abnormalities of the stimulus-response relationships which have been noted in disease. Impaired pancreatic responses to acid[17] and amino acids[47] in the small intestine have been noted in coeliac disease and the reaction to small intestinal acidification is also abnormally impaired in patients with duodenal ulceration[17]. It is not possible, at present, to decide whether the functional abnormalities represent endocrinological disorders, associated with defective production or release of small intestinal hormones or denote neural dysfunction, affecting mucosal receptors or the autonomic innervation of the small intestine.

Do Conditions in the Small Intestine under Physiological Circumstances Permit the Release of Secretin?

It has been suggested, on the basis of the bicarbonate secretory reaction of the pancreas, that the threshold for secretin release is about pH 4·5 in dogs[48], since no pancreatic secretion can be elicited by intestinal perfusion of buffers with pH greater than 4·5[49]. At pH less than 4·5, Meyer *et al*[49] have noted that the total quantity of acid infused into the intestine determines the magnitude of secretin release (that is, pancreatic secretory response), presumably because a greater area of intestinal mucosa is exposed to acid as the acid load increases.

No information is available about the threshold of pH required to stimulate pancreatic secretion in man. However, a number of studies have shown that in normal subjects, the pH of the postampullary duodenum[50,51,52,53,54] and of the remainder of the small intestine[51,55,56] is usually near neutral. The normal small intestine is therefore exposed for only brief periods, if at all, to contents with a pH below 5, in response to which secretin release can occur if the human intestine reacts like the canine. On the other hand, it has been shown that L-amino acids evoke a pancreatic secretory response when perfused in near-neutral solution through the small intestine both of man[47,57] and dog[36]. It seems possible, therefore, that postcibal pancreatic secretion is determined more by breakdown products of food and perhaps even by bile salts[58,59] than by acid. Indeed, it is perhaps because the acid-stimulated element of pancreatic exocrine secretion is relatively unimportant that patients with achlorhydria rarely suffer from maldigestion[13].

With the evidence available at present, it must be concluded that in man it seems quite likely that normal physiological circumstances are inappropriate for the release of secretin, while even under experimental conditions, involving the introduction of abnormally large amounts of acid into the small intestine, the pattern of reaction to acid is incompatible with the release of more than small amounts of secretin.

If There is So Little Evidence for the Release of Secretin, What is the Function of Secretin?

Recent computer-based analysis of the sequence of homologous amino acids of the stimulant polypeptides derived from the gut has shown that the 27 amino acids composing secretin correspond to the sequence which stops just at the point where the sequence of amino acids of gastrin and the effective amino acids of CCK-PZ start, in the postulated composition of a primitive precursor polypeptide of gut origin[60].

It is perhaps worth speculating, at this point, that the consecutive nature of the amino acid sequences of secretin and gastrin may represent an evolutionary development of polypeptide fragments which are 'useful' (for survival purposes). As an extreme and improbable alternative, it may be argued that secretin is a 'waste product', like the C-peptide of proinsulin[61], which requires removal before the gastrin-like peptides can be released. In this connexion it may be relevant that CCK-PZ (and cholinergic activity) depolarizes pancreatic acinar cells, while secretin has no such effect[62].

Although possible, it seems improbable that a peptide as biologically active as secretin has no functional significance. Indeed, present uncertainty can probably best be summarized by suggesting that if secretin is involved in physiological events, then it is possible that its very marked potency serves to augment the efficiency of the response to intraluminal, small intestinal stimuli by potentiating the neurohormonal mechanisms which mediate the response.

Summary

Under experimental conditions, eg, acid in isolated, denervated small intestine with intact pancreas or in intact small intestine with denervated transplanted pancreas, a hormonal mechanism has been shown to be involved in mediating the pancreatic response to small intestinal stimuli. In seeking to identify the

hormonal mechanism, a group of polypeptides with possible hormonal activity has been isolated from the small intestine. When one of these polypeptides—secretin—is introduced into the circulation, the resulting pancreatic secretion of bicarbonate is quantitatively similar to the pancreatic response to small intestinal acidification. The similarity of the bicarbonate secretory responses has been interpreted as indicating that the pancreatic response to acid in the small intestine is mediated by secretin.

The inference may be correct, but has not been substantiated and has been queried, for two principal reasons. In the first place, it has been shown that the stimulation of pancreatic bicarbonate secretion is not a unique property of secretin. Although secretin is the most potent known stimulant of pancreatic bicarbonate secretion, other polypeptides and combinations of polypeptides can stimulate the secretion of bicarbonate. Secondly, the demonstration of a hormonal mechanism under experimental circumstances does not tell us anything about the importance of this mechanism under physiological circumstances, particularly since the similarity in response to secretin and to acid in the small intestine is only apparent. The integrated, overall response to the two modes of stimulation is sufficiently different to emphasize that it remains necessary to keep an open mind when considering the mechanisms which control the functions of the upper alimentary tract.

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