EDITORIAL REVIEW

Two of the newer ‘gastrointestinal hormones’

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There has been an explosive increase in information pertaining to the biologically active peptides located in the gut: two recent symposia (Thompson, 1975; Bloom, 1978a) together amount to 1330 pages, giving comprehensive accounts of knowledge in this field. In this review two of these peptides will be considered, which are likely to be of most immediate clinical importance.

Vasoactive intestinal polypeptide

This peptide (VIP) was first isolated from porcine duodenum (Said & Mutt, 1970) and has been shown to be widely distributed throughout the gastrointestinal tract from lower oesophagus to rectum (Polak, Pearse, Garaud & Bloom, 1974). Later it was discovered in the pancreas (Buffa, Capella, Solcia, Feigerio & Said, 1977) and in the brain (Bryant, Bloom, Polak, Albuquerque, Modlin & Pearse, 1976). With the establishment of antibodies against VIP a more precise localization of the peptides has been possible with immunocytochemical techniques.

High concentrations are present in the cerebral cortex, hypothalamus, amygdaloid nucleus and corpus striatum with immunofluorescence present in neurons and nerve terminals (Giachetti, Rosenberg & Said, 1976; Larsson, Fahrenkrug, Schaffalitzky de Muckadell, Sundler, Häkanson & Rehfeld, 1976; Said & Rosenberg, 1976). Concentrations in rat anterior and posterior hypothalamus were found to be 31·8 + 1·36 pmol/g wet weight (mean ± SEM) and the subcellular distribution is consistent with a synaptic vesicular localization (Emson, Fahrenkrug, Schaffalitzky de Muckadell, Jessell & Iversen, 1978). High potassium concentrations (47 mmol/l) release VIP from superfused hypothalamic tissue, a calcium-dependent effect, which provides additional evidence for a physiological role for VIP as a neurotransmitter and/or a neurohormone.

Its presence in cortical synaptosomes has also been reported by Giachetti, Said, Reynolds & Koniges (1977), and in human cerebrospinal fluid, where its concentration is 10 times that in plasma (Fahrenkrug, Schaffalitzky de Muckadell & Fahrenkrug, 1977). The peptide has also been located in the autonomic nervous system, the mesenteric ganglia and in the enteric nerve plexi (Bryant et al., 1976; Larsson et al., 1976). In the gut, however, VIP is not confined to nervous tissue, but is present in the endocrine cells which have been classified as type H (Pearse, Polak & Bloom, 1977). These cells are pyramidal in shape, with a long apical process extending towards the lumen of the intestine (Polak et al., 1974), suggesting that they could be influenced by stimuli acting from the intestinal lumen. However, a meal, or ingestion of amino acids, glucose or saline did not increase the concentrations of VIP in peripheral blood, but hydrochloric acid, fat and ethanol were all effective in increasing the concentration above the normal mean resting value of 4·3 pmol/l in man (Schaffalitzky de Muckadell, Fahrenkrug, Holst & Lauritsen, 1977b). Similar effects were obtained with intraduodenal acid, hypertonic saline and phenylalanine in the dog (Ebeid, Murray & Fischer, 1977). A study of the pharmacokinetics in the pig demonstrates that VIP has a very short life in the circulation, being rapidly destroyed (Modlin, Mitchell & Bloom, 1978), and this has been confirmed in man (Domschke, Domschke, Bloom, Mitznegg, Mitchell, Lux, Strunz & Demling, 1978). Destruction occurs not only in the liver but also in other tissues. This means that VIP may not act as a circulating peptide hormone. The available evidence is more in
favour of a local action, and is in keeping with VIP having the function and properties of a neurotransmitter. Indeed, as noted above, VIP is present in nervous structures in the gut, and electrical excitation of the peripheral cut end of the abdominal vagus leads to a rise in its concentration in pig portal blood from 21 to 50 pmol/l (Schefallitzky de Muckadell, Fahrenkrug & Holst, 1977a). Atropine does not abolish the response and this therefore gives rise to further speculation as to the cause of other atropine-resistant effects in the gut, such as vagal stimulation of pancreatic electrolyte secretion in the pig (Hickson, 1970) and vagal potentiation of the action of secretin in the cat (Brown, Harper & Scratcherd, 1967). However, Mailman (1978) has recently found that atropine inhibited the secretory effects on ileal secretion which were elicited by intravenous infusion of VIP in the dog. VIP when injected intravenously has a very wide spectrum of actions on smooth muscle and glands (Said, 1974, 1975). It has potent vasodilator actions on almost all vascular beds and will cause coronary vasodilatation in doses which are too small to affect total blood flow or blood pressure (Yoshida, Geumei, Schmitt & Said, 1974), and this effect is not dependent on an increase in cardiac metabolism. It has positive inotropic actions on cardiac muscle. The respiratory system is also influenced by VIP, both as a bronchodilator but possibly also by stimulating chemoreceptors (Said, 1975). Metabolic effects are not immune from the influence of VIP, as it stimulates both lipolysis (Desbuquois, Laudat & Laudat, 1973; Frandsen & Moody, 1973) and glycogenolysis (Kerins & Said, 1973). It also stimulates adenylate cyclase in membrane preparations of liver fat cells, colon, ileum and jejunum in a number of species (Desbuquois et al., 1973; Schwartz, Kimberg, Sherrin, Field & Said, 1974). In the gastrointestinal tract VIP inhibits gastric secretion stimulated by either pentagastrin or histamine, but it stimulates pancreatic secretion, although it is much less potent than secretin (Konturek, Thor, Dembinsky & Krul, 1975; Scratcherd, Case & Smith, 1975). It also causes a choleresis in the dog (Thulin, 1973). On intestinal secretion it has an effect qualitatively similar to that of cholera toxin (Krejs, Walsh, Morawski & Fordtran, 1977) and stimulates adenylate cyclase in rabbit ileal mucosa as recorded above, which is probably the biochemical basis for its association with watery diarrhoea. VIP relaxes the isolated muscle of stomach and gall bladder. It has an action on the endocrine pancreas by stimulating insulin and glucagon secretion in the isolated perfused cat pancreas (Schebalin, Said & Makhlouf, 1977).

In spite of this plethora of information, the physiological significance of VIP is still uncertain, despite various suggestions which all so far remain unproven. Perhaps the most attractive suggestion which fits many of the facts is that the peptide may be a neurotransmitter both in the central nervous and the autonomic nervous system. The clinical importance is that very high concentrations of VIP have been reported in the plasma of patients with the severe diarrhoea associated with endocrine tumours, which are usually of pancreatic origin. The clinical features are watery diarrhoea, hypokalaemia and achlorhydria (WDHA) and the syndrome was described by Verner & Morrison (1974), from whom it takes its name. It is important to emphasize that WDHA is a syndrome, which has many causes, and therefore it is not surprising that the primary role of VIP has been contested (Gardner & McCarthy, 1978). The main arguments put forward by these authors against VIP are as follows: (i) the lowest concentration of VIP which will activate adenylate cyclase is 10–100 times the concentration found in the plasma of a patient with watery diarrhoea; (ii) to reproduce the effects on transport of water and electrolytes VIP has to be infused at higher doses than those found in patients with WDHA; (iii) in confirmation of (i), some patients with WDHA have had neither activation of adenylate cyclase nor increase in intracellular concentrations of cyclic AMP in the intestinal mucosa; (iv) the immunoassay for VIP by many authors has not been adequately validated, with consequent lack of agreement between various laboratories; (v) most surprisingly, the clinical criteria by which patients were diagnosed as having WDHA have not always been documented and therefore comparison and clarification is difficult, if not impossible.

Moreover, all tumours are not pancreatic in origin, and phaeochromocytoma, ganglioneuroma and bronchogenic carcinoma have all been implicated. It would also appear to be the case that not all patients with these diarrhoeal syndromes have high plasma concentrations of VIP. A WDHA-syndrome has been attributed to the secretion of pancreatic polypeptide (PP) by a tumour of the pancreas in which almost all cells were pancreatic polypeptide cells (Fahrenkrug & Schaffalitzky de Muckadell, 1978). Welbourn, Polak, Bloom, Pearse & Galland (1978), in a discussion on apudomas (peptide- and amine-secreting tumours) of the
pancreas, make passing reference to having seen one such case of WDHA-syndrome with an elevated plasma concentration of pancreatic polypeptide and a normal concentration of VIP. Medullary thyroid carcinoma (MTC) is often associated with diarrhoea. O'Dorosio (1978) has described cases in which a WDHA-syndrome was present but with no elevation of plasma VIP. However, MTC tissue and also C-cell hyperplastic tissue had elevated VIP concentrations. He suggested that as the VIP cell in the gut has a common ancestry with the C cell of the thyroid, abnormalities may occur simultaneously in the gut and thyroid.

It is clear that many technical problems have to be overcome in relation to VIP assays, which require rigorous validation (Bloom, 1975b; Gardner & McCarthy, 1975). Finally, thorough documentation of the clinical and biochemical criteria, on which diagnosis depends, is of fundamental importance in this difficult area of clinical medicine.

**Gastric inhibitory polypeptide**

Gastric inhibitory polypeptide (GIP) has a sequence of 43 amino acids (Brown, 1971; Brown & Dryburgh, 1971). It was discovered as a contaminant of CCK-PZ preparations and it was from this source that it was first isolated (Brown, Pedersen, Jorpes & Mutt, 1969; Brown, Mutt & Pedersen, 1970). The name was derived from the first property known, that of inhibiting acid secretion by the stomach, and it appeared to be a likely candidate for the elusive 'enterogastrone'. Acid secretion from denervated pouches of body of the stomach in the conscious dog is inhibited by the intravenous injection of GIP. It is most effective on pentagastrin-stimulated secretion, by the innervated stomach, but has less effect on the secretion stimulated by histamine or insulin hypoglycaemia (Pedersen & Brown, 1972). The doses of GIP which were used produced plasma concentrations similar to those observed under physiological conditions.

GIP is located in cells which have been named as K cells, according to an international agreement made at Lausanne (Polak, Bloom, Kuzio, Brown & Pearse, 1973; Solcia et al., 1978), which are distributed throughout the small intestine from duodenum to ileum, with the highest density of cells in the jejunum (Bloom & Polak, 1978). Perfusion of various segments of gut, with glucose as the stimulant for GIP release, confirms the anatomical distribution of immunoreactivity (Thomas, Shook, O'Dorosio, Cataland, Mekhjian, Caldwell & Mazzaferrri, 1977). The polypeptide is released into the portal blood by the ingestion of a meal (Cleator & Gourlay, 1975). When the components of the meal were examined separately, the effective stimulants were glucose and triglyceride fat (Brown, Dryburgh, Moccia & Pedersen, 1975a). The amount of GIP released depends upon the concentration of glucose perfusing the lumen of the small intestine. The release of GIP may also be related to the rate of absorption of glucose or fat. In patients with untreated coeliac disease there is only a small increase in plasma concentration after a meal (Creutzfeldt, Ebert, Arnold, Frerich & Brown, 1976). Oral fat administered to patients with steatorrhoea caused by chronic pancreatitis also produces a smaller rise than in normal subjects, an effect which reverts towards normal if the fat is given with pancreatic enzyme supplements. Finally, inhibition of the intestinal disaccharidase sucrase by Tris buffer also reduces the response of plasma GIP to glucose in otherwise healthy subjects (Ebert & Creutzfeldt, 1975).

Protein and meat extracts do not stimulate the release of GIP and, as these two stimuli are important secretagogues for acid secretion, this suggests that acid in the small intestine does not release GIP. Direct experiments on both man and dog have now confirmed this. Whereas GIP inhibits acid secretion when injected intravenously, there was no increase in plasma GIP concentration when acid was introduced into the small intestine, yet inhibition of stimulated gastric secretion occurred. The effect of acid is therefore not mediated by GIP. Normal fasting concentrations are about 250 pg/ml, which rise in excess of 1000 pg/ml after a meal (Brown et al., 1975a). In addition to its enterogastrone effect, GIP also stimulates the secretion of water and electrolyte by Thiry-Vella intestinal fistulae (Barbezat & Grossman, 1971) and stimulates the secretion of insulin (Dupré, Ross, Watson & Brown, 1973) and glucagon (Pedersen, Dryburgh, Brown & Dupré, 1978). It is its role in absorption and metabolism of glucose which is attracting most attention at the moment.

The observation that orally administered glucose releases more insulin than intravenous glucose, despite a smaller increase in plasma glucose concentrations, suggests that some factor from the gut potentiates insulin secretion. Secretin, gastrin and cholecystokinin—pancreozymin have a spectrum of biological actions (Gregory, 1974) and...
have all been implicated in stimulating insulin secretion. It is unlikely that any of these hormones is physiologically involved, as the doses needed to achieve insulin release are many times higher than those observed during meals. When purified porcine GIP is injected intravenously in man (Dupré et al., 1973) and dog (Pedersen, Schubert & Brown, 1975), in doses within the above physiological range, the release of immunoreactive insulin is stimulated. However, this effect is dependent upon the plasma concentration of glucose which pertains at the time, release only occurring in man when the glucose is more than 1.39 mmol/l above basal values. It is because of this dependence upon glucose that an alternative name for GIP has been proposed: ‘glucose-dependent insulinotropic peptide’. The now-established link between GIP and insulin secretion raises important questions not only in regard to the physiological interaction between these two peptides, but also to their role in the pathophysiology of diabetes mellitus. The basal concentration of GIP in the blood of obese subjects

Fig. 1. Increase in serum amounts of immunoreactive GIP (IR-GIP) and immunoreactive (IR) insulin and glucose with the ingestion (at arrows) of 30 g of glucose (○), 100 g of triglyceride (●) and 30 g of glucose plus 100 g of triglyceride (▲) in the same normal-weight control subjects (n = 16) and obese (42% overweight) subjects with normal glucose tolerance (n = 16). Significant differences between glucose and glucose plus triglyceride are indicated (*P = 0.02 or less).

does not differ from that of normal subjects, unless glucose intolerance is present or the patients have an overt maturity-onset diabetes (Crockett, Mazzaferri & Cataland, 1976b; Ebert & Creutzfeldt, 1978), in which case the concentrations are higher. High basal values are also found in obese subjects after starvation, in untreated ketotic juvenile diabetes, in uraemic patients and after truncal vagotomy (Ebert, Frerichs & Creutzfeldt, 1976a; Ebert & Creutzfeldt, 1978).

An exaggerated release of GIP occurs in patients with maturity-onset diabetes in response to a test meal (Crockett et al., 1976b; Ebert et al., 1976a). An exaggerated GIP release in response to the ingestion of a glucose test meal was observed in obesity, but only if glucose intolerance was present, the amount of GIP being related to the degree of hyperglycaemia. However, an increase in GIP occurred after a test meal of fat in the obese, and this was independent of glucose intolerance. As the obese patients, who responded to an oral load of glucose with an exaggerated secretion of GIP, also had hyperinsulinaemia, the question arises: is the hypersecretion of GIP involved in the hyperinsulinism of obesity? This has been investigated by using a small glucose load and a high fat load, separately and together (Fig. 1). With the small glucose load the insulin response was similar in both the obese and normal groups. After oral fat loads, the serum concentration of insulin did not change in either group, whereas the GIP concentrations in the obese were almost double the control values. When both fat and glucose were ingested together, the obese patients responded with an increased concentration of insulin typical of that found in the hyperinsulinaemia of obesity. It is therefore concluded that, as fat is a strong stimulus for GIP release, the hyperinsulinaemic response is due to the excessive GIP release. The factors which lead to hypersecretion of GIP in obesity are unknown, and a reducing diet, even for only 7 days, reduces the GIP response to a test meal (Ebert, Willms, Brown & Creutzfeldt, 1976b).

Brown, Dryburgh, Ross & Dupré (1975b) have proposed that insulin inhibits GIP release by means of a negative-feedback mechanism, as intravenous insulin decreases fat-induced GIP release. In order to examine the effect of endogenous insulin release on GIP concentrations, intravenous glucose was infused in subjects who had elevated plasma concentrations of GIP after an oral fat load. In the normal subjects there was a fall in GIP concentration, but the values were unaffected in the obese subjects with glucose intolerance. From these observations it has been concluded that insulin inhibits the release of GIP and that the exaggerated GIP response observed in obesity is due to defective feedback between insulin and GIP release (Crockett, Cataland, Falko & Mazzaferri, 1976a; Cleator & Gourlay, 1975; Ebert & Creutzfeldt, 1978).

In a new and rapidly advancing area of physiology and medicine it is all too easy to draw conclusions from inadequate evidence. As detection and diagnoses rely heavily on radioimmunoassay, these new methods must first be validated. Unfortunately, enthusiastic pathophysiological reports have often preceded publication of reliable and definitive assay procedures, making it difficult to come to an objective judgement of work presented. Lessons should be drawn from established assays, for basal values continue to fall with each publication, and multiple forms of the peptide are being discovered. This would appear to be the story with VIP and GIP, particularly the former. Dimaline & Dockray (1978) have published evidence that there are two different molecular forms of VIP, one in the endocrine type cell, the other in nerve cells, and Brown, Dryburgh, Frost, Otte & Pedersen (1978) have also described more than one molecular form of GIP.

References


