THE PHYSIOLOGY OF
CHOLECYSTOKININ IN BRAIN AND GUT

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1 Chemical relationships of cholecystokinin in brain and gut
   a Characterized forms
   b Immunochemical studies
   c Biosynthesis
2 Cellular origins and release
3 Cholecystokinin receptors
4 Cholecystokinin as a gut hormone
5 Cholecystokinin as a neurotransmitter
6 Satiety and other central actions of cholecystokinin 
7 Overview 

Since the identification in brain extracts of the carboxyl
(C)-terminal octapeptide of cholecystokinin (CCK8) much
evidence has arisen to suggest that CCK-related peptides have
neuroregulatory roles in the central nervous system (c.n.s.) in
addition to their well-known hormonal functions in controlling
digestion. Sufficient information now indicates the existence of
both similarities and important differences in the mechanisms of
production and action of CCK-like peptides in brain and gut
(Dockray, 1982a). In part the differences may reflect the need
to maintain specificity when the same substance has control
functions in such diverse systems as brain and gut. The
information available from studies of CCK may therefore
illustrate points of general interest that will be of value in
considering other brain-gut peptides, e.g. somatostatin,
substance P, neurotensin, the enkephalins. I propose to consider
here fundamental aspects of organization relating to the identity,
synthesis, storage, release and actions of CCK in brain and gut,
and to evaluate the extent to which members of the CCK family
of peptides have developed independent hormonal and neuro-
transmitter functions.

1 Chemical Relationships of Cholecystokinin in Brain and Gut

a Characterized Forms

The chemically identified forms of CCK in gut are the
peptides of 33 (CCK33) and 39 (CCK39) residues, isolated and
sequenced by Mutt and Jorpcs over a decade ago (see review by
Mutt, 1980). During the isolation procedure it was found that
the biological activity of CCK, i.e., gall-bladder contraction,
always moved in parallel with that of pancreozymin, i.e.,
pancreatic enzyme release. This evidence strongly suggested
that the two factors which had hitherto been considered separate
hormonal entities were in fact identical. Confirmation of this
idea came when it was discovered that the C-terminal
octapeptide, CCK8, produced by prolonged trypsinization of
CCK33, had full biological activity on both pancreas and gall
bladder. The name "cholecystokinin" is now used irrespective
of the action under consideration. Synthetic CCK8 was widely
used in biological studies before it became clear that this
fragment existed naturally in its own right. The identification
of CCK8 was made first in extracts of brain of the rat, pig, dog and
man, and followed reports of gastrin-like immunoreactivity in
brain (Vanderhaeghen et al. 1975; Dockray, 1976; Muller et al.
1977; Rehfeld, 1978). The latter material was reported to occur in
high concentrations in cerebral cortex and to have the gel-filtration properties of a molecule smaller than the main
forms of gastrin. It is now clear that this material is attributable
to CCK8, which cross-reacts with some C-terminal specific
gastrin antisera because of the common C-terminal penta-
peptide of the two substances (fig. 1). Soon after the
identification of CCK8 in brain this material was isolated and
shown to possess the full chemical and biological properties of the
synthetic peptide (Dockray et al. 1978). A closely related
variant of CCK8 that is also biologically active, but on
anion-exchange chromatography appears to be slightly less
acidic, was isolated as well, but has not yet been fully
characterized.

All the characterized forms of CCK have a sulphated tyrosine
residue at position seven counting from the C terminus.
Radioimmunoassay studies using antisera that react equally
with sulphated and unsulphated CCK8 indicate that the
desulphated form does not occur naturally in detectable
amounts (Dockray, 1980). In contrast, the structurally related
hormone gastrin, which also has a tyrosine in the C-terminal
region (although in this case at position six from the C
terminus), occurs in antral mucosa in about equal proportions of
sulphated and unsulphated forms (see Gregory, 1982). The
sulphate group is essential for the main gastrointestinal actions
of CCK8, but its significance for the neuronal actions of this
peptide are less obvious (see section 3).

True gastrin may well occur outside the gut in low
concentrations in certain specific locations, notably in the pars
nervosa and in corticotrophs and melanotrophs of the pig
pituitary (Larsson & Rehfeld, 1981), and in the vagus nerve
(Uvnäs-Wallensten et al. 1977). This distribution is apparently
erratic, since gastrin is absent from the rat pituitary (Beinfeld et al.
1980), and in the vagus nerve in dog and cat occurs in
detectable amounts in only a few animals (Dockray et al. 1981a).
On present evidence gastrin should be regarded as absent from the c.n.s., and the predominant representative of this
peptide has been identified as CCK8.

b Immunochemical Studies

A number of radioimmunoassays for CCK and related
peptides have been developed. These have proved invaluable
not just for estimation of the peptides, but also for the
identification and initial characterization of various molecular
forms. The results of immunochemical studies indicate that
CCK8 probably occurs in high concentrations in gut as well as
brain, and that forms of intermediate size between CCK8 and
CCK33 may also exist in gut (Dockray, 1977; Rehfeld, 1978;
Straus & Yalow, 1978). In human intestinal mucosal biopsies it
has been estimated that CCK8 occurs in concentrations of
about 100 pmol/g, compared with about 30 pmol/g for CCK33
(Calam et al. 1982). In brain, there seem to be relatively lower
concentrations of larger forms of CCK, e.g. in rat cerebral
cortex CCK8 occurs in concentrations of about 500 pmol/g,
and larger-molecular-weight forms account for less than 5% of
total CCK activity. Recent studies suggest that a variant of
CCK33 that could correspond to either a C-terminally
elongated form, or an amino (N)-terminal fragment, occurs in
high concentration in pig brain (Ryder et al. 1981). The biological activity of this material is unknown, but on present evidence (see below) it would not be expected to be active in the common CCK bioassays, e.g. gall bladder or pancreas.

The larger-molecular-weight forms of CCK are presumed to be biosynthetic precursors of the smaller forms. In addition, there may also exist fragments smaller than CCK8. The possible occurrence in brain and gut of the C-terminal tetrapeptide common to CCK and gastrin (G4) is controversial (Rehfeld et al. 1980). The evidence available from antisera that are highly specific for either the C terminus or the N terminus of G4 leaves no doubt that this molecule is unlikely to occur in brain or gut in concentrations within one or two orders of magnitude of those of the main forms of gastrin or CCK (Dockray et al. 1981b). There may, however, exist in CCK-producing cells of brain or gut other small fragments, but these have yet to be isolated and characterized. Cleavage of CCK to yield G4 may occur during transport in blood, or across the synaptic cleft, but as yet there is no experimental support for this idea.

c Biosynthesis

Because CCK occurs in relatively high concentrations in brain and gut, and because its concentrations in plasma are relatively low, it seems unlikely that it is synthesized in one system and transported to the other. Although a start has been made in the study of CCK biosynthesis in brain (Goltermann et al. 1980), little has been done to study synthesis in the intestine. Assuming that a single gene codes for CCK in brain and gut, it would appear that the different proportions of molecular forms that occur in these systems arise from different patterns of post-translational processing. In brain, the larger forms are presumed to be efficiently converted to CCK8, whereas in gut endocrine cells the conversion is incomplete and leads to accumulation of CCK33 and CCK39 as intermediates. The mechanisms of conversion are still largely unknown, although a preparation that specifically converts CCK33 to CCK8 has been obtained from bovine brain (Ryder et al. 1980). Recently Mutt (1982) reported that enterokinase cleaves CCK33 to yield CCK8, but the relationships between enterokinase and the endogenous converting enzymes are still uncertain.

2 Cellular Origins and Release

Both brain and gut CCKs are stored in their cells of origin in secretory granules and are generally thought to be released by exocytosis. Several studies have demonstrated that high concentrations of CCK occur in the synaptosomal fraction of brain homogenates which corresponds to pinched-off nerve endings. The capacity for protein and peptide synthesis in neuropeptides is limited to the cell soma, and so CCK must be transported to nerve endings intra-axonally; the existence of axonal transport mechanisms has been demonstrated in several systems, including the vagus nerve and the medial forebrain bundle by showing that ligation or lesion of nerve fibres leads to CCK accumulation on the side of the cell body (Dockray et al. 1981a; Williams et al. 1981). In the medial forebrain bundle it is clear that CCK8 is transported from cell bodies of the mid-brain to terminal regions in the limbic forebrain (fig. 2). However, in the vagus nerve CCK is located within afferent nerve fibres and is transported in a retrograde manner from the cell bodies of the nodose ganglion towards the gastrointestinal tract. The significance of this type of transport remains to be established. CCK8 is released from synaptosomes and brain slices by depolarizing stimuli, e.g., high potassium concentrations, in the presence of calcium (Dodd et al. 1980; Emson et al. 1980). Studies in intact dogs in which pancreatic enzyme secretion was used as an index of circulating CCK concentrations suggest that the main stimuli for CCK release from endocrine cells are the products of protein and fat digestion in the intestinal lumen (Meyer, 1981); the possibility that vagovagal cholinergic reflexes account for some of these responses cannot however be excluded. The mechanisms of hormone release at the cellular level are largely unknown, although there is evidence that CCK can be released from ferret jejunum in vitro by depolarizing concentrations of potassium, and as in neuropeptides calcium is apparently required (Scratcherd et al. 1976).

The endocrine cells of the gut have long been known to possess histochemical properties associated with amine metabolism. In particular they actively take up amine precursors which are decarboxylated and stored in secretory granules. Pearse (1969) described these properties, which are shared by many other endocrine cells elsewhere in the body, by the acronym APUD (amine precursor uptake and decarboxylation). The significance of these properties in terms of endocrine cell function is largely obscure. However, for certain CCK-containing neuropeptides the relationships between amine metabolism and peptide production are more apparent. Thus, in some meso-limbic neurons CCK8 coexists with dopamine (Hökfelt et al. 1980). The relationship is flexible as many dopaminergic cells do not contain CCK8 and vice versa. Skirboll et al. (1981) have shown that CCK8 excites neurons in mid-brain regions where the two substances coexist while it has little action on
The black columns indicate concentrations on the same side as lesions of the medial forebrain bundle made earlier, at the times indicated. The white columns show concentrations in the other, control side of the brain. Note the 14-fold accumulation seven days after lesion. The results demonstrate axonal transport from the mid-brain to the forebrain along the medial forebrain bundle.

Immunohistochemical methods are widely used for the localization of peptides, and there have been several such studies on CCK in brain (Innis et al. 1979; Larsson & Rehfeld, 1979; Løren et al. 1979; Vanderhaeghen et al. 1980) and gut (Buffa et al. 1976). Many of the results obtained from immunohistochemistry agree well with those from radioimmunoassay of extracts or micro-punch material. There is, for instance, general agreement that abundant CCK occurs in the cortex, hypothalamus, thalamus and basal ganglia (fig. 3). However, considerable caution needs to be applied in dealing with detailed immunohistochemical findings. Recent studies in our laboratory illustrate this finding, and highlight a discrepancy between radioimmunoassay and immunohistochemical results that has particular bearing on the interpretation of data obtained with the latter technique (Schultzberg et al. 1982). Thus in spinal cord there can be localized by immunohistochemistry abundant nerve terminals in the superficial laminae of the dorsal horn, and this accords with the finding that by radioimmunoassay concentrations of CCK in the dorsal half of the spinal cord (about 100 pmol/g) are 2–3 times higher than those in the ventral half. When capsaicin, the active ingredient of Hungarian red peppers, is administered to newborn rats there is irreversible damage to certain sensory neurones, notably those containing substance P, as demonstrated by immunohistochemistry and radioimmunoassay. However, while capsaicin causes a loss of CCK8-like activity in the dorsal half of the spinal cord revealed by immunohistochemistry, there is no change in the concentrations of material measured by radioimmunoassay, either in dorsal spinal cord or spinal ganglia. The latter material can be characterized as CCK8 by column chromatography and patterns of cross-reactivity with several antisera. Evidently, (i) CCK8 may not be readily demonstrable even when it is present in a tissue, e.g. in dorsal spinal cord of capsaicin-treated rats, and (ii) immunohistochemical localization of "CCK-like peptides" may sometimes reveal material that is plainly not CCK8—although its identity is still to be established.

3 Cholecystokinin Receptors

The structure–activity relationships of CCK and gastrin-related peptides on gastrointestinal targets, e.g. gall bladder, pancreatic acinar cells and gastric parietal cells, are well established. The results obtained from both in-vivo and in-vitro studies are in broad agreement, and recently have been supplemented by studies on receptor binding. In the exocrine pancreas (which has been studied in most detail) the results of receptor studies indicate high-affinity binding of radiolabelled CCK33 that is saturable and reversible. The sulphated C-terminal heptapeptide of CCK is the smallest fragment with appreciable activity, so that CCK8 and CCK33 have similar potencies. However, potency is decreased more than a 1000-fold by desulphation of the tyrosine or shifting this residue towards the C terminus (as in gastrin) (Innis & Snyder, 1980; Jensen et al. 1980). Several studies have demonstrated in brain homogenates binding sites for radiolabelled CCK33; again these are of high affinity, are saturable and binding is reversible (Hays et al. 1980; Innis & Snyder, 1980; Saito et al. 1981). The localization of binding sites revealed by autoradiography of brain sections suggests a distribution that broadly matches that of CCK8 (Zarbin et al. 1981a). However, the affinity of brain binding sites for the C-terminal tetrapeptide, and for gastrins, is only 3–50 times less than that for CCK8 or CCK33, and desulphation of the tyrosine has relatively little effect on potency. There is a further difference between c.n.s. binding sites and pancreas: Peikin et al. (1979) first observed that...
dibutylryl cyclic GMP (Bt_2GMP) inhibited the action of CCK-related peptides on the exocrine pancreas, and since then Bt_2GMP has been shown to act as a specific and reversible competitive antagonist of binding of CCK to its pancreatic receptors (Jensen et al. 1980; Robberecht et al. 1980). Other analogues, including cyclic GMP itself, have little or no effect, and non-CCK stimulants of the pancreatic acinar cells are not inhibited by Bt_2GMP. In contrast, Bt_2GMP does not specifically antagonize CCK binding to brain receptors (Saito et al. 1981). Together then, these results provide evidence for differences in central and peripheral CCK receptors.

In addition to direct actions on smooth muscle, e.g. gall bladder, glandular cells and c.n.s. neurones, CCK also acts on peripheral neurones. Thus CCK causes contraction of the longitudinal smooth muscle of the guinea-pig ileum by a mechanism that involves the release of acetylcholine and probably substance P from the myenteric plexus, as indicated by the observation that CCK8 is inactive on denervated muscle or tetrodotoxin-treated preparations, and its actions are inhibited by atropine and substance P tachyphylaxis (Vizi et al. 1973; Hutchison & Dockray, 1980). The structure—activity relationships for CCK on the guinea-pig ileum closely resemble those for pancreas and gall bladder, i.e., sulphation of the tyrosine is important and gastrins and gastrins are only weakly active. Moreover, Bt_2GMP specifically and reversibly antagonizes the action of CCK on the guinea-pig ileum (Hutchison & Dockray, 1981). These results suggest that the receptors on the myenteric neurones resemble those on other peripheral cells more closely than those on c.n.s. neurones. It is not yet possible to ascribe any physiological significance to these differences in receptor specificity, but it is worth bearing in mind that they might in some way be related to the need to ensure specificity of the hormonal and c.n.s. actions of CCK.

At least two other receptor types that bind CCK-related peptides may exist. The gastrin receptor on parietal cells shows higher affinity for gastrins compared with CCKs (Takeuchi et al. 1979). The existence of the other may be inferred from studies on hormone release from the isolated pig pancreas. In this preparation, the C-terminal tetrapeptide has been shown to stimulate insulin and glucagon release with markedly higher potency compared with N-terminal extended analogues, i.e., gastrin and CCK (Rehfeld et al. 1980). Little else is known of the receptor involved, and direct studies on binding are clearly needed.

With the exception of Bt_2GMP little is known of specific antagonists for the various types of receptor mentioned above. Recent studies suggest, however, several interesting compounds that deserve further detailed evaluation. For example, pralumide (DL-4-benzamido-3',5',diacetylamidobutanoic acid) and benzotript (N-p-chlorobenzoyl-L-tryptophan) have been reported to act as specific antagonists of CCK binding to pancreatic acinar cells; in view of their structural differences compared with Bt_2GMP these compounds probably belong to a different class of antagonist (Hahne et al. 1981). Moreover, they may also act as antagonists of gastrin binding to parietal cells (Weiss & Miederer, 1979). Clearly further progress in understanding the physiology of CCK, particularly with regard to its neuro-regulatory functions, will depend on the vigorous development of these and other possible specific antagonists.

**4 Cholecystokinin as a Gut Hormone**

The idea that the main hormonal function of CCK is to control gall-bladder contraction and pancreatic enzyme secretion is widely accepted; yet recently this idea has been challenged. In order to establish hormonal function it is necessary to demonstrate that the concentrations and molecular species of hormone circulating after a physiological stimulus are sufficient to account for the observed target organ responses. In the case of CCK this means demonstrating that the amounts and types of plasma CCK seen after a normal meal are comparable to those found during infusion of exogenous peptides which produce responses of the gall bladder and pancreas matching those occurring in digestion. Recent studies suggest that this may not be the case. Technical improvements have now made it possible to determine the low concentrations of CCK that occur in plasma after feeding and to identify the molecular forms. The determination may be readily achieved by immunoaffinity adsorption of plasma CCK to specific antisera immobilized on Sepharose beads; after elution of the peptide the different forms can be separated by chromatography and estimated by radioimmunoassays. It is preferable to use C-terminal specific antisera in radioimmunoassays, since these will react with biologically active forms. However, they may also react with gastrins. The latter should be identified and estimated by means of a second radioimmunoassay using gastrin-specific antiserum (Calam et al. 1982; Walsh et al. 1982). Using this method, we have found fasting CCK in normal subjects to be less than 0.8 pmol/l; one to two hours after a light meal plasma CCK concentrations increased to 2–3 pmol/l. The predominant molecular form in plasma was identified as CCK8, and in our hands CCK33 was undetectable. The failure to identify CCK33 in plasma was not due to degradation during sample processing since, when CCK33 was added to plasma, the material was recovered in high yield. Essentially similar results have been found by Walsh et al. (1982). In addition they found circulating concentrations of CCK8-like immunoreactivity after intraduodenal instillation of fat (5–10 pmol/l) that were higher than after a normal meal. When CCK8 was infused intravenously (together with secretin to provide a potentiating background) the threshold plasma concentration needed for stimulation of pancreatic enzyme secretion was about 5 pmol/l, and for 50% of maximal response the plasma concentration was about 10 pmol/l. Pancreatic responses to the exogenous CCK8 were comparable to those after intraduodenal instillation of fat giving similar plasma levels. These observations suggest that while the responses of the exocrine pancreas to fat can be accounted for in terms of CCK release, the plasma CCK concentrations after a normal light meal are unlikely to be sufficient to account for the pancreatic enzyme response.

These data need to be taken together with recent studies on vagovagal reflex control of the pancreas in dogs. Solomon (1981a) has reviewed the evidence for these reflexes. In dogs with a transplanted pancreas the response of the transplant to intraduodenal stimuli is about 50% of the intact gland (expressed as a proportion of the maximum response to exogenous stimuli). The former is regulated only by blood-borne stimuli, whereas the latter obviously receives both hormonal stimuli and a vagal innervation. In normal dogs, both atropine and vagotomy decrease the response of the in-situ pancreas to intraduodenal stimuli. Together these results suggest that vagovagal cholinergic reflexes are important in the normal control of pancreatic enzyme secretion. Further evidence for this view comes from detailed studies of the latency of the pancreatic responses to feeding and to exogenous hormones. When fat or protein is instilled into the duodenum in dogs, there is a prompt increase in the flow of juice with a latency of about
20s. But when CCK is infused exogenously into a peripheral vein (which may be taken to be a model for the secretion of gut CCK into the hepatic portal vein) the latency is at least 30 s. Administration of atropine or vagotomy greatly prolongs the latency to intraduodenal stimuli. Taken as a whole, these studies establish the importance of vagovagal reflexes in the control of pancreatic enzyme secretion, and leave in doubt the extent to which plasma CCK normally regulates enzyme release. However, circulating CCK may determine other aspects of pancreatic function, for example control the growth of the gland (Solomon, 1981b). As reliable methods become more widely available for the estimation and identification of different forms of plasma CCK, these issues should be clarified. Obviously, comparable information on the relationships between plasma CCK and gall bladder contraction are urgently needed.

5 Cholecystokinin as a Neurotransmitter

Considerable progress has been made recently towards satisfying the criteria needed to establish a neurotransmitter role for CCK8. As already mentioned CCK is synthesized in neurones, packaged into granules or vesicles, transported to nerve endings, and stored there until released by mechanisms similar to those determining the release of other transmitters. CCK8 also exerts postsynaptic effects in several systems, both in vitro and in vivo. Thus Dodd & Kelly (1981) have shown that CCK8 administered by iontophoresis has excitatory actions on pyramidal cells of rat hippocampal slices in vitro. The responses were characterized by short latency, decrease in input resistance, depolarization and action potentials. Prolonged application of CCK8 appeared to produce desensitization. In other parts of the c.n.s., CCK8 also has excitatory actions: for example in spinal cord of cat and rat, CCK8 depolarized about 50% of neurones studied (Jeftinija et al. 1981). It is too early to identify specific functions for CCK in brain at the level of single neurones. However, some possibilities are worth detailed consideration; amongst these must be counted a possible function as an excitatory mediator of cortical interneurones, possibly acting to integrate functions within particular cortical barrels or columns. The coexistence with dopamine also prompts detailed studies on the interrelationships in this system.

6 Satiety and Other Central Actions of Cholecystokinin

One of the effects of CCK that is sometimes said to unite its functions in brain and gut is that on feeding behaviour. In the rat, peripheral administration of CCK (intraperitoneal or intravenous) produces a satiety effect, i.e., it inhibits feeding (Gibbs et al. 1973). This observation, which has been confirmed many times, has led to the suggestion that circulating CCK after a meal not only exerts effects on digestive organs, but also on the brain, to inhibit further feeding. In the rat, CCK given directly into the cerebral ventricles has little effect on feeding. In other species, however, notably the sheep, CCK8 administered into the cerebral ventricles has a potent satiety effect (Della-Fera & Baile, 1979). The mode of action of CCK in producing satiety is uncertain, and in consequence the physiological importance of this effect is unclear. In seeking to interpret the significance of these actions it is plainly important to know the precise site of action of CCK and, in particular, whether intravenous or intraperitoneal CCK is acting at a peripheral site or is penetrating the blood–brain barrier and acting centrally. Conversely, the possibility should not be too readily dismissed that CCK administered into the cerebral ventricles subsequently leaks into the blood stream and acts peripherally; Debas et al. (1982) have recently shown that labelled CCK8 given to rabbits intracerebroventricularly rapidly appears in the plasma. Several recent studies have a direct bearing on three questions. In the rat, it has now been demonstrated that vagotomy abolishes the satiety effect of CCK, indicating a peripheral, and very likely a gastrointestinal, site of action (Smith et al. 1981). It is not yet known whether CCK acts directly on vagal afferent endings or indirectly via changes in gut motility or secretion. Both possibilities are worth considering. It is known that CCK receptors occur on vagal fibres and are apparently transported towards the gut (Zarbin et al. 1981b). In addition, however, it is well established that vagal afferent endings respond to distension of the gut wall or chemical stimulation of the mucosa (see reviews by Leek, 1972; Newman, 1974). Given the potent effects of CCK on gut motility it would not be surprising if the vagally mediated effects were secondary to changes in gut movement or in the composition of the luminal contents. In keeping with the idea that the satiety effects of CCK are not exerted directly on the c.n.s., it has recently been shown in sheep that administration of CCK33 into the carotid artery was no more effective in producing satiety than administration into the jugular vein, although concentrations of CCK33 in the cerebral circulation would obviously be much higher after intracarotid administration than after intravenous administration (Grovum, 1981). Regardless of the site of action of CCK, it is clear that the satiety effect produced by peripheral administration is unlikely to be a physiological hormonal action. The doses of exogenous peptide needed to evoke these effects give plasma concentrations far above those seen after a normal meal. However, the possibility cannot yet be excluded that a small pool of neuronal CCK in the gut, either in intrinsic neurones, or perhaps in the vagal fibres (Dockray et al. 1981a), might act on vagal afferent endings to regulate feeding behaviour.

The peripheral administration of CCK produces many other c.n.s. effects in addition to those on feeding. One is a decrease in exploratory behaviour. This effect, like that on satiety, is inhibited by vagotomy, again suggesting a peripheral site of action, and raising the possibility that the effects are secondary to changes in gut function (Crawley et al. 1981). These findings serve to emphasize the importance of studying the effect of vagotomy on other apparently c.n.s.-mediated actions of CCK. Another action deserving particular mention is that producing analgesia. Analgesic effects in rat or mouse hot-plate and tail-flick tests can be evoked by either central or peripheral administration of CCK8 or its amphibian analogue, caerulein (Zeller, 1980; Iurna & Zeller, 1981). CCK8 is found in several areas of the c.n.s. known to be important in the processing of nociceptive information: these include the dorsal horn of the spinal cord and the periaqueductal grey region. Micro-injection into the latter region, as well as into other c.n.s. regions, e.g. caudate, ventromedial thalamus, produces antinociceptive effects. The opioid antagonist, naloxone, abolishes this response, suggesting that CCK might act locally in these regions by releasing endogenous opiates. The alternative possibility that CCK acts on opioid receptors seems at first sight unlikely, but is still worth serious consideration. Thus a CCK analogue, the desulphated C-terminal heptapeptide of CCK8 (Tyr-Met-Gly-Trp-Met-Asp-Phe-NH2), is somewhat related in sequence to Met-enkephalin (Tyr-Gly-Gly-Phe-Met) sharing three of five residues from the N terminus, and this fragment has been shown to possess weak opioid actions (Schiller et al. 1978). It is conceivable that CCK could be enzymically processed to the
PHYSIOLOGY OF CHOLECYSTOKININ IN BRAIN AND GUT

G J Dockray

7 Overview

The accumulated evidence of the last few years leaves no doubt that peptides of the CCK group, particularly the smaller forms such as CCK8, are widely distributed in central and peripheral neurones, and in gut endocrine cells. Although the endocrine functions of CCK are not usually questioned, there is still much to learn of the quantitative relationships between circulating forms of CCK and target organ responses. Until these relationships are established the hormonal role of CCK should not be uncritically accepted. Methods now exist to measure CCKs with sensitivity and specificity, and to study their effects at the cellular and molecular level. It should therefore soon be possible to study these questions in detail.

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