Pancreatic Pathology

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This section, entitled “Pancreatic Pathology,” includes a spectrum of topics on normal and abnormal pancreatic tissue. Specifically, two presentations deal with characterization of cholecystokinin (CCK) receptors on normal tissues. Wank has recently reported the purification, cloning, and expression of the CCKα receptor from rat pancreas, and the article by Miller deals with the biochemical characterization of the CCKα receptor, primarily in gallbladder and pancreatic membranes. The article by Logsdon et al. deals with the effects of CCK on activating immediate early gene expression in normal pancreas, and the other with pancreatic cancer, including recent results of studies in animal models of pancreatic carcinoma (by Longnecker et al.) and the relationship between pancreatic cancer and diabetes mellitus (by Pour and colleagues).

Before considering a few concluding remarks on each paper and points that arose in the questions, because a significant proportion of the papers deal with CCK receptors, Table 1 is included, which summarizes a number of points about the classification of CCK receptors that should be kept in mind in assessing these presentations. CCK and gastrin share the same COOH terminal pentapeptide, and they cause changes in biologic activity or interaction with receptors in binding experiments examining different relative affinities with a number of tissues [1,2]. It is generally agreed, from numerous pharmacological studies, that there are at least two classes of CCK/gastrin receptors [2,3]; one is a CCKα subtype, which interacts with high affinity only with CCK/gastrin analogs sulfated in the seventh position from the COOH terminus. Because gastrin, even when sulfated (gastrin-17-II) is sulfated in the sixth position from the COOH terminus, this receptor has a low affinity for all forms of gastrin [3,4]. This receptor is thought to be the physiologically important receptor mediating the action of CCK on gallbladder contraction, pancreatic secretion, and satiety [1,2,5,6]. Both selective agonists and antagonists now exist for the CCKα subtype; this subtype is found on a number of other tissues, as shown in Table 1, and in the central nervous system (CNS) is present in only a few specific locations, such as the area postrema, certain intrapenduncular nuclei, and the nucleus tractus solitarius [6,7]. Extensive studies have demonstrated that occupation of this receptor causes activation of phospholipase C with changes in cellular calcium and phosphoinositides [2,8]. It is unclear at present whether one subtype, a CCKβ/gastrin, or two subtypes, a CCKβ and a gastrin receptor, or more, mediate the high-affinity interactions with gastrin and non-sulfated CCK analogs seen in the CNS and various tissues (Table 1) [2,3]. The CCKβ receptor was characterized primarily in the CNS by binding studies, where it is widely distributed, especially in the cerebral cortex, and is distinguished by having a high affinity for CCK, gastrin, and various antagonists.

Abbreviations: CCK: cholecystokinin  CNS: central nervous system  ECL: enterochromaffin-like (cells)
TABLE 1
Classification of Receptors for Cholecystokinin/Gastrin-Related Peptides

| Agonists:          | CCK<sub>A</sub> | CCK<sub>B</sub> | ? Gastrin |
|--------------------|-----------------|-----------------|-----------|
| General            | CCK-8 ⇒ Gastrin (1,000×) | CCK-8 > Gastrin (3–10×) | CCK = Gastrin |
| Selective          | A71387           | SNF8702         | Gastrin   |
| Antagonists        | L-364,718, Lorglumide | L-365,260, PD134,308 | Parietal |
| Location           | Pancreas         | Cerebral cortex | GI smooth muscle |
|                    | Gallbladder      | GI smooth muscle| Pancreas |
|                    | Anterior pituitary| Cell lines AR42J and human | GI smooth muscle |
|                    | Gastric smooth muscle | Cell lines AR42J | small-cell Cushion |
|                    | LES inhibit neurons |        |          |
|                    | Area postrema—CNS |        |          |
|                    | Pyloric sphincter |        |          |
|                    | Cell lines—AR42J |        |          |
| Cellular Mediator  | IP<sub>3</sub>   | IP<sub>3</sub>  | IP<sub>3</sub> |
|                    | Ca<sup>2+</sup>  | ?            | CA<sup>2+</sup> |

(Modified from [1,3])

(Table 1) [6,7,9]. At present, the cellular basis of action of this receptor in the cerebral cortex is unclear, although a pharmacologically similar receptor exists on human small-cell lung cancer cells and occupation of this receptor activates phospholipase C (refer to Table 1) [10,11]. The action of gastrin was originally described on gastric acid secretion [1]; subsequent studies demonstrated that parietal cells possessed a receptor with equal high affinity for CCK and gastrin, and later studies demonstrated that the cellular basis of action of these peptides was by activating phospholipase C [12,13]. A particularly important point to remember is that CCK or its COOH terminal octapeptide (CCK-8) has high affinity for all classes of CCK receptors and, therefore, any given physiological or pharmacologic action by these peptides described in the various papers can be through any or all of these receptors [2,4,14].

The recent report by Wank and colleagues represents a particularly important advance: this study reports for the first time the cloning of the CCK<sub>A</sub> receptor through which CCK alters pancreatic acinar cellular function. That study [5], coupled with the recent cloning of the gastrin receptor from dog parietal cells [15], unequivocally establishes that the CCK<sub>A</sub> and gastrin receptors are distinct receptors. What remains not as yet established is whether there is a distinct CCK<sub>B</sub> receptor or how many additional subclasses of CCK receptors mediate the actions of CCK/gastrin peptides. Within the next year, it is likely that this question will be answered. It is also likely, with the availability of cells transfected with these receptors, that the pharmaceutical companies will rapidly develop increasingly selective compounds, which should prove useful in exploring the actions of CCK in mediating various physiological processes. The cloning of this family of receptors not only allows the cell biology of the CCK receptor to be studied in detail, it also opens the possibility that disease states may be found with alterations in this receptor, such as in some neoplasias, obesity, or possibly gastric secretory or intestinal motility disorders.
The article by Miller summarizes his extensive studies, using various cross-linking techniques to characterize CCK receptors on a number of tissues as well as recent research on possible regulation of the CCK receptor by phosphorylation. These studies have provided important findings, which can now be confirmed and extended more easily because of the recent cloning of the CCK\textsubscript{A} receptor. For example, cross-linking studies suggest that gallbladder and pancreatic CCK\textsubscript{A} receptors are probably the same, even though some previous pharmacological studies\cite{16}, usually performed in different species, have raised the possibility they may be pharmacologically distinct. This question will presumably be unequivocally answered in the next year with the recent cloning of the CCK\textsubscript{A} receptor. Another important area highlighted by this study is that CCK and a number of secretagogues, which act via a similar intracellular cascade to CCK (i.e., carbachol, TPA) that cause activation of phospholipase C, mobilization of cellular calcium, or protein kinase C activation, can cause specific phosphorylation of the CCK receptor, suggesting that protein kinase C may be involved as well as a kinase analogous to the \(\beta\)-adrenergic receptor kinase. A number of studies have shown that CCK can induce desensitization\cite{17,18} and whether this phosphorylation relates to this phenomenon or contributes to the unusual biphasic dose-response curve caused by CCK with enzyme secretion will probably be answered in the future by extensions of these researches. Furthermore, the availability of possible antibodies generated against specific CCK\textsubscript{A} receptor areas will likely allow these studies of the regulation of the CCK\textsubscript{A} receptor by phosphorylation and phosphatases to be investigated in detail more easily in the future.

The article by Logsdon et al. presents their recent important studies involving non-secretory effects of CCK. It is known that long-term CCK administration causes pancreatic growth effects and adaptative changes in the pancreatic acinar cell with changes in digestive enzyme genes. These researches clearly demonstrate that CCK in normal pancreas has effects on activation of the immediate early genes c-fos, c-myc, and c-Jun, and that probably cAMP, protein kinase C, and calcium-sensitive response elements are important in mediating these effects. This paper has important implications for the action, not only of CCK/gastrin-related peptides in the pancreas, but also in other tissues. CCK-related peptides are known to affect the growth of a number of normal tissues as well as to affect growth of a number of tumors\cite{19-21}. Various different experimental protocols demonstrate that CCK can promote the development of pancreatic neoplasms such as those in animals treated long-term with trypsin inhibitors, which result in elevated CCK levels\cite{22,23}. Furthermore, administration of CCK analogs promote azaserine-induced carcinogenesis\cite{24,25}. These studies, as well as the results reported by Logsdon et al., clearly emphasize the importance of understanding the molecular basis for long-term cellular changes induced by CCK in the pancreas and other tissues. Other reports suggest that similar studies will be equally important with respect to gastrin. Recent researches show that chronic hypergastrinemia induces hyperplasia of enterochromaf-fin-like cells (ECL cells) in the gastric mucosa and, in some cases, malignant carcinoid tumors develop\cite{26,27}. Because of the widespread increased long-term use of potent gastric anti-secretory agents such as the gastric H\textsuperscript{+}/K\textsuperscript{+}-ATPase inhibitor omeprazole, which can cause achlorhydric and chronic hypergastrinemia\cite{26,27}, the molecular basis for the long-term growth effects of gastrin on the stomach have important clinical implications.

The article by Longnecker et al. discusses recent results in animal models of
pancreatic cancer, reviews the differences that are being found with these diverse models, and also points out the difficulty in establishing the cell of origin of the various histologic types of pancreatic tumors found in these models. It is important to remember that pancreatic cancer is the fifth most common cause of cancer death, with an average survival of only three months. Therefore, current therapeutics are clearly unsatisfactory. One of the main difficulties in studying the biology of pancreatic cancer is the relative inaccessibility of tissue until late in the course of the disease. These tumors almost all present late in their course, and, because of the inaccessibility of the gland, detection of asymptomatic early lesions almost never occurs. Therefore, in contrast to such tumors as gastric or colon adenocarcinoma, where various early stages of the tumor can be easily approached endoscopically, this procedure is not possible in pancreatic cancer and thus, only by developing adequate animal models of this tumor, will unique features of its cell biology and pathogenesis be resolved. The development of appropriate animal models of this tumor would probably prove to be extremely helpful in better understanding the cellular origin of these tumors and studying their cell biology.

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