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CHOLECYSTOKININ AND GASTROINTESTINAL CANCER

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Summary—The gut hormone cholecystokinin exerts various actions on the gastrointestinal tract, including the regulation of growth. The hormone has been reported to induce hypertrophy and hyperplasia of the pancreas and to enhance chemically-induced pancreatic carcinogenesis in animals. Stimulation of endogenous cholecystokinin secretion through the induction of deficiency of intraintestinal proteases and bile salts by trypsin-inhibiting nutrients, bile salt-binding drugs or surgical intervention is also capable of stimulating growth and tumour development in the rat. In man, factors suggested to increase the risk of pancreatic cancer, such as a high-fat and high-protein diet or gastrectomy, are known to stimulate plasma cholecystokinin secretion. Receptors for cholecystokinin have been demonstrated on human pancreatic adenocarcinomas, and cholecystokinin has been demonstrated to enhance the growth of xenografted pancreatic cancer and to inhibit growth of gastric and bile duct cancer. The recently developed cholecystokinin-receptor antagonists inhibit not only pancreatic growth but also pancreatic carcinogenesis in animals. These new drugs may be valuable new tools for inhibiting pancreatic cancer growth in humans.

CHOLECYSTOKININ

Cholecystokinin belongs together with gastrin and secretin to the classical gut hormones [1]. Cholecystokinin is produced by the I-cells in the upper small intestinal mucosa and is released into the circulation in response to ingestion of nutrients or infusion of the neurotransmitter bombesin/gastrin releasing peptide. The polypeptide hormone is named cholecystokinin because of its property to stimulate gallbladder contraction. In addition to its gallbladder contracting property, cholecystokinin has been shown to be a potent stimulus of pancreatic growth and pancreatic enzyme and hormone secretion, to affect motility of the gastrointestinal tract and to play a role in the regulation of satiety. Because of its pancreatic growth promoting action, cholecystokinin has been studied in pancreatic carcinogenesis [2–4]. The recent development of highly effective and specific cholecystokinin-receptor antagonists has enabled us to delineate the various actions of cholecystokinin in great detail [5]. Two types of cholecystokinin-receptor antagonists can be used in *in vivo* studies, glutaramic derivates (proglumide, lorglumide, loxiglumide) and non-peptide compounds (asperlicin, L-364,718). Studies on the role of cholecystokinin on gastrointestinal tumours have been concentrated on the role of cholecystokinin in pancreatic cancer.

CHOLECYSTOKININ AND PANCREATIC CANCER

The effect of cholecystokinin on pancreatic cancer can be studied by various approaches (Table 1). Several studies have shown that cholecystokinin not only stimulates the growth of the normal pancreas but also promotes pancreatic carcinogenesis and tumour growth of the pancreas [6, 7]. In fact, long-term administration of cholecystokinin to rats induces pancreatic hypertrophy, hyperplasia and premalignant changes [8]. Furthermore, cholecystokinin has been reported to enhance azaserine-induced pancreatic carcinogenesis in rats [9] and nitrosamine-induced carcinogenesis of the pancreas in hamsters [10]. In addition, several studies indirectly point to an important role of cholecystokinin in the development of pancreatic cancer. In man, factors suggested to increase the risk of pancreatic cancer, such as high-fat and high-protein intake and previous gastrectomy, are known to be accompanied by a raised plasma cholecystokinin secretion [4]. In animals, especially in rats but also in hamsters, there are numerous studies pointing to a role of

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Table 1. Effect of cholecystokinin on pancreatic tumour growth

1. Effect of exogenous cholecystokinin on tumour growth
   —Pancreatic cancer *in vitro*
   —Xenografted pancreatic cancer
   —Chemically-induced pancreatic carcinogenesis
2. Effect of endogenous cholecystokinin (surgery, drugs or nutrients) on tumour growth
   —Xenografted pancreatic cancer
   —Chemically-induced pancreatic carcinogenesis
3. Characterization of cholecystokinin receptors on pancreatic tumours
4. Effect of specific cholecystokinin-receptor antagonists on tumour growth
   —Pancreatic cancer *in vitro*
   —Xenografted pancreatic cancer
   —Chemically-induced pancreatic carcinogenesis
   —Advanced pancreatic cancer

cholecystokinin in pancreatic carcinogenesis and tumours can be induced by various manipulations that increase plasma cholecystokinin, such as dietary manipulations (nutrients with trypsin-inhibiting properties such as raw soya flour) and camostate, bile-salt binding drugs, such as cholestyramine and surgical interventions inducing deficiency of intestinal proteases or bile salts (pancreaticobiliary diversion and, possibly, cholecystectomy [11–14]). Furthermore, these plasma cholecystokinin secretion-stimulating manipulations promote pancreatic carcinogenesis induced by chemical carcinogens. It has been shown that azaserine-induced pancreatic carcinogenesis in rats can be enhanced by raw soya flour and a high-fat diet [15–17] and that nitrosamine-induced pancreatic carcinogenesis in hamsters can be stimulated by dietary fat [18]. Furthermore, receptors for cholecystokinin have been demonstrated on human pancreatic adenocarcinomas [19]. Upp *et al.* [20] have shown that the presence or absence of cholecystokinin receptors on such cancers may predict the responsiveness of the tumour to hormonal treatment. It has further been shown that cholecystokinin stimulates the growth of xenografted human pancreatic cancer [19, 21, 22].

The recent availability of specific cholecystokinin-receptor antagonists have enabled us to study the role of cholecystokinin in pancreatic cancer in more detail. Furthermore, in analogy with the growth-inhibiting effect of steroid receptor antagonists in breast cancer, the effects of these cholecystokinin-receptor antagonists in pancreatic cancer are presently studied. Recent studies by Alexander *et al.* [21] and Maani *et al.* [23] have demonstrated that the specific cholecystokinin-receptor antagonists asperlicin and L-364,718 inhibit the growth of xenografted human pancreatic carcinomas. Furthermore, Douglas *et al.* [9] have shown that enhancement of asazerine-induced pancreatic carcinogenesis by the trypsin inhibitor camostate in rats can be reduced by treatment with the specific cholecystokinin-receptor antagonist lorglumide (Fig. 1).

It is apparent from the above and several other studies that cholecystokinin may be involved in the development and growth of pancreatic cancer and that the availability of specific cholecystokinin-receptor antagonists may open a new area of research on pancreatic cancer and may ultimately offer new hope to the desperate patients afflicted by this dismal disease.

CHOLECYSTOKININ AND NON-PANCREATIC TUMOURS

Cholecystokinin and gastric carcinoma

Cholecystokinin is structurally related to gastrin [1], which is known to possess growth

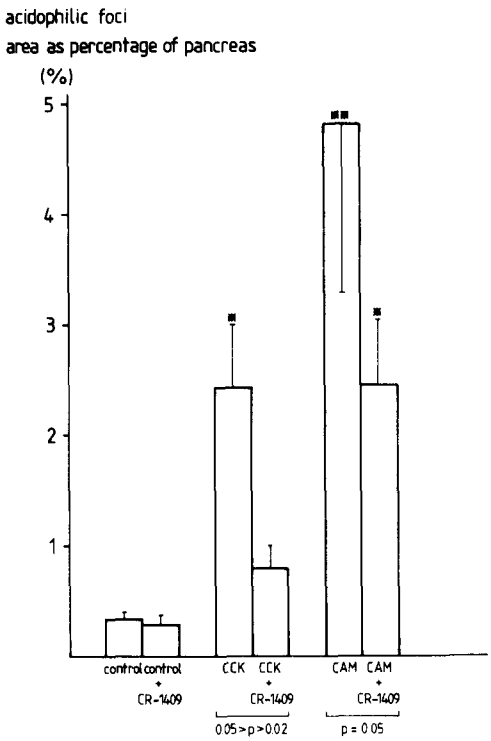

Fig. 1. Stimulation of azaserine-induced preneoplastic acidophilic lesions by exogenously administered cholecystokinin (CCK) and by endogenously released cholecystokinin during stimulation by oral administration of the trypsin inhibitor camostate (CAM), and the partial inhibition of cholecystokinin- and CAM-stimulated pancreatic carcinogenesis by the specific cholecystokinin-receptor antagonist lorglumide (CR1409) in rats. Asterisks denote significant differences from the control studies (*$P < 0.05$; **$P < 0.01$; analysis of variance).

promoting actions on certain gastric carcinomas [2, 3]. With regard to gastric acid secretion, cholecystokinin is known to be a partial agonist, i.e. the hormone stimulates basal but inhibits gastrin-stimulated gastric acid secretion. Yasui *et al.* [24] have shown that cholecystokinin inhibited the growth of a xenotransplantable gastrin-sensitive human gastric carcinoma in nude mice. Hudd *et al.* [22] studied two gastric carcinomas transplanted into nude mice and found that growth of one of these cancers was inhibited by cholecystokinin.

Cholecystokinin and hepatobiliary cancer

Administration of cholecystokinin did not affect the growth of a hepatic and biliary human cancer transplanted in nude mice [22]. However, Hugh *et al.* [25] could inhibit growth of a xenotransplanted cholangiocarcinoma with cholecystokinin receptors by the cholecystokinin analogue caerulein. This inhibition by caerulein was abolished by treatment with the cholecystokinin-receptor antagonist lorglumide (CR1409).

SUMMARY

In summary, cholecystokinin is able to modulate growth of gastrointestinal cancers possessing cholecystokinin receptors. In general, the effect of the hormone on pancreatic cancer is stimulatory, whereas it inhibits growth of certain non-pancreatic gastrointestinal cancers. The recent development of highly specific cholecystokinin-receptor antagonists has enabled further studies on hormonal manipulation of gastrointestinal cancers. However, much work has to be done before the place of cholecystokinin and cholecystokinin-receptor antagonists in the treatment of gastrointestinal cancer in man can be fully evaluated.

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