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Sounding Board

Role of Gastrin and Cholecystokinin in Tumours of the Gastrointestinal Tract

CORNELIS B.H.W. LAMERS and JAN B.M.J. JANSEN
Department of Gastroenterology and Hepatology, University Hospital Leiden, The Netherlands

THE GASTROINTESTINAL hormones gastrin and cholecystokinin are polypeptides with structural homologies in the biologically active carboxy-terminal part of the molecules [1]. Both hormones are released into the circulation after ingestion of food. The main physiological function of gastrin, produced by G-cells in the mucosa of the gastric antrum and proximal duodenum, is the stimulation of gastric acid secretion, while the predominant action of cholecystokinin, produced by the I-cells in the upper small intestinal mucosa, is the stimulation of gall-bladder contraction and secretion of digestive enzymes by the pancreas [1]. In addition, both hormones have trophic actions on the gastrointestinal tract [2]. The trophic actions of gastrin are mainly directed towards the gastric and colonic mucosa, while cholecystokinin predominantly stimulates pancreatic growth [2].

Gastrin and cholecystokinin are produced by certain tumours and these hormones may serve as a hormonal marker of such a tumour. Furthermore, by their property of influencing mucosal growth the hormones may interfere with the development and growth of various tumours of the gastrointestinal tract.

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Correspondence to: Prof. Dr. C.B.H.W. Lamers, Head, Department of Gastroenterology and Hepatology, University Hospital Leiden, Bldg 1 C4-P, P.O. Box 9600, 2300 RC Leiden, The Netherlands.
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PRODUCTION OF GASTRIN AND CHOLECYSTOKININ BY TUMOURS

Gastrin is produced by endocrine tumours belonging to the so-called apudomas [3]. These tumours are usually malignant, although their growth may be relatively slow [4]. The tumours mostly arise from the pancreas and the proximal duodenum, but the hormone has also been reported to be produced by parathyroid, renal and gastric tumours and by ovarian cystadeno(carcino)ma pseudomucinosum [5, 6]. The hypersecretion of gastrin by these tumours leads to the so-called Zollinger–Ellison syndrome [4, 7], characterized by gastric acid hypersecretion, peptic ulcers and often diarrhoea. In about a third of the patients is the Zollinger–Ellison syndrome a component of the multiple endocrine neoplasia type I syndrome [8, 9]. This is an autosomal dominant inherited entity in which tumours of the parathyroid glands, pancreatic islets and pituitary gland are prominent. Unfortunately, surgical attempts to resect all tumour tissue are successful in only 10–20% of the patients with gastrin-producing tumours. Since the introduction of potent antisecretory drugs, preventing death from peptic ulcer complications [4, 10], most patients will eventually die from tumour spread. Apart from streptozotocin, which has been reported to induce temporary tumour reduction in only a minority of the patients [11], no effective antitumour drugs are available.

Cholecystokinin has recently been reported to be present in pituitary tumours [12]. It is not known whether these cholecystokinin containing pituitary tumours are accompanied by increased plasma concentrations of the hormone. In this respect it is important to note that both cholecysto-

kinin and gastrin occur in the normal pituitary gland as well [13, 14]. Furthermore, cholecystokinin has been demonstrated in cloned cell lines from a transplantable islet cell tumour [15].

EFFECT OF GASTRIN AND CHOLECYSTOKININ ON TUMOURS

Carcinomas of the gatrointestinal tract occur frequently and contribute considerably to death from cancer. Treatment of patients with gastrointestinal cancer relies heavily on adequate surgical resection. However, this therapy is only effective when localized tumour is present. There is no effective systemic treatment for widespread or metastatic gastrointestinal cancer.

It is well known that breast cancers are often successfully treated by endocrine manipulation, when specific receptors for steroid hormones that stimulate growth of the normal breast are present in the cancer. Since gastrointestinal hromones have trophic effects on the normal gastrointestinal tract [2], the possibility of influencing the growth of gastrointestinal cancer by gastrointestinal hormones is gaining increasing interest. Indeed, recent studies in animals have demonstrated that gastrointestinal hormones can influence the development and growth of gastrointestinal tumours [16–18]. Gastrointestinal hormones may either stimulate or inhibit growth of the normal gastrointestinal tract. For example, cholecystokinin has a trophic effect on the pancreas which can be inhibited by somatostatin.

Several types of studies have been performed to demonstrate the effect of gastrointestinal hormones on tumour growth. First, studies on the effect of exogenously administered hormones on tumour growth. This can be done by evaluating the effect of gastrointestinal hormones on tumour cells *in vitro*, on the growth of tumour cells transplanted into suitable animal models, and on the development of (pre) malignant changes induced by carcinogens. Second, studies on the effect of manipulation of endogenous hormone secretion on the growth of transplanted tumours or the development of tumoural changes by carcinogens. Hormonal manipulation can be achieved by feeding of specific nutrients or surgical intervention. Third, studies on the effect of growth-inhibiting hormones on tumour development and growth in the models mentioned above. Fourth, studies on the effect of recently developed specific hormonal receptor antagonists in the various models. Fifth, the demonstration and characterization of specific receptors for gastrointestinal hormones on cancers. Depending on the model the influence of hormones on development and growth of tumours can be quantitated by various means, such as the number, size or weight of tumours, DNA synthesis, uptake of labelled thymidine or leucine, production of cAMP or cAMP-dependent protein kinase.

Gastric carcinoma

Studies on the promotion of gastric carcinogenesis and tumour growth by gastrointestinal hormones are mainly restricted to the effects of gastrin. Several studies have shown that gastrin stimulates the growth of rat and human stomach cancer cells *in vitro* [19–23]. Furthermore, exogenously administered gastrin promotes the growth of rat and human gastric cancer transplanted into the nude mouse [20, 21, 24, 25]. Less convincing are the reports on the tumour-promoting effect of gastrin on gastric carcinogenesis induced by carcinogens. Tahara and Haizuka [26] reported that prolonged administration of gastrin resulted in a remarkable increase in the production of scirrhous gastric cancer in rats produced by *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG). Other workers, however, were unable to demonstrate a growth promoting effect of gastrin in this model [27, 28]. In a later report, Tahara *et al* [29] demonstrated that the timing of gastrin administration is of utmost importance and this finding may explain the apparent discrepancies between the studies. Kurihura *et al.* [30] succeeded by administration of *N*-ethyl-*N'*-nitrosoguanidine and gastrin in producing scirrhous carcinoma in the stomach of the dog, a species known to be relatively resistant to gastric carcinogenesis by the carcinogen only. The results of the effect of endogenous gastrin on gastric carcinogenesis are conflicting as well. Deveney *et al.* [27] failed to find an increased incidence of gastric cancer induced by MNNG in rats made hypergastrinaemic by antral transposition. The absence of any apparent effect in that study may have been due to the model selected, because hypersecretion of gastric acid induced by the high gastrin levels in this model may protect the animals against gastric carcinogens [17]. This suggestion is supported by the finding that endogenous hypergastrinaemia induced by atrophic gastritis, a condition known to be accompanied by low gastric acid secretion, does promote MNNG induced gastric carcinogenesis in rats [31].

Cancer of the pancreas

These studies have mainly been concentrated on the hormone cholecystokinin. As mentioned before, cholecystokinin has trophic effects on the gastrointestinal tract, especially on the pancreas [32, 33]. In fact, long-term administration of cholecystokinin to rats induces pancreatic hypertrophy, hyperplasia and premalignant changes [34, 35]. Cholecystokinin stimulates the growth of a human pancreatic carcinoma *in vitro* [36]. In addition, this hormone promotes the growth of this tumour after

transplantation into the nude mouse [36]. Furthermore, cholecystokinin in combination with secretin, another gastrointestinal hormone, stimulates the growth of a hamster pancreatic cancer transplanted into the cheek pouch of another hamster [37]. In this respect it is interesting to note that there is also potentiation between cholecystokinin and secretin in the stimulation of growth of the normal pancreas [32]. In studies on the effect of cholecystokinin on pancreatic carcinogenesis by carcinogens, two animal models should be distinguished. First, the acinar cell-type adenocarcinoma in rats and, second, the ductal/ductular cell-type adenocarcinoma induced by certain nitrosamines in hamsters. Acinar cell-type adenocarcinoma in rats is induced by azaserine [38], while the ductal/ductular cell adenocarcinoma in hamsters develops after administration of nitrosamines [39]. It has recently been shown that the effect of azaserine on pancreatic carcinogenesis in the rat is enhanced by cholecystokinin [40]. Studies on a possible promoting effect of cholecystokinin on the induction of ductular cell carcinoma by nitrosamines in hamsters have shown contrasting results. Johnson *et al.* [41] reported that cholecystokinin inhibits pancreatic carcinogenesis induced by diisopropanolnitrosamine, while Andrén-Sandberg *et al.* [42] were unable to demonstrate any effect of cholecystokinin on the development of pancreatic cancer by *N*-nitrosobis(2-hydroxypropyl)amine. On the other hand, Howatson and Carter [43] found a marked enhancement by cholecystokinin of pancreatic carcinogenesis induced by *N*-nitrosobis(2-oxopropyl)amine. Several differences in the design of the studies may be responsible for the contrasting results. Stimulation of endogenous cholecystokinin by feeding of raw soya flour or fat promotes the development of acinar cell adenocarcinoma in rats induced by carcinogens [35, 44, 45].

Colon carcinoma

Gastrin promotes the *in vitro* growth not only of stomach cancer but also of rat and human colon cancer [21, 46]. Furthermore, exogenously administered gastrin stimulates growth of transplanted mouse and rat colon cancer in the nude mouse [47, 48]. This stimulation by gastrin of colon cancer growth was accompanied by a significantly decreased survival due to accelerated tumour growth in the mice [47]. Studies on the effect of gastrin administration on the growth of colon cancer induced by carcinogens are contrasting. McGregor *et al.* [49] reported a significantly raised tumour concentration of DNA, RNA and protein in rats treated with gastrin after previous tumour induction with methylazoxymethanol, while Tatsuta *et al.* [50] failed to demonstrate enhancement by gastrin of colon cancer growth induced by intrarectal instillation of MNNG. Endogenous hypergastrinaemia, produced by antral exclusion or small bowel resection in rats, increases DNA synthesis in colon tumours or increases the incidence of tumours in carcinogen-treated rats [39, 51, 52]. Oscarson *et al.* [53], however, failed to demonstrate a promoting effect of endogenous hypergastrinaemia, resulting from gastric fundectomy, on colon tumour growth induced by dimethylhydrazine in rats.

Endocrine gastro-intestinal tumours

It has recently been shown that endogenous hypergastrinaemia is involved in the development of gastric carcinoid tumours in rats [54]. Since these tumours arise from ECL cells in the gastric body, they are also named ECLomas. In these experiments marked hypergastrinaemia was secondary to achlorhydria induced by long-term administration of very high doses of the antisecretory drug omeprazole. The development of gastric carcinoids was preceded and accompanied by ECL cell hyperplasia. When hypergastrinaemia was prevented by antrectomy, omeprazole did not induce ECL cell hyperplasia or carcinoid tumours [55]. In this respect it is interesting to note that ECL cell hyperplasia and gastric carcinoids are extremely rare in normogastrinaemic human subjects but occur more frequently in hypergastrinaemic patients with pernicious anaemia [56].

Inhibition of gastrointestinal tumour growth by hormonal manipulation

Secretin inhibits the *in vitro* growth of both gastric and colon adenocarcinoma stimulated by gastrin [21]. Such an inhibitory effect on gastrin-stimulated growth of gastric cancer has also been shown for cholecystokinin [20]. Furthermore, secretin inhibits the effect of endogenous hypergastrinaemia on colon cancer growth induced by carcinogens in the rat *in vivo* [38]. Somatostatin, a polypeptide with inhibitory effects on the gastrointestinal tract, inhibits the growth of transplanted pancreatic carcinoma in rats and hamsters and of colon carcinoma in mice [57–59]. Another important finding is that the gastrin-receptor antagonist Proglumide inhibits the stimulatory effect of gastrin on transplanted mouse colon cancer [48]. This inhibition of tumour growth was accompanied by prolonged survival of the animals. In humans it has been reported that the somatostatin analogue SMS 201-995 is able to induce transient inhibition of growth of hormone-producing gastrointestinal tumours [60]. In this respect it is noteworthy that it has been suggested that gastrin-producing tumours that co-secrete somatostatin

have a slower growth tendency than such tumours without somatostatin secretion [61].

Hormonal receptors on gastrointestinal cancers

The findings that gastrin stimulates growth of gastric and colon cancers and that cholecystokinin promotes growth of pancreatic cancer suggest the presence of receptors for the respective hormones on such cancers. In fact, gastrin was found to stimulate leucine uptake in five of 17, and protein production by four of 13 gastric cancers [21]. This stimulatory action of gastrin could especially be demonstrated on poorly differentiated gastric cancers. In another sudy using radiolabelled gastrin, receptors for gastrin were demonstrable on seven of eight human colon cancers [62]. In that study the binding of gastrin to the cancer cells could be inhibited by secretin. In another study from the same group, high-affinity binding sites specific for gastrin were identified on a human stomach cancer cell line, a human colon cancer cell line and a mouse colon cancer cell line, while a human pancreatic and duodenal cancer cell line were found to be slightly positive for gastrin receptors [63]. Exogenously administered gastrin has been shown to stimulate growth of one of two gastric cancers and one of three colon cancers transplanted into the nude mouse [21]. Interestingly, the binding affinity and capacity of gastrin receptors on a transplanted mouse colon cancer could be maintained by the administration of exogenous gastrin, whereas in the absence of gastrin the binding affinity decreased [64]. Recently receptors for cholecystokinin have been identified on small cell lung cancer cells [65].

Possible role of gastrointestinal hormones in the effect of food on gastrointestinal cancer

Feeding raw soya flour to rats stimulates pancreatic growth, resulting in hypertrophy, hyperplasia, adenomas and adenocarcinomas of the pancreas [66]. Heating the soya flour reduces but does not abolish the trophic effect of the diet on the pancreas. It is suggested that the trypsin-inhibiting potency of raw soya flour interferes with a postulated luminal trypsin–plasma cholecystokinin feedback mechanism, resulting in increased plasma cholecystokinin concentrations [67]. In fact, high plasma concentrations of cholecystokinin have been reported during a raw soya flour diet by both radioimmunoassay [68] and bioassay [69]. An important role of cholecystokinin as mediator of the effect of raw soya flour on the pancreas is further supported by the finding that long-term administration of cholecystokinin is reported to have similar growth stimulating properties as raw soya flour [34, 35]. As mentioned earlier, a raw soya flour diet enhances pancreatic carcinogenesis induced by azaserine [45]. Interestingly, a combination of di(2-hydroxypropyl) nitrosamine and raw soya flour induces acinar cell tumours in rats, while the nitrosamine alone does not produce pancreatic tumours in these animals [35]. Furthermore, the promoting effect of a high fat diet on azaserine-induced pancreatic tumours may also be mediatd by cholecystokinin, since, in contrast to a study using a bioassay system for cholecystokinin, we have recently found that fat stimulates release of cholecystokinin, measured by radioimmunoassay, in the rat [70].

CONCLUSIONS

Gastrin and cholecystokinin are produced by certain endocrine tumours belonging to the apudomas. Elevated serum gastrin concentrations are crucial for the diagnosis of gastrin-producing tumours, giving rise to the Zollinger–Ellison syndrome, characterized by gastric acid hypersecretion, peptic ulcers and diarrhoea. In addition, several studies both *in vitro* and in animals *in vivo* have pointed to a possible role for gastrin and cholecystokinin in influencing gastrointestinal carcinogenesis and tumour growth. However, the question as to whether these results can be extrapolated to humans cannot be answered at present. In humans, the important role of gastrin in the development of gastric carcinoids in patients with pernicious anaemia seems to be well established. Whether gastrin is also involved in the development of gastric adenocarcinomas, which occur more frequently in such patients, is not known. An important consequence of a tumour growth promoting effect of gastrin and cholecystokinin is the possibility of inhibiting tumour growth by specific antagonists of the receptors for such hormones. In this respect, the recent development of synthetic long-acting somatostatin analogues and specific hormone receptor antagonists may open a new area in research on gastrointestinal cancer.

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