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REVIEW

Gastric cancer: Animal studies on the risk of hypoacidity and hypergastrinemia

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Abstract

Gastric hypoacidity and hypergastrinaemia are seen in several conditions associated with an increased risk of gastric malignancy. Hypoacidity and hypergastrinaemia are closely related and their long-term effects are difficult to study separately in patients. Studies using animal models can provide valuable information about risk factors and mechanisms in gastric cancer development as the models allow a high degree of intervention when introducing or eliminating factors possibly affecting carcinogenesis. In this report, we briefly review findings from relevant animal studies on this topic. Animal models of gastric hypoacidity and hypergastrinaemia provide evidence hypergastrinaemia is a common causative factor in many otherwise diverse settings. In all species where sufficient hypoacidity and hypergastrinaemia have been induced, a proportion of the animals develop malignant lesions in the gastric oxyntic mucosa.

Key words: Gastrin; Gastric cancer; Proton pump inhibitors; Acid secretion; Animal model

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INTRODUCTION

Gastric hypoacidity and subsequent hypergastrinaemia occur in patients with parietal cell loss due to atrophic gastritis as well as in patients using drugs inhibiting gastric acid secretion. The increased risk of developing gastric carcinoids as well as adenocarcinomas is well documented in patients with pernicious anemia[1-4], whereas there is no direct evidence that hypoacidity and hypergastrinaemia caused by proton pump inhibitors promote gastric carcinogenesis in humans. Proton pump inhibition for up to five years has led to enterochromaffin-like (ECL) hyperplasia related to hypergastrinaemia[5]. Patients with gastrinomas often develop ECL cell carcinoids secondary to hypergastrinaemia, as well as signet ring cell carcinoma[6]. ECL cell carcinoids develop more often in patients with multiple endocrine neoplasia type 1 (MEN1)[7], but are also found in patients without MEN1[8,9]. The common factor in the above mentioned conditions is prolonged hypergastrinaemia, and it has been presumed that hypergastrinemia in itself increases the risk of gastric neoplasia in humans[10,11].

However, gastric carcinogenesis in humans is a process that progresses over years to decades and may be influenced by numerous factors. Dissecting the mechanisms of gastric carcinogenesis in humans is therefore difficult and several animal models have been used to reduce the number of variables affecting this process. Various animal models have demonstrated that regulation of acid secretion and oxyntic mucosal growth are interwoven and animal models have provided detailed knowledge regarding the role of hypoacidity as well as hormones and signal substances in gastric carcinogenesis. In this report, we briefly review findings from animal studies on the role of gastric hypoacidity and hypergastrinaemia in gastric carcinogenesis.

GASTRIN AND THE GASTRIN RECEPTOR

Gastrin, which stimulates gastric acid secretion, was the second hormone to be postulated to exist[12]. The release of gastrin from G cells is inhibited by hydrochloric acid. Gastrin exerts its effect on the CCK-B receptor, which was first localised in the brain[13], but later found to be identical to the gastric gastrin receptor[14]. Gastrin regulates gastric acid secretion through a cellular sequence in which gastrin stimulates ECL cells to secrete histamine, which in turn stimulates secretion of hydrochloric acid from parietal cells[15,16]. However, parietal cells have also been reported to express gastrin receptors[17,18] and whether or not these are functional has been debated. Very high concentrations of gastrin potentiates histamine-stimulated acid secretion from isolated parietal cells[19], suggesting the existence of a functional gastrin receptor on parietal cells. However,

fluorescein-labeled CCK-8 binds to rat ECL cells, but not to parietal cells[20], and gastrin does not stimulate acid secretion in either histidine decarboxylase (HDC)-deficient[21] or H2 receptor-deficient[22] mice. Altogether, this implies the physiological effect of gastrin is fully mediated by histamine secreted by the ECL cell and that only the gastrin receptors on ECL cells are of physiological importance. These observations are also relevant to understanding the trophic and carcinogenic effects of gastrin on the oxyntic mucosa.

GASTRIC HYPOACIDITY, HYPERGASTRINEMIA AND GASTRIC NEOPLASIA

Gastrin was shown early to have a general trophic effect on the oxyntic mucosa[23]. In 1985 it was first published that rats develop ECL cell carcinoids after lifelong inhibition of gastric acid secretion by administration of the long-acting insurmountable histamine 2 receptor antagonist loxtidine[24]. At the time, it was speculated whether this effect was specific for one drug, but the following year it was found that life-long administration of the proton pump inhibitor omeprazole also caused hyperplasia of the oxyntic mucosa and carcinoids in rats[25]. Even the short-acting histamine 2 receptor antagonist ranitidine was later shown to cause ECL cell carcinoids in 19 of 100 rats after 2-year of administration, and these animals showed a 3-fold increase in plasma gastrin[26].

Short-term administration of omeprazole (400 μmol/kg) to rats caused a 15-fold increase in plasma gastrin as well as hyperplasia of the oxyntic mucosa[27-29]. The ECL cell density was tripled after 10 wk, whereas the total oxyntic mucosal thickness increased 20%[28].

Hypoacidity and hypergastrinaemia are closely related in the normal state, but the effects of each factor can be studied separately in several animal models. Infusion of gastrin has been mentioned and is feasible for short-term proliferation studies in which the specific proliferative effect on ECL cells has been documented[30-32].

Low pH in the antrum inhibits gastrin release, and, by removal of a large proportion of the oxyntic mucosa by partial corpectomy, the antral pH is raised and gastrin release is stimulated. Rats develop carcinoids in the remaining 25% of the oxyntic mucosa[33] demonstrating that acid-inhibiting drugs per se do not cause neoplasia, but antral hypoacidity and subsequent hypergastrinaemia. Furthermore, oral administration of ciprofibrate, which is a peroxisome proliferator and a hypolipidemic compound, induces hypergastrinemia and carcinoid formation after 2 years in rats[34]. Ciprofibrate does not cause gastric hypoacidity[35], but induces hypergastrinemia through a direct effect on the antral G cell[36]. Altogether, there is evidence that hypergastrinaemia induced by either method, whether accompanied by gastric hypoacidity or not, causes ECL cell carcinoids in rats.

After carcinoid development due to hypergastrinemia was demonstrated in the rat, similar experiments were performed in mice to examine possible species differences. Administration of loxtidine to mice at various doses for 2 year induced carcinoid tumors of the gastric corpus[37], whereas long-term studies with proton pump inhibitors in mice have been inconclusive, as mice require much higher doses of proton pump inhibitors than rats to maintain a high gastric pH[38].

Transgenic (INS-GAS) mice over-express gastrin and have a 4-fold increase in plasma gastrin at age 6 mo, which leads to an increased gastric acid secretion[39]. In this animal model it is possible to study the effects of hypergastrinemia without gastric hypoacidity, mimicking human gastrinomas. Young INS-GAS mice have an increased ECL cell number and a proportion of these mice develop adenocarcinomas in the gastric corpus at the end of their lifespan[39]. Inoculation with *Helicobacter felis* increases gastrin levels 7-fold and accelerates carcinogenesis considerably[39], but mice without *Helicobacter* infections also develop carcinomas, demonstrating that carcinogenesis does not depend on infection and inflammation. The reason why INS-GAS mice develop malignancy in the oxyntic mucosa with an adenocarcinoma phenotype, whereas mice and rats develop ECL cell carcinoids after long-term acid inhibition or ciprofibrate administration, is not known. A synergistic inhibitory effect of gastrin and histamine receptor antagonists on hypergastrinemia-driven carcinogenesis has been found in INS-GAS mice[40], suggesting a role for both gastrin and histamine, but leaves questions regarding the cellular location of the histamine 2 receptor, and thus, the cellular origin of the adenocarcinomas. It has been found *H pylori* lipopolysaccharides stimulate ECL cell proliferation and secretion in the rat[41], supporting a concept of synergism of gastrin and *H pylori* infection on ECL cell growth.

INS-GAS mice have been inoculated with a *H pylori* strain and only inoculated males developed gastric cancer, whereas serum gastrin concentrations did not differ between the sexes[42].

HDC-deficient mice show gastric hypoacidity and a threefold increase in plasma gastrin levels[21]. This model has been mainly used for studying acid secretion, and long-term studies examining the possible carcinogenetic effects of hypergastrinemia in the absence of histamine have not been published to date. However, in animals aged 8 to 12 wk there was no difference in mucosal thickness[21].

Another genetically modified mouse model is H^+K^+ATPase beta subunit-deficient mice. These mice are anacidic, show a 7-fold increase in serum gastrin levels and hyperplasia in the oxyntic mucosa[43,44]. H^+K^+ATPase-deficient mice have been followed for up to 14 wk only, and changes in the gastric mucosa in old mice have not been published. Gastrin and H^+K^+ATPase double knockout mice are anacidic without gastrin and do not develop hypertrophic changes in the oxyntic mucosa, demonstrating that gastrin is responsible for these changes[43].

Gastrin-deficient mice show no basal acid secretion[45] and provide a model for studying the effect of gastric hypoacidity without hypergastrinemia. Gastrin-deficient mice develop antral adenocarcinomas[46] through a mechanism that must be different from carcinogenesis in the oxyntic mucosa in hypoacidic and hypergastrinemic mice. The development of carcinomas in the absence of gastrin is attributed to bacterial overgrowth and subsequent formation

of carcinogenic substances[47,48]. However, gastric hypoacidity is also found in H^+K^+ATPase-deficient mice which do not develop antral carcinomas (Fossmark R *et al* unpublished observations) and it is possible the lack of gastrin itself induces the carcinomas.

GROWTH PROMOTION MEDIATED BY ECL CELLS

In the oxyntic mucosa, only ECL cells have gastrin receptors shown to have a functional role in mucosal growth regulation. Several studies mentioned have described the trophic effects of gastrin on the oxyntic mucosa, and the trophic effect on the ECL cell in particular, but less is known about the further mediation of the gastrin effect. It has been shown administration of gastrin has a proliferative effect in the neck region of the oxyntic glands[49], where stem cells are located. However, it has not been possible to settle whether this proliferative effect is a direct effect or mediated by growth factors released by ECL cells[50]. Several ECL cell products have been suggested to stimulate growth of the oxyntic mucosa, either on parietal cells, stem cells or ECL cells themselves.

Histamine was the first ECL cell product to be identified and has been suggested to have a trophic effect[50], but the effects of histamine are not fully understood. Histamine has been shown to stimulate proliferation of gastric cancer cell lines[51], but the histamine 1 receptor antagonist astemizole has an additional trophic effect when administered to rats with omeprazole-induced hypergastrinemia[52]. Histamine 2 receptor-deficient mice are hypergastrinemic and develop hypertrophy of the oxyntic mucosa[22], supporting previous studies suggesting the mediation of histamine's trophic effect does not involve the H2 receptor[53]. However, in histamine decarboxylase-deficient mice there was no difference in parietal and ECL cell numbers compared with controls, in animals aged 8 to 12 wk, and no increase in oxyntic mucosal thickness[21], indicating an important role for histamine as a mediator of hypergastrinaemia-driven mucosal growth.

The regenerating gene (Reg) cDNA was first isolated from regenerating pancreatic islets in rats and its human homologue was named RegI alpha[54], but Reg protein is also expressed in ECL cells[55]. Gastrin stimulates Reg protein expression in ECL cells, and Reg protein is mitogenic to gastric mucosal cells[56], suggesting Reg protein is involved in gastrin-induced gastric mucosal cell growth. Reg expression is also increased in healing gastric mucosa[57]. Reg protein receptors are found on parietal cells and chief cells in the lower part of the corpus glands[58]. A recent study using INS-GAS mice has found expression of Reg1 is controlled through separate promoter elements by gastrin and *Helicobacter*[59], implying that these factors affect carcinogenesis through Reg protein. RegI alpha protein is also found in 35% of human gastric adenocarcinomas, particularly in those that are less well differentiated[60], and Reg protein expression is associated with higher proliferation rates in early gastric cancers[61]. Altogether, this makes Reg protein a strong candidate for mediating the general trophic effects of gastrin on the oxyntic mucosa.

OTHER ANIMAL MODELS OF HYPOACIDITY AND HYPERGASTRINEMIA IN GASTRIC CARCINOGENESIS

A strain of Japanese cotton rats develops spontaneous carcinomas in the oxyntic mucosa with a marked female predominance[62]. Animals developing carcinomas have gastric hypoacidity of an unknown cause and secondary hypergastrinemia[63]. The tumors develop from an oxyntic mucosa with marked hyperplasia of chromogranin A, synaptophysin and HDC-immunoreactive cells, and a proportion of the tumor cells are chromogranin A-, pancreastatin-, HDC- and Sevier-Munger-positive[63-66]. Carcinomas develop after 4 mo of hypergastrinemia, but are prevented by the gastrin receptor antagonist YF486[64], demonstrating gastrin is essential in carcinoma development in cotton rats. Carcinomas can also be induced in male cotton rats by administration of the histamine 2 receptor antagonist loxtidine[67], as well as by partial corpectomy[68], two different methods of inducing pronounced hypergastrinemia. It has also been found ECL cells in hypergastrinemic animals gradually lose ultrastructural characteristics as well as chromogranin A and pancreastatin immunoreactivity[66] suggesting ECL cells dedifferentiate during long-term stimulation by gastrin. The cotton rat model is important as it demonstrates tumors with an adenocarcinoma phenotype, but with neuroendocrine differentiation, are induced by gastric hypoacidity and hypergastrinemia and develop through dedifferentiation of ECL cells.

In the African rodent Mastomys, multicentric gastric carcinoids frequently develop in the oxyntic mucosa of a proportion of aging animals. Serum gastrin levels in Mastomys developing tumors is normal[69] and the development of spontaneous ECL cell tumors is most likely related to a gastrin receptor mutant which shows ligand-independent activity; that is, the receptor is constitutively activated[70]. However, endogenous gastrin is involved in the growth of ECL cell carcinoids in Mastomys as the development of these tumors is significantly enhanced by loxtidine-induced hypoacidity and hypergastrinemia[71,72] and carcinoid development is inhibited by a gastrin receptor antagonist[73]. There is no sex-difference in the occurrence of such tumors. The development of carcinoids in Mastomys is prevented by a somatostatin analogue[74].

Mongolian gerbils inoculated with *H pylori* are used extensively in research on *H pylori*-related gastric carcinogenesis. In the context of this paper, Mongolian gerbils are interesting as they become hypergastrinemic in response to *H pylori* infection and develop mainly ECL cell carcinoids, but also gastric adenocarcinomas[75,76]. Inoculated animals show a five to ten-fold rise in serum gastrin, increasing with time after inoculation[77]. An increasing proportion of the gerbils develop ECL cell hyperplasia and carcinoids from 12 to 24 mo after inoculation[76]. Atrophic gastritis and focal intestinal metaplasia and dysplasia also appear 6 mo after inoculation, and premalignant changes can be reversed after *H pylori* eradication[78]. Hypergastrinemia in *H pylori*-infected animals is associated with increased Reg gene expression, and both plasma gastrin and Reg mRNA levels are normalized after *H pylori* eradication[79].

Finally, the possibility of species differences in relation to carcinoid development after long-term administration of acid inhibitors has also been studied in dogs. Beagle dogs were given omeprazole daily for 7 years, but there were no changes in the gastric mucosa at termination and there were specifically no increases in ECL cell numbers[80]. However, dogs receiving omeprazole had fasting and meal-stimulated plasma gastrin levels at the same level as controls, and changes in the oxyntic mucosa should therefore not be expected.

CONCLUSION

Animal models can provide valuable information about risk factors for gastric cancer as the models allow a high degree of intervention when introducing or eliminating factors possibly affecting carcinogenesis. The various animal models of gastric hypoacidity and hypergastrinemia provide evidence hypergastrinemia is a common causative factor in many otherwise diverse settings. In all species where sufficient hypoacidity and hypergastrinemia has been induced, a proportion of the animals develop neoplastic lesions. Bearing in mind that gastrin acts on gastrin receptors located on ECL cells, which are stimulated to secretion and proliferation, we find it obvious ECL cells have a pivotal role in the gastric carcinogenesis associated with hypergastrinemia. Findings in Japanese cotton rats and Mongolian gerbils in particular suggest carcinoids and adenocarcinomas develop though a similar mechanism, and derive from ECL cells. Hypergastrinemia induces gastric neoplasia whether accompanied by gastric hypoacidity or not, and experiments using the above-mentioned models could explain why carcinoids develop in some situations, whereas tumors with an adenocarcinoma phenotype develop in other models.

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