Histamine Metabolism of Gastric Carcinoids in *Mastomys natalensis*

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Pharmacological inhibition of gastric acid secretion and subsequent hypergastrinemia in *Mastomys natalensis* is an experimental model well suited for the study of gastric carcinoid formation. The genetic susceptibility of *Mastomys* to develop such tumors is a feature reminiscent of the situation in patients with the MEN-1 Zollinger Ellison syndrome, in whom tumor-induced hypergastrinemia promotes the development of gastric carcinoids. Chronic hypergastrinemia, induced by the irreversible H\textsubscript{2}-receptor antagonist loxtidine will cause carcinoid formation in *Mastomys* already after four to six months. As in humans, gastric carcinoids in *Mastomys* are mainly composed of enterochromaffinlike (ECL) cells and have low malignant potential. Administration of exogenous gastrin to normal young animals increases the expression of histidine decarboxylase (HDC) mRNA in the oxyntic mucosa within 30 minutes. Endogenous hypergastrinemia, induced by short-time loxtidine treatment (three to 29 days) enhances the expression of HDC mRNA, histamine contents and ECL cell numbers in the oxyntic mucosa. Long-term loxtidine treatment (seven to 21 months) results in sustained hypergastrinemia and tumor formation. Tumor-bearing animals exhibited an increase in HDC mRNA and histamine content in the oxyntic mucosa as well as increased urinary excretion of the main histamine metabolite, tele-methylimidazole acetic acid (MelMAA). Subsequent to cessation of loxtidine treatment for two weeks, all parameters of histamine metabolism were normalized in tumor-bearing animals. These results indicate that gastric carcinoids developing during hypergastrinemia are well-differentiated neoplasms whose histamine synthesis and metabolism is regulated by plasma gastrin.

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**INTRODUCTION**

In recent years, great interest has been focused on the pathogenesis of human gastric carcinoids, their early diagnosis and optimal treatment [1, 2, 3]. Our understanding of the mechanisms behind gastric carcinoid has been promoted by access to a suitable animal model for induction of gastric carcinoids in *Mastomys natalensis* [4]. Originally, *Mastomys*, "the multimammate mouse," was used as a vector for tropical diseases, i.e., Lassa fever, bilharzia and plague [5]. It was soon discovered that a laboratory strain of *Mastomys* was prone to develop gastric tumors [6, 7]. At first, these tumors were described as adenocarcinomas, but later they were shown to originate from histamine producing enterochromaffin like (ECL)\textsuperscript{e} cells and, therefore, were reclassified as gastric carcinoids. Several strains of *Mastomys* have been characterized. The Z strain develops spontaneous antral adenocarcinomas and fundic carcinoids, while the Y strain, like the wild type, develops solely fundic carcinoids [8, 9]. The gastric carcinoids in *Mastomys* have shown the capacity to grow after transplantation to both *Mastomys* and nude mice [8-13]. Spontaneous formation

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\textsuperscript{e} Abbreviations: ECL, enterochromaffin like; HDC, histidine decarboxylase; MelMAA, tele-methylimidazole acetic acid.
of gastric carcinoids increase with increasing age in *Mastomys*. Some authors have reported an incidence of carcinoids as high as 40-60 percent in older animals (one to two years of age) [14]. The malignant potential of the tumors varies significantly between strains. In our own colony of *Mastomys natalensis*, we have not observed spontaneous development of a gastric carcinoids within the first year of age [7].

**INDUCTION OF TUMORS**

The morphological changes occurring during spontaneous tumor formation have been described in detail by Soga and collaborators [14]. During stage I, the ECL cells proliferate within the basal portion of the fundic glands with chain formations (linear hyperplasia). During the pre-neoplastic stage II, the ECL cells form nodules, which are still located within the gland (nodular hyperplasia). The neoplastic stage III comprises ECL growth across the basal lamina of the gland into the lamina propria as well as formation of micro- and macrocarcinoids. A detailed staging and classification of human gastric carcinoids was initiated by Solcia et al., and the classification has been successfully applied to this animal model [7, 15, 16]. The principal differences compared to the original staging are that isolated tumor growth in the lamina propria is referred to as dysplasia and that microcarcinoid formation is required for classification of the lesion as neoplasia.

The rate at which the tumors are formed can be greatly enhanced by hypergastrinemia. Administration of the insurmountable H₂-receptor blocker loxtidine to the drinking water reproducibly induces hypergastrinemia both in rats and *Mastomys*. The mechanism involves blockade of parietal H₂-receptors, resulting in decreased secretion of gastric acid and subsequent sustained hypergastrinemia due to loss of feed back-control of antral G cells [7, 17, 18]. *Mastomys*, subjected to long-term loxtidine treatment (2 g/l drinking water), develop gastric carcinoids composed of ECL cells in a reproducible manner. Neoplastic changes (micro- or macrocarcinoids) occur in about 25 percent and dysplastic changes occur in about 50 percent of the animals subjected to loxtidine treatment for 24 weeks (classified according to Solcia et al.) [15]. The formation of tumors is to a certain extent reversible. If loxtidine is administered for 24 weeks and thereafter withdrawn and followed by drinking water alone for another 24 week period, the plasma gastrin levels return to normal and practically all morphological changes up to the stage of dysplasia disappear during this second period. However the vast majority of neoplastic lesions remain unchanged [16]. This indicates that the neoplastically transformed ECL cells are less sensitive to the trophic effects of circulating gastrin than normal or hyperplastic ECL cells.

**RELEVANCE OF THE MASTOMYS MODEL**

The *Mastomys* model is in several aspects well suited for the study of gastric carcinoids. Firstly, the induction of carcinoids is much more rapid and results in higher incidence of tumors than in other species, e.g., the rat [7, 17, 18, 19]. Secondly, the tumor development in *Mastomys* shows considerable similarity to the formation of type I (associated with chronic atrophic gastritis, ACAG) and type III (associated with the MEN-I Zollinger-Ellison syndrome) gastric carcinoids in man. Moreover, the animals are easy to maintain and reproduce well in captivity. In both man and *Mastomys* these tumors are mainly composed of ECL cells [1, 2]. Furthermore, the tumors are of low malignant potential and appear in multiple foci together with precursor lesions (precarcinoids) throughout the entire oxyntic mucosa in a background setting of linear and nodular hyperplasia. The inborn susceptibility to hypergastrinemia in *Mastomys* may correspond to the MEN-1 genetic trait, which in man predisposes such patients to development of gastric carcinoids in response to the
hypergastrinemia generated by the gastrinoma. Both for ACAG- and MEN-1 associated human gastric carcinoids, as well as for Mastomys tumors, a period of hypergastrinemia is thus required for the tumor formation [20-24].

**TISSUE DISTRIBUTION OF HISTAMINE AND METABOLIC PATHWAYS**

The two major cellular sources of gastric histamine are the ECL cells and the mast cells. The relative contribution of histamine from these sources vary between species [25]. In man, endocrine cells of gastric mucosa (characterized by the presence of chromogranin A) are relatively few in comparison with the numerous mast cells. On the other hand, in the rat, endocrine cells outnumber mast cells. In the Mastomys, the relative distribution of these cells resembles that seen in the rat. The histamine-containing ECL cells constitute the vast majority of the oxyntic endocrine cells (Figure 1), and from depletion studies in the rat it has been estimated that ECL cells contribute at least 80 percent of the oxyntic mucosal histamine [26]. In our own preliminary morphological studies in Mastomys, mast cells are very sparsely distributed within the fundic wall and thus appear to contribute minimally to the tissue pool of histamine (Figure 2).

Histamine is formed by conversion of the amino acid histidine by the rate limiting enzyme histidine decarboxylase (HDC). One physiological role of histamine released from ECL cells is to stimulate the parietal cell to secrete gastric acid. In the hypergastrinemic state, stimulation of the ECL cells leads to activation of HDC with enhanced production of histamine, reflected by increased levels of mucosal histamine. Histamine can be degraded by several different pathways. In man, although a small portion of histamine can be methylated and excreted as methylhistamine, the major pathway involves methylation and oxidative deamination resulting in tele-methylimidazole acetic acid (MeImAA), which is excreted in the urine. In rats, the methylation step is less important than in man. Non-methylated ImAA is a less specific product since it can also be generated by metabolism of histidine. A very small portion of histamine may also be excreted unmetabolized [27, 28].

**HISTAMINE METABOLISM IN MASTOMYS NATALENSIS**

As described above ECL cells in the gastric oxyntic mucosa of Mastomys are particularly sensitive to hypergastrinemia. They respond rapidly to elevated gastrin levels with increased histamine synthesis, followed by ECL cell hyperplasia and formation of gastric carcinoids after sustained hypergastrinemia. Within 30 minutes of a single injection of gastrin (500 μg/kg s.c.) an enhanced expression of HDC mRNA could be detected in the oxyntic mucosa.

When animals were given oral loxtidine (10 g/l drinking water) for periods up to 29 days, sustained hypergastrinemia was induced. Plasma gastrin levels were significantly elevated in all loxtidine-treated animals compared to untreated controls and reached a peak after 14 days of treatment (10-fold increase), which declined somewhat after 29 days of treatment. The expression of oxyntic mucosal HDC mRNA was significantly elevated (two to four times) in all loxtidine-treated animals, and a significant positive correlation between the plasma gastrin levels and the mucosal HDC mRNA was evident (Figure 3).

To investigate the importance of plasma gastrin levels on mucosal HDC mRNA expression and histamine metabolism in gastric carcinoids of Mastomys, two separate groups of animals were given loxtidine for seven to 21 months. This resulted in prolonged sustained hypergastrinemia and tumor formation. In one group, the long-term loxtidine treatment was discontinued, and the animals thereafter received standard drinking water without loxtidine for a period of two weeks before sacrifice. In both groups, only animals
Figure 1. Consecutive sections of the fundic wall in *Mastomys* harboring a small intramucosal carcinoid tumor. Following 24 hr of EDAC fixation the sections were stained with a) antisera against histamine, (Delichon Ltd, Finland, no 2121 C, dil. 1:80000); b) HDC (Euro-Diagnostica, the Netherlands, no B 260-1, dil 1:5000); c) and chromogranin A+B, (Euro-Diagnostica, the Netherlands, no B 315-1, dil 1:500), respectively. The vast majority of chromogranin-immunoreactive cells were also demonstrated to display HDC- and histamine-immunoreactivities, indicating that the majority of the endocrine cells of the oxyntic mucosa were ECL cells.

Figure 2. a) Representative sections of the normal oxyntic mucosa of *Mastomys* following 24 hr of EDAC fixation and staining with histamine antiserum (Delichon Ltd, Finland, no 2121 C, dil. 1:80000) [42]. There are numerous histamine-immunoreactive ECL cells located in the basal portion of the glands as well as very few histamine-immunoreactive mast cells in the submucosa. b) Following 4 hr of IFAA fixation the section was stained with toluidine blue with specific staining of the mast cells [43, 44]. Note the discrepancy in cell number between the two cell types.
Figure 3. Effect of short-term loxtidine treatment (10 g/l drinking water) on plasma gastrin levels and oxyntic mucosal expression of HDC mRNA. Four groups of animals were given loxtidine for periods up to 29 days, resulting in mild hyperplasia of mucosal ECL cells. Plasma gastrin levels were significantly elevated after three days and reached a maximum after 14 days compared with untreated controls (c). The expression of HDC mRNA was also significantly elevated after three days and reached a peak at seven days of treatment. There was thus a significant correlation between circulating plasma gastrin levels and the mucosal expression of HDC mRNA.

with gross, macroscopic tumors were included. In the group still receiving loxtidine at sacrifice, the plasma gastrin levels remained elevated. A concomitant increase in mucosal HDC mRNA expression, mucosal histamine levels and urinary excretion of MeImAA was observed. In contrast, in the group of animals receiving only water (no loxtidine) for two weeks prior to sacrifice, the plasma gastrin levels had returned to levels seen in untreated controls. This normalization of plasma gastrin levels was accompanied by a simultaneous normalisation of mucosal HDC mRNA expression, mucosal histamine levels and of urinary excretion of MeImAA (Table 1).
Table 1.

|                  | C              | TL             | TW             |
|------------------|----------------|----------------|----------------|
| Plasma gastrin (pM) | 51.7 ± 9.5 (n = 7) | 102.1 ± 25.1 (n.s., n = 7) | 50.1 ± 10.5 (n = 7) |
| HDC expression (relative values) | 1 (n = 7) | 4.9 ± 0.77 (p < 0.001, n = 7) | 1.6 ± 0.56 (n = 7) |
| Mucosal histamine (µg/g tissue) | 6.0 ± 3.0 (n = 3) | 24.7 ± 2.2 (p < 0.05, n = 3) | 6.1 ± 0.93 (n = 5) |
| U-MeImAA (mmol/mol C) | 17.9 ± 2.0 (n = 12) | 33.0 ± 4.1 (p < 0.01, n = 32) | 19.5 ± 1.0 (n = 8) |

*Mastomys* subjected to long-term loxtidine treatment resulting in development of gastric carcinoids. Only animals with large, macroscopic tumors were included. C, control animals; TL, tumor-bearing animals on loxtidine at sacrifice; TW, tumor bearing animals on water at sacrifice. Values are given as Mean ± S.E.M. Student’s two-tailed test was used for statistical comparison.

**COMMENTS**

Our experiments in *Mastomys* have demonstrated that the HDC mRNA expression and histamine metabolism of the gastric oxyntic mucosa are controlled by the plasma gastrin levels, and in addition, that expression of HDC mRNA can rapidly be induced by injection of exogenous gastrin. Furthermore, in animals with ECL cell tumors, the plasma gastrin levels are capable of modulating the HDC mRNA expression and histamine metabolism.

The histamine metabolism of gastric ECL cells during formation of gastric carcinoids is a complex process influenced by many stimuli. Carcinoids in man, whether associated with ACAG or the MEN-I Zollinger Ellison syndrome or in the available animal models (rat and *Mastomys*) seem to require a period of hypergastrinemia for tumor formation. In man this period of hypergastrinemia may be several years, or even decades [20, 24, 29]. In the rat, gastric carcinoids develop during a period of one to two years of sustained hypergastrinemia [17, 19]. In the *Mastomys*, the carcinoids are rapidly induced over a period of four to six months with hypergastrinemia [7, 18]. Experimental hypergastrinemia may be accomplished in several ways including pharmacological reduction of gastric acid secretion, which is a reproducible method for the induction of hypergastrinemia and is associated with increased histamine synthesis and ECL cell proliferation. In the rat, a similar state has been achieved by direct infusion of gastrin via osmotic minipumps [30]. In this species, partial colectomy also results in compensatory hypergastrinemia and ECL cell proliferation [31]. Using *in vitro* systems with elutriated rat- and *Mastomys*-ECL cells, gastrin causes a rapid release of histamine together with an enhanced HDC activity and DNA synthesis [32-34]. There is thus substantial evidence for an important role of gastrin in stimulating the ECL cells to increase both histamine synthesis and cell proliferation. In gastrin-stimulated mucosa, the ratio between proliferating ECL cells and non-proliferating somatostatin-producing D cells increases, leading to the possibility that decreased inhibition by somatostatin on ECL cells may accentuate the effects observed [7].

There is a discrepancy between the plasma gastrin levels and the expression of HDC mRNA between the different experimental situations. Thus, in experiments with an acute injection of gastrin, a very high peak in plasma gastrin levels (2000-4000 pmol/l) was followed by a moderate increase of HDC mRNA expression (two-fold increase) compared to the chronic situation, where hypergastrinemia sustained for three to 29 days caused an increase in plasma gastrin (300-500 pmol/l) which was associated with a three to four-fold increase in HDC mRNA expression. A possible explanation for this observation may be
that gastrin exerts its action via indirect mechanisms. Thus, in a state of hypergastrinemia prolonged over months, we observed a different relation between the plasma gastrin levels and the increase in HDC mRNA expression, i.e., a relatively moderate increase in plasma gastrin (100 pmol/l) was associated with a pronounced (five-fold) increase in HDC mRNA expression. This effect may be explained by an upregulation of CCK-B/gastrin receptors on the ECL cells during tumor development, which has been identified in isolated Mastomys ECL cells. Similarly other local growth factors such as TGF-α may be involved [34]. The possibility that other non-humoral factors may be involved in this process has not been excluded. The relative importance of neuronal stimuli seems to vary among species. In the rat, vagal innervation has been showed to interact with gastrin in the trophic control of ECL cells since in animals subjected to unilateral vagotomy the ECL cell density decreased on the vagotomized side [35]. This contrasts to the findings in the Mastomys, where unilateral vagotomy had no obvious influence on ECL cell density [36]. Nevertheless, in isolated ECL cell populations, neurotransmitters were demonstrated to be highly effective modulators of ECL cell function [37].

The possibility of histamine as an intermediate growth factor has also been discussed. In favor of this theory is the observation that treatment with H1-receptor blockers, e.g., cyproheptadine, decreases the ECL hyperplasia observed in response to hypergastrinemia [38]. On the other hand, depletion of histamine from ECL cells using α-fluoromethylhistamine resulted in an unchanged hyperplastic response to hypergastrinemia [39]. Also, different receptor subtypes, different binding sites of receptors or receptors in different states of affinity, may use separate intracellular second messenger systems. This has been noted for histamine release as compared to DNA synthesis in ECL cells stimulated with gastrin [32]. It is also probable that activation of different somatostatin receptor subtypes, expressed by the ECL cells, operates via separate second messenger systems [40]. In this respect, separate subtypes of somatostatin receptors are involved in the secretory modulation and proliferative regulation of other neuroendocrine tumors [41].

CONCLUSIONS

It could be concluded that the Mastomys is an animal model with unique biological characteristics and is very well suited for the study of ECL cell physiology and ECL cell tumor formation. Gastrin seems to be the single most important factor in controlling ECL cell function, including synthesis and secretion of biogenic amines as well as ECL cell proliferation. However the regulation of ECL cell function is complex, and other factors such as locally produced growth factors or cytokines as well as neuronal stimuli may be of importance. The Mastomys model is of great relevance because of its biological similarities to the situation in humans suffering from MEN-I/Zollinger-Ellison syndrome and will be of importance when trying to explore the complex ECL cell pathophysiology.

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