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Control of Histidine Decarboxylase Gene Expression in Enterochromaffin-Like Cells

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The ability of histamine to stimulate gastric acid secretion was recognized over 75 years ago by Popielski [1]. The central importance of this action in the physiological regulation of acid secretion was established with the development of histamine H_2 receptor antagonists by Black and colleagues in the early 1970s [2]. There has, however, been intense debate about the precise mechanisms of action, and relative importance of, histamine and the other major gastric acid secretagogues, gastrin and acetylcholine. The currently favored view proposes that gastrin and acetylcholine act principally by releasing histamine, which then acts directly on the acid-secreting parietal cell. This idea is supported by pharmacological studies on histamine H_2 antagonists *in vivo* and in isolated perfused stomachs, and by the fact that gastrin and muscarinic agonists release histamine from the isolated perfused stomach, and increase activation of gastric histidine decarboxylase (HDC, EC 4.1.1.22), the enzyme that converts histidine to histamine [3-7]. However, there is also evidence for separate receptors for gastrin, histamine and acetylcholine on canine parietal cells [8], suggesting that in some circumstances all three agents may be able to act directly on this cell type.

Kahlson and colleagues were the first to demonstrate increases in histidine decarboxylase (HDC)[b] activity in rodent gastric mucosa in response to gastrin and cholinergic agents [4], and it is now well recognized that this response is localized to the enterochromaffin-like (ECL) cell [4, 9, 10]. Since ECL cells represent a relatively high proportion of gastric corpus mucosal endocrine cells in rodents, these species are well suited to studies of ECL cell function. The relative scarcity of ECL cells in some other species raised questions about the generality of the gastrin-induced increases in HDC activity in this cell type [10, 11]. Nevertheless, in all species where purified ECL cells have been studied, gastrin-induced activation of HDC activity has been observed [12-14].

Increases in HDC activity could, in principle, arise by *de novo* synthesis of enzyme, or by activation of a pre-existing but inactive enzyme pool, since it is known that HDC activity can be modulated by phosphorylation [15]. In addition, there exists the possibility that translation rates are regulated. The opportunity to examine in more detail the regulation of HDC expression arose with the cloning of a cDNA encoding the enzyme in 1990 [16], and subsequent elucidation of the genomic sequence [17, 18].

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[b]*Abbreviations:* HDC, histidine decarboxylase; ECL, enterochromaffin-like; CCK, cholecystokinin; CGA, chromogranin A; VMAT, vesicular monamine transporter; MEN, multiple endocrine neoplasia; PCR, polymerase chain reaction.

PHYSIOLOGICAL REGULATION OF HDC MRNA ABUNDANCE IN ECL CELLS

HDC mRNA abundance is strongly regulated *in vivo* by changes in the gastric luminal environment. Thus, in rats fasted for periods of up to 48 hours there was about a four-fold decrease in corpus HDC mRNA, which was accompanied by a marked reduction of circulating gastrin concentrations [19, 20] (Figure 1). The depression of gastrin and of HDC mRNA is probably due largely to the effects of unbuffered gastric acid rather than withdrawal of food, since it did not occur in animals made achlorhydric by administration of the proton pump inhibitor omeprazole, during the food withdrawal [18, 19] (Figure 1). The role of gastrin in mediating the responses to luminal pH is supported by the finding that fasted, achlorhydric animals did not express high levels of HDC mRNA when treated concomitantly with a specific gastrin/CCK-B receptor antagonist [19]. When rats fed *ad libitum* were made achlorhydric there was little further increase in HDC mRNA for periods of up to 48 hours, suggesting that under normal circumstances gastrin regulates HDC mRNA over its physiological range of circulating concentrations [19] (Figure 1). There is, however, a marked progressive increase in HDC mRNA abundance in fed rats in the face of chronic hypergastrinaemia induced by prolonged achlorhydria [21, 22].

The fasting-evoked reduction in HDC mRNA develops gradually over 48 hours, with significant depression first evident after about 12 hours [20]. In contrast, re-feeding induced a rapid two-fold upregulation of HDC mRNA within 30 minutes [20]; thereafter, there was a gradual sustained increase over the following 48 hours until control levels of expression were achieved. The rapid response to feeding of HDC mRNA suggests that there may be functionally important changes in HDC gene expression over the time course of a single meal. Gastrin modulates, at least in part, the rapid response to feeding since it was significantly attenuated in animals pre-treated with potent and specific gastrin/CCKB-receptor antagonists (Figure 2). Evidence that gastrin is also involved in mediating the sustained response to feeding is provided by the observation that this

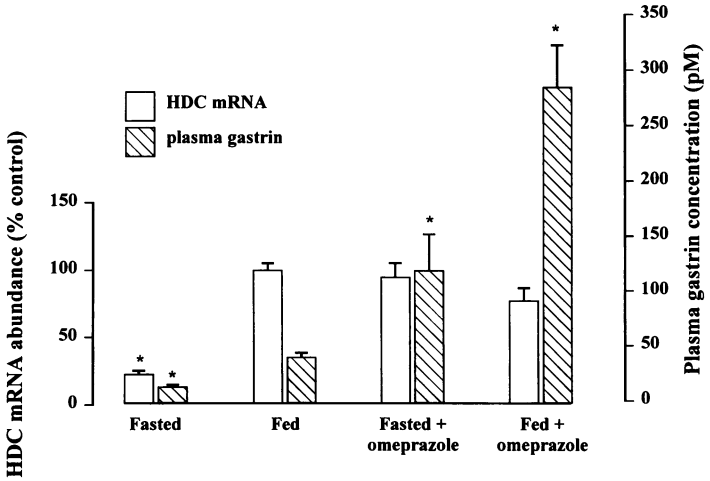

Figure 1. Changes in HDC mRNA abundance and plasma gastrin concentrations in response to changes in the gastric luminal environment. Groups of six rats were fed *ad libitum* or fasted for 48 hr and treated with omeprazole (400 μmol/kg daily, by gavage) or vehicle (0.5 percent methyl cellulose). HDC mRNA in gastric corpus (open bars) was determined by Northern blot, and plasma gastrin by specific radioimmunoassay [20]. Values are mean ± SEM, n = 6). * = significantly different from control (fed rats) values, $P < .05$, one-way ANOVA).

response was reduced in animals passively immuno-neutralized with gastrin-specific antisera [20]. Moreover, infusion of exogenous gastrin in conscious fasted rats led to elevation of both HDC activity and mRNA abundance within two hours [23, 24]. But, the responses to exogenous peptide were slower and of lower magnitude than those elicited in response to feeding, suggesting that other endogenous factors are involved [23]. Further evidence for a substantial gastrin-independent component to the feeding response, is provided by the finding that this response was also significantly reduced by pre-treatment with the muscarinic antagonsist atropine, in a dose that did not reduce circulating gastrin concentrations (Figure 3).

REGULATION OF OTHER ECL CELL mRNAS: THE CO-ORDINATED ECL CELL RESPONSE

While HDC is undoubtedly the key determinant of histamine production, there are a number of other proteins expressed in ECL cells that are likely to have important roles in the sequestration and storage of the secretory product. Chromogranin A (CGA) is a large, soluble, acidic protein that in gastric corpus appears to be localized exclusively to ECL cells and has been used as a marker for them in health and disease [25]. CGA is the biosynthetic precursor of a number of biologically active peptides, e.g., pancreastatin, although there appears to be limited processing of CGA in rat stomach [26]. However, it has been suggested that CGA may play a role in the condensation of material during formation of secretory granules of the regulated pathway [27] and may help stabilize the granule interior in amine secreting cells [28]. In this context, it is, therefore, of interest that CGA mRNA abundance changed in parallel with that of HDC, in response to both changes in gastric luminal pH, and to fasting and feeding [29]. One possibility is that the changes in CGA biosynthesis reflect a response to changes in either the numbers or amine content of the ECL secretory granules.

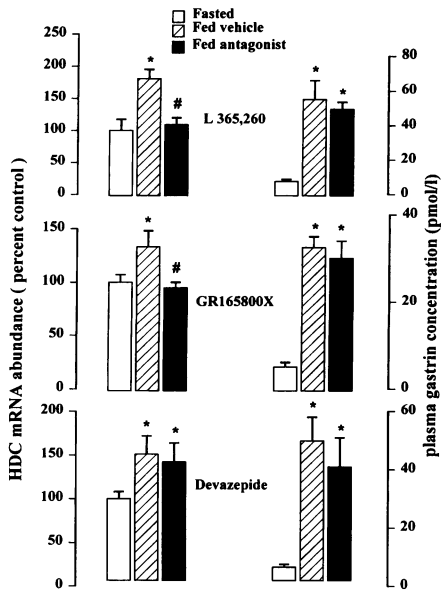

Figure 2. Effect of gastrin antagonists on HDC mRNA and plasma gastrin responses to feeding. Groups of six rats were fasted for 48 hr (water *ad lib*) then refed for 30 min. One hour before feeding, they received by tail vein injection, vehicle alone (50 µl formamide, 20 percent cremaphor, 80 percent saline; solid bars), or the gastrin/CCK_B antagonist L265,260 (5 mg/kg, hatched bars, upper panel), or the gastrin/CCK_B antagonist GR165800X ([1 mg/kg] hatched bars, center panel) or the CCK_A antagonist devazepide (1 mg/kg, hatched bars, lower panel). HDC mRNA in gastric corpus was determined by Northern blot and plasma gastrin by specific radioimmunoassay [20]. Values are mean (± SEM, n = 6). * = significantly different from fasted control $P < .05$, one-way ANOVA. # = significantly different from re-fed vehicle treated group, $P < .05$. GR165800X= 2-{3-[-(1H-Indazol-7-yl)-ureido]-5-methyl-2-oxo-2,3-dihydro-benzo[e][1,4]diazepin-1-yl}-N-methyl-N-phenyl-acetamide, isomer 1.

It seems unlikely that ECL cells possess a plasma membrane histamine transporter, but there is evidence that they can accumulate histidine, possibly utilizing amino acid transport system N [30], and convert it to histamine in the cytosol [31]. There must exist, therefore, mechanisms to transport histamine into the secretory granules. In other comparable systems, vesicular transporters have been identified specific for acetylcholine, GABA and biogenic amines [32-35]. A transporter specific for histamine has not yet been identified, but one of the two vesicular monoamine transporters cloned ($VMAT_2$) is able to transport histamine [36], and a number of lines of evidence suggest that it may function as a histamine transporter in the ECL cell. First, there is immuocytochemical evidence for the presence of $VMAT_2$ in ECL cells [37]. Second, $VMAT_2$ has been cloned from rat gastric corpus and identified by Northern blot in ECL cell-enriched fractions of gastric corpus mucosa [22]. Finally, the energy required for transport of amines by $VMAT_2$ is provided by a proton gradient, and there is direct evidence for such a gradient, generated by a V-type ATPase in the secretory granule of the ECL cell [14]. The affinity for histamine of $VMAT_2$ is about 10-fold lower that its affinity for other biogenic monoamines such as dopamine, serotonin and noradrenaline [38]. However, ECL cells are normally devoid of serotonin and catecholamines [39, 40], and it seems likely that the high levels of HDC ensure that histamine is the only effective substrate accessible to $VMAT_2$.

Unlike HDC, the abundance of gastric corpus $VMAT_2$ mRNA was not affected by fasting for up to 48 hours, or by subsequent refeeding [22]. It was however elevated significantly, like HDC and CGA mRNA, in rats treated with omeprazole for five days to induce achlorhydria and hypergastrinaemia [22] (Figure 4), suggesting that chronic, but not acute stimulation of the ECL cell upregulates vesicular monoamine transporters. Presumably, upregulation of $VMAT_2$ in response to prolonged hypergastrinaemia secures

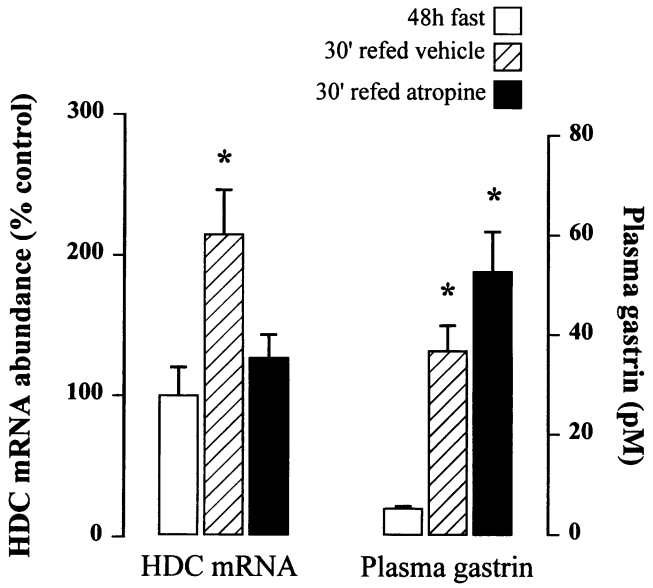

Figure 3. Effects of atropine on HDC mRNA and plasma gastrin responses to feeding. Groups of six rats were fasted for 48 hr (water *ad lib*) then re-fed for 30 min. One hour before feeding animals received by subcutaneous injection either vehicle alone (saline, hatched bars) or atropine (400 μg/kg, solid bars). HDC mRNA in gastric corpus was determined by Northern blot and plasma gastrin by specific radioimmunoassay [20]. Values are mean (± SEM. * = significantly different from control (fasted) group, $P < .05$, one-way ANOVA.

enhanced capacity to efficiently transport the increased cytoplasmic histamine into secretory granules. The ECL cell responses to hypergastrinaemia are not part of a non-specific response of gastric corpus mucosa because somatostatin mRNA abundance in the D-cell for example, was unaffected (Figure 4).

It seems then that on stimulation by gastrin, and perhaps other endogenous factors, the ECL cell exhibits a co-ordinated response in which all aspects of histamine biosynthesis and its sequestration and storage in secretory granules are upregulated (Figure 5).

PATHOPHYSIOLOGICAL REGULATION OF HDC mRNA ABUNDANCE

When rats are treated with high doses of gastric acid inhibitors for up to two years, they develop ECL cell hyperplasia, dysplasia and ultimately gastric carcinoid tumors [41]. It is generally agreed that hypergastrinaemia is a key determinant of the pathological changes induced by achlorhydria [42]. ECL cell hyperplasia is also seen in humans in response to the hypergastrinaemia associated with long term use of proton pump inhibitors such as omeprazole, but progression to carcinoid tumors has not, so far, been documented [43,44]. This progression is however seen in some patients with pernicious anemia or with gastrinoma; in the latter case, ECL cell carcinoids only occur in association with multiple endocrine neoplasia (MEN) type-I [44, 45]. Both surgical removal of the gastric antrum, and treatment with somatostatin or its analogues (e.g., octreotide) have been used as therapeutic strategies to control gastrin-dependent ECL cell growth. [46, 47].

In pernicious anemia patients with multiple ECL cell nodules, expression of HDC and CGA mRNAs determined by Northern blot of total RNA from endoscopic biopsies, was greatly elevated within the nodules compared with adjacent corpus mucosa (Table 1). Following a 72-hour octreotide infusion, both nodule and corpus mucosal HDC was dramatically downregulated with an associated reduction of plasma gastrin concentrations;

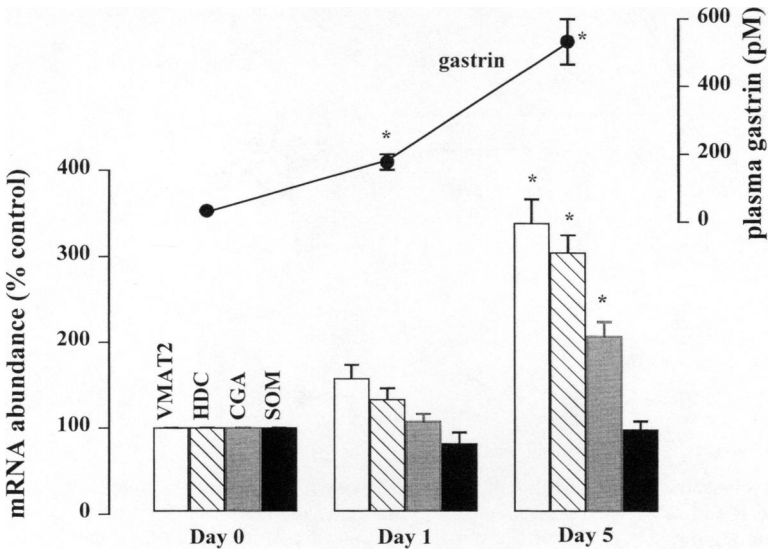

Figure 4. The co-ordinated ECL cell response to hypergastrinaemia. Groups of six rats were treated with omeprazole (400 μmol/kg daily by gavage) for 0, 1 or 5 days. Upper line graph, plasma gastrin concentrations determined by specific radioimmunoassay [20]. Lower bar chart, mRNA abundance for HDC, CGA, $VMAT_2$ and somatostatin in gastric corpus determined by Northern blot [20, 22, 29]. Values are mean (± SEM. * = significantly different from control (untreated) group, $P < .05$, one way ANOVA.

Table 1. HDC and CGA mRNA in human gastric corpus in response to octreotide.

	HDC mRNA	CGA mRNA	Plasma gastrin (pM)
Nodule: Pre-octreotide	100	100	850
Nodule: Post-octreotide	3.5	25	250
Corpus: Pre-octreotide	5.4	15	850
Corpus: Post-octreotide	<1	7	250

Samples of normal mucosa and nodule were removed by endoscopic biopsy from the gastric corpus of a pernicious anemia patient, before and after a 72 hr octreotide infusion (25 μg/hr). mRNA abundance was determined by Northern blot and expressed relative to pre-infusion levels; plasma gastrin was determined by specific radioimmunoassay [20, 29].

CGA was also downregulated, but less markedly (Table 1). It seems possible that the downregulation by octreotide results from a combination of inhibitory effects on both the antral G-cell and the ECL cell itself. The relatively smaller responses seen with CGA compared with HDC are perhaps unsurprising given that in rats, CGA is less strongly regulated in response to changes in gastric luminal pH (and, therefore, somatostatin release) than is HDC [19, 20, 29]. Determination of HDC mRNA abundance in biopsies from gastric corpus mucosa and from nodules, may be a useful adjunct to conventional methods for assessing ECL cell dysfunction in these tissues. In addition, evaluation of the HDC mRNA response to octreotide therapy provides some indication of the susceptibility of the nodules to neuroendocrine control. This information may be of value in predicting the outcome of more permanent therapeutic strategies such as antrectomy.

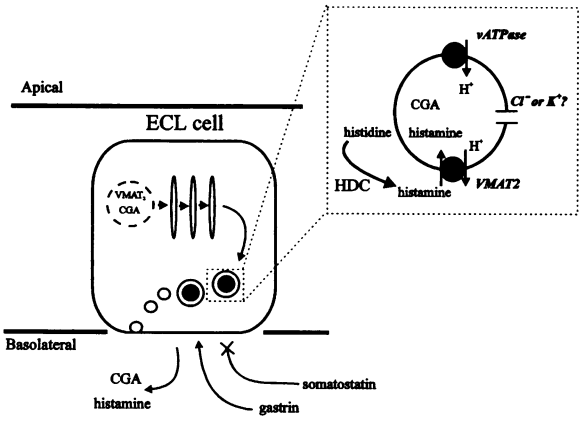

Figure 5. Schematic representation of histamine biosynthesis in the ECL cell. Chomogranin A and $VMAT_2$ reside in the dense cored secretory granule and its membrane, respectively, after transport through the regulated pathway of secretion. Cytosolic histamine enters the granule via $VMAT_2$ in exchange for intragranular protons. The proton gradient is generated by a V-type ATPase; a chloride or potassium channel may be present in the granule membrane. HDC, $VMAT_2$ and CGA mRNAs are upregulated by gastrin; HDC and CGA mRNAs are downregulated by luminal acid, presumably mediated by somatostatin.

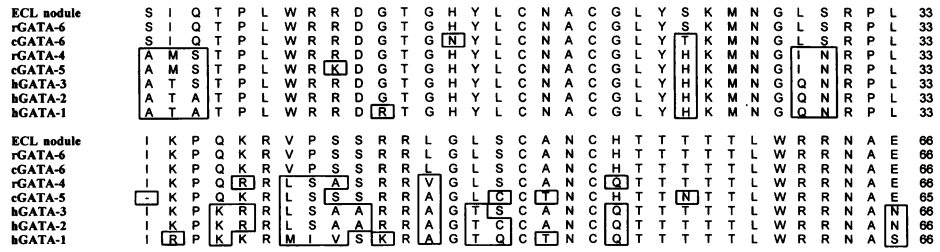

Figure 6. Cloning of human GATA-6 from an ECL cell nodule. The protein sequence predicted by cDNA generated by PCR from a human ECL cell nodule is aligned with the corresponding regions of other members of the GATA family. The human ECL cell sequence is identical with rat GATA-6, but differs from all other members of the family.

GENOMIC REGULATION OF HDC

Examination of molecular mechanisms and intracellular signalling pathways involved in regulation of the HDC promoter by gastrin have been hampered to some extent by the lack of a permanent ECL cell line. Wang and colleagues used a poorly differentiated gastric cancer cell line (AGS) permanently transfected with the gastrin/CCK-B receptor to investigate transcriptional activation of HDC. Using this approach they were able to demonstrate regulation of the rat and human HDC promoters by gastrin, through a protein kinase C pathway [18, 48]. In the human promoter, they localized the *cis*-acting gastrin response element to downstream of the transcriptional start site and identified a potentially novel transcription factor that bound to it [48].

In addition, however, expression of HDC mRNA in ECL cells is regulated by gastrin-independent mechanisms (see above, Figure 3), and this is also plainly the case in other histaminergic systems. In this context, it is of interest that the human HDC promoter contains a number of canonical *cis*-acting elements, notably, four GATA consensus sequences of the type (A/T)GATA(A/G) [17]. The GATA consensus sequences are recognized by a family of at least six vertebrate proteins that all contain two zinc finger-binding domains of the type C-X-N-C-(X_{17})-C-N-X-C [49, 50]. GATA-1 and GATA-2 are crucial regulators of hematopoiesis, and GATA-3 is implicated in T-cell development [49, 51]. GATA-4, -5 and -6 have been proposed to represent a distinct subfamily that may regulate gene expression in a range of developing tissues including gut epithelium [50, 52, 53].

GATA-4 and GATA-6 have been shown to bind functionally to sequences in the promoter of gastric proton pump genes and their mRNAs have been localized by *in situ* hybridization to parietal cells [54, 55]. Recently, however, it has also become clear that GATA proteins are expressed in gastric endocrine cells [56]. Several lines of evidence are consistent with the idea that GATA-6 is preferentially located in gastric endocrine cells in general, and in ECL cells in particular. Thus, GATA-6 mRNA was detected in rat corpus mucosal cells, enriched with ECL cells by centrifugal elutriation and in an endocrine cell line (STC-1) derived from mouse gut epithelium [56]. Moreover, when mixed oligonucleotide primers to a conserved region of the GATA family were used in PCR with a cDNA template derived from a human ECL cell nodule, a single band of the appropriate size was obtained. Cloning and sequencing of the PCR product revealed that it corresponded to human GATA-6 [56] (Figure 5).

The role of GATA proteins in ECL or other gastric endocrine cells is not yet clear. However, in gel shift assays, proteins in nuclear extracts from STC-1 cells bound specifically to the GATA consensus sequence AGATAT, that occurs three times in the human HDC

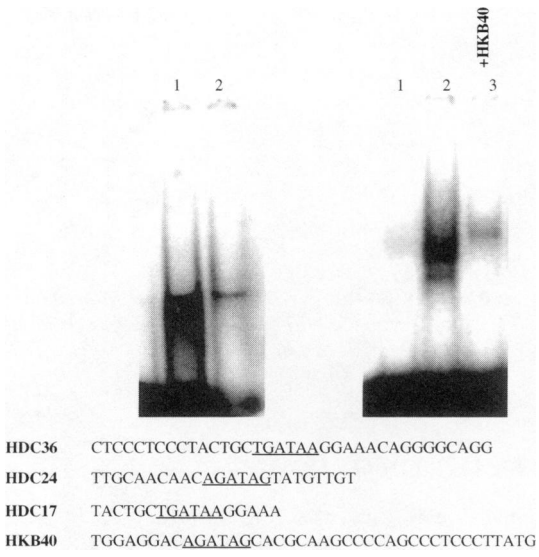

Figure 7. Identification of GATA-binding factors in the STC-1 cell line. Proteins binding GATA consensus sequences of the human HDC promoter were identified in STC-1 cells by gel mobility shift assays [56]. Left panel, STC-1 cell nuclear protein extracts bound to a ^{32}P-labelled oligonucleotide (HDC36) containing the consensus sequence TGATAA that occurs three times in the hHDC promoter (lane 1), and to a labelled oligonucleotide (HDC24) containing the sequence AGATAG, that occurs once in hHDC (lane 2). Right panel, binding of the labelled oligonucleotide HDC17 to STC-1 nuclear protein extract. Lane 1, no extract present; lane 2, protein extract present; lane 3 protein extract present together with unlabelled oligonucleotide (HKB40) corresponding to the GATA consensus region of the HK-ATPase ß subunit promoter. Arrows indicate retardation of the labelled probe induced by protein binding; free unbound probe appears at the lower border of the gel. Sequences of oligonucleotides used in the assays are given below.

promoter, and to the sequence TGATAA, that occurs once [56] (Figure 7). Furthermore, expression of GATA-6 mRNA in rat gastric corpus was upregulated by feeding, in concert with HDC mRNA [56]. GATA transcription factors and GATA-6 in particular, therefore, have a potential role in physiological regulation of HDC expression . In addition, however, they may be involved in regulating development of the gastrointestinal tract. The GATA-4, -5, -6 subfamily have been linked to control of development in a number of vertebrate tissues, including heart, gut epithelium, primitive endoderm and gonads [50,52,53]. In rat gastric corpus, GATA-6 and GATA-4 were upregulated at the time of terminal differentiation of the stomach, and the development of its responsiveness to gastric acid secretagogues, raising the possibility that they may play a regulatory role in this process [56].

PERSPECTIVES

The central importance of the ECL cell in the physiological regulation of gastric acid secretion is now beyond any doubt. Stimulation of the ECL cell, primarily by gastrin, increases histamine secretion, HDC enzyme activity, and HDC gene expression. Increases in HDC mRNA abundance in response to feeding are sufficiently rapid to account for changes in histamine biosynthesis over the time course of a single meal. Expression in ECL cells, of other genes such as CGA and $VMAT_2$, whose products facilitate sequestration and storage of histamine, is also upregulated as part of a coordinated response.

Prolonged hypergastrinaemia in rat or man induces progressive increases in HDC mRNA abundance and ECL cell hyperplasia. Determination of HDC mRNA in endoscopic biopsies may be useful in assessing ECL cell dysfunction. It also provides a means to evaluate responses to pharmacological and surgical strategies designed to reduce stimulation of the ECL cell.

Elucidation of genomic sequences central to ECL cell function has provided the opportunity to examine at the molecular level their regulation by gastrin and other agents. Evidence is now emerging for control of ECL cell function and development by known regulators such as the GATA proteins, as well as by other novel transcription factors.

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