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FOOD STIMULATION OF HISTIDINE DECARBOXYLASE MESSENGER RNA ABUNDANCE IN RAT GASTRIC FUNDUS

BY R. DIMALINE*, A. K. SANDVIK†, DEBRA EVANS, E. R. FORSTER AND G. J. DOCKRAY

From the MRC Secretory Control Research Group, Physiological Laboratory, University of Liverpool, Liverpool L69 3BX

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SUMMARY

1. Histidine decarboxylase in the enterochromaffin-like cells of the gastric corpus mucosa converts histidine to histamine which in turn stimulates gastric acid secretion. The control of histidine decarboxylase activity is poorly understood. We have examined how fasting and refeeding influence the abundance of the messenger RNA encoding histidine decarboxylase in the gastric corpus of the rat.
2. The polymerase chain reaction was used to generate a probe for detection of histidine decarboxylase messenger RNA in Northern and slot blots of total RNA from the gastric corpus of rats fasted for up to 48 h, or fasted and then refed. A gastrin monoclonal antibody was used to neutralize the action of endogenous gastrin.
3. Fasting progressively reduced histidine decarboxylase messenger RNA abundance by 3- to 4-fold after 48 h. Refeeding induced a rapid increase in histidine decarboxylase messenger RNA abundance which was detectable after 30 min.
4. There was a significant correlation between histidine decarboxylase messenger RNA abundance and plasma gastrin. Administration of gastrin antibody inhibited the increase in histidine decarboxylase activity after 6 h refeeding, but not after refeeding for 30 min.
5. The results suggest that histamine-mediated changes in postprandial acid secretion depend on control of histidine decarboxylase mRNA levels, and that gastrin regulates production of this enzyme in the rat over periods of a few hours.

INTRODUCTION

It has been known since 1920 that histamine is a potent stimulant of gastric acid secretion (Popielski, 1920). Histamine H_2 receptor antagonists inhibit the acid response to a meal, indicating that endogenous histamine is a physiologically important regulator of gastric function (Black, Duncan, Durant, Ganellin & Parsons, 1972; Grossman & Konturek, 1974). Histamine is produced from histidine by the

* To whom correspondence should be addressed at Physiological Laboratory, Crown Street, University of Liverpool, PO Box 147, Liverpool L69 3BX.
† Present address: Department of Medicine, University Hospital Trondheim, Norway.

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action of histidine decarboxylase (HDC; EC 4.1.1.22) and there is an impressive body of evidence to suggest functional modulation of HDC enzyme activity in the rodent stomach (Kahlson & Rosengren, 1971). It is clear, for example, that gastric HDC activity is rapidly increased when fasted rats are refed, and that both vagal-cholinergic stimulation and circulating gastrin are potential physiological regulators of enzyme activity (Rosengren & Svensson, 1969; Kahlson & Rosengren, 1971; Lundell, 1974; Hakanson, Kroesen, Liedberg, Oscarson, Rehfeld & Stadil, 1974). However, the cellular mechanisms responsible for changes in HDC activity remain unclear. Recently, we reported evidence to indicate that gastric HDC mRNA levels were controlled by circulating gastrin in the rat, suggesting that control of synthesis of new enzyme was one point of regulation (Dimaline & Sandvik, 1991). These experiments were performed in rats with depressed, or elevated, plasma gastrin concentrations for periods of 48 h and it is not clear whether HDC mRNA abundance might be regulated over shorter periods, for instance from meal to meal. In the present study we have examined the effect of food intake on HDC mRNA abundance, and have sought to define whether HDC mRNA abundance is regulated at meal-to-meal intervals. Some of this work has already appeared in abstract form (Dimaline, Sandvik & Evans, 1992).

METHODS

Experimental protocols

Female Wistar rats weighing 240–260 g were used. Animals were fed with standard rat chow (rat and mouse diet, Bantin & Kingman, Hull, England) and tap water *ad libitum* until the start of the experiment. They were kept on a 12 h light–dark cycle and were routinely housed on sawdust floor cages; for experiments involving fasting they were transferred to individual wire bottomed cages. Groups of six rats were fasted for 6, 12, 24 or 48 h; alternatively they were fasted for 48 h and refed for 0·5, 1, 2, 4, 6, 12, 24 or 48 h. Fasted rats had free access to water. In some experiments, rats were treated with gastrin monoclonal antibody (generous gift of Dr J. H. Walsh) by tail vein injection, under halothane anaesthesia, 60 min prior to refeeding. The monoclonal antibody is specific for the C-terminal of amidated gastrins and neutralizes the acid-secretory response to a meal (Kovacs, Walsh, Maxwell, Wong, Azuma & Katt, 1989). In these experiments control rats received antibody to a biologically inactive Gly-extended gastrin (gift from Dr J. H. Walsh).

Animals were killed by decapitation. Trunk blood was collected in chilled heparinized plastic tubes, centrifuged and plasma removed then stored at -80 °C for subsequent gastrin radioimmunoassay. A wedge-shaped piece of the gastric corpus with the short side corresponding to the border of the corpus and non-glandular stomach was rapidly excised from the major curvature, and homogenized in RNA extraction buffer (4 mol/l guanidinium isothiocyanate containing 25 mmol/l sodium acetate pH 6·0 and β-mercaptoethanol 0·84% v/v); the extract was then rapidly frozen and stored at -80 °C until further processing.

Probes

Gastric HDC mRNA was detected in Northern and slot blots using a radiolabelled cDNA probe generated by the polymerase chain reaction (PCR). Complementary DNA was made by reverse transcription of total RNA from liver of fetal rats at 20 days gestation (which is an abundant source of HDC) using a commercial cDNA synthesis kit (Boehringer Mannheim, Lewes, Sussex). The histidine decarboxylase cDNA probe was simultaneously synthesized and radiolabelled with ^{32}P by PCR performed in 100 μl 1 × Taq (*Thermus aquaticus*) polymerase buffer (Promega, Southampton, Hants) containing deoxyadenosine triphosphate (200 μmol/l), deoxyguanidine triphosphate (200 μmol/l), deoxythymidine triphosphate (200 μmol/l) (Pharmacia, Uppsala, Sweden), [α-^{32}P]deoxycytosine triphosphate (100 μCi; 3000 Ci/mmol, Amersham, Bucks), oligonucleotide

primers (50 pmol each), fetal rat liver cDNA template (2 μg) and Taq DNA polymerase (2 units, Promega). After initial denaturation, 30 cycles of amplification (55 °C for 1 min, 72 °C for 2 min, 95 °C for 1 min) were performed followed by a 10 min extension step at 72 °C; the probes were purified on NICK Spin Columns (Pharmacia, Uppsala, Sweden). Primers used for PCR were synthesized on an Applied Biosystems 391 oligonucleotide synthesizer (Warrington, Cheshire) and corresponded to bases 1114–1135 (sense) and 1585–1564 (antisense) of rat HDC cDNA (Joseph *et al.* 1990). They were purified by ion exchange high-performance liquid chromatography. Electrophoresis of the unlabelled and ^{32}P radiolabelled HDC cDNA fragments on 1·5% agarose gels gave bands consistent with the predicted size of 471 base pairs.

A 32 mer oligonucleotide of the rat 18S ribosomal subunit was 5′ end-labelled using 100 μCi [γ-^{32}P]ATP (3000 Ci/mmol, Amersham) and T4 polynucleotide kinase (Promega). The labelled oligonucleotide was purified using NICK Spin Columns (Pharmacia).

Quantification of mRNA

Guanidinium isothiocyanate homogenates were adjusted to 2·3 mol/l caesium chloride (CsCl), layered onto a cushion of 5·4 mol/l CsCl and centrifuged at 156000 *g* for 20 h. Pellets of RNA were dissolved in Tris–ethylenediaminetetraacetic acid (EDTA) (10 mmol/l and 1 mmol/l, pH 7·4) containing 0·2% sodium dodecyl sulphate (SDS), precipitated overnight with 0·3 mol/l sodium acetate and ethanol, centrifuged and the RNA pellet dissolved in water. Samples of total RNA were quantified by absorbance at 260 nm and aliquots of 20 μg (5 μl) denatured at 55 °C for 15 min by incubation with 8 μl deionized formamide, 3·5 μl formaldehyde, and 2 μl 10 × 3-(*N*-morpholino)propanesulphonic acid (Mops) buffer (0·2 mol/l, pH 7·0).

Total RNA samples (20 μg) were blotted onto Hybond N, nylon membranes (Amersham, Bucks) prewet with 10 × standard saline citrate (SSC; 1·5 M NaCl, 0·15 M sodium citrate, pH 7·4) buffer, using a commercial slot blotting apparatus (BioRad, Hemel Hempstead, Herts). The RNA was cross-linked to the membrane using ultraviolet light. Posthybridization washing stringency was tested on Northern blots of 20 μg total RNA that was electrophoresed in 1 × Mops on 1% agarose formaldehyde gels and electroblotted onto Hybond N membranes. Washing at room temperature (23 °C) twice for 20 min with 2 × standard sodium phosphate EDTA buffer (SSPE; 0·3 M NaCl, 0·02 M sodium phosphate, 2 mM EDTA, pH 7·4) containing 0·1% SDS and once at 65 °C with 0·1 × SSPE and 0·1% SDS, was routinely used for HDC. Similar washing conditions were used after 18S hybridization except that the final wash was 20 min at 55 °C. The linearity of signal intensity was assessed on both Northern blots and slot blots of graded amounts of total RNA. Northern and slot blots were first hybridized with the HDC probe, washed and exposed to Kodak X-AR film (Rochester, NY, USA) for 24–48 h at −80 °C using an intensifying screen. The HDC probe was then stripped with boiling 0·1% SDS and membranes rehybridized with 18S oligonucleotide probe to monitor for equal loading and transfer efficiency. The slot blot signals were quantified by video densitometry.

Gastrin radioimmunoassay

Plasma was assayed for C-terminal gastrin immunoreactivity as previously described using antibody L2 and ^{125}I-labelled human heptadecapeptide gastrin (Dockray, Best & Taylor, 1977; Dockray, Hamer, Evans, Varro & Dimaline, 1991).

Statistics

Results are expressed as means ± S.E.M., and comparisons between treatments were made by one-way analysis of variance (ANOVA). Correlations between plasma gastrin and HDC mRNA from individual animals were evaluated by linear regression analysis.

RESULTS

Histidine decarboxylase mRNA

Northern blots revealed two species of HDC mRNA of approximately 2·7 (major band) and 3·5 kilobases (minor band) corresponding to those described by Joseph *et al.* (1990) in fetal rat liver (Fig. 1). The two varied in parallel under all conditions

studied, and their sum was taken in quantifying HDC mRNA in the studies described below. Signal intensity, as determined from absorbance using video densitometry, was linearly related to the amount of total RNA loaded (Fig. 2).

Effect of fasting and refeeding on HDC mRNA abundance

Fasting produced a progressive reduction in HDC mRNA abundance which was significant after 12 h (62 ± 10% of control; $P < 0{\cdot}05$), and after 48 h was 37 ± 5% of

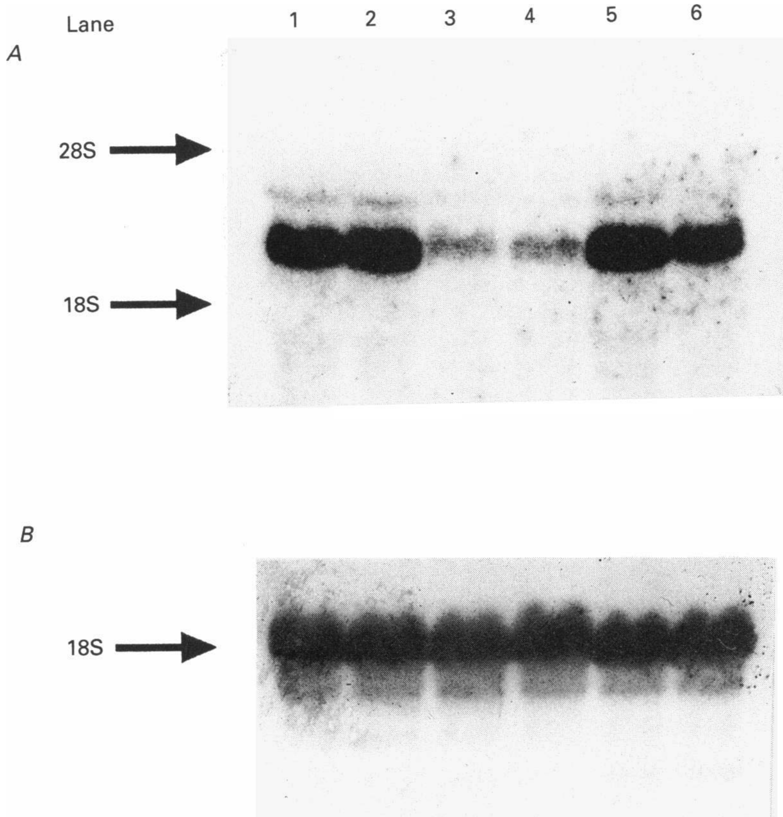

Fig. 1. Representative Northern blots of HDC mRNA levels in 20 μg samples of total corpus RNA from control rats (lanes 1 and 2), rats fasted for 48 h (lanes 3 and 4) and rats refed for 6 h following a 48 h fast (lanes 5 and 6). *A*, membrane hybridized with HDC probe. *B*, the same membrane rehybridized with an oligonucleotide probe for the 18S ribosomal subunit. Arrows indicate the position of the ribosomal subunits.

control (Fig. 3). Refeeding rats that had been fasted for 48 h induced a rapid increase in HDC mRNA abundance which was significant 30 min after refeeding ($P < 0{\cdot}05$) and was followed by a more gradual increase that approached control levels 48 h after the start of refeeding (Fig. 4).

Plasma gastrin

During fasting there was a decrease in plasma gastrin, which was significant after 12 h and reached stable low levels at 24 h ($P < 0{\cdot}05$, ANOVA) (Fig. 3). There was a

significant positive correlation between plasma gastrin concentration and HDC mRNA abundance in individual rats that were fasted from 0 to 48 h or were refed for up to 48 h after fasting ($r = 0{\cdot}580$, $P = 0{\cdot}00077$, $n = 60$) (Fig. 5). Refeeding rats fasted for 48 h induced an initial surge in plasma gastrin which peaked at 30 min and subsequently declined to a nadir at 4 h before rising again over the following 2 days (Fig. 4).

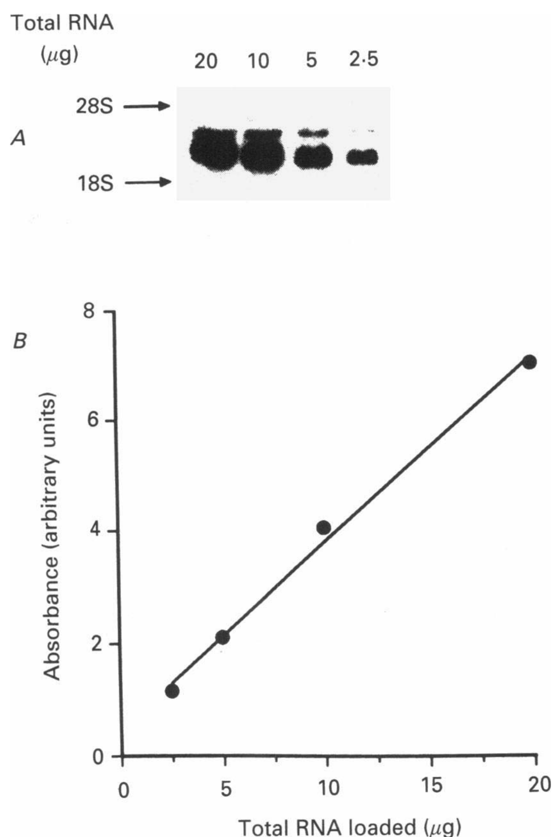

Fig. 2. Quantification of HDC mRNA in Northern blots of samples of total RNA from fundus of rats fed *ad libitum*. *A*, samples of 20, 10, 5 and 2·5 μg total RNA (lanes 1–4, respectively). Arrows indicate the position of ribosomal subunits. *B*, relationship between video densitometer signal intensity and quantity of RNA loaded.

Gastrin neutralization

In order to examine the role of gastrin in the control of HDC mRNA levels after refeeding we treated rats with a gastrin monoclonal antibody 60 min before the refeeding trial. Control rats received antibody to an inactive fragment of gastrin. In control rats, the HDC mRNA levels after refeeding for 30 min were increased to $127{\cdot}3 \pm 11{\cdot}4$ % of those in fasted rats ($100 \pm 10{\cdot}9$ %; $n = 6$) and in animals receiving

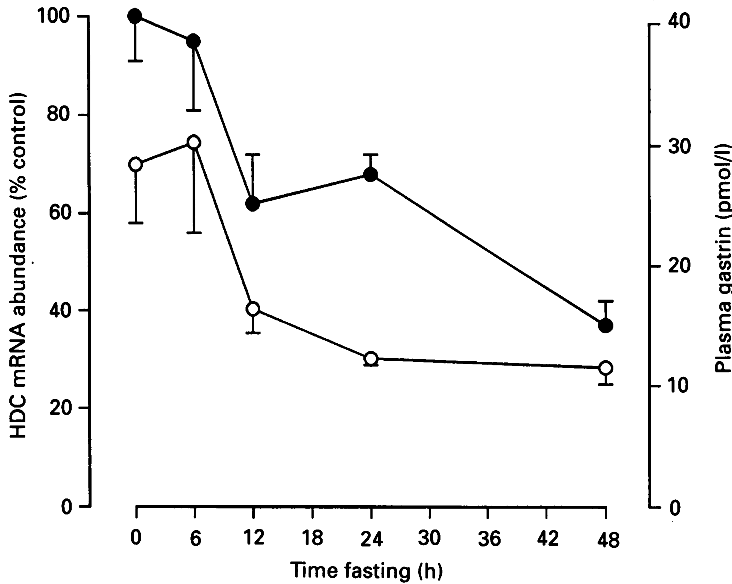

Fig. 3. Histidine decarboxylase mRNA abundance (●) and plasma gastrin concentrations (○) in rats fasted from 0 to 48 h. Messenger RNA abundance is expressed as percentage of that in control animals that were allowed free access to food. Values are means ± S.E.M., $n = 6$.

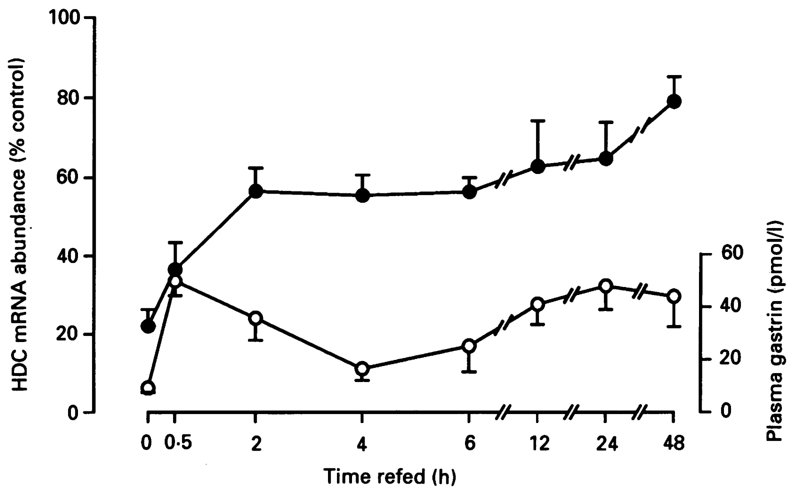

Fig. 4. Histidine decarboxylase mRNA abundance (●) and plasma gastrin concentrations (○) in rats refed from 0–48 h following a 48 h fast. Messenger RNA abundance is expressed as percentage of that in control animals allowed free access to food. Values are means ± S.E.M., $n = 6$.

gastrin antibody the increase was if anything slightly greater (154·8 ± 19·2 %) but the difference was not significant. In contrast, after 6 h of refeeding the increase in HDC mRNA abundance in control rats (172·3 ± 20·3 %) was significantly greater than in rats treated with anti-gastrin antibodies (124·7 ± 11·7 %; $P < 0·05$).

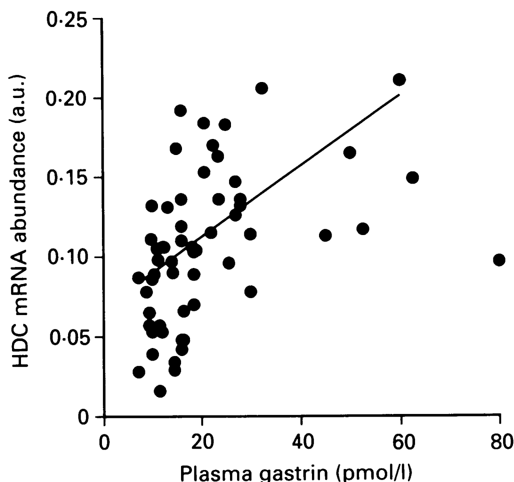

Fig. 5. Correlation between corpus HDC mRNA abundance (arbitrary units, a.u.) and plasma gastrin in individual animals fasted from 0 to 48 h, or refed for periods up to 48 h following a 48 h fast. The line was fitted by linear regression analysis. Correlation coefficient = 0·58, $P = 0{\cdot}00077$, $n = 60$.

DISCUSSION

The control of histamine production is now widely recognized to be of central importance in the regulation of gastric acid secretion. The main finding of the present study is that the abundance of the mRNA encoding HDC can be rapidly regulated and in particular can increase over periods as short as the time required for gastric digestion of a single meal. The factors that might regulate HDC enzyme activity have been studied for many years, but the cellular mechanisms involved have so far been largely unexplored. Our data suggest that synthesis of new HDC is likely to be an important factor in accounting for the stimulation of histamine production after a meal.

There are two sources of histamine in the acid-secreting part of the stomach: mast cells and enterochromaffin-like (ECL) cells (Hakanson *et al.* 1986; Soll, Toomey, Culp, Shanahan & Beaven, 1988); it is the histamine originating from ECL cells that is generally thought to be important in the control of gastric acid secretion. There is abundant evidence that acid secretagogues release histamine in rodents, and recently direct evidence for similar actions in dog have been reported (Soll, Chuang & Chen, 1991; Sandvik, Waldum, Kleveland & Schulze Sognen, 1987). Previously we reported that HDC mRNA levels are much lower in the antral part of the stomach compared with the corpus, and since ECL cells are restricted to the corpus this suggests that HDC mRNA is predominantly of ECL cell origin (Dimaline & Sandvik, 1991). Moreover, in antrum there are no feeding-associated changes in HDC mRNA, which is compatible with the idea that histamine outside the corpus is associated with mast cells that are not under the control of gastrin (Soll *et al.* 1988).

Many years ago gastric mucosal HDC enzyme activity in the rat was shown to fall

with fasting and increase with refeeding (Kahlson, Rosengren, Svahn & Thunberg, 1964). In principle, the increased HDC activity could be due to synthesis of new enzyme or to activation of stored forms. There is evidence, for example, that HDC activity can be altered by phosphorylation and this could provide a regulatory mechanism for activation of cellular stores of enzyme (Savany & Cronenberg, 1990). Our data do not discount this; they do, however, firmly indicate that production of new enzyme is an early and potentially important component in the food-induced increase of activity. Interestingly, in the study of Kahlson *et al.* (1964) the increase in HDC activity in refed rats peaked at about 3 h and was virtually undetectable after 1 h. In the present study, HDC mRNA abundance was shown to increase within 30 min of refeeding; it seems possible, therefore, that the prompt increase in HDC mRNA on refeeding leads to increased levels of enzyme about 3 h later.

The present experiments revealed broadly similar changes in plasma gastrin concentrations and HDC mRNA abundance when rats were fasted for up to 48 h or refed for up to a further 48 h. In a previous report, depressed plasma gastrin and HDC mRNA were described in rats fasted for 48 h; moreover, when fasted rats were treated with the H^+–K^+-ATPase inhibitor omeprazole (which enhances plasma gastrin by removing inhibitory feedback by gastric acid) there was a marked increase in HDC mRNA and this was blocked by the gastrin antagonist CI 988. In rats fed *ad libitum* and treated with omeprazole there were extremely high plasma gastrin concentrations but HDC mRNA was not substantially different to control rats fed *ad libitum* (Dimaline & Sandvik, 1991). Taken together with the present results, the data suggest that gastric HDC mRNA levels are regulated by plasma gastrin concentrations in the physiological range, but at supra-physiological levels there is no further stimulation of HDC mRNA abundance. Our observation that immunoneutralization of gastrin was associated with inhibition of the food-induced increase of HDC mRNA 6 h after refeeding, indicates that meal-related fluctuations in plasma gastrin might be linked to phasic control of HDC production. There was a significant positive correlation between plasma gastrin and HDC mRNA levels throughout the fasting and refeeding experiments. However, while both plasma gastrin and HDC increased promptly after refeeding, gastrin immunoneutralization did not reduce HDC mRNA abundance after 30 min refeeding, which suggests that while gastrin might control HDC mRNA over periods of a few hours, or longer, there is at least one meal-induced factor that regulates gastric HDC over shorter periods, e.g. < 1 h. The changes in HDC mRNA with fasting are unlikely to reflect a general reduction in mRNA levels because rats treated similarly showed no change in fundic somatostatin mRNA levels, and an increase in antral somatostatin mRNA levels was observed (Wu, Sumii, Tari, Mogard & Walsh, 1990; Sandvik, Dimaline, Forster & Dockray, 1993).

The rapid postprandial increase in HDC mRNA that we have described extends reports of comparable changes in mRNA species encoding other substances important in the control of gastric acid secretion. Thus in isolated parietal cells *in vitro*, the three main acid secretagogues, gastrin, histamine and muscarinic agonists, rapidly increased abundance of mRNAs for H^+–K^+-ATPase, carbonic anhydrase and β actin (Campbell & Yamada, 1989). Moreover, refeeding of fasted rats produced rapid changes in gastrin and somatostatin mRNA abundance over intervals

comparable to those described for postprandial HDC mRNA described here (Wu, Sumii, Tari, Mogard & Walsh, 1990; Wu, Sumii, Tari, Sumii & Walsh, 1991). Thus in all the major cell types involved in physiological control of acid secretion, i.e. the gastrin, somatostatin, ECL and parietal cells there is not simply acute modulation of secretory events but also concomitant control of the synthesis of proteins important for the secretory response. Further work is needed to elucidate the relevant mechanisms and on present evidence it seems possible that multiple points of control are involved since there is direct evidence for control of both gene expression and mRNA stability (Wu, Giraud, Mogard, Sumii & Walsh, 1990).

It is now clear that gastrin influences several different aspects of ECL cell function, including stimulation of histamine release, HDC enzyme activity and mRNA abundance, chromogranin A production, and (after prolonged hypergastrinaemia) ECL cell numbers which in extreme cases progresses to carcinoid tumours (Kahlson *et al.* 1964; Larsson *et al.* 1986; Sandvik, Waldum, Kleveland & Schulze Sognen, 1987; Sandvik & Waldum, 1991; Dimaline, Sandvik, Watkinson & Dockray, 1992). Our data raise the possibility that physiological concentrations of circulating gastrin control gene expression in ECL cells over relatively short periods of time. During stimulation by gastrin or cholinomimetics there is a rapid increase in histamine release in the isolated perfused rat stomach, followed by a lower plateau of histamine release that is maintained with continuous stimulation (Sandvik *et al.* 1987). It seems possible that the initial histamine release is attributable to secretion of stored material and that maintenance of the plateau phase of secretion depends on production of new histamine by stimulation of HDC. An important part of the latter response would appear to involve synthesis of new enzyme due to increased mRNA levels.

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