Interrelationships between circulating gastrin and iron status in mice and humans

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Kovac S, Smith K, Anderson GJ, Burgess JR, Shulkes A, Baldwin GS. Interrelationships between circulating gastrin and iron status in mice and humans. Am J Physiol Gastrointest Liver Physiol 295: G855–G861, 2008. First published August 28, 2008; doi:10.1152/ajpgi.90359.2008.—The observations that the peptide hormone gastrin interacts with transferrin in vitro and that circulating gastrin concentrations are increased in the iron-loading disorder hemochromatosis suggest a possible link between gastrin and iron homeostasis. This study tested the hypothesis that gastrin and iron status are interrelated by measurement of iron homeostasis in mice and humans with abnormal circulating gastrin concentrations. Intestinal iron absorption was determined by 59Fe uptake following oral gavage, and concentrations of duodenal divalent metal transporter-1 (DMT-1) and hepatic hepcidin mRNAs were determined by quantitative real-time PCR in agastrinemic (GasKO), hypergastrinemic (Ggly), and wild-type mice. Iron status was measured by standard methods in the same mice and in hypergastrinemic humans with multiple endocrine neoplasia type 1 (MEN-1). Iron absorption was increased sixfold and DMT-1 mRNA concentration fourfold, and transferrin saturation was reduced 0.8-fold and hepcidin mRNA expression 0.5-fold in juvenile GasKO mice compared with age-matched wild-type mice. In mature mice, few differences were observed between the strains. Juvenile CCK2RKO mice were hypergastrinemic and had a 5.4-fold higher DMT-1 mRNA concentration than wild-type mice without any increase in iron absorption. In contrast to juvenile GasKO mice, juvenile CCK2RKO mice had a 1.5-fold greater transferrin saturation, which was reflected in a twofold increase in liver iron deposition at maturity compared with wild-type mice. The correlation between transferrin saturation and circulating gastrin concentration observed in mutant mice was also observed in human patients with MEN, in whom hypergastrinemia correlated positively (P = 0.004) with an increased transferrin saturation. Our data indicate that in juvenile animals when iron demand is high, circulating gastrin concentrations may alter iron status by a CCK2R-independent mechanism.

anemia; ferric; hemochromatosis

THE PEPTIDE HORMONE GASTRIN exists in several forms, all of which are derived from an 80-amino acid precursor, progastrin (14). COOH-terminal amidation to form amidated gastrin17 (Gamide) is essential for the biological activities of Gamide as a stimulant of gastric acid secretion and a growth factor for the gastric mucosa (14). Nonamidated gastrins such as glycine-extended gastrin17 (Ggly) are also biologically active as growth factors for the colorectal mucosa (2). Gamide acts via the cholecystokinin type 2 receptor (CCK2R), but the structure of the Ggly receptor has not yet been determined (2). We have previously reported that gastrins bind two ferric ions (7). In the case of Ggly, ferric ion binding is essential for biological activity (29), but the removal of ferric ions has no effect on binding of Gamide to the CCK2R or on CCK2R-mediated biological activity (31). Furthermore, Gamide has been demonstrated to interact with the iron-transport protein transferrin in vitro (22), and previous studies in both mice and humans with the iron-overload disease hemochromatosis demonstrated a connection between high-iron status and increased circulating gastrin concentrations (35). The link between Gamide and iron status is potentially of great interest because Gamide is a major stimulant of acid secretion. A requirement for either gastrin or gastric acid released in response to gastrin for optimal dietary iron uptake by the duodenum was demonstrated 50 years ago by the observation that anemia is a long-term consequence of partial gastrectomy (5).

Dietary iron uptake is crucial to the regulation of iron homeostasis because of the lack of a physiological mechanism for iron excretion (4, 25). Ferric ions in the lumen of the gastrointestinal tract are first reduced by a duodenal cytochrome b (Dcytb) before import into enterocytes as ferrous ions by the divalent metal ion transporter DMT-1. Ferrous ions are subsequently exported across the basolateral membrane of the enterocyte by ferroportin (FPN), oxidized by hephaestin, and bound by transferrin for transport throughout the body. The process is regulated in response to iron requirements by alteration of DMT-1 and Dcytb mRNA synthesis (13, 38) and by internalization and degradation of the complex formed between FPN and the hepatic iron regulatory peptide hepcidin (28). For example, DMT-1 expression is known to be upregulated in low-iron conditions and downregulated in high-iron conditions (15, 16).

Iron (11) and gastrins (2) have been independently implicated in the initiation and progression of colorectal carcinoma (CRC). The risk of CRC is up to threefold greater in patients with hemochromatosis (1, 32), and there is an association between iron intake and CRC risk in normal subjects (24, 27). Intracellular iron concentrations (9) and circulating concentrations of gastrins (12) are increased in patients with CRC, and a circulating gastrin concentration above normal is associated with a 3.9-fold greater risk of developing CRC (39). In animal models, progastrin and Ggly stimulated proliferation of the normal colonic mucosa (2, 40) and increased the number of cells...
GASTRIN AND IRON STATUS ARE RECIROCALLY RELATED

CRC after treatment with the carcinogen azoxymethane (3, 33). Conversely, stable expression of antisense gastrin mRNA inhibited proliferation of CRC cell lines in vitro (20) and blocked development of tumor xenografts in vivo (30).

To study further the connection between gastrins and iron status we characterized iron homeostasis in two mouse models. GasKO mice lack all forms of gastrin (18), and CCK2RKO mice have increased concentrations of circulating gastrins as a result of deficiency of the CCK2R (26). To study the regulation of iron homeostasis GasKO and the CCK2RKO mice were investigated at two ages that differed in their iron requirements. Juvenile (4 wk old) mice have a high iron requirement because of their high growth rate and the low iron content of the breast milk that formed their diet until weaning (21), whereas mature mice (10 wk old) have lower iron requirements and sufficient dietary iron. To investigate the link between gastrin and iron status in humans serum transferrin saturation was measured in patients with hypergastrinemia as a consequence of multiple endocrine neoplasia (MEN).

MATERIALS AND METHODS

Patients. Patients with MEN-1 have been described previously (10). The study group of 41 consenting patients consisted of 14 men (mean age 54.4 ± 3.6 yr) and 27 women (mean age 50.8 ± 3.2 yr). This study was approved by the Ethics Committee of the Royal Hobart Hospital.

Mouse strains. Balb/c mice with a deletion of the gastrin gene (18) or C57BL/6J mice with a deletion of the CCK2R gene (26) were obtained from Dr. Linda Samuelson (Department of Physiology, University of Michigan, Ann Arbor, MI) and Professor Tetsuo Noda (Department of Cell Biology, Cancer Institute, Tokyo, Japan), respectively. Wild-type Balb/c and C57BL/6J mice were used as controls. All mice were fed a commercially prepared pelleted diet, were given water ad libitum, and were anesthetized with ethrane before euthanasia. Samples from juvenile (4 wk old) mice were taken within 3 days of weaning onto the pelleted diet. All experiments described in this study were approved by the Austin Health or the Queensland Institute of Medical Research Ethics Committees.

Radioimmunoassay. Concentrations of Ggly in the plasma of CCK2R-deficient and wild-type C57BL/6J mice were measured as described previously by radioimmunoassay against a Ggly standard curve with 125I-glycine-extended gastrin17 as label with antiserum 7270, which does not cross-react with Ggly (12). Concentrations of Gamide in the plasma of patients with MEN-1 and of CCK2R-deficient and wild-type C57BL/6J mice were measured as described previously by radioimmunoassay against a gastrin17 standard curve with 125I-gastrin17 as label with antiserum 1296, which does not cross-react with Ggly (12).

Iron uptake assays. Uptake of 55Fe2+ was measured as described previously (16). Briefly, mice were administered an intragastric dose of iron consisting of 10 mM ferrous sulfate in 10 mM HCl containing 2 μCi/ml 55Fe in a volume of 100 μl. Approximately one hour after dosing, the total 55Fe administered to each animal was measured by whole-body counting with a Ram DA Counter with a PM-11-tube (Rotem Industries, Arava, Israel) at a distance of 20 cm. A second whole-body count was conducted 7 days later, at which time iron that has not been absorbed has been excreted. Iron absorption was calculated as the percentage of the initial iron dose remaining after 7 days.

Real-time PCR. Total RNA was isolated from frozen liver or duodenum with TRIzol reagent (Invitrogen, Melbourne, Australia) according to the manufacturer’s instructions. RNA concentration and purity were determined by spectrometry and gel electrophoresis, respectively. Total RNA (5 μg) was used for cDNA synthesis with the Superscript III First Strand Synthesis system (Invitrogen). The resulting cDNA transcripts were used for real-time PCR using an ABI PRISM 7700 Sequence Detector (Applied Biosystems, Melbourne, Australia). Specific primer and probe pairs were designed from the mouse sequences for DMT-1 and the gene encoding hepcidin antimicrobial peptide 1 (Hamp1). 5′→3′ Primer/probe sequences for hepcidin (GenBank accession no. NM032541) were sense AGGCCCAC-CTATCTCCATCAACA, antisense GCTTTCTCAGGCGTCAA, probe AGACAGACTACAGAGCCCTG. 5′→3′ Primer/probe sequences for DMT-1 (GenBank accession no. L33415) were sense CGGGCCAGT-GATGAGTGAAT, antisense AGATTCGCGTGGGCAT, probe TTC-CAATGGAATAGGC.

Iron status assays. Serum ferritin concentrations and transferrin saturation were measured by the Division of Laboratory Medicine, Austin Health (Heidelberg, Australia). Hepatic iron concentrations were determined by Analytical Reference Laboratories (Melbourne, Australia).

Statistics. Data are means ± SE. Statistical significance relative to the control (∗∗P < 0.01; **P < 0.01; #P < 0.001) was assessed by one-way ANOVA, followed by Student’s t-test with Bonferroni correction.

RESULTS

To test the hypothesis that iron status is related to circulating gastrin concentration we characterized iron homeostasis in juvenile and mature mice with altered circulating gastrin concentrations, either as a consequence of deletion of the gastrin gene (18) or deletion of the CCK2R gene (26). One of the consequences of the reduced acid secretion caused by deletion of the CCK2R gene is removal of the feedback inhibition of gastric acid on gastrin production. The end result is a three- to fivefold increase in the circulating Gamide concentration and a twofold increase in the circulating Ggly concentration in the CCK2RKO mice compared with age-matched wild-type mice (Table 1).

Iron absorption in gastrin-modified mice. We first measured iron absorption in juvenile and mature mice with altered circulating gastrin concentrations (Fig. 1). The results revealed a sixfold increase (P < 0.001) in iron absorption in the juvenile GasKO mice compared with age-matched wild-type mice (Fig. 1A). By the time the mice had reached maturity (10 wk), no significant difference was observed between the strains (Fig. 1A). No significant difference in iron absorption was observed between the CCK2RKO and wild-type C57BL/6J mice at either 4 or 10 wk of age although iron absorption decreased by approximately fourfold in both strains over the 6-wk period (Fig. 1B), presumably as a result of a decline in iron requirements.

Table 1. Concentrations of Gamide and Ggly in CCK2 receptor-deficient mice

<table>
<thead>
<tr>
<th>Combination</th>
<th>n</th>
<th>Gamide</th>
<th>Ggly</th>
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<tbody>
<tr>
<td>CCK2R KO (4 wk old)</td>
<td>12</td>
<td>140 ± 22</td>
<td>50 ± 12</td>
</tr>
<tr>
<td>CCK2R KO (10 wk old)</td>
<td>12</td>
<td>363 ± 45</td>
<td>71 ± 6</td>
</tr>
<tr>
<td>Wild-type (4 wk old)</td>
<td>8</td>
<td>57 ± 10</td>
<td>24 ± 5</td>
</tr>
<tr>
<td>Wild-type (10 wk old)</td>
<td>8</td>
<td>84 ± 11</td>
<td>38 ± 5</td>
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Data are means ± SE. Concentrations of glycine-extended gastrin17 (Ggly) in the plasma of CCK2 receptor-deficient and wild-type C57BL/6J mice were measured by radioimmunoassay as described in MATERIALS AND METHODS. The values for [Ggly] in CCK2R KO and wild-type mice are in reasonable agreement with the values reported by Nagata et al. for 12–20-wk-old mice (750 ± 120 and 140 ± 30 pM, respectively) (26).
between the GasKO and the wild-type Balb/c mice in any of plasma ferritin concentrations revealed no significant difference in the absence of inflammation, the concentration of ferritin in the circulation is a reliable measure of body iron stores. Measurement of plasma ferritin concentrations revealed no significant difference between the GasKO and the wild-type Balb/c mice in any of the age groups studied (Fig. 3A) although values were lower in the wild-type mice. In contrast, in the juvenile CCK2RKO mice, ferritin concentrations were reduced by 0.23-fold \( (P < 0.01) \) compared with the wild-type C57BL/6J mice (Fig. 3B). No significant differences were observed in mature mice.

**Transferrin saturation in the plasma of gastrin-modified mice.** Transferrin saturation is an alternative measurement of iron status. In 4-wk-old GasKO mice, the transferrin saturation was reduced by 0.76-fold \( (P < 0.001) \) compared with age-matched wild-type Balb/c mice. In mature GasKO mice, no significant difference in transferrin saturation was observed compared with the wild-type mice (Fig. 4A). In juvenile CCK2RKO mice, the transferrin saturation was increased by 1.5-fold \( (P < 0.001) \) compared with the age-matched wild-type C57BL/6J mice. At 10 wk of age, no difference in the transferrin saturation was apparent between the mice (Fig. 4B).

The observation that transferrin saturation is significantly increased in juvenile CCK2RKO mice and reduced in juvenile GasKO mice compared with the appropriate wild-type strains is striking, particularly because both transgenic strains had increased DMT-1 mRNA expression. One of the consequences of the reduced acid secretion caused by deletion of the CCK2R gene is an increase in the circulating concentrations of Gamide and Gly. Hence our data indicate a relationship between transferrin saturation and the concentrations of circulating gastrins in young mice with increased iron demand.

**Hepatic iron concentration of gastrin-modified mice.** Since a persistently increased transferrin saturation should result in an increased DMT-1 mRNA expression. One of the consequences of the reduced acid secretion caused by deletion of the CCK2R gene is an increase in the circulating concentrations of Gamide and Gly. Hence our data indicate a relationship between transferrin saturation and the concentrations of circulating gastrins in young mice with increased iron demand.

**Expression of DMT-1 mRNA in the duodenum of gastrin-modified mice.** Concentrations of the mRNA encoding the divalent metal transporter DMT-1 were then measured by quantitative real-time PCR in duodenal extracts from GasKO and CCK2RKO mice and their wild-type counterparts. In juvenile GasKO mice, the concentration of DMT-1 mRNA was significantly increased by fourfold \( (P < 0.05) \) compared with age-matched wild-type Balb/c mice (Fig. 2A). In contrast, the concentration of DMT-1 mRNA in mature GasKO mice was significantly reduced by 2.1-fold \( (P < 0.05) \) compared with wild-type Balb/c mice. In juvenile CCK2RKO mice, the concentration of DMT-1 mRNA was significantly increased by 5.4-fold \( (P < 0.01) \) compared with age-matched wild-type C57BL/6J controls. As the CCK2RKO and wild-type C57BL/6J mice matured, the concentrations of DMT-1 mRNA decreased significantly \( (P < 0.001) \) by 32-fold and 6.5-fold, respectively, and no difference was observed between the CCK2RKO and wild-type mice at maturity (Fig. 2B).

**Ferritin concentration in the plasma of gastrin mutant mice.** In the absence of inflammation, the concentration of ferritin in the circulation is a reliable measure of body iron stores. Measurement of plasma ferritin concentrations revealed no significant difference between the GasKO and the wild-type Balb/c mice in any of the age groups studied (Fig. 3A) although values were lower in the wild-type mice. In contrast, in the juvenile CCK2RKO mice, ferritin concentrations were reduced by 0.23-fold \( (P < 0.01) \) compared with the wild-type C57BL/6J mice (Fig. 3B). No significant differences were observed in mature mice.

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increase in hepatic iron stores, hepatic iron was also measured. Juvenile and mature GasKO mice have similar hepatic iron stores to age-matched wild-type Balb/c mice (Fig. 5A). In addition, hepatic iron concentrations did not change with age in either strain. In CCK2KO mice, although no difference in hepatic iron was found at 4 wk, at 10 wk the hepatic iron stores were increased by twofold ($P < 0.05$) compared with age-matched wild-type C57BL/6J mice (Fig. 5B).

Expression of hepcidin mRNA in the livers of gastrin-modified mice. Since the small antimicrobial peptide hepcidin is an important regulator of iron homeostasis, the concentrations of hepcidin mRNA in hepatic extracts were measured by quantitative real-time PCR. In juvenile GasKO mice, the concentrations of hepcidin mRNA were reduced by 0.54-fold ($P < 0.05$) compared with age-matched wild-type Balb/c mice (Fig. 6A). With increasing age the concentrations of hepcidin mRNA increased by 3.9-fold ($P < 0.001$) in GasKO and by 2.5-fold ($P < 0.05$) in wild-type Balb/c mice. In 4-wk-old CCK2KO mice, the concentrations of hepcidin mRNA were not significantly different to wild-type C57BL/6J mice. The concentrations of hepcidin mRNA increased by 4.7-fold ($P < 0.001$) in CCK2KO mice with increasing age (Fig. 6B).

Transferrin saturation in the plasma of MEN-1 patients. To investigate whether or not the connection between circulating gastrin concentrations and iron status observed in mice was also present in humans, transferrin saturation was determined in the sera from patients with MEN-1. Approximately 40% of such patients develop hypergastrinemia by age 40 as a result of enteropancreatic gastrinomas (8). In patients with a circulating Gamide concentration greater than 50 pM, transferrin saturation was significantly correlated with the concentration of Gamide ($r^2 = 0.197, P = 0.021, n = 27$, Fig. 7A). This relationship was improved if the analysis was limited to patients with a circulating Gamide concentration greater than 100 pM ($r^2 = 0.543, P = 0.004, n = 13$, Fig. 7A). To eliminate the contribution to circulating Gamide concentration from bacterial infection the comparison was then restricted to *Helicobacter pylori* (*H. pylori*)-negative patients with a circulating Gamide concentration greater than 50 pM. A significant correlation was still observed for the *H. pylori*-negative patients ($r^2 = 0.485, P = 0.017, n = 11$, Fig. 7B) but not for the *H. pylori*-positive patients ($r^2 = 0.175, P = 0.106, n = 16$, data not shown). No such correlation was observed between the concentrations of serum ferritin and of Gamide (data not shown). The hypergastrinemic MEN-1 patients did not show any increase in the plasma concentrations of progastrin, Ggly, or the COOH-terminal flanking peptide of progastrin (36), and hence there was no correlation between the plasma concentrations of any of these peptides and transferrin saturation. We conclude that the correlation between the circulating Gamide concentration and transferrin saturation observed in juvenile mice is also present in humans with disturbed gastrin homeostasis.

**DISCUSSION**

Several independent lines of evidence suggest that interrelationships may exist between gastrins and iron status. First, Gamide and Ggly both bind ferric ions in vitro (7), and the interaction is essential for the biological activity of nonamidated gastrins such as Ggly (29). Second, both Gamide (22) and Ggly (S. Kovac, unpublished data) bind to the iron-transport protein transferrin. Third, our in vivo data demonstrate that circulating Gamide and Ggly concentrations are increased in hemochromatotic mice and humans (35). Fourth, a microarray comparison of
gastric gene expression profiles has revealed that the concentration of gastrin hepcidin mRNA in gastrin-knockout mice is only 40% of the value in wild-type mice and that the hepcidin mRNA concentration returns to 150% of the wild-type value after subcutaneous infusion of Gamide for 1 wk (17). The aim of the present paper was therefore to test the hypothesis that gastrins and iron status are interrelated by measurement of iron homeostasis in mice and humans with abnormal circulating gastrin concentrations.

The relationship between circulating gastrin concentrations and iron uptake is not clear cut, perhaps because of the confounding effects of changes in acid secretion. Both the absorption of radioactive iron and DMT-1 mRNA expression are dramatically increased in juvenile GasKO mice compared with wild-type mice. Since basal acid output is abolished in GasKO mice (KO, undetectable; wild-type, 36 ± 3.3 meq/h) (26). This residual acid secretion is presumably sufficient to maintain the higher rate of iron absorption observed in wild-type C57BL/6J mice compared with Balb/c mice. Nevertheless, the significant reduction in serum ferritin and the significant upregulation of DMT-1 mRNA expression suggest that juvenile CCK2RKO mice are iron deficient.

There is no obligatory relationship between acid secretion and iron status. For example, in humans absorption of dietary iron is reduced after reduction of acid secretion by vagotomy (23) or by treatment with the histidine H2 receptor antagonist cimetidine (34). However, long-term treatment with the proton pump inhibitor omeprazole does not result in iron deficiency in humans (37) or in rats unless the animals are fed an iron-deficient diet (19).

The data in this paper further suggest that gastrins have the ability to modulate transferrin saturation. In young mice and in humans, a correlation was observed between circulating Gamide concentrations and the percentage saturation of serum transferrin. Thus serum transferrin saturation was reduced in agastremic GasKO mice at 4 wk and was increased in hypergastrinemic CCK2RKO mice at 4 wk. The increase in transferrin saturation in the CCK2RKO mice was unexpected because these mice had increased DMT-1 and reduced serum ferritin, both of which are
and that apotransferrin binds two molecules of Gamide with a 0.197, \( P = 0.021, n = 27 \). A better correlation was observed if the analysis was limited to patients with a circulating Gamide concentration greater than 100 pM (\( r^2 = 0.543, P = 0.004, n = 13 \)). B: when the analysis was restricted to \( H. pylori \)-negative patients with a circulating Gamide concentration greater than 50 pM, transferrin saturation was still significantly correlated with the concentration of Gamide (dashed line, \( r^2 = 0.485, P = 0.017, n = 11 \)). However, because of the low number of patients remaining, the correlation was no longer significant if the analysis was limited to patients with a circulating Gamide concentration greater than 100 pM (solid line, \( r^2 = 0.243, P = 0.261, n = 7 \).

Fig. 7. Transferrin saturation and serum gastrin concentration are correlated in patients with multiple endocrine neoplasia-1 (MEN-1) syndrome. The study group of 41 patients consisted of 14 men (mean age 54.4 ± 3.6 yr) and 27 women (mean age 50.8 ± 3.2 yr). A: when no allowance was made for \( Helicobacter pylori \) (\( H. pylori \)) status in the ~40% of patients with a circulating Gamide concentration greater than 50 pM (the accepted upper limit of normal), transferrin saturation was significantly correlated with the concentration of Gamide (\( r^2 = 0.197, P = 0.021, n = 27 \)). A better correlation was observed if the analysis was limited to patients with a circulating Gamide concentration greater than 100 pM (solid line, \( r^2 = 0.543, P = 0.004, n = 13 \)). B: when the analysis was restricted to \( H. pylori \)-negative patients with a circulating Gamide concentration greater than 50 pM, transferrin saturation was still significantly correlated with the concentration of Gamide (dashed line, \( r^2 = 0.485, P = 0.017, n = 11 \)). However, because of the low number of patients remaining, the correlation was no longer significant if the analysis was limited to patients with a circulating Gamide concentration greater than 100 pM (solid line, \( r^2 = 0.243, P = 0.261, n = 7 \)).

Gastrin and iron status are reciprocally related

The physiological consequences of an increased transferrin saturation are clearly seen in the mature CCK2RKO mice, which have significantly greater hepatic iron content than age matched wild-type mice. The increased iron deposition in the liver of CCK2RKO mice from 4 to 10 wk is presumably responsible for the significant increase in the expression of hepcidin mRNA in this strain over the same period. Interestingly the reduced transferrin saturation observed in juvenile GasKO mice does not appear to result in a reduction in hepatic iron content. Presumably sufficient iron is deposited in the homozygous fetal liver from the maternal circulation to tide the pups over the weaning period when their iron requirements are maximal. Although the concentrations of hepcidin mRNA were significantly decreased in juvenile GasKO mice, no differences in iron parameters were observed between mature GasKO mice and wild-type animals, presumably because iron homeostasis had stabilized and the mice were no longer iron deficient. The observed reduction in the concentration of hepatic hepcidin mRNA in GasKO mice is consistent with a previous report that the concentration of gastric hepcidin mRNA from gastrin-deficient mice is only 40% of the value in wild-type mice and that the hepcidin mRNA concentration returns to 130% of the wild-type value after subcutaneous infusion of gastrin for 1 wk (17).

Our results also shed light on the connections between iron, gastrins, and the development of CRC. The risk of CRC is up to threefold greater in patients with hemochromatosis (1, 32), and a circulating Gamide concentration above normal is associated with a 3.9-fold greater risk of developing CRC (39). We previously reported that circulating Gamide and Ggly concentrations are increased in mice and humans with hemochromatosis (35), and in animal models Ggly accelerates the development of CRC (2). The data presented herein indicate that an increased circulating Gamide and/or Ggly concentration may lead to an increased saturation of serum transferrin. The resultant increase in availability of ferric ions may also accelerate tumor growth. In conclusion, our observations establish that the link previously established between iron homeostasis and circulating gastrin concentrations (35) may also operate in the reverse direction. Thus the results presented herein demonstrate that iron status is modulated by changes in circulating gastrin concentrations. This conclusion opens new perspectives on the control of mechanisms of iron homeostasis in vivo.
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