Immune control of food intake: enteroendocrine cells are regulated by CD4⁺ T lymphocytes during small intestinal inflammation

J R McDermott, F C Leslie, M D'Amato, D G Thompson, R K Grencis, J T McLaughlin

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See end of article for authors' affiliations

Correspondence to:
Dr J T McLaughlin, GI
Sciences, CSB, Hope
Hospital, University of
Manchester, Salford M6
8HD, UK;
john.mclaughlin@
manchester.ac.uk

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Background and aims: Gastrointestinal inflammation reduces food intake but the biological mechanisms explaining suppressed feeding during inflammation are unknown. We have used a model of upper gut infection (*Trichinella spiralis* in the mouse) to study the effect of inflammation on food intake, and explored the role of a key enteroendocrine cell (EEC) in the regulation of feeding by the immune response.

Methods: Food intake of NIH mice infected with the intestinal nematode *Trichinella spiralis* was measured. Duodenal cholecystokinin (CCK) cells were counted. Plasma CCK was measured. Infected mice were treated with a specific CCK₁ receptor antagonist, and food intake reassessed. The influence of the immune response on food intake and CCK was mechanistically examined by treating mice with CD4 or mast cell neutralising antibodies. The role of the T helper 2 response was further explored in mice genetically deficient for interleukin (IL)-4, IL-13, or IL-4R α (receptor α subunit).

Results: Food intake of infected mice was significantly reduced at the temporal peak of intestinal inflammation. CCK expressing EEC were upregulated in infected mice, and plasma CCK levels were increased. A CCK₁ receptor antagonist restored the food intake of infected mice to a significant degree. Furthermore, suppression of food intake was completely abolished in the absence of CD4⁺ T lymphocytes or IL-4R α .

Conclusions: The data show for the first time that intestinal inflammation results in reduced food intake due to upregulation of CCK. Moreover, following infection, food intake and CCK expressing cells are under the specific control of CD4⁺ T-cells, via release of IL-4 and IL-13.

Inflammatory episodes in the intestine are strongly associated with reduced food intake,^{1–3} an important clinical issue with major nutritional consequences. Surprisingly, the physiological and cellular mechanisms that underpin this hypophagic response remain obscure.

In the short term control of normal food intake, the proximal small intestine is the key sensory region of the gut. Neuroendocrine factors are released from epithelial enteroendocrine cells (EEC) in direct response to luminal nutrients,⁴ and activate vagal afferent neurones inputting to feeding control centres in the brain. EEC, along with enterocytes, goblet cells, and Paneth cells, are derived from crypt stem cells. Differentiation into the EEC pathway is a highly regulated lineage commitment decision followed by a minority of cells (~1% of total), and crucially dependent on expression of several transcription factors.^{5–7} Cholecystokinin (CCK) is a key regulatory peptide secreted by a subset of predominantly duodenal EEC during eating to coordinate pancreatobiliary secretomotor responses, but which also induces satiety and limits ingested meal size. In large part these effects are achieved via a delay in gastric emptying.⁸

A role of EEC in reducing food intake during intestinal disease episodes has not been investigated. In a proof of concept study, we have recently shown that plasma CCK levels are raised in symptomatic humans with a common small bowel infection, *Giardiasis*.⁹ This returned to normal once the infection resolved. To explore this link mechanistically, we have now employed a mouse model of small intestinal infection, the nematode parasite *Trichinella spiralis*, in order to investigate the role and function of CCK during small intestinal inflammation. This infection invokes a marked but transient inflammatory response, characterised by influx of T cells,¹⁰ mast cells,¹¹ and eosinophils.¹² Intestinal

parasite expulsion is mast cell and T cell dependent, and in the absence of either cell type parasite expulsion is delayed.^{10–13} *T spiralis* evokes a Th2 dominated inflammatory response in which interleukin (IL)-4 and IL-13 are pivotal.^{15–16} This infection is also usefully characterised by a delayed wave of secondary inflammation when the parasite invades skeletal muscle. This represents a valuable internal control of extraintestinal inflammation induced by the same biological agent.

Using this model we have identified and characterised a novel aspect of intestinal immunoregulation, showing for the first time that Th2 cytokines mediate the control of food intake via altered EEC function during local inflammatory responses.

METHODS

Mice and infection

NIH and BALB/c mice were purchased from Harlan Olac (Bicester, UK). IL-13, IL-4, and IL-4R α (receptor α subunit) deficient mice were generated as previously described.^{17–19} Mice were maintained under pathogen free conditions. Experiments obeyed the regulations of the UK Home Office Scientific Procedures Act (1986). Male mice (aged 6–8 weeks) were infected with *T spiralis* larvae by oral gavage of 300 larvae (day 0).

Food intake, and stomach and body weight

Chow (B and K, Hull, UK) was repeatedly weighed. The daily amount consumed per mouse was derived. Mice were weighed on day 0 and on day 9 post infection. In some, the

Abbreviations: CCK, cholecystokinin; 5-HT, 5-hydroxytryptamine; EEC, enteroendocrine cell; IL, interleukin; VCU, villus-crypt unit

stomach was removed whole and weighed. Small intestines were removed to recover and count parasites.

Immunohistochemistry

Duodena were removed and immediately fixed in 4% paraformaldehyde for one hour before transfer to 20% sucrose solution for a further four hours. Fixed tissues were frozen in liquid nitrogen cooled isopentane and 5 µm transverse sections cut and attached to polylysine coated glass slides. Sections were passed through graded 50% and 75% ethanol before blocking with 10% donkey serum (Jackson ImmunoResearch, Westgrove, Pennsylvania, USA) and then incubated with rabbit polyclonal anti-proCCK antibody L421 (kind gift from Dr Andrea Varro, University of Liverpool, UK) or anti-5-hydroxytryptamine (5-HT) (Sigma Chemical Co, St Louis, Missouri, USA) for 90 minutes at room temperature or overnight at 4°C. Following washing, sections were incubated with Alexafluor 594 goat antirabbit antibody (Molecular Probes, Oregon, USA) for 60 minutes at room temperature and mounted (Vectashield, Vector Labs, Peterborough, UK). Slides were examined on a Zeiss Axioplan 2 microscope and positive cells counted. Results are expressed as fluorescent (CCK positive) cells per 15 villus-crypt units (VCU).

CCK radioimmunoassay

Plasma CCK was determined using a commercially available kit (Euro-Diagnostica, Malmo, Sweden).

CCK₁ antagonism

Mice were injected once, intraperitoneally at 18:00 (to coincide with the predominantly nocturnal feeding pattern) on day 9 with either sterile distilled water or the CCK₁ receptor antagonist loxiglumide 20 mg/kg (Rotta Research Laboratorium, Monza, Italy). In a small pilot study, loxiglumide was shown not to affect overnight food intake in mice not infected with a parasite. The amount of food consumed overnight was calculated. A subset of animals was later retreated with loxiglumide or a control injection on day 22 post infection, long after the enteritis had resolved.

Antibody neutralisation of candidate cellular mediators

NIH mice were treated with an anti-CD4 antibody derived from rat hybridoma YTS 191. Infected mice received 0.5 mg anti-CD4 intraperitoneally on days -1, 1, 3, 5, and 7 post infection. Control infected mice were simultaneously administered 0.5 mg non-specific rat IgG (Sigma, UK). Similar experiments were performed using an anti-c-kit antibody, which prevents the pronounced mastocytosis observed following infection with *T. spiralis*.^{13 14}

Figure 1 Effect of infection on feeding. Food intake was measured following *Trichinella spiralis* infection. Points represent the mean (SEM) of 4 mice/group from at least three independent experiments. ** $p < 0.01$.

Figure 2 Effect of infection on enteroendocrine cells. Duodenal cholecystokinin (CCK) cells (A) significantly increased in number during the course of infection, as did duodenal 5-hydroxytryptamine (5-HT) cells (B). Data are mean (SEM) of 4 mice/group, from at least three independent experiments. * $p < 0.05$. VCU, villus-crypt unit.

Results are expressed as mean (SEM). The Student's *t* test or the Mann U Whitney test was used to assess statistical significance, as appropriate. A value of $p < 0.05$ was deemed significant.

RESULTS

Small intestinal inflammation induces hypophagia

NIH mice were infected with *T. spiralis* and food intake was measured over the subsequent 30 days (fig 1). Infected mice became hypophagic by day 7 post infection, eating least on day 9 post infection, and then returned to normal. Day 9 post infection corresponded to the peak of intestinal inflammation.^{10 13 20} These events were associated with effective expulsion of worms from the intestine by day 9 post infection (0.8 (0.5) worms/mouse on day 9, compared with 82.5 (9.4) on day 6; $n = 4$). Body weight was also markedly reduced by day 9 post infection, infected mice losing 1.8 (0.1) g from day 0. In contrast, uninfected mice gained 1.5 (0.1) g over the matched time period. Total gastric weights were lower in infected animals (naïve 0.71 (0.1) g/mouse; infected 0.48 (0.05) g/mouse; $p < 0.05$). This supports a direct inhibitory effect on feeding, rather than simple limiting of food intake secondary to a delay in gastric emptying.

At day 25 post infection, a second fall in food intake was observed (fig 1), despite resolution of epithelial inflammation.^{10 13 20} This is when *T. spiralis* larvae encyst in skeletal muscle, representing an extraintestinal inflammatory response to the same biological agent.²¹

CCK cell numbers and secretion are increased during intestinal inflammation

Numbers of duodenal CCK cells increased (fig 2A), again peaking on day 9 post infection. By day 20, CCK cell numbers had returned to naïve or pre-infected levels. Plasma CCK immunoreactivity was also elevated at this time point (naïve 1.1 (0.3) pM *v* infected 4 (0.4) pM). This was not confined to CCK cells: serotonin staining enterochromaffin cells were similarly increased in number (fig 2B).

Figure 3 Effect of a cholecystikinin (CCK) antagonist on feeding, during and after small intestinal inflammation. Five groups of 3–4 infected mice were treated with either sterile water or the CCK₁ receptor antagonist loxiglumide intraperitoneally. Feeding was measured 15 hours later. Control mice, but not loxiglumide treated mice on day 9 post infection, consumed significantly less than naïve animals. * $p < 0.05$ versus naïve day 9 animals.

Inhibition of CCK₁ receptors improves food intake of infected mice

A single treatment with the antagonist loxiglumide produced significant, although not complete, restoration of food intake in parasitised animals (fig 3), which was recorded over a 15 hour period overnight from day 9 post infection. Gastric weights were also increased on the morning following loxiglumide (0.32 (0.1) g/mouse, loxiglumide v 0.25 (0.01) g/mouse, control), suggesting a dominant effect of improving food intake via satiety and appetite mechanisms, rather than a purely gastropromkinetic effect of loxiglumide.

Interestingly, in contrast, inhibition of CCK₁ receptors had no effect on feeding on day 22 post infection, the time point corresponding to the beginning of the second wave of hypophagia when *T. spiralis* larvae encyst extraintestinally in skeletal muscle (naïve 3.4 (0) g/mouse/15 hours; infected, saline intraperitoneally 2.4 (0.03) g/mouse/15 hours; infected, loxiglumide 1.6 (0.10) g/mouse/15 hours). This indicates that CCK directly contributes to intestinal inflammation induced hypophagia but that it does not mediate the hypophagia observed at this later extraintestinal inflammatory stage.

Feeding and CCK cells are under the control of CD4⁺ T cells but not mast cells during inflammation

CD4⁺ T cells play a decisive role in the resolution of intestinal infections. In the absence of functional CD4⁺ T cells, resolution of *T. spiralis* infection was significantly delayed (fig 4A). The antibody had no intrinsic effect on food intake in a pilot study in uninfected mice (data not shown). Infected mice treated with non-specific IgG were hypophagic as before (fig 4B). The hypophagic effect was completely abolished in infected mice treated with CD4 neutralising antibodies. Gastric weights were also increased by anti-CD4 (0.60 (0.07) g/mouse v 0.48 (0.05) g/mouse with control IgG).

In parallel, administration of CD4 neutralising antibodies significantly inhibited the increase in CCK expressing cells in the duodenum of infected animals (naïve mice 3.8 (1.0) cells/15 VCU, increasing in infected mice treated with IgG to 6.6 (1.5) but not in infected mice treated with α CD4, 4.3 (0.5)) (fig 4C), and attenuated the rise in plasma CCK (1.5 (0.5) pM at day 9 compared with 3.3 (0.1) following control IgG).

Efficient resolution of *T. spiralis* infection is also dependent on mast cells (also under the control of CD4⁺ T cells), which can curiously degranulate in response to CCK.²² Anti-*c-kit* antibodies abrogate mucosal mastocytosis but leave the T cell response intact.¹⁴ Food intake reduced after anti-*c-kit* treatment, as in previous groups of infected animals (to 2.76 (0.21) g/mouse/day, anti-*c-kit* v 2.34 (1.04) g/mouse/day,

Figure 4 The role of CD4 T cells in controlling food intake during small intestinal inflammation. Naïve and infected mice received repeated doses of neutralising CD4 antibody or rat IgG (control) intraperitoneally. Two independent experiments were undertaken, with 4 mice/group. (A) Mice treated with α CD4 failed to expel their parasites by day 9 post infection. ** $p < 0.002$. (B) However, their food intake remained comparable with naïve mice. * $p < 0.05$. (C) Infected mice treated with control IgG had significantly more cholecystikinin (CCK)⁺ cells/15 villus-crypt units (VCU) than naïve or α CD4 treated infected mice. ** $p < 0.01$.

control IgG). Anti-*c-kit* treatment was effective as worm burdens on day 8 were appropriately increased by anti-*c-kit* antibody (147.3 (15.0) compared with 66.0 (5.4) after control IgG; $p = 0.006$).

Inflammation induced T cell cytokines regulate food intake

T. spiralis induces strong Th2-type cytokine responses in the intestine. Given that CD4⁺ T cells mediated food intake and CCK⁺ cell hyperplasia in parasitised mice, we sought to investigate the influence of IL-4 and IL-13 on these parameters. Mice genetically deficient for IL-4, IL-13, or IL-4R α were infected, and food intake again measured during the course of infection. There was no significant difference in food intake between infected wild-type mice or IL-4 or IL-13 deficient mice (fig 5A). In the absence of IL-4R α however, infection induced hypophagia was fully abolished. IL-4 and IL-13 deficient mice lost less body weight over the course of infection compared with wild-type animals, and this effect was again completely abolished in IL-4R α deficient mice

Figure 5 The role of Th2 cytokines in controlling food intake during small intestinal inflammation. Wild-type (WT), interleukin (IL)-4^{-/-}, IL-13^{-/-}, and IL-4R α ^{-/-} (receptor α subunit) mice were infected with *Trichinella spiralis*. On day 9 post infection, food intake of infected IL-4^{-/-}, IL-13^{-/-}, and wild-type mice was again reduced compared with IL-4R α ^{-/-} mice, which consumed the same as naive mice (A). Weight loss was reduced in infected IL-4^{-/-} and IL-13^{-/-} wild-type mice and abolished in infected IL-4R α ^{-/-} mice on day 9 post infection (B). Histograms represent the mean (SEM) of 4 mice/group from two independent experiments.

(fig 5B). These results demonstrate that either IL-4 or IL-13 can influence nutritional parameters during inflammation, and only in the functional absence of both cytokines together is this signal abolished. IL-4 and IL-13 exhibit some mutual redundancy, but both converge to signal via the IL-4R α subunit.²³

DISCUSSION

Given the adverse nutritional consequences of gut inflammation widely observed in clinical practice, elucidation of specific molecular pathways causally linking inflammation to reduced nutrient intake would be of fundamental importance, particularly if accessible to existing therapeutic agents. Much recent physiological research has focused on the role of EEC factors in the short term regulation of food intake in health, with evidence available from both human and animal models. The brain-gut axis peptide CCK has received the most attention; its physiological role in the control of food intake is widely accepted. CCK is most highly expressed in the duodenum which bears the most nutrient chemosensitive epithelium gut. CCK is believed to influence meal size, in part via a delay in gastric emptying rate, and in part via direct signals to brain feeding centres.^{8 24 25}

However, the possibility that increased CCK release is mechanistically implicated in inflammatory gut diseases associated with reduced food intake has not been explored.

In a preliminary study, we recently demonstrated that humans with upper gut infections, such as *Giardia lamblia*, have elevated circulating plasma CCK concentrations during infection, and that this returns to normal afterwards.⁹ This raised the possibility that hyperCCKaemia may causally

account for some of the observed symptoms, such as anorexia. In keeping with this, it is well established that intravenous infusion of high dose CCK to healthy humans induces similar symptoms.²⁶

Mice infected with the nematode parasite, *T. spiralis*, present a powerful model in which to dissect the molecular mechanisms operating in small bowel inflammation, including those underpinning reduced food intake. This model has three key advantages. Firstly, the inflammation is transient and reproducible, and most marked in the key region of interest, the upper small intestinal mucosa. Secondly, the regulatory cell types and cytokines elicited in response to this parasite are very well characterised, and amenable to intervention, including immunoneutralisation and transgenics. Thirdly, the biphasic nature presents an internal control, with a delayed extraintestinal inflammatory phase.

As previously documented, infection causes initial proximal enteritis which peaks at around days 9–10, when the parasites have just been expelled from the gut. Intestinal inflammation then resolves^{10 20}: the epithelium is functionally normalised by day 21, even by highly sensitive parameters such as epithelial permeability.¹³ However, some neuromuscular dysfunction persists after the epithelial changes have resolved,²⁰ but this continues well beyond the transient hypophagia we have observed in this study. Given the degree of intestinal inflammation observed in these mice, it was unsurprising to initially demonstrate that food intake fell significantly, in a time course paralleling the well documented inflammatory response described above. However, this basic observation had not been reported previously. Our study confirms that the *T. spiralis* parasitised mouse presents a tractable model to identify the biological effectors responsible.

Increased CCK cell numbers were evident from day 6 post infection, despite villus atrophy. This increase is absolute since the data are normalised to a numeric sample of crypt-villus functional units. CCK cells clearly remain functional as plasma CCK concentration is elevated fourfold. This can be directly linked to reduced food intake as this is partially abrogated by the specific CCK antagonist loxiglumide. Failure of loxiglumide to reverse the second phase of hypophagia, when skeletal muscle inflammation is active, is also of importance in confirming a specific mechanism of hypophagia in gut centred inflammation. This demonstrates that the CCK-immune interaction is in large part mediated locally, in the intestinal epithelium, rather than representing a purely systemic effect, for example via circulating hypercytokinaemia. Loxiglumide is in phase III clinical trials for functional human gastrointestinal disorders, but has not yet been evaluated in the context of inflammatory disease or of nutritional status.

As crypts are the stable niche for the stem cells which populate all four cell lineages in daughter villi, the data suggest a shift in lineage differentiation commitment. Given that both goblet cells and Paneth cells are increased in this model,^{10 27} the data suggest a shift in lineage differentiation commitment: from absorptive to secretory cell types. The transcription factor Math 1 has been reported as essential to commitment to the three secretory cell types rather than enterocytes,⁷ and its role in mediating stem cell responses to inflammation now requires study. Subsequent endocrine cell differentiation is controlled by the Notch signalling pathway, neurogenin 3, pax 4, and pax 6.⁶ Factors governing final differentiation to a CCK cell are not yet known. The lag of six days before the CCK cell count increases is in keeping with the time course of epithelial cell turnover, which has been estimated at 3–4 days by kinetic studies.²⁸ This rapid cell turnover probably also underpins the transient effect on EEC, unlike the neuromuscular changes which persist for months²⁰

in these subepithelial cells of far greater longevity. The lag also suggests that it is necessary for the inflammatory response to be activated before cell lineage commitment is altered, rather than representing a direct effect of the parasite. It will be interesting to ascertain whether CCK cells have become hypersecretory basally, hyperfunctional only in response to nutrient exposure, or whether the increased plasma level purely mirrors increased cell numbers. However, pure primary EEC preparations to answer these questions cannot be obtained at present.

The role of the immune system we have now characterised is novel. A single previous report showed that orally administered glucocorticoids reduced hypophagia in nematode infected rats.²⁹ However, corticosteroids are intrinsically highly orexigenic and thus do not allow discrimination between this property and their immunosuppressive effects. We adopted a more specific approach, investigating the role of CD4⁺ T cells on infection induced hypophagia and CCK expression by treating infected animals with CD4 neutralising antibodies. In the absence of functional CD4⁺ T cells, inflammation was much reduced and resolution of *T. spiralis* infection was significantly delayed. Infected mice treated with non-specific IgG were hypophagic but, strikingly, this was completely abolished in infected mice treated with CD4 neutralising antibodies. Indeed, eating proceeded normally despite a very large worm burden. CD4 neutralising antibody had no independent effect on food intake in uninfected mice.

We have demonstrated that CD4⁺ T lymphocytes are as pivotal to the enteroendocrine and hypophagic response as they are to worm clearance. This functional coupling via a single effector cell type suggests that the EEC-CD4 cell pathway represents an innate immunoregulatory role, rather than an aberrant response. IL-4R α has a pivotal role here, and is activated by both IL-4 and IL-13: hence the redundancy observed when either cytokine is absent alone.²³ The current model is at present most relevant to events coupled to a predominantly Th2 type immune response. However, it is likely that other inflammatory mediators are coupled to EEC biology. For example, T cell receptor alpha chain knockout mice have reduced EEC numbers in the colon,³⁰ suggesting that this interaction may be constitutively important in health for epithelial cell differentiation, or in the response to endogenous bacterial flora. Gnotobiotic animals have been shown to have reduced EEC numbers, which increase when recolonised with flora.³¹

It is also clear that this effect is not restricted to CCK cells: enterochromaffin cells were increased in number in parallel. Secretion of 5-HT by human enterochromaffin cells is linked to induction of nausea and vomiting in a variety of situations, particularly in chemotherapy and postoperative patients.³² Mice are not able to vomit, but the presence of nausea contributing to the reduction in food intake is highly plausible. This aversive sensation may in part be mediated via enterochromaffin 5-HT hypersecretion. 5-HT is also implicated in diarrhoea in some infections and in functional gastrointestinal disorders.³²⁻³³ Normal faecal pellets are still observed in our model, but with additional looser and mucoid material present in the cage, all observed for a few days at the time of peak inflammation. This may indeed be partly due to 5-HT hypersecretion, but difficult to unravel in the presence of an inflammatory enteropathy, villus atrophy with probable malabsorption, enhanced smooth muscle contractility, and increased mucus secretion due to goblet cell hyperplasia. However, mast cells infiltrate the gut in this model, and murine mast cells are also an abundant source of 5-HT. In addition, the amine operates at multiple receptor subtypes, so it is not tractable to pharmacologically unravel these confounding factors. It will be interesting to discover whether all EEC lineages are affected in parallel, as seems likely given

the general secretory switch to include increased goblet and Paneth cells,²⁷ or only a restricted subset.

An immunoregulatory role of EEC may have short term advantages, such as reduced energy expenditure and avoidance of ingestion of contaminated feed sources. CCK may have additional defensive roles, such as increased mucosal immunoglobulin secretion³⁴ and enhanced mucosal blood flow.³⁵ If trial therapeutic interventions with CCK₁ antagonists were undertaken for anorexia triggered by gut inflammation, the possibility of adverse outcomes must therefore be considered. However, this must be balanced against possible additional beneficial effects of CCK₁ antagonists, particularly in the presence of infection. For example, gut propulsion is accelerated by CCK₁ antagonism,³⁶ and could contribute to a faster elimination of parasites or other pathogens. There is evidence that other EEC products, such as GLP-2, are restitutive to damaged epithelia,³⁷ and studies are planned to assess other EEC lineages in this model.

However, beyond initial short term adaptive responses, ongoing inflammation may prove counterproductive to the health of the host organism. It would be detrimental to nutritional status if food intake remained suppressed. This may be of considerable importance when considering the prevalence of intestinal nematode infection in humans³⁸⁻³⁹ and, indeed, in domestic stock⁴⁰ where food intake and weight gain have economic implications in addition to health considerations. Conversely, subverting the molecular basis of this immunoregulatory pathway would present a novel therapeutic target for purposefully increasing satiety, thereby impairing food intake and inducing weight loss.

In summary, we have discovered and characterised for the first time an important aspect of enteric immunoregulation. We have shown that the reduction in food intake during small intestinal inflammation is linked to an increase in CCK expressing EEC, and under the control of IL-4 and IL-13 secreting CD4⁺ T cells.

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Authors' affiliations

J R McDermott, R K Grencis, Faculty of Life Sciences, University of Manchester, Manchester, UK
F C Leslie, D G Thompson, J T McLaughlin, Gastrointestinal Sciences, University of Manchester, Manchester, UK
M D'Amato, Rotta Research Laboratorium, Monza, Italy

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REFERENCES

- 1 Rigaud D, Angel LA, Cerf M, et al. Mechanisms of decreased food intake during weight loss in adult Crohn's disease patients without obvious malabsorption. *J Clin Nutr* 1994;**60**:775-81.
- 2 Gee MI, Grace MG, Wensel RH, et al. Protein-energy malnutrition in gastroenterology outpatients: increased risk in Crohn's disease. *J Am Diet Assoc* 1985;**85**:1466-74.
- 3 McHugh K, Castonguay TW, Collins SM, et al. Characterization of suppression of food intake following acute colon inflammation in the rat. *Am J Physiol Gastrointest Liver Physiol* 1993;**265**:R1001-5.
- 4 Best L, McLaughlin JT. 2005. Nutrients as regulators of endocrine and neuroendocrine secretion. *Top Curr Genet* 2004;**7**:79-111.
- 5 Jenny M, Uhl C, Roche C, et al. Neurogenin3 is differentially required for endocrine cell fate specification in the intestinal and gastric epithelium. *EMBO J* 2002;**21**:6338-47.
- 6 Schonhoff SE, Giel-Moloney M, Leiter AB. Minireview: development and differentiation of gut endocrine cells. *Endocrinology* 2004;**145**:2639-44.
- 7 Yang Q, Bermingham NA, Finegold MJ, et al. Requirement of Math1 for secretory cell lineage commitment in the mouse intestine. *Science* 2001;**294**:2155-8.

- 8 Lal S, McLaughlin J, Barlow J, *et al.* Cholecystokinin pathways modulate sensations induced by gastric distension in man. *Am J Physiol Gastrointest Liver Physiol* 2004;**287**:G72–9.
- 9 Leslie FC, Thompson DG, McLaughlin JT, *et al.* Plasma cholecystokinin concentrations are elevated in acute upper gastrointestinal infections. *Q J Med* 2003;**96**:870–1.
- 10 Garside P, Grecis RK, Mowat AM. T lymphocyte dependent enteropathy in murine *Trichinella spiralis* infection. *Parasite Immunol* 1992;**14**:217–25.
- 11 Alizadeh H, Murrell KD. The intestinal mast cell response to *Trichinella spiralis* infection in mast cell-deficient w/wv mice. *J Parasitol* 1984;**70**:767–73.
- 12 Lammas DA, Wakelin D, Mitchell LA, *et al.* Genetic influences upon eosinophilia and resistance in mice infected with *Trichinella spiralis*. *Parasitology* 1992;**105**:117–24.
- 13 McDermott JR, Bartram RE, Knight PA, *et al.* Mast cells disrupt epithelial barrier function during enteric nematode infection. *Proc Natl Acad Sci U S A* 2003;**100**:7761–6.
- 14 Donaldson LE, Schmitt E, Huntley JF, *et al.* A critical role for stem cell factor and *c-kit* in host protective immunity to an intestinal helminth. *Int Immunol* 1996;**8**:559–67.
- 15 Grecis RK, Hultner L, Else KJ. Host protective immunity to *Trichinella spiralis* in mice: activation of Th cell subsets and lymphokine secretion in mice expressing different response phenotypes. *Immunology* 1991;**74**:329–32.
- 16 Urban JF Jr, Schopf L, Morris SC, *et al.* Stat 6 signaling promotes protective immunity against *Trichinella spiralis* through a mast cell- and T cell-dependent mechanism. *J Immunol* 2000;**164**:2046–52.
- 17 Mohrs M, Ledermann B, Köhler G, *et al.* Differences between IL-4- and IL-4 receptor-deficient mice in chronic leishmaniasis reveal a protective role for IL-13 receptor signalling. *J Immunol* 1999;**162**:7302–8.
- 18 Noben-Trauth N, Kropf P, Müller I. Susceptibility to *Leishmania* major infection in interleukin-4-deficient mice. *Science* 1996;**271**:987–90.
- 19 McKenzie GJ, Bancroft A, Grecis RK, *et al.* A distinct role for interleukin-13 in Th2-cell-mediated immune responses. *Curr Biol* 1998;**8**:339–42.
- 20 Barbara G, Vallance BA, Collins SM. Persistent intestinal neuromuscular dysfunction after acute nematode infection in mice. *Gastroenterology* 1997;**113**:1224–32.
- 21 Ko RC, Fan L, Lee DL, *et al.* Changes in host muscles induced by excretory/secretory products of larval *Trichinella spiralis* and *Trichinella pseudospiralis*. *Parasitology* 1994;**108**:195–205.
- 22 Juanola C, Giral M, Jimenez M, *et al.* Mucosal mast cells are involved in CCK disruption of MMC in the rat intestine. *Am J Physiol Gastrointest Liver Physiol* 1998;**275**:G63–7.
- 23 Hershey GK. IL-13 receptors and signaling pathways: an evolving web. *J Allergy Clin Immunol* 2003;**111**:677–90.
- 24 Moran TH, Kinzig KP. Gastrointestinal satiety signals II. Cholecystokinin. *Am J Physiol Gastrointest Liver Physiol* 2004;**286**:G183–8.
- 25 Zittel TT, Glatzle J, Kreis ME, *et al.* c-fos protein expression in the nucleus of the solitary tract correlates with cholecystokinin dose injected and food intake in rats. *Brain Res* 1999;**846**:1–11.
- 26 Chua AS, Bekkering M, Rovati LC, *et al.* Clinical efficacy and prokinetic effect of the CCK-A antagonist lorglumide in nonulcer dyspepsia. *Ann N Y Acad Sci* 1994;**713**:451–3.
- 27 Kamal M, Wakelin D, Ouellette AJ, *et al.* Mucosal T cells regulate Paneth and intermediate cell numbers in the small intestine of *T. spiralis*-infected mice. *Clin Exp Immunol* 2001;**126**:117–25.
- 28 Cheng H, Leblond CP. Origin, differentiation and renewal of the four main epithelial cell types in the mouse small intestine. III. Entero-endocrine cells. *Am J Anat* 1974;**141**:503–19.
- 29 Faro CJ, Reidelberger RD, Palmer JM. Suppression of food intake is linked to enteric inflammation in nematode-infected rats. *Am J Physiol Regul Integr Comp Physiol* 2000;**278**:R118–24.
- 30 Rubin DC, Zhang H, Qian P, *et al.* Altered enteroendocrine cell expression in T cell receptor alpha chain knock-out mice. *Microsc Res Tech* 2000;**51**:112–20.
- 31 Sharma R, Schumacher U. The diet and gut microflora influence the distribution of enteroendocrine cells in the rat intestine. *Experientia* 1996;**52**:664–70.
- 32 Gershon M. Review article: serotonin receptors and transporters—roles in normal and abnormal gastrointestinal motility. *Aliment Pharmacol Ther* 2004;**20**(suppl 7):3–14.
- 33 Spiller R. Effects of serotonin on intestinal secretion and motility. *Current Opin Gastroenterol* 2001;**17**:99–103.
- 34 Freier S, Eran M, Alon Y, *et al.* Verapamil and furosemide prevent cholecystokinin-induced translocation of immunoglobulins in rat intestine. *Dig Dis Sci* 1991;**36**:1619–24.
- 35 Rozsa Z, Varro V. Mechanism of action of cholecystokinin on intestinal blood flow; interactions with opioid peptides and vasoactive intestinal peptide. *Neuropeptides* 1985;**6**:71–81.
- 36 Meyer BM, Werth BA, Beglinger C, *et al.* Role of cholecystokinin in regulation of gastrointestinal motor functions. *Lancet* 1989;**2**:12–15.
- 37 Drucker DJ, Lovshin J, Baggio L, *et al.* New developments in the biology of the glucagon-like peptides GLP-1 and GLP-2. *Ann N Y Acad Sci* 2000;**921**:226–32.
- 38 Chan MS. The global burden of intestinal nematodes—50 years on. *Parasitol Today* 1997;**13**:438–43.
- 39 Montessoro A, Crompton DW, Gyorkos TW, *et al.* *Helminth control in school age children. A guide for managers of control programmes.* Geneva: WHO, 2002.
- 40 Newton SE, Munn EA. The development of vaccines against gastrointestinal nematode infections, particularly *Haemonchus contortus*. *Parasitol Today* 1999;**15**:116–22.

EDITOR'S QUIZ: GI SNAPSHOT

Answer

From question on page 443

The clue to the diagnosis in this case was provided by video capsule endoscopy. Apart from a very fast gastric emptying time of five minutes and rapid passage through the small bowel (82 minutes), video capsule endoscopy revealed 17 polyps starting from the second part of the jejunum. By open surgical procedure we resected 110 cm of small bowel. All polyps in the resection specimen were histologically proven lipomas. The operation resulted in complete recovery of the patient.

Lipomas are often asymptomatic incidental findings but they also can lead to intestinal obstruction causing an acute abdominal emergency. Small bowel lipomatosis to the extent present in our case is an extremely rare condition.

Abdominal computed tomography detected several intraluminal structures with a density characteristic of fat. However, capsule video images displayed more polyps and allowed us to suspect their submucosal origin and the extent of the polyposis.

Our case indicates that in patients with symptoms suggestive of recurrent intestinal pain of unknown origin, small bowel polyposis should be considered in the differential diagnosis.

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