

Discuss the hormones secreted by the stomach

The hormones secreted by the stomach have two major roles; acid secretion and appetite control. This essay will discuss both roles in turn.

An introduction to acid secretion

Gastric acid is secreted from parietal cells in the corpus of the stomach (Martinsen *et al*, 2005) under the regulation of gastrin, histamine, acetylcholine and somatostatin. Gastric acid is important for denaturing proteins which are then broken down by pepsin (Waldum *et al*, 2014), and for the destruction of ingested microorganisms (Martinsen *et al*, 2005).

Regulation of acid secretion

Gastrin, histamine and acetylcholine are stimulators of gastric acid secretion, whereas somatostatin is a gastric acid inhibitor (Lindström & Håkanson, 2001). Gastrin is secreted from G cells in the antrum of the stomach (Choi *et al*, 2013) in response to food intake, which triggers excitation of the vagus nerve and acetylcholine secretion (Norlén *et al*, 2005). Acetylcholine activates the M3 receptors on G cells to initiate gastrin release (Bitziou & Patel, 2012). Gastrin stimulates histamine secretion from the enterochromaffin-like cells (ECL) via cholecystokinin-2 (CCK2) receptors on the ECL surface membrane (Bitziou & Patel, 2012). Histamine then activates the H2 receptor on the parietal cells, resulting in gastric acid secretion (Bitziou & Patel, 2012). Fykse *et al* (2006) suggests that histamine travels to the parietal cell from the ECL via diffusion. Their study showed that after gastrin stimulation, there were higher concentrations of histamine in rat stomach tissue than in the blood. They indicate that their results do not reject the possibility of a vascular pathway for histamine transport, but highlight the importance of the paracrine pathway.

The link between gastrin and histamine secretion is illustrated by the effect of feed intake and vagal stimulation on the concentration of both hormones (Norlén *et al*, 2005). The study showed that food intake caused vagal excitation, which at 5 and 20 Hz, increased gastrin and histamine concentration greatly. This relationship between gastrin and histamine is further supported by the fact that gastrin receptor blockades reduced histamine concentration, indicating that gastrin is responsible for histamine secretion (Norlén *et al*, 2005).

Alternatively, **Fig. 1** illustrates that gastrin can also directly activate gastric acid secretion in the guinea pig stomach by stimulating CCK2 receptors on parietal cells. This occurs under basal conditions, when gastrin is responsible for the majority of gastric acid output (~55% compared to ~35% from histamine and ~10% from acetylcholine) (Bitziou & Patel, 2012). This study differs from most as it also looks at the output of gastric acid under basal conditions as well as under stimulated conditions. Under stimulated conditions, gastrin and histamine are responsible for ~40% of total acid secretion whereas acetylcholine is responsible for ~20% (Lloyd *et al*, 1992). The other 60% can most likely be accounted for by other factors that stimulate gastric acid secretion such as noradrenaline and neuropeptides (Norlén *et al*, 2005). Under stimulated conditions, acetylcholine from the vagus nerve directly stimulates gastric acid secretion (Bitziou *et al*, 2008) via the m3 receptors as illustrated in **Fig. 1** and **Fig. 2**. This is confirmed by stimulating acetylcholine secretion, resulting in

a significant increase in gastric acid secretion with no alteration gastrin or histamine concentration (Bitziou & Patel, 2012).

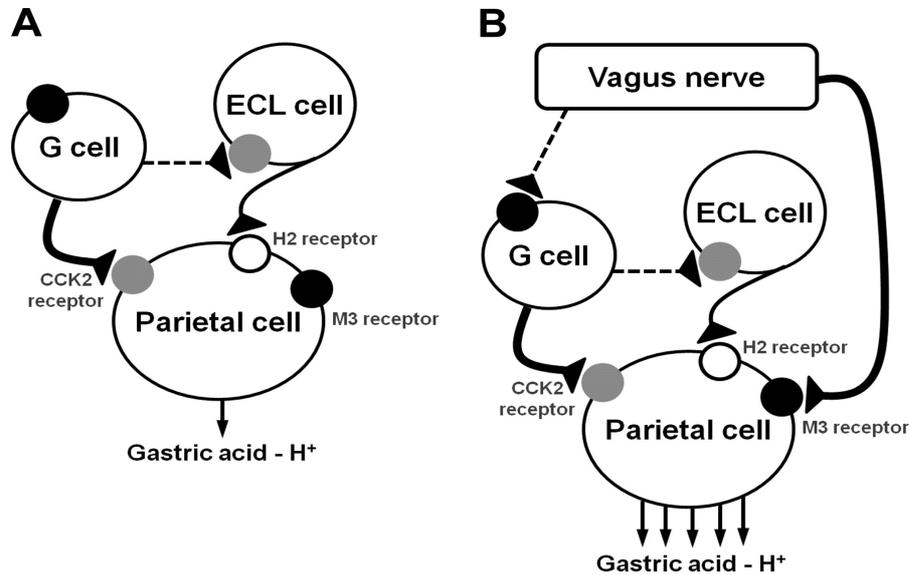


Fig. 1: A schematic diagram of the gastric acid secretion mechanism in the guinea pig stomach under basal and stimulated conditions. The solid lines show direct stimulation of the parietal cell and the dashed lines represent the indirect route to parietal stimulation. A- basal conditions, B- stimulated conditions. (Source: Bitziou & Patel, 2012).

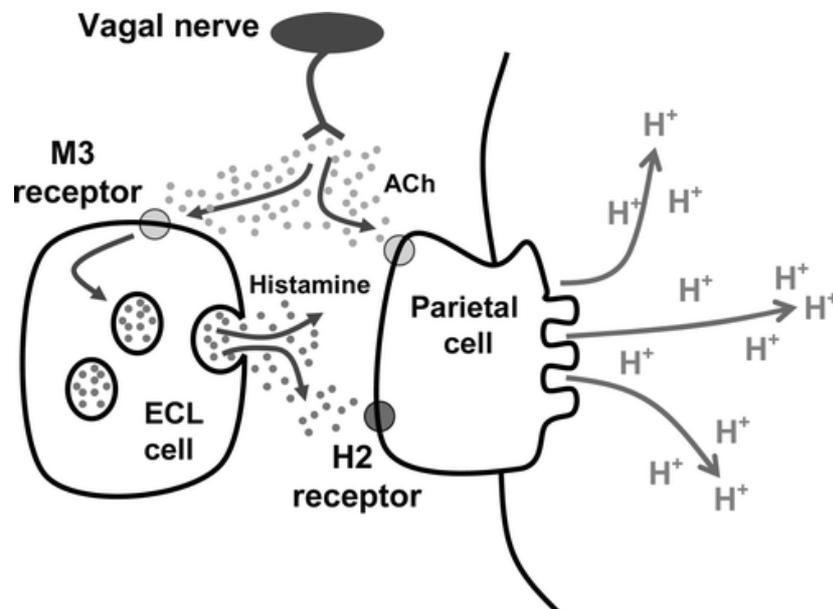


Fig. 2: A schematic diagram showing the direct and indirect stimulation of gastric acid secretion by the vagal nerve. The direct route involves stimulation of the parietal cell by acetylcholine from the vagal nerve. The indirect route involves stimulation of the M3 receptor on the enterochromaffin-like (ECL) cells by acetylcholine from the vagal nerve, resulting in histamine secretion which activates the H2 receptor on the parietal cell. (Source: Bitziou et al, 2008)

Acetylcholine has an indirect effect on histamine concentration by inhibiting the release of somatostatin (Bitziou & Patel, 2012), suggesting that somatostatin prevents gastric acid secretion by inhibiting histamine. As well as

this, somatostatin can also directly inhibit parietal cell function (Komasaka *et al*, 2002). The study showed that histamine activated acid secretion in isolated mouse stomach was inhibited, whereas acid secreted in response to direct stimulation of parietal cells was not. This suggests that the inhibition via the histamine pathway is more important than direct parietal cell inhibition.

Long term inhibition of gastric acid secretion stimulates somatostatin from D cells in the fundus mucosa of the rat stomach (Bolkent *et al*, 2001). As somatostatin is an acid inhibitor, we would expect reduced acid secretion to correlate with reduced somatostatin concentration. Despite this, Bolkent *et al* (2001) found that after treatment with omeprazole (a gastric acid inhibitor) there was an increase in somatostatin mRNA, suggesting that somatostatin secretion is regulated by stomach pH. It is important that somatostatin is sensitive to gastric pH because if the pH becomes too low there is risk of acid related diseases such as peptic ulcer or acid reflux. Older studies, e.g. Allen *et al* (1986) found no change in somatostatin concentration in response to omeprazole. Bolkent *et al* (2001) proposes that the varied results are caused by varying concentrations of omeprazole and length of treatments, which is a plausible explanation. Both studies found that omeprazole increased the concentration of gastrin, suggesting that the increase in somatostatin concentration observed by Bolkent *et al* (2001) is possibly caused by the increase in gastrin levels.

Ghrelin and obestatin control appetite

Another role of hormones secreted by the stomach is appetite control and energy regulation. This is the role of ghrelin and obestatin. Ghrelin is a 28 amino acid peptide, produced in the oxyntic glands of the stomach (Kojima *et al*, 1999). Obestatin is a 23 amino acid peptide (Lauwers *et al*, 2006) that is derived from the ghrelin gene (Zhang *et al*, 2005). Ghrelin has an orexigenic effect and so increases appetite; whereas obestatin appears to be anorexigenic and so reduces appetite (Zizzari *et al*, 2007). Fasting has been shown to raise ghrelin levels and significantly reduce obestatin levels (Zizzari *et al*, 2007). Obestatin treatment in rodents suppresses food intake, inhibits jejunal contraction and decreases weight gain (Zhang *et al*, 2005), whereas ghrelin has been found to increase food intake, weight gain and adipogenesis (Zizzari *et al*, 2007). Zizzari *et al* (2007) also explains that ghrelin upregulates the secretion of growth hormone from the anterior pituitary gland, but obestatin has no effect. Together, this evidence confirms that despite their similar origin, the two hormones have opposing effects.

Ghrelin stimulates appetite by activating the GHSR1 alpha receptor on neuropeptide Y (NPY) neurones (Zizzari *et al*, 2007). NPY neurones are involved in the increase of feed intake and fat storage. Ghrelin has been found to stimulate activity of NPY neurons and to mimic NPY neurone effect in the paraventricular nucleus of the hypothalamus (Cowley *et al*, 2003). This suggests that ghrelin stimulates appetite by causing the release of appetite stimulating neurotransmitters. Whilst much is known about the actions of ghrelin, obestatin is a newly discovered hormone and its mechanism is still debated. It has been proposed that obestatin is the ligand for the orphan G protein-coupled receptor, GPR39 (Zhang *et al*, 2005). However this has been disproven by multiple studies (e.g. Lauwers *et al* (2006) and Chartrel *et al* (2007)) that have found no significant increase in cAMP levels after following similar processes as Zhang *et al* (2005). The studies used the same receptor and ligand in the same cell line (HEK293T) for the same incubation period (16 hours) and assayed the same second

messenger (cAMP) (Lauwers *et al*, 2006). However, there was a difference in the methods of measuring cAMP concentration. Zhang *et al* (2005) used ELISA where as Lauwers *et al* (2006) used a luciferase detection system. But Lauwers *et al* (2006) persists that this would not have caused their opposing results as the luciferase system has a higher sensitivity than the ELISA. Nonetheless, it is clear that more research into the mechanism of obestatin is needed.

Ghrelin and obestatin are regulated by thyroid hormones

Studies have indicated an association between gut hormones and thyroid hormones, proposing there may be regulatory interactions between them. This is confirmed by changes in ghrelin and obestatin concentration observed in subclinical hypo- and hyper- thyroidism (Emami *et al*, 2014). This study found a significant correlation between serum ghrelin and obestatin with TSH, T4 and T3. Ghrelin concentration had a positive relationship with serum thyroid hormone concentration but had a negative relationship with TSH (Emami *et al*, 2014). This suggests that thyroid hormones are involved in the secretion of gut hormones, which then feedback to the hypothalamus, pituitary and thyroid **Fig. 3**. The positive relationship between ghrelin and thyroid hormones accounts for the characteristic increase in appetite and body weight in hypothyroidism (Altinova *et al*, 2006). In contrast, it has been reported that there is no correlation between ghrelin and thyroid hormone concentration (Giménez-Palop *et al*, 2005). Emami *et al* (2014) justly explains that conflicting results may be due to differences in the individuals, fat mass and degree of thyroid dysfunction.

The relationship between obestatin and thyroid hormone has not been confirmed. Emami *et al* (2014) proposes that because ghrelin and obestatin are derived from the same gene, their actions may be similar. However, this may not be the case. As the two hormones have opposing effects on appetite, they may also have opposing effects on thyroid hormone concentration. Undoubtedly, more research is needed in this area to make a confirmed judgment.

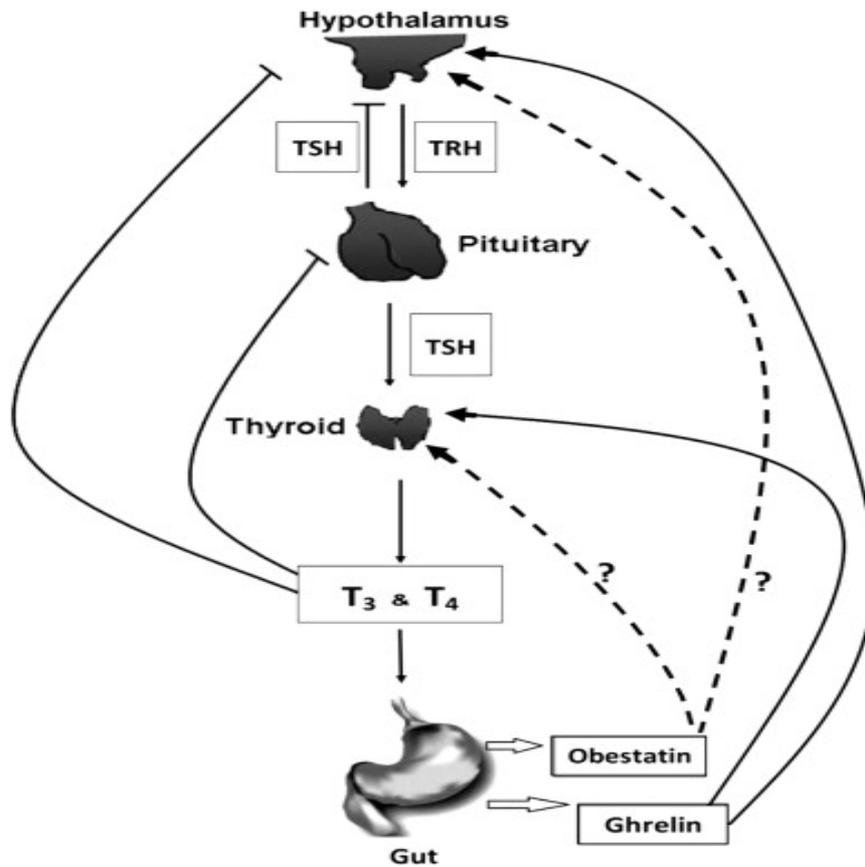


Fig.3: A schematic diagram of the regulatory relationship between T₃ and T₄, secreted by the hypothalamic-pituitary-thyroid (HPT) axis, and the gut hormones, obestatin and ghrelin. (Dashed lines indicate speculated action of obestatin). (Source: Emami *et al*, 2014).

Conclusions

There are two distinct roles of the stomach that are regulated by gut hormones; acid secretion and appetite control. Gastrin, histamine and acetylcholine interact to achieve acid secretion, permitting the destruction of ingested microorganisms and digestion. The interactions between these hormones differ between basal and stimulated conditions. It is known that somatostatin inhibits gastric acid secretion and the most likely mechanism is inhibition of histamine secretion. Long term inhibition of gastric acid is shown to upregulate somatostatin gene expression. The regulation of somatostatin concentration due to altered pH is important in the prevention of acid reflux and peptic ulcers. Ghrelin is identified as an orexigen and obestatin as an anorexigen. The expression of these hormones may be regulated by thyroid hormones, which can be observed by the effects of hyper- and hypo- thyroidism on their concentration. Overall, there are many unanswered questions about the mechanisms of hormones secreted by the stomach and there is much further research to be done.

Word count= 1646

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