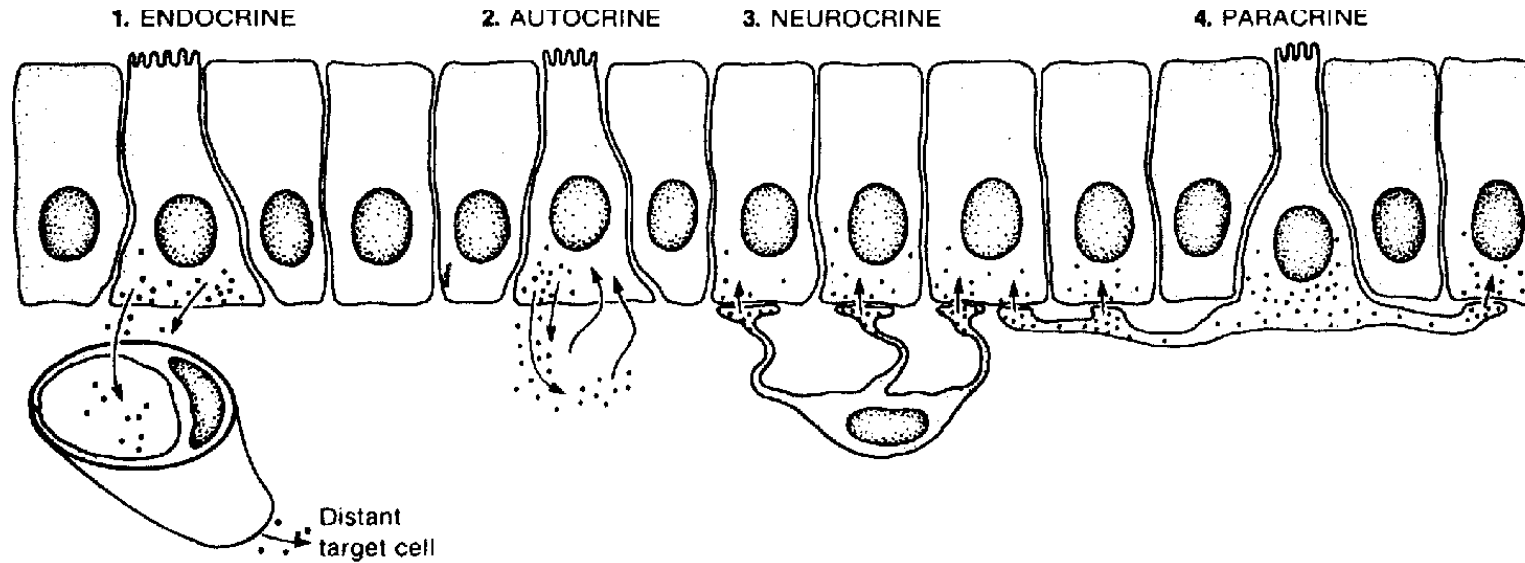




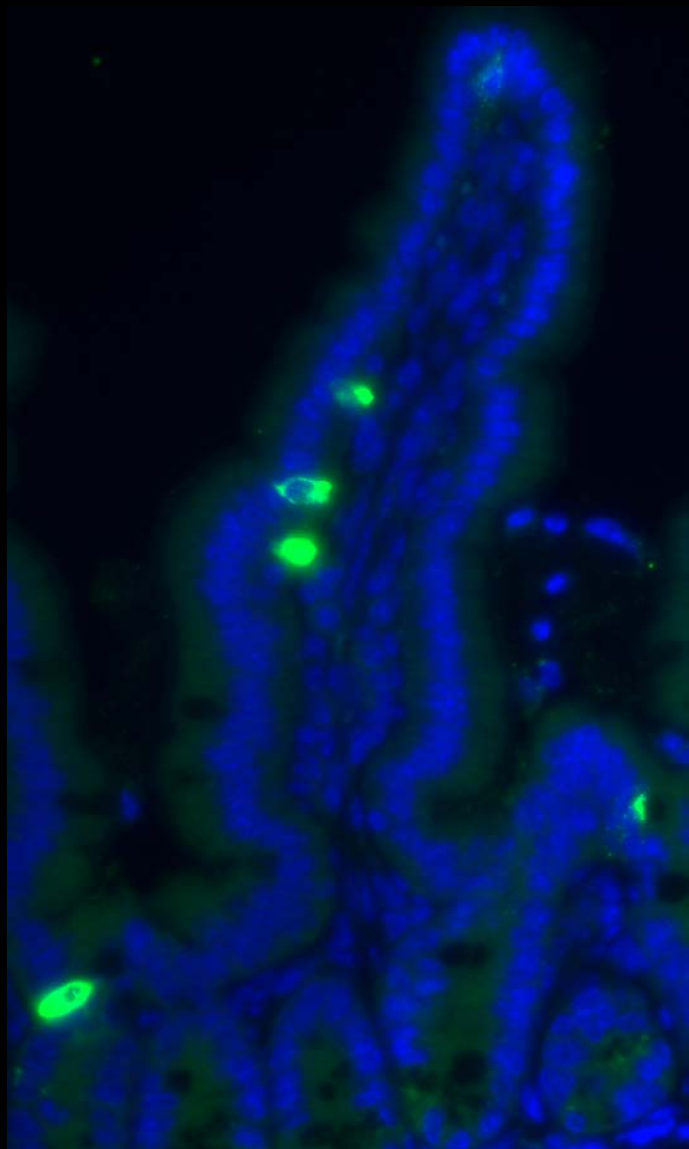
Gastrointestinal Hormones

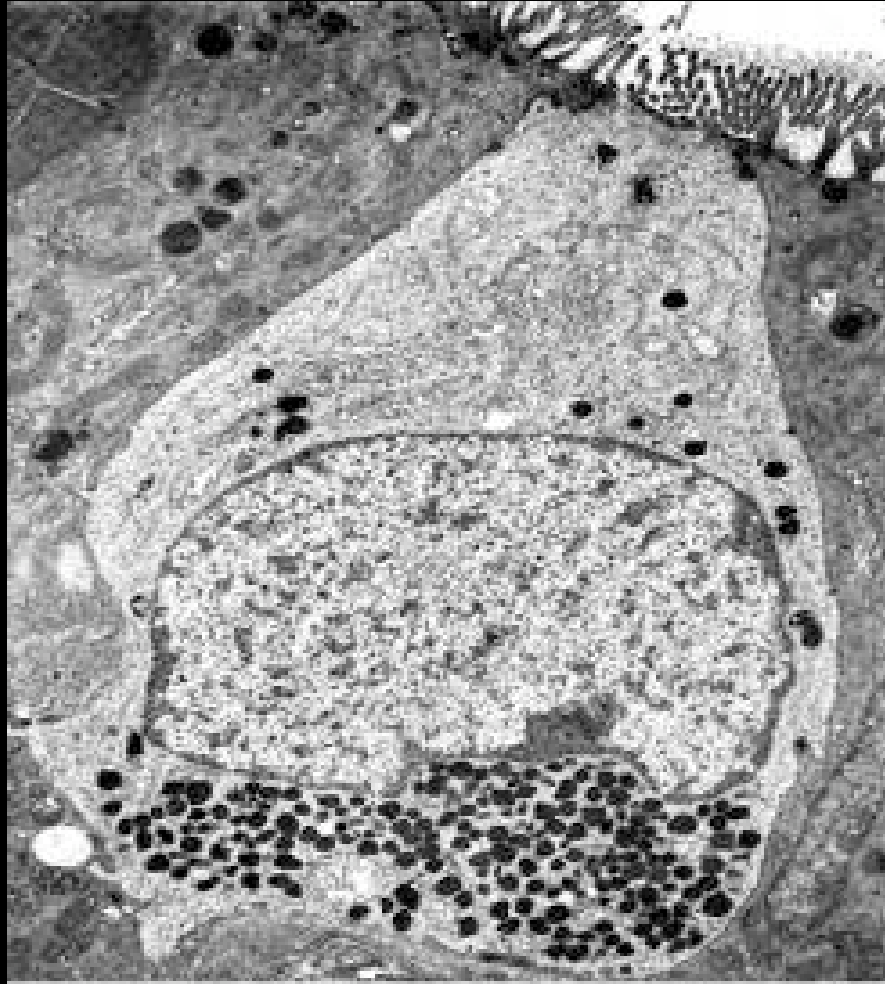


-
- 1. An understanding of the advantages of the GI hormone system over other regulatory systems.
 - 2. An understanding of the “Classic” GI hormones that are members of the gastrin and secretin families
 - 3. An understanding of those GI hormones that are clinically important (e.g. somatostatin, VIP, GIP)
 - Gastrointestinal hormone; cck; gastrin; secretin; vip; somatostatin

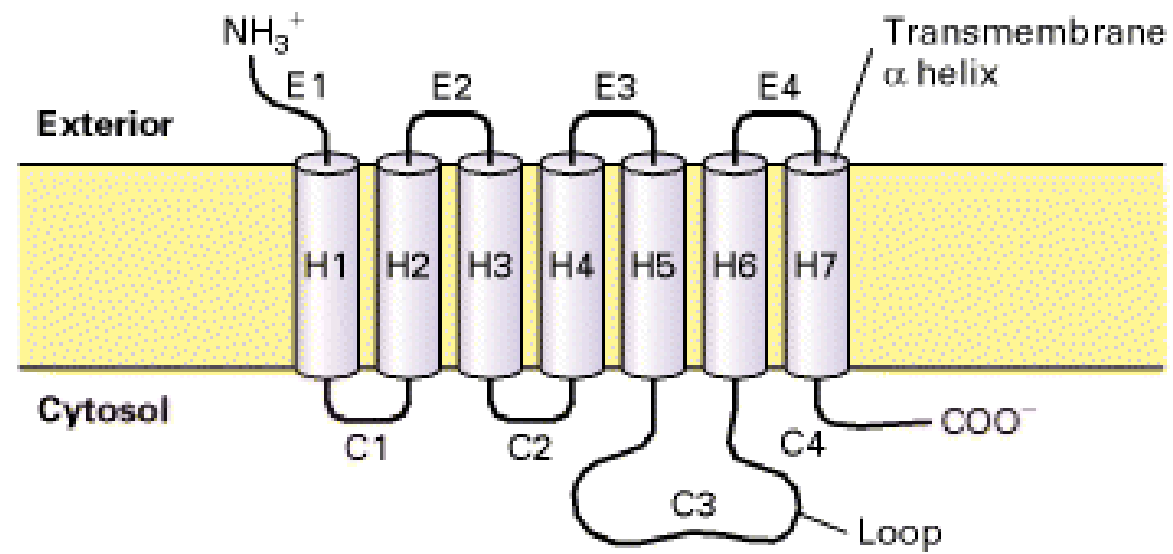


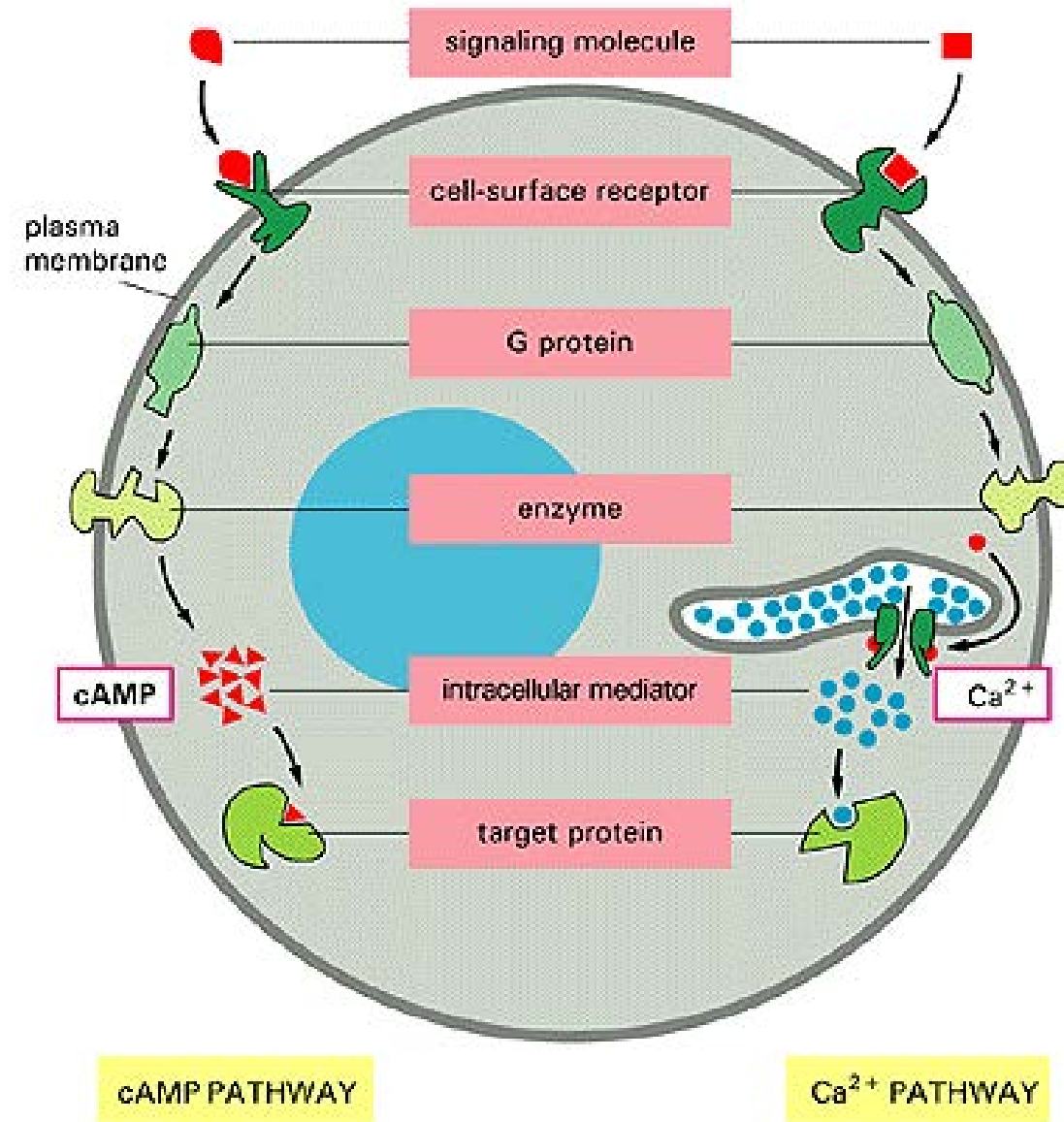
- Hormones have relatively long half-lives as signaling molecules (minutes).
- They act on targets at a site often distant from the site of hormone release.
- Expression of the appropriate receptor dictates whether a cell responds to a hormone.

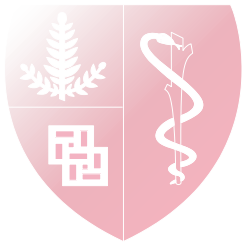




Junqueira and Carneiro, Basic Histology, a text and atlas, p. 307, Figure 15-18







Hormone

Neurotransmitters
Paracrine Hormones

Candidate Regulators

Gastrin

VIP

Motilin

CCK

Somatostatin

Pancreatic Polypeptide

Secretin

CCK

Neurotensin

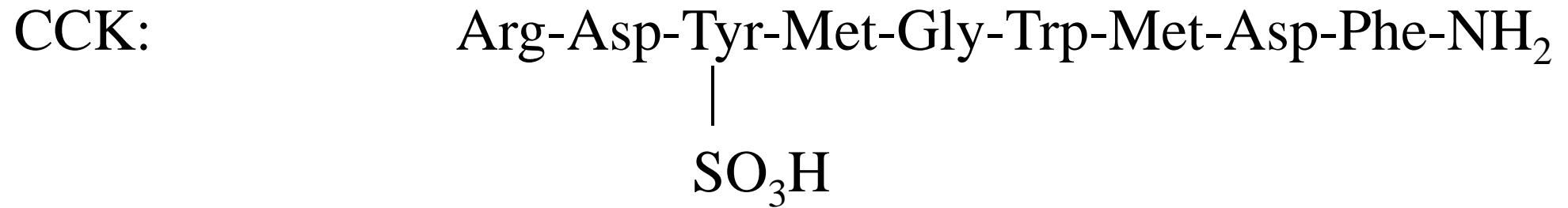
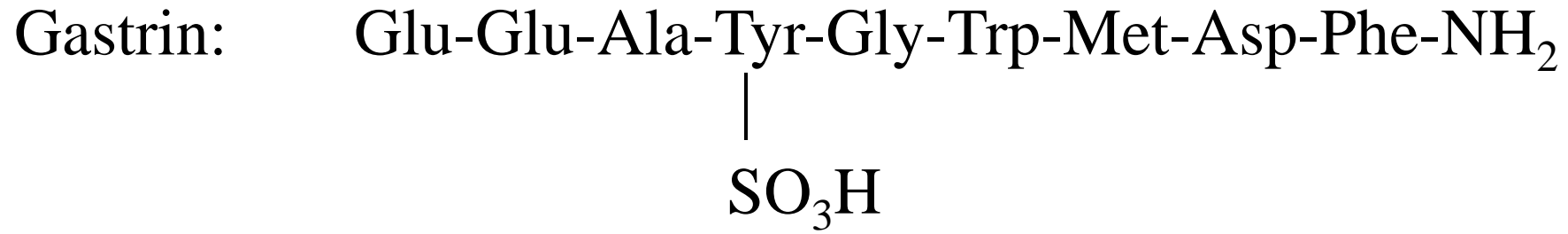
GIP

Ghrelin



Cholecystokinin & Gastrin families

- Share a common COOH terminal peptide
- The COOH terminal end is amidated
- The terminal 4 amino acids are shared and possess biologic activity





Gastrin

- Synthesized as several different isoforms (G-34, G-17, G-14)
- Source: G cells of the gastric antrum
- Actions:
 - Stimulation of gastric acid secretion
 - Trophic effects on parietal cell mass



Gastrin

- Regulation
 - Digestive products, especially Phe and Trp
 - Neural via the vagus nerve
 - $\text{pH} > 3.0$

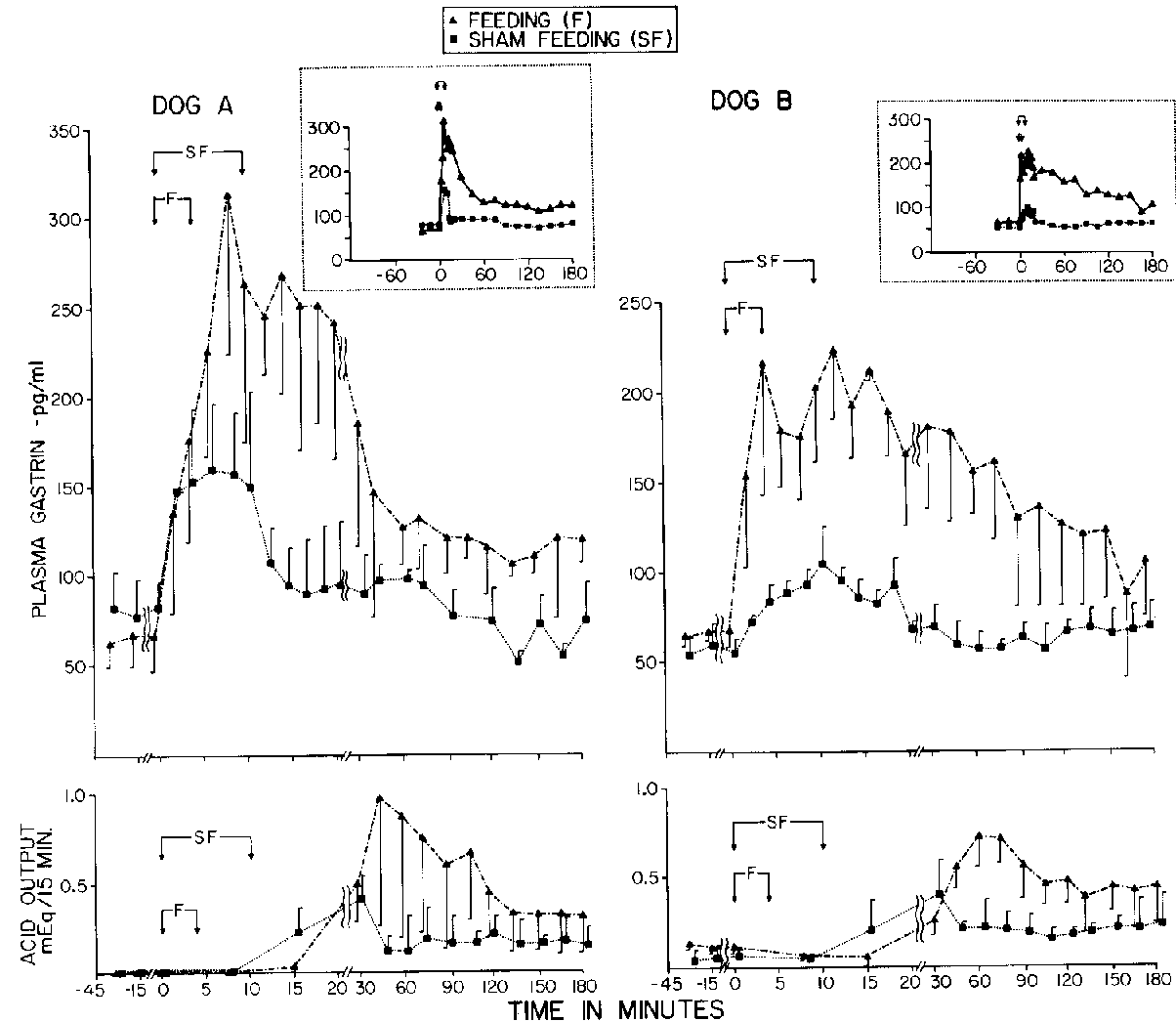


FIG. 3. Gastric acid secretions from Pavlov pouches and plasma gastrin concentrations before and after feeding and sham feeding. Each symbol represents the mean of three experiments. Gastric fistulae were closed in all experiments. Vertical bars represent 1 SD. Gastrin concentration are repeated with linear time scale in *small drawings*.



Gastrin Receptor

- also known as the CCK_B receptor
- 7 transmembrane G protein coupled receptor
- expressed in the gastric parietal cell and the brain.



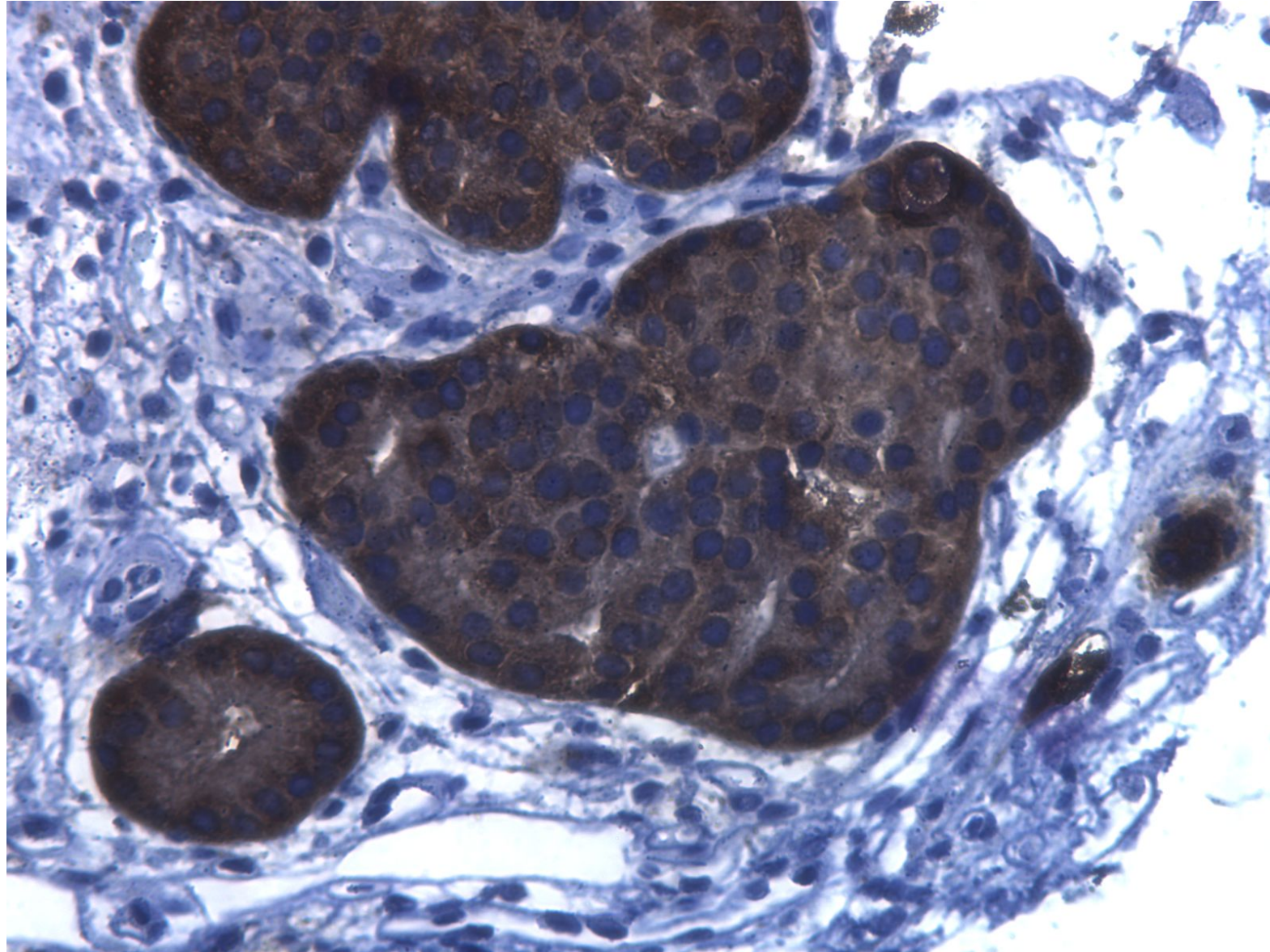
Knockout mice of gastrin or its receptor

- Knockout mice for gastrin or its receptor produced similar results
 - marked atrophy of the gastric mucosa
 - elevation of gastric pH
 - acid secretion could not be stimulated with acetylcholine or histamine.



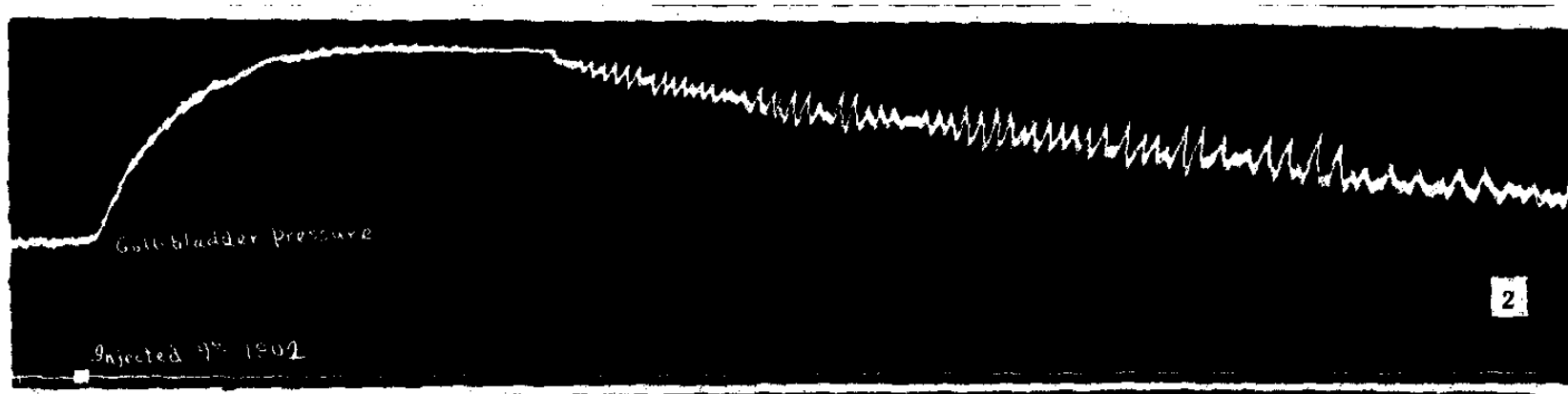
Zollinger-Ellison Syndrome

- Gastrin secreting tumors
- Hypertrophy of the parietal cell mass
- Excessive acid secretion
 - Multiple gastric ulcers resulting in bleeding
 - Death from hemorrhage





Cholecystokinin

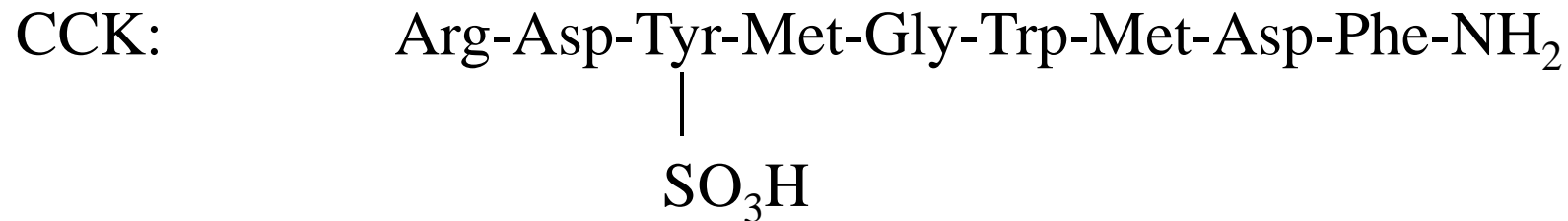


1923 - original experiment by Ivy and Oldberg demonstrating gallbladder contraction with duodenal extracts.



Cholecystokinin (CCK)

- 115 amino acid prepropeptide that undergoes post-translational processing into multiple biologically active forms
 - CCK 58, 39, 33, 22, 12, 8, and 4
- Specificity determined by a sulfated tyrosine





Cholecystokinin (CCK)

- Source: I cells of the duodenum and jejunum. Also made in the brain and the enteric nervous system. CCK functions in an endocrine and paracrine manner.
- Mechanism: Increases $[Ca^{+2}]$
- Regulation
 - Fat and protein digestive products, especially Phe and Trp



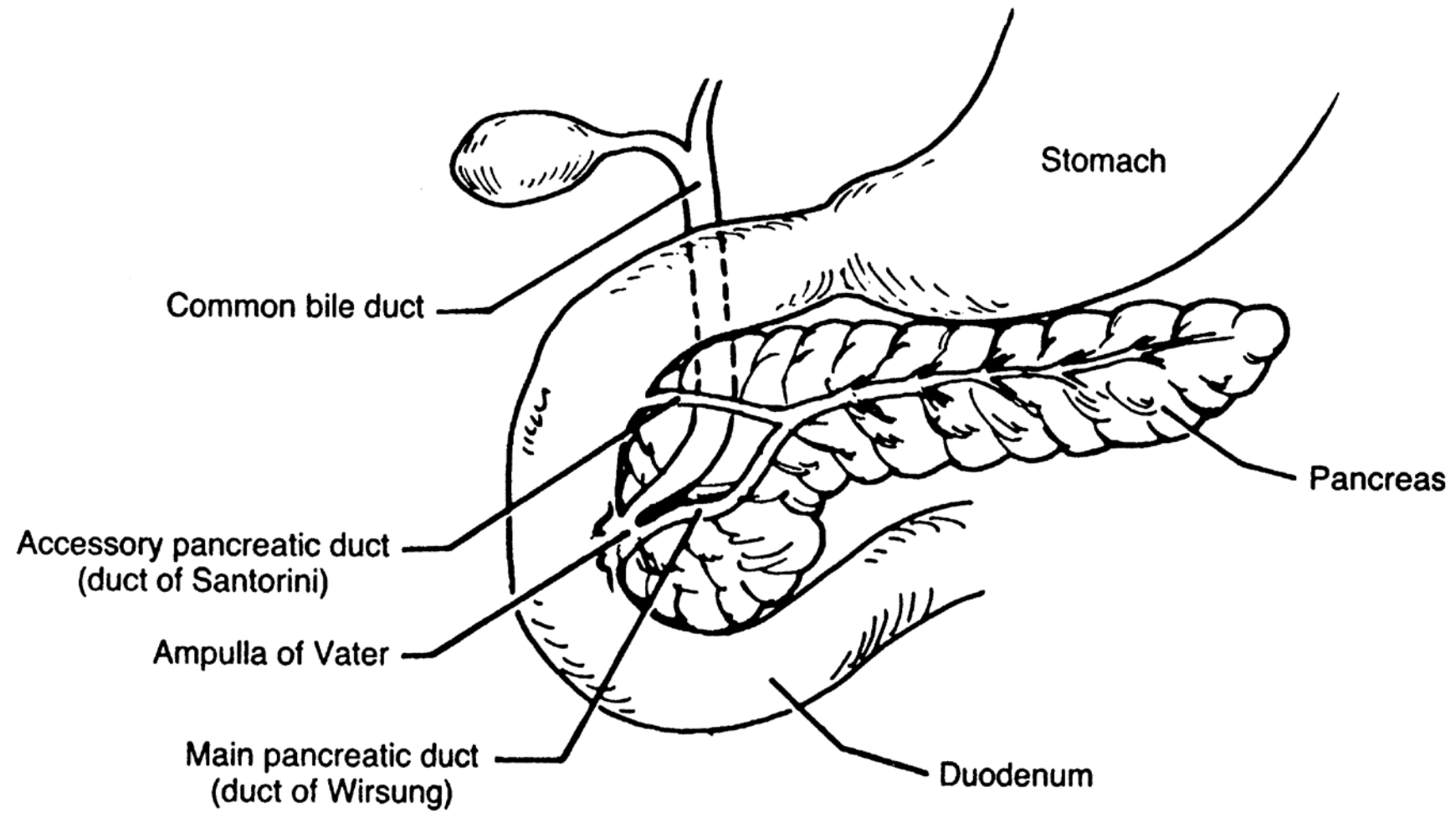
Cholecystokinin (CCK) Receptors

- CCK_A receptor is present in the gallbladder and pancreas.
- CCK_B (gastrin) receptor is expressed in the brain and gastric fundus



Cholecystokinin (CCK)

- Actions:
 - Indirectly stimulates pancreatic exocrine secretion
 - Stimulates gallbladder contraction
 - Inhibits gastric emptying
 - Trophic effects on the pancreas
 - Influences sensation of satiety





Secretin Family

- Secretin
- Vasoactive intestinal peptide (VIP)
- Glucose-Dependent Insulinotropic Polypeptide (previously known as Gastric inhibitory peptide, GIP)
- Exhibit sequence similarities
- No common biologic peptide

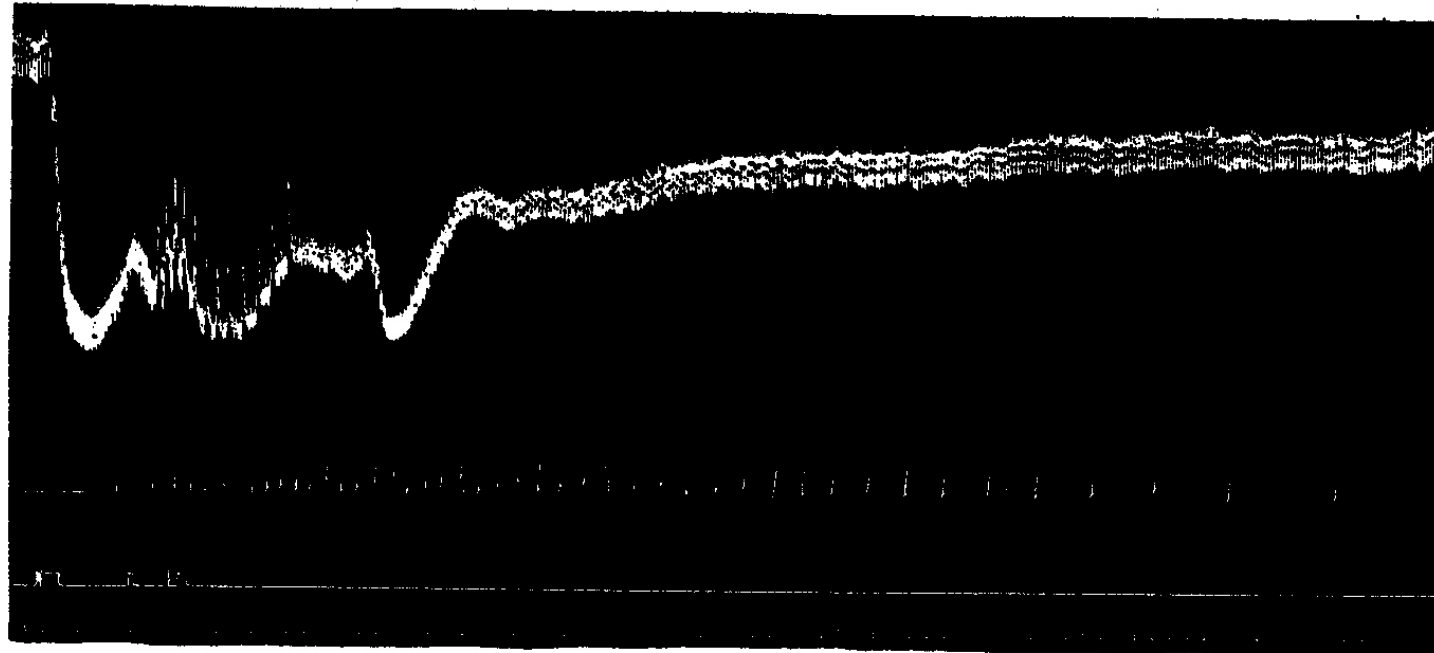


Fig. 2. *Effect of injecting acid extract of jejunal mucous membrane into vein.* Explanation as Fig. 1. The steps on the drop-tracing are due to a gradual accumulation of secretion on the lever of the drop-recorder, which fluid falls off at intervals. Blood-pressure zero=level of drop recorder.



Secretin

- Structure: 27 amino acids
- Source: S cells of the jejunum
- $T_{1/2}$ = 4-5 minutes
- Mechanism: increases cAMP



Secretin

- Stimulation of pancreatic water and bicarbonate secretion



Secretin Regulation

- Secretin secretion is stimulated by
 - acidification of the duodenum
 - products of fat digestion



Secretin Regulation

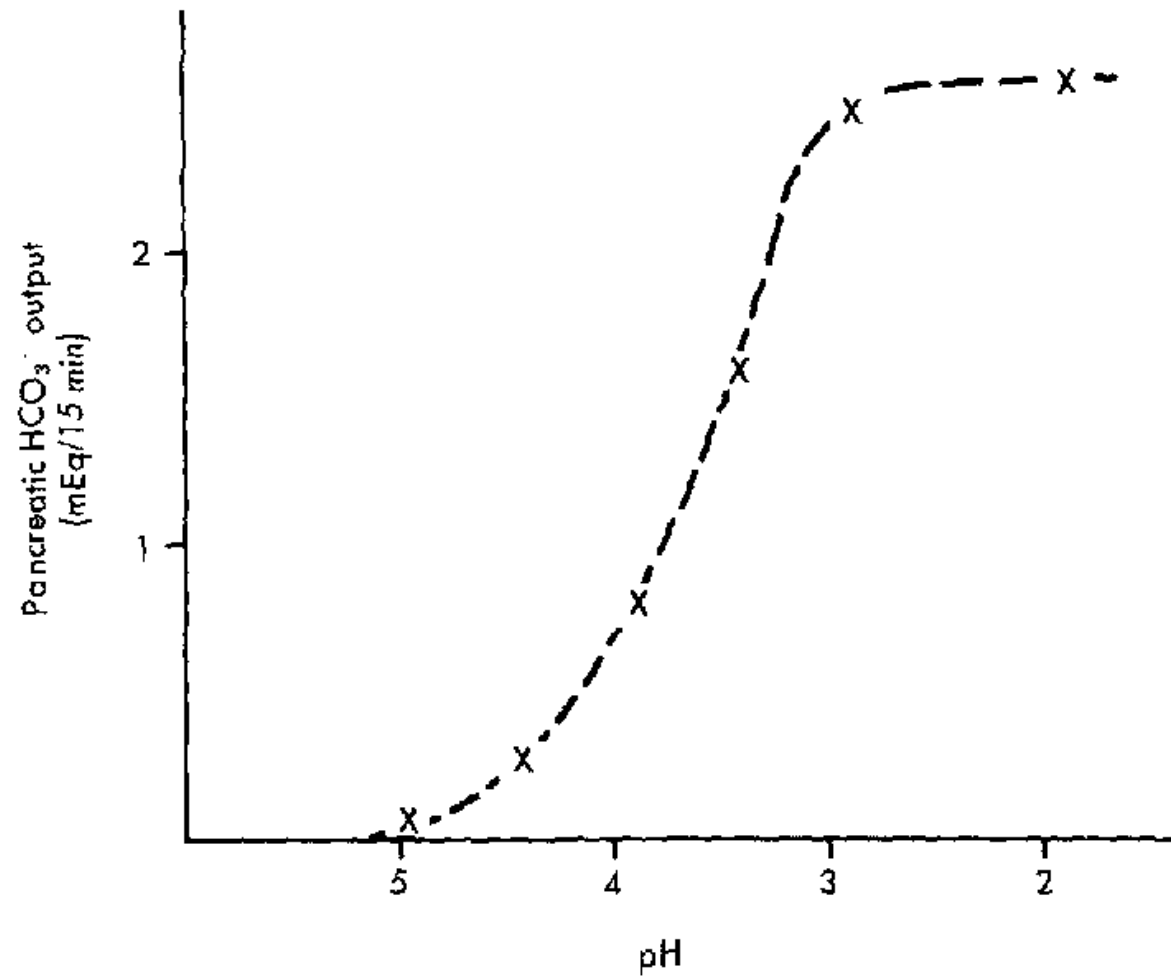
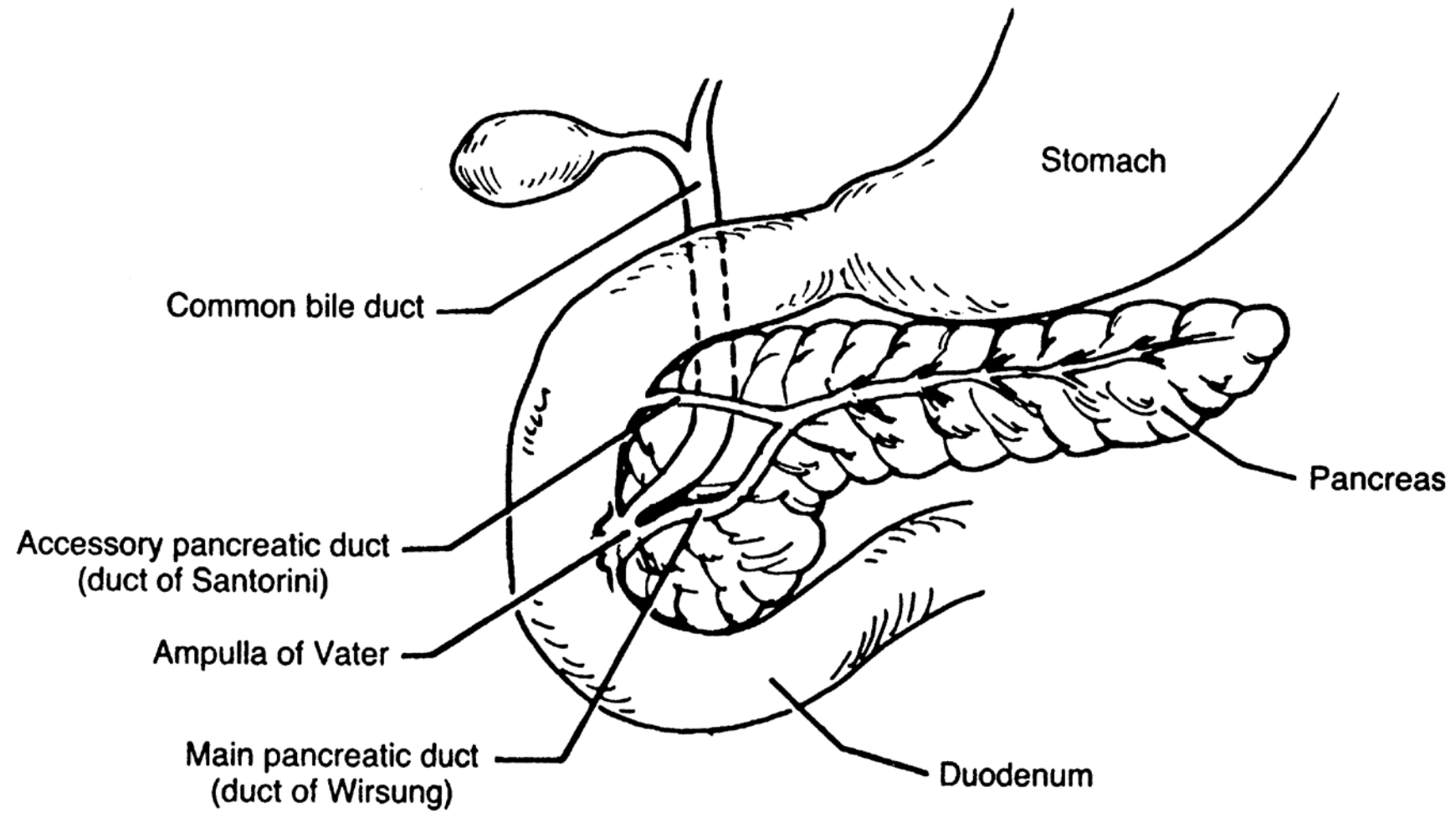


Fig. 9-5. Pancreatic bicarbonate output in response to various duodenal pH values. The output of bicarbonate is used as an index of secretin release.



Secretin

- Response to secretin administration is used to test for pancreatic function
 - Secretin stimulation test: measure total amount of bicarbonate secreted
 - MRCP with secretin stimulation: measure change in duct size with secretin stimulation





VIP

- 28 amino acids
- Source: neurons of the intestine, CNS, and urogenital tract
- Actions: increase in intracellular cAMP
 - Intestinal secretion
 - Smooth muscle relaxation
- Receptor: present in the small intestine, colon, brain, heart, lung, kidney, and spleen



WDHA SYNDROME

(watery diarrhea hypokalemia achlorhydria)

- VIP peptide secreting tumors
- Results in an increase in cAMP levels
- Effects are identical to that of cholera toxin
- Intestinal secretion is greatly increased, resulting in massive secretory diarrhea



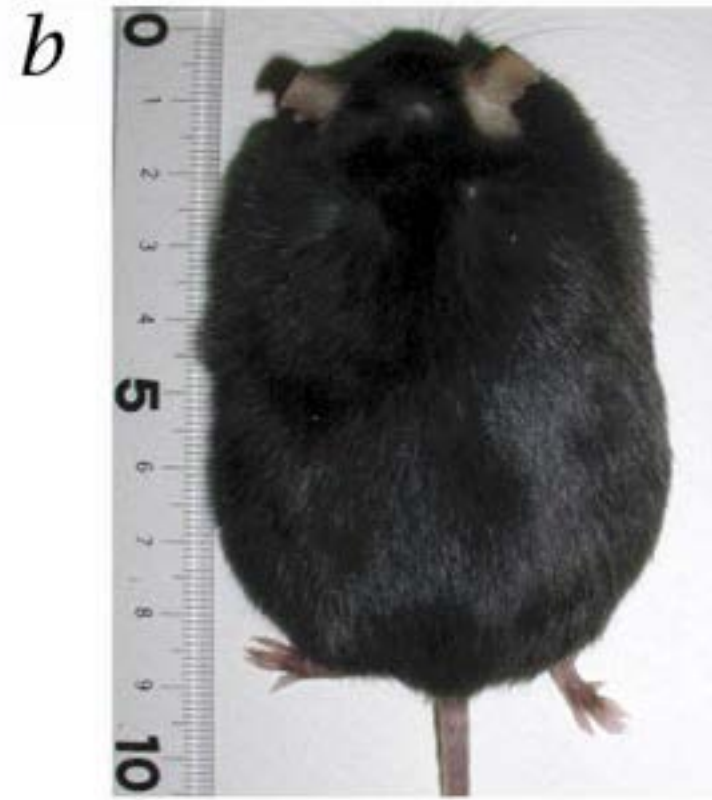
Glucose-Dependent Insulinotropic Polypeptide (GIP)

- A much greater response in serum insulin levels is observed when glucose is administered orally versus an intravenous route.
- Hormonal factors thought to mediate the signaling from the intestine to the pancreatic beta cells have been called incretins and include GIP and glucagon-like peptide (GLP-1)



GIP

- 42 amino acid
- Source: K cells of the duodenum
- Regulation: oral fat or glucose in the intestine stimulates GIP secretion
- GIP enhances insulin secretion from pancreatic beta cells



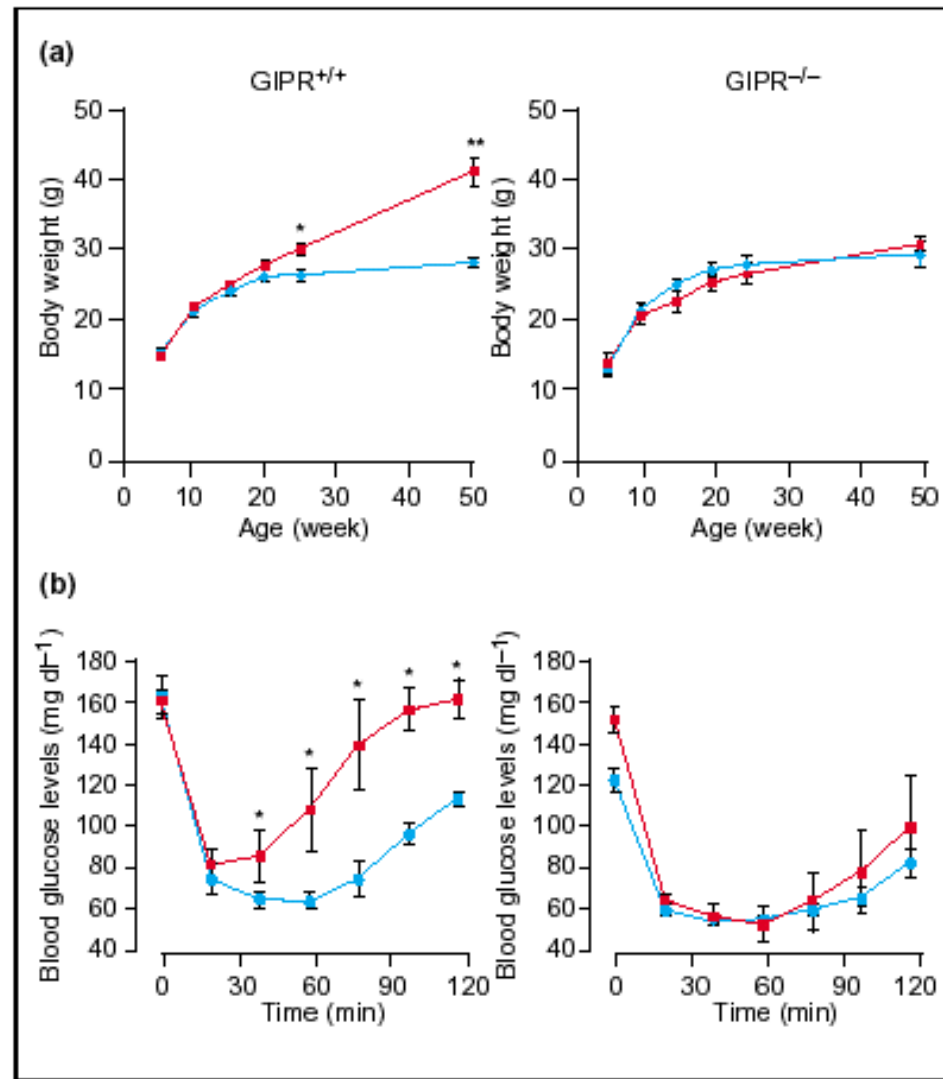
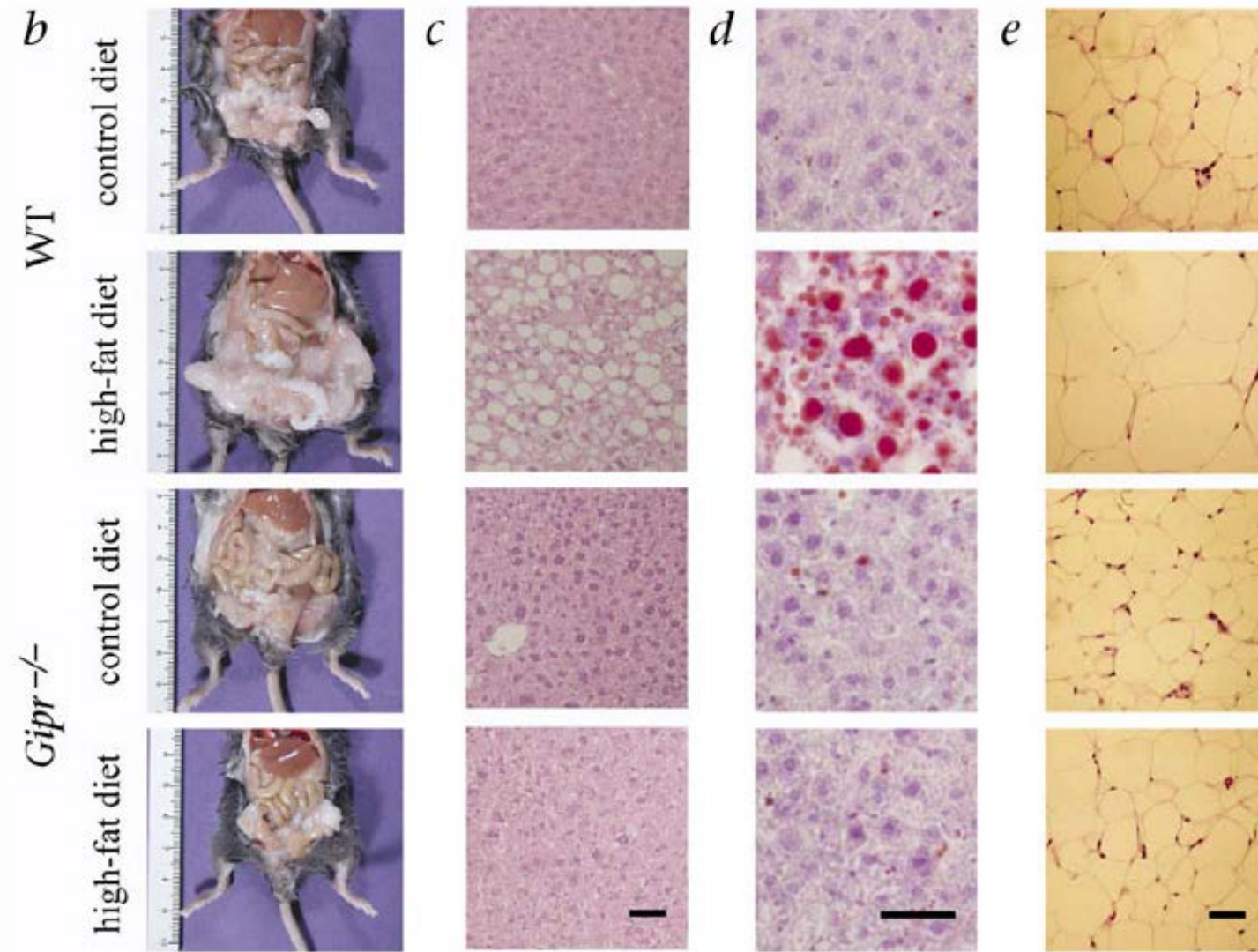
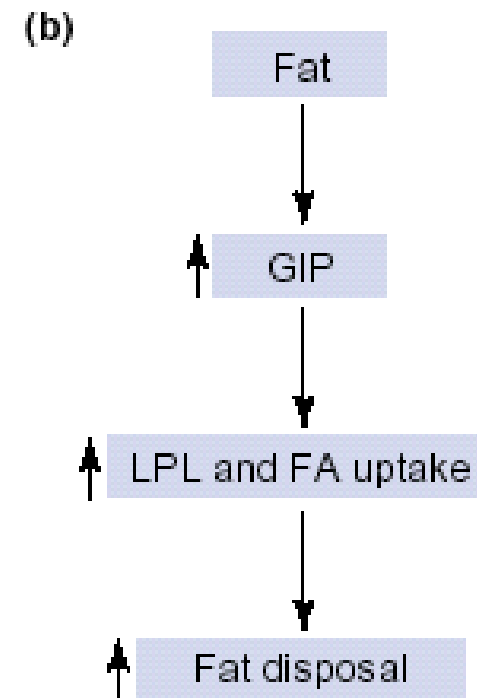
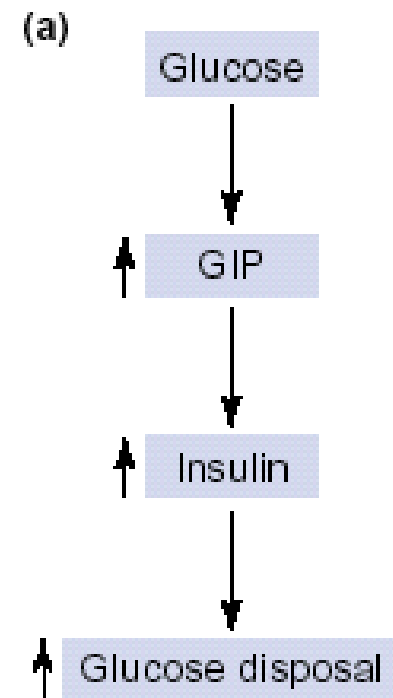


Fig. 2. Inhibition of the glucose-dependent insulinotropic polypeptide (GIP) signal prevents high-fat-induced obesity. Body-weight gain (a) and insulin sensitivity (b) in wild-type mice (GIPR^{+/+}; left panels) and GIP receptor knockout mice (GIPR^{-/-}; right panels) fed either a control diet (cyan) or a high-fat diet (red) are shown. Insulin tolerance tests were administered to mice on either diet at 50 weeks. Values are means \pm SEM, $n = 4$ per group. * $P < 0.05$, ** $P < 0.01$, compared with control mice. Modified, with permission, from [16]. ©Nature (<http://www.nature.com>).





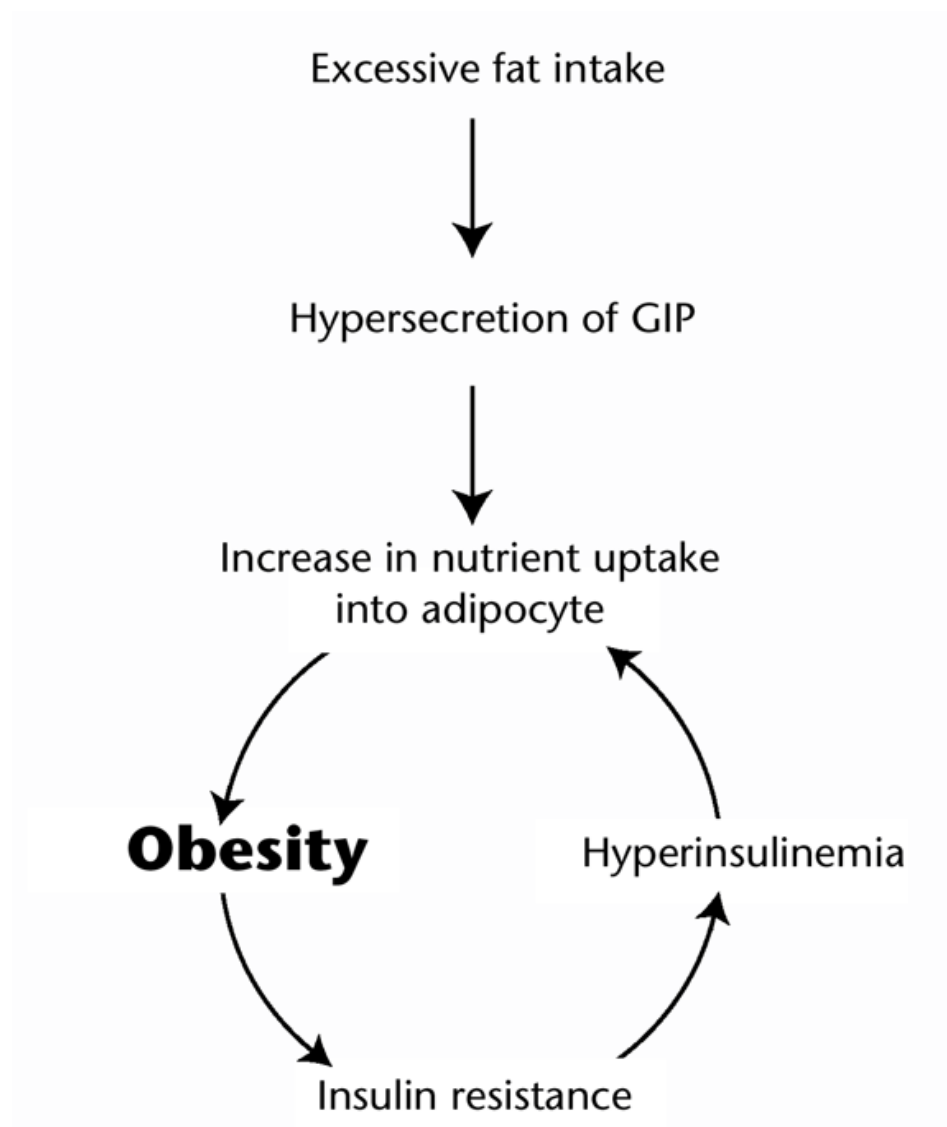
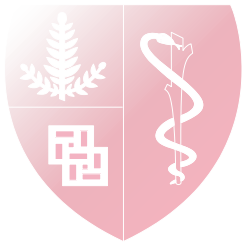
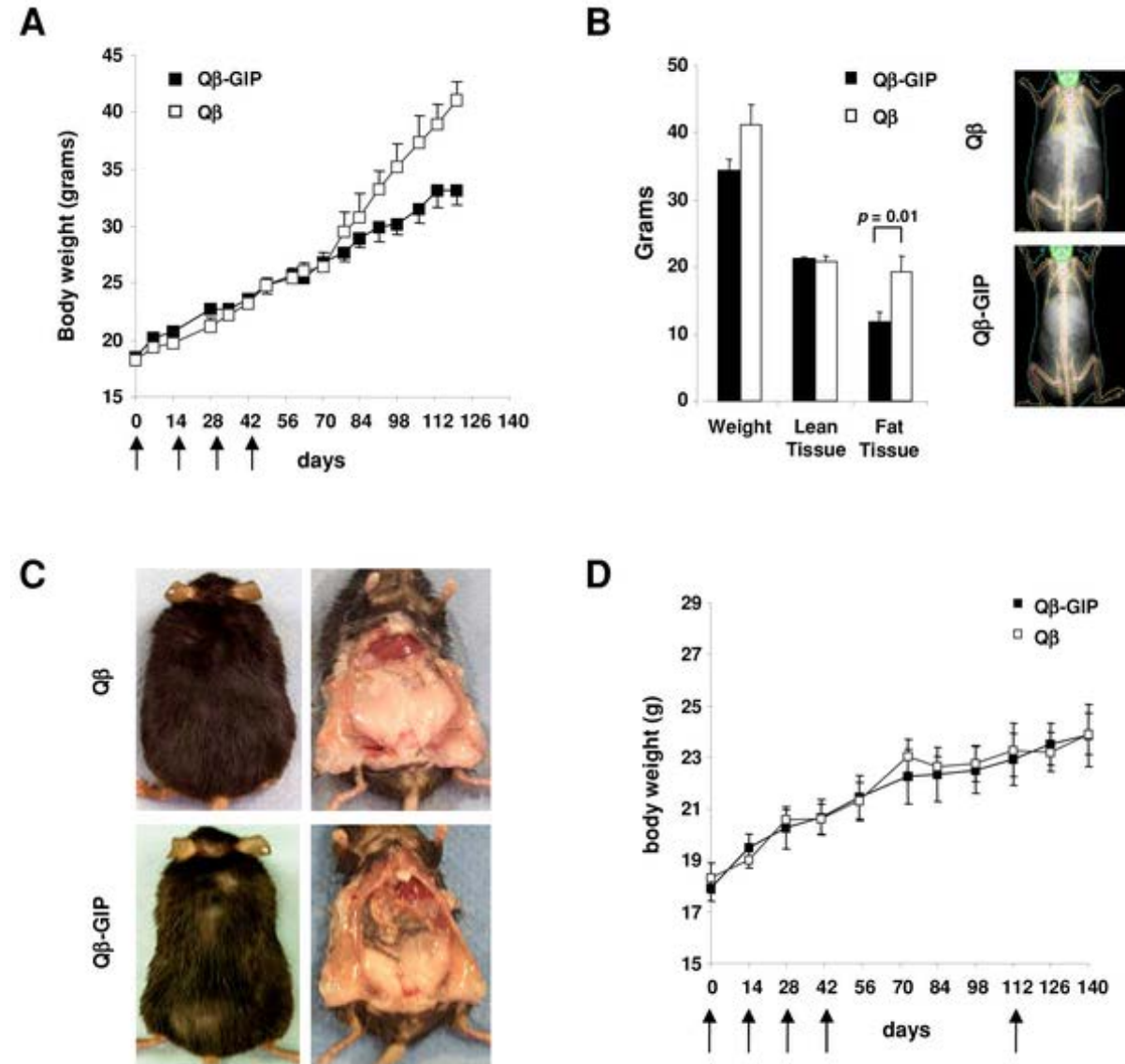




Figure 2. Vaccination against GIP protects against diet-induced obesity.



Fulurija A, Lutz TA, Sladko K, Osto M, et al. (2008) Vaccination against GIP for the Treatment of Obesity. PLoS ONE 3(9): e3163.
doi:10.1371/journal.pone.0003163

<http://www.plosone.org/article/info:doi/10.1371/journal.pone.0003163>



Somatostatin

- Source:
 - Neurons of CNS and PNS
 - Endocrine cells of the pancreas (D cells) and stomach
- Actions in the GI tract
 - Inhibition of transport
 - Inhibition of secretion
 - Splanchnic vasoconstriction



Somatostatin

- Clinical Applications
 - Secretory diarrhea
 - Pancreatic secretions
 - Gastrointestinal hemorrhage (variceal bleeding)
 - induces splanchnic vasoconstriction



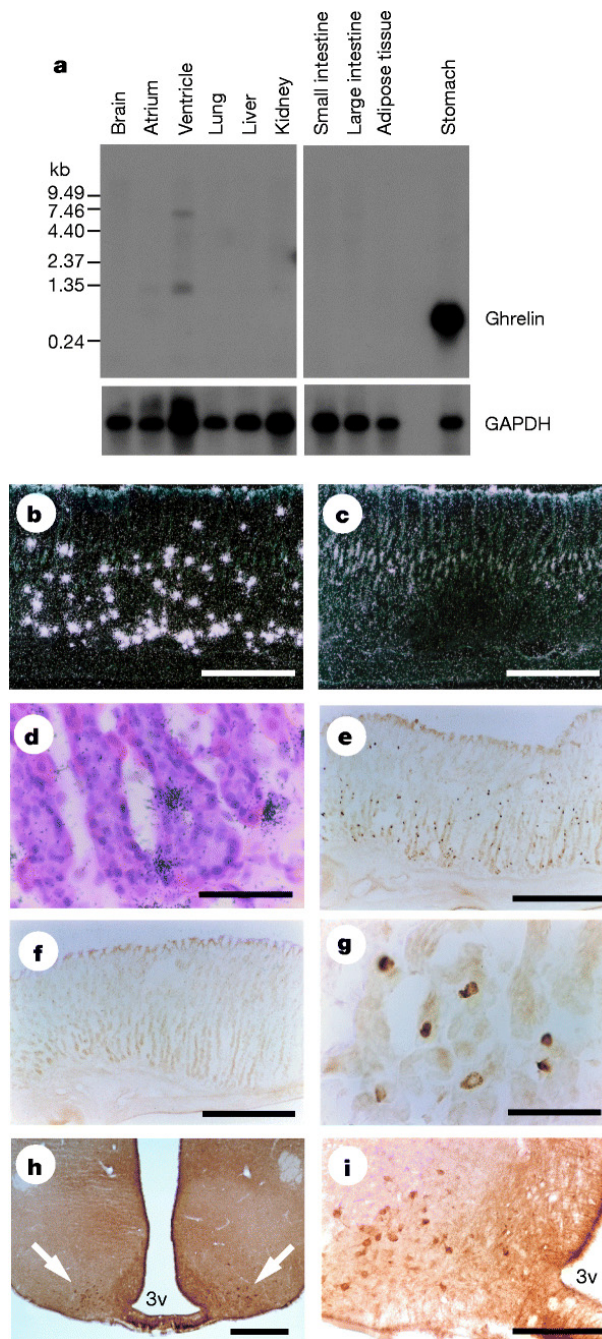
Motilin

- 22 amino acids
- Source: small intestine
- Actions: serum levels parallel that of the interdigestive motor complex
- Pharmacology: erythromycin binds to the motilin receptor and acts as an agonist
- Used in the clinical setting to promote motility



Ghrelin

- Discovered in 1999 as a ligand for the growth hormone secretagogue receptor
- Source: enteroendocrine cells within the stomach oxyntic glands
- Regulation: levels rise before meals and fall after meals. Fasting results in elevated ghrelin levels.





Actions

- Stimulates growth hormone release. More potent than growth hormone releasing hormone.
- Affects hypothalamic regulation of energy homeostasis.
Induces feeding
 - Induces feeding and efficient nutrient assimilation
 - Induction of feeding is independent of growth hormone



Prader-Willi Syndrome

- Characterized by a voracious appetite, hyperphagia, and obesity
 - Associated with gene deletions on chromosome 15
 - Patients have ghrelin levels 3 times higher than controls



Bariatric Surgery for Obesity

- Gastric bypass or resection has been used as an approach for the treatment of obesity.
 - Results in decrease ghrelin levels

