NUTRIENT SENSING MECHANISMS

IN THE

SMALL INTESTINE:

Localisation of taste molecules in mice and

humans with and without diabetes

Kate Sutherland, B.Sc. (Hons)

A thesis submitted in fulfilment of the Degree of Doctor of Philosophy

Discipline of Physiology

School of Molecular and Biomedical Sciences

Adelaide University

October 2008

APPENDIX
5-HT IMMUNOREACTIVITY IN OTHER REGIONS OF THE GASTROINTESTINAL TRACT; ALTERATIONS IN 5-HT SIGNALLING PATHWAYS IN DISEASE

A1 Introduction

5-HT is an important paracrine signalling molecule and neurotransmitter in the gastrointestinal tract which activates intrinsic primary afferent neurons involved in peristaltic and secretory reflexes and extrinsic primary afferents involved in transmission of sensory information to the central nervous system system (105). 5-HT is synthesised in the gastrointestinal tract in enterochromaffin cells, myenteric neurons and mast cells (375). In the upper gastrointestinal tract 5-HT is released from enterochromaffin cells, and activates adjacent vagal afferent endings which have been shown to alter gastric motility patterns (22, 270, 381, 382). In the colon 5-HT also activates extrinsic primary afferents (130) and is implicated in the signalling of pain (376). The symptoms of abdominal discomfort and pain associated with functional bowel disorders such as dyspepsia and irritable bowel syndrome (IBS), are thought to result from a hypersensitivity of primary afferent neurons (32). An initial insult, such as inflammation, may lead to longstanding phenotypic and functional alterations in sensory signalling pathways. Expression of key molecules in serotonin synthesis are altered in IBS patients suggesting changes in the metabolism of 5-HT occur in this disease disease (49). Electrophysiological single-fibre recordings from colonic lumbar splanchnic afferents in both the normal and inflamed rat colon performed in our laboratory have shown increased responsiveness to 5-HT during and after dextran sulphate sodium (DSS)-induced inflammation (50). In the treated rats only, application of mast cell degranulator mimicked the response to 5-HT, suggesting that mast cell released 5-HT is involved in this increased responsiveness of primary afferents in inflammation.

Immunohistochemistry for 5-HT was used in studies outlined in this thesis to identify intestinal enterochromaffin cells in investigations of the role of 5-HT as a mediator in intestinal taste signalling. The 5-HT primary antibody used produced reliable and strong immunolabelling of these cells in the gastrointestinal mucosa. Based on a possible role of alterations in 5-HT signalling in mast cells and sensory neurons contributing to symptoms in functional bowel disorders dual immunolabelling was performed for 5-HT and calcitonin gene-related peptide (CGRP) in the colon of rats subjected to experimental inflammation. The aim of this study was to explore whether increased sensitivity of serotonergic signalling in inflammation (50) may be associated with changes in the relationship between sensory fibres, labelled by CGRP, and 5-HT-releasing cells in the colonic serosa.

A2 Methods

All experiments were performed using adult male Sprague-Dawley rats weighing approximately 200g, housed conventionally with free access to water and a standard laboratory rodent diet. All studies were performed in accordance with the Australian code of practice for the care and use of animals for scientific purposes and with the approval of the Animal Ethics Committees of the Institute of Medical & Veterinary Science (Adelaide, Australia) and the University of Adelaide.

Colonic inflammation was induced in two Sprague-Dawley rats by the addition of 2%w/v dextran sulphate sodium (DSS) (MW 40000, ICN Biochemicals, Cleveland, Ohio) to drinking water for a period of 7 days. An additional two animals used as controls were housed in identical conditions but without DSS treatment for the same duration.

Following deep anaesthesia with sodium pentobarbitone (60 mg/kg, ip) and transcardial perfusion with 4% paraformaldehyde, the distal colon was removed from rats. The most distal 4-5 cm, corresponding to the region used in electrophysiological studies, was retained including the mesenteric attachment, was then post-fixed for 2 hrs at room temperature (RT) in fresh fixative, washed three times for 20 min with phosphate-buffered saline (PBS) at pH7.4, then cryoprotected with 30% sucrose in PBS for 24 hrs at 4ºC. The colon was subsequently frozen and 20 µm transverse sections cut. Sections were air dried for 10 min, after which the tissue was washed with PBS including 0.1% TritonX-100 (PBS-T). Tissue was then blocked with 2% goat serum, 1% bovine serum albumin, 0.05% Tween 20 and 0.1% gelatine in PBST for 60 mins at RT and subsequently incubated with monoclonal anti-5-HT (1:100; Dako, Sydney, Australia) and rabbit anti-CGRP (1:200; Calbiochem) in blocking solution in PBS-T overnight at 4ºC. Tissue was then washed three times with PBS-T, and then incubated with a mixture of secondary antibodies: goat anti-rabbit Alexa Fluor 350 and donkey anti-mouse Alexa Fluor 555 (1:200; Molecular Probes, USA) for 45 min at RT. The tissue was then washed three times with PBS-T and mounted with ProLong Antifade (Molecular Probes, USA). Negative controls were prepared as above with the primary antibody omitted. Slides were allowed to dry overnight before viewing with an Olympus BX51 epifluorescence microscope. Images were taken with a Photometrics CoolSnap *fx* monochrome camera then pseudo-coloured.

Associations between CGRP containing nerve fibres and 5-HT containing mast cells were counted in the serosa from 15 randomly selected sections from each of the four rats. CGRP immunopositive nerve fibres were counted as associated with a mast cell if they were within 20 - 25 µm of each other, this distance corresponding to the diameter of the average mast cell over which 5-HT would be expected to diffuse readily.

A3 Results

Immunoreactivity for 5-HT was contained within individual cells in the mucosal epithelium, submucosa and in the serosa and mesentery of rat colon sections. CGRP immunoreactive nerve fibres were observed in all regions of the colon, in the mucosa, muscle layers and mesentery.

The DSS inflammatory protocol was validated by disease activity index score, histopathological assessment and myeloperoxidase (MPO) assay (50). Colonic sections from DSS-treated rats showed an increased level of background labelling for 5-HT and an increased number of 5-HT-cells in the mucosa and submucosa (data not shown). 5-HT immunoreactive cells in the serosa and mesentery were observed in thick sections from both inflamed and normal tissue. These cells had a granular appearance, and a morphology consistant with mast cells when examined under phase contrast (Nomarski) optics. No other 5-HT-immunoreactive structures were seen in these layers. Mast cells were frequently found in clusters of up to six cells surrounding mesenteric blood vessels in the serosa. CGRP-immunoreactive nerve fibres were also observed surrounding blood vessels entering the gut wall, and frequently in association with 5-HT immunolabelled mast cells (Figure A3.1). In inflamed specimens, the number of mast cells associated with CGRP fibres per section was higher ($34 \pm 6.3\%$) than in non-inflamed specimens ($17.0 \pm 4.9\%$, t-test, $p < 0.05$).

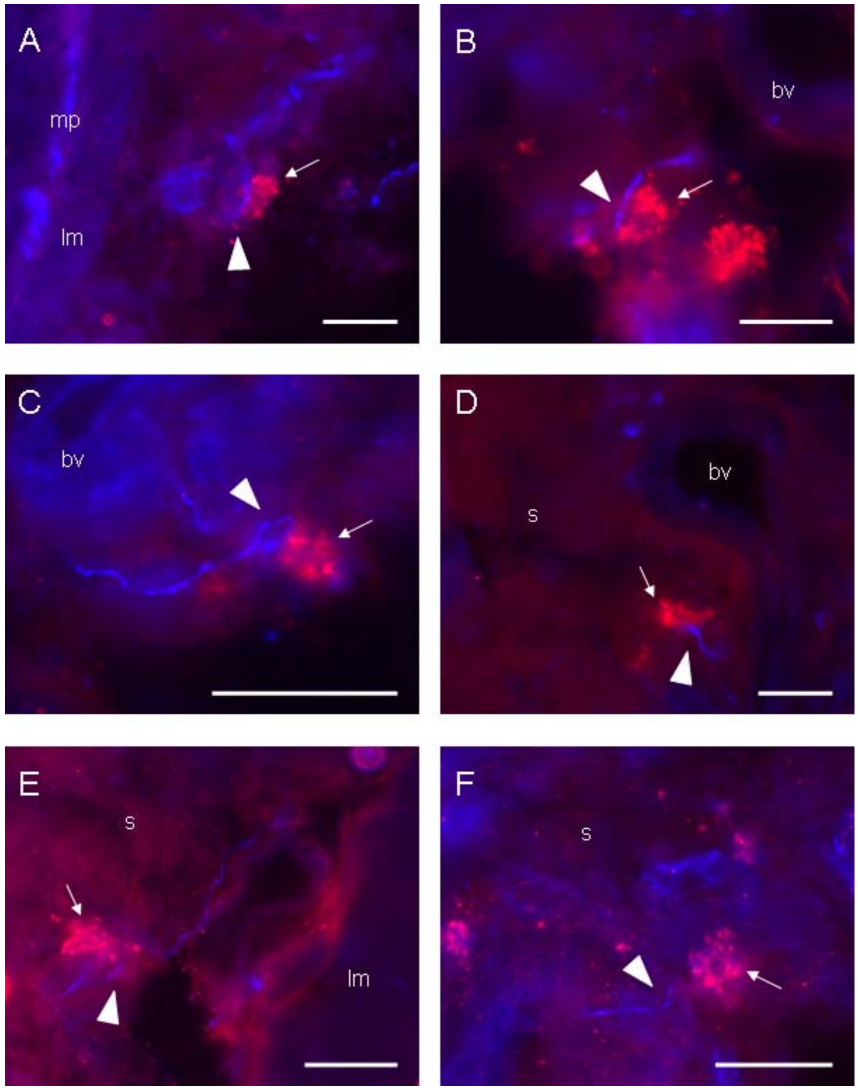

Figure A3.1 Immunohistochemistry for 5-HT and CGRP in the mesenteric border of rat colon.
Double label immunohistochemistry for 5-HT (red fluorescence) and CGRP (blue fluorescence) are shown in sections from dextran sulphate sodium (DSS)-treated rats (A-F). Arrows indicate 5-HT immunopositive mast cells which are in close association with CGRP immunoreactive nerve fibres (arrowheads). Mast cells and fibres are all located beyond the longitudinal muscle (lm) on the serosal (s) side of the mesenteric border region. Fibres and 5-HT immunopositive mast cells were frequently associated with mesenteric blood vessels (bv). Myenteric plexus; mp. Scale bars = 50µm.

A4 Discussion

It is well described that 5-HT activates colonic splanchnic afferents, and this process has been implicated in symptoms in postinfectious and postinflammatory states in humans (105). Functional studies performed in our laboratory show that colonic serosal and mesenteric extrinsic afferent endings exhibit increased sensitivity to 5-HT in inflammation, with an increase in proportion of responders and an increase in sensitivity reported, which is maintained after healing from inflammation (50). Immunohistochemical studies were undertaken in the current study to visualise associations between the 5-HT-containing mast cells and sensory nerves in the colonic serosa and mesentery, tissue regions where afferent electrophysiological recordings were obtained in in vitro colonic preparations (50).

5-HT-immunoreactive cells were identified in thick sections of the colonic serosa and mesentery from control and DSS - treated rats, as were colonic afferent nerve fibres labelled by CGRP (45). 5-HT cells were morphologically similar in appearance to mast cells, based on previous findings (230, 375). An increased number of these cells were observed in the colonic mucosa and submucosa, which were of comparable size and distribution to mast cells previously described in the inflamed rat colon (249). The number of close associations (20 μm) between 5-HT-immunoreactive mast cells and CGRP immunopositive nerve fibres in the current study was also significantly higher in colons form DSS-treated rats compared to controls, and may underestimate the actual number of close associations (332).

Electrophysiological studies showed that robust responses to mast cell degranulation occurred exclusively in inflamed preparations, which may be attributable to altered 5-HT release. The immunohistochemical data indicates a higher probability of functional associations between sensory nerves and mast cells in this region of the inflamed rat colon, as has been shown anatomically in IBS in humans (11) and by others in the rat model of DSS-induced colitis (249). The initial insult of DSS affects only the mucosa at the level of the epithelial cells (54, 245) and therefore changes in the serosa or mesentery reflect signalling of the mucosal injury. This finding supports a role for 5-HT in responses to mast cell degranulation but does not exclude the possibility of involvement of other mediators such as histamine and proteases.

The increased probability of association between 5-HT-releasing cells and sensory afferent fibres in inflammation illustrates a potentially maladaptive response of 5-HT signalling that may increase gastrointestinal symptoms. Experimental models of diabetes in the rat have also shown an increase in the 5-HT content of enterochromaffin cells in the duodenum (338). This increase may lead to an increased activation of vagal afferents in the small intestine and gastrointestinal sensory and motor dysfunctions in diabetes. However changes in enteroendocrine cell populations in diabetes have yet to be thoroughly investigated. A technical issue to be resolved prior to use of such an immunohistochemical approach is the fact that gastrointestinal vagal afferents have no unifying immunohistochemical marker. As a consequence, an assessment of 5-HT signalling to gastrointestinal vagal afferents may require a combined approach of 5-HT immunolabelling with anterograde nerve tracing from the nodose ganglion.

In conclusion electrophysiologyical studies in our laboratory have shown that colonic serosal and mesenteric primary afferent endings exhibit increased sensitivity to 5-HT in inflammation. The current immunohistochemical studies add to this and suggest this may be due to increased associations between 5-HT immunopositive serosal mast cells and colonic sensory fibres in inflammation. These findings illustrate how altered 5-HT signalling in the gastrointestinal tract may contribute to sensory and motor dysfunctions in disease states.

REFERENCES

1.Adler E, Hoon MA, Mueller KL, Chandrashekar J, Ryba NJ, and Zuker CS. A novel family of mammalian taste receptors. *Cell* 100: 693-702, 2000.

2.Affleck JA, Helliwell PA, and Kellet GL. Immunocytochemical detection of GLUT2 at the rat intestinal brush-border membrane. *J Histochem Cytochem* 51: 1567-1574, 2003.

3.Akkermans LM, Vos A, Hoekstra A, Roelofs JM, and Horowitz M. Effect of ICS 205-930 (a specific 5-HT3 receptor antagonist) on gastric emptying of a solid meal in normal subjects. *Gut* 29: 1249-1252, 1988.

4.Andrews JM, Rayner CK, Doran S, Hebbard GS, and Horowitz M. Physiological changes in blood glucose affect appetite and pyloric motility during intraduodenal lipid infusion. *Am J Physiol* 275: G797-804, 1998.

5.Anini Y and Brubaker PL. Muscarinic receptors control glucagon-like peptide 1 secretion by human endocrine L cells. *Endocrinology* 144: 3244-3250, 2003.

6.Annese V, Bassotti G, Caruso N, De Cosmo S, Gabbrielli A, Modoni S, Frusciante V, and A. A. Gastrointestinal motor dysfunction, symptoms, and neuropathy in noninsulin-dependent (type 2) diabetes mellitus. *J Clin Gastroenterol* 29: 171-177, 1999.

7.Azpiroz F and Malagelada JR. Intestinal control of gastric tone. *Am J Physiol* 249: G501-509, 1985.

8.Azpiroz F and Malagelada JR. Vagally mediated gastric relaxation induced by intestinal nutrients in the dog. *Am J Physiol* 251: G727-735, 1986.

9.Baggio LL and Drucker DJ. Biology of incretins: GLP-1 and GIP. *Gastroenterology* 132, 2007.

10.Baggio LL, Huang Q, Brown TJ, and Drucker DJ. A recominant human glucagon-like peptide (GLP)-1-albumin protein (albugon) mimics peptidergic activation of GLP-1 receptor-dependent pathways coupled with satiety, gastrointestinal motility, and glucose homeostasis. *Diabetes* 53: 2492-2500, 2004.

11.Barbara G, Stanghellini V, De Giorgio R, Cremon C, Cottrell GS, Pasquinelli G, Morselli-Labate AM, Grady EF, Bunnet NQ, Collins SM, and Corinaldesi R. Activated mast cells in proximity to colonic nerves correlate with abdomical pain in irritable bowel syndrome. *Gastroenterology* 126: 693-702, 2004.

12.Barbera R, Feinle C, and Read NW. Abnormal sensitvity to duodenal lipid infusion in patients with functional dyspepsia. *Eur J Gastroenterol Hepatol* 7: 1051-1057, 1995.

13.Barnett JL and Owyang C. Serum glucose as a modulator of interdigestive gastric motility. *Gastroenterology* 94: 739-744, 1988.

14.Belai A, Calcutt Na, Carrington AL, Diemel LT, Tomlinson DR, and Burnstock G. Enteric neuropeptides in streptozocin-diabetic rats; effects of insulin and aldose reductase inhibition. *J Auton Nerve Syst* 58: 163-169, 1996.

15.Bernhardt SJ, Naim M, Zehavi U, and Lindemann B. Changes in IP3 and cytostolic Ca2+ in response to sugars and non-sugar sweeteners in transduction of sweet taste in the rat. *J Physiol* 490: 325-336, 1996.

16.Berthoud HR, Kressel M, Raybould HE, and Neuhuber WL. Vagal sensors in the rat duodenal mucosa: distribution and structure as revealed by in vivo DiI-tracing. *Anat Embryol (Berl)* 191: 203-212, 1995.

17.Berthoud HR and Neuhuber WL. Functional and chemical anatomy of the afferent vagal system. *Auton Neurosci: Basic and Clinical* 85: 1-17, 2000.

18.Berthoud HR and Patterson LM. Anatomical relationship between vagal afferent fibers and CCK-immunoreactive entero-endocrine cells in the rat small intestinal mucosa. *Acta Anat (Basel)* 156: 123-131, 1996.

19.Bertrand PP. Real-time detection of serotonin release from enterochromaffin cells of the guinea-pig ileum. *Neurogastroenterol Motil* 16: 511-514, 2004.

20.Bezencon C, le Coutre J, and Damak S. Taste-signaling proteins are coexpressed in solitary intestinal epithelial cells. *Chem Senses* 32: 41-49, 2007.

21.Blackshaw LA, Brookes SJH, Grundy D, and Schemann M. Sensory transmission in the gastrointestinal tract. *Neurogastroenterol Motil* 19: 1-19, 2007.

22.Blackshaw LA and Grundy D. Effects of 5-hydroxytryptamine (5-HT) on the discharge of vagal mechanoreceptors and motility in the upper gastrointestinal tract of the ferret. *J Auton Nerve Syst* 45: 51-59, 1993.

23.Blackshaw LA and Grundy D. Effects of 5-hydroxytryptamine on discharge of vagal mucosal afferent fibres from the upper gastrointestinal tract of the ferret. *J Auton Nerve Syst* 45: 41-50, 1993.

24.Blackshaw LA and Grundy D. Effects of cholecystokinin (CCK-8) on two classes of gastroduodenal vagal afferent fibre. *J Auton Nerve Syst* 31: 191-201, 1990.

25.Blake BL, Wing MR, Zhou JY, Lei Q, Hillmann JR, Behe CI, Morris RA, Harden TK, Bayliss DA, Miller RJ, and Siderovski DP. G beta association and effector interaction selectivities of the divergent G gamma subunit G gamma(13). *J Biol Chem* 276: 49267-49274, 2001.

26.Bo X, Alavi A, Xiang Z, Oglesby I, Ford A, and Burnstock G. Localization of ATP-gated P2X2 and P2X3 receptor immunoreactive nerves in rat taste buds. *Neuroreport* 10: 1107-1111, 1999.

27.Boughter JD, Jr., Pumplin DW, Yu C, Christy RC, and Smith DV. Differential expression of alpha-gustducin in taste bud populations of the rat and hamster. *J Neurosci* 17: 2852-2858, 1997.

28.Brierley SM, Jones RCW, Gebhart GF, and Blackshaw LA. Splanchnic and pelvic mechanosensory afferents signal different qualities of colonic stimuli in mice. *Gastroenterology* 127: 166-178, 2004.

29.Brubaker PL. The glucagon-like peptides: pleiotropic regulators of nutrient homeostasis. *Ann N Y Acad Sci* 1070: 10-26, 2006.

30.Bubenik GA, Ball RO, and Pang SF. The effect of food deprivation on brain and gastrointestinal tissue levels of trypothan, serotonin, 5-hydroxyindoleacetic acid, and melatonin. *J Pineal Res* 12: 7-16, 1992.

31.Buchan AM. Nutrient Tasting and Signaling Mechanisms in the Gut III. Endocrine cell recognition of luminal nutrients. *Am J Physiol* 277: G1103-1107, 1999.

32.Bueno L, De Ponti F, Fried M, Kullak-ublick GA, Kwiatek MA, Pohl D, Quigley EM, Tack J, and Talley NJ. Serotonergic and non-serotonergic targets in the pharmacotherapy of visceral hypersensitivity. *Neurogastroenterol Motil* 19: 89-119, 2007.

33.Bulbring E and Crema A. The release of 5-hydroxytryptamine in relation to pressure exerted on the intestinal mucosa. *J Physiol* 146: 18-28, 1959.

34.Burdyga G, Lal S, Varro A, Dimaline R, Thompson DG, and Dockray G. Expression of cannabinoid CB1 receptors by vagal afferent neurons is inhibited by cholecystokinin. *J Neurosci* 24: 2708-2715, 2004.

35.Burdyga G, Varro A, Dimaline R, Thompson DG, and DocKray GJ. Feeding-dependent depression of melanin-concentrating hormone and melanin-concentrating hormone receptor-1 expression in vagal afferent neurons. *Neuroscience* 137: 1405-1415, 2006.

36.Burdyga G, Varro A, Dimaline R, Thompson DG, and Dockray GJ. Ghrelin receptors in rat and human nodose ganglia: putative role in regulating CB-1 and MCH receptor abundance. *Am J Physiol Gastrointest Liver Physiol* 290: 1289-1297, 2006.

37.Bustin SA. Absolute quantification of mRNA using real-time reverse transcription polymerase chain reaction assays. *J Mol Endocrinol* 25: 169-193, 2000.

38.Bustin SA. Quantification of mRNA using real-time reverse transcription PCR (RT-PCR): trends and problems. *J Mol Endocrinol* 29: 23-39, 2002.

39.Bytzer P, Leemon M, Young LJ, Jones MP, Horowitz M, and Talley NJ. Diabetes mellitus is associated with an increased prevalence of gastrointestinal symptoms: results from a population-based survey of 15,000 adults *Arch Int Med* 86: 5836-5837, 2001.

40.Cetin Y and Grube D. Topology of chromogranins in secretory granules of endocrine cells. *Histochemistry* 96: 301-310, 1991.

41.Chandrashekar J, Hoon MA, Ryba NJ, and Zuker CS. The receptors and cells for mammalian taste. *Nature* 444: 288-294, 2006.

42.Chaudhri O, Small C, and Bloom S. Gastrointestinal hormones regulating appetite. *Philos Trans R Soc Lond B Biol Sci* 361: 1187-1209, 2006.

43.Cheeseman C. Role of intestinal basolateral membrane in absorption of nutrients. *Am J Physiol* 263: R482-488, 1992.

44.Chen MC, Wu SV, Reeve JR, Jr., and Rozengurt E. Bitter stimuli induce Ca2+ signaling and CCK release in enteroendocrine STC-1 cells: role of L-type voltage-sensitive Ca2+ channels. *Am J Physiol Cell Physiol* 291: C726-739, 2006.

45.Christianson JA, Traub RJ, and Davis BM. Differences in spinal distribution and neurochemical phenotype of colonic afferents in mouse and rat. *J Comp Neurol* 494: 246-259, 2006.

46.Clapp TR, Medler KF, Damak S, Margolskee RF, and Kinnamon SC. Mouse taste cells with G protein-coupled taste receptors lack voltage-gated calcium channels and SNAP-25. *BMC Biol* 4: 7, 2006.

47.Clapp TR, Yang R, Stoick CL, Kinnamon SC, and Kinnamon JC. Morphologic characterization of rat taste receptor cells that express components of the phospholipase C signaling pathway. *J Comp Neurol* 468: 311-321, 2004.

48.Clarke GD and Davison JS. Mucosal receptors in the gastric antrum and small intestine of the rat with afferent fibres in the cervical vagus. *J Physiol* 284: 55-67, 1978.

49.Coates MD, Mahoney CR, Linden DR, Sampson JE, Chen J, Blaszyk H, Crowell MD, Sharkey KA, Gershon MD, Mawe GM, and Moses PL. Molecular defects in mucosal serotonin content and decreased serotonin reuptake transporter in ulcerative colitis and irritable bowel syndrome. *Gastroenterology* 126: 1657-1664, 2004.

50.Coldwell JR, Phillis BD, Sutherland K, Howarth GS, and Blackshaw LA. Increase responsiveness of rat colonic splanchnic afferents to 5-HT after inflammation and recovery. *J Physiol* 579: 203-213, 2007.

51.Conigrave AD and Brown EM. Taste receptors in the gastrointestinal tract II. L-amino acid sensing by calcium-sensing receptors: implications for GI pysiology. *Am J Physiol Gastrointest Liver Physiol* 291: 753-761, 2006.

52.Conigrave AD, Quinn SJ, and Brown EM. L-amino acid sensing by the extracellular Ca2+-sensing receptor. *Proc Natl Acad Sci U S A* 97: 4814-4819, 2000.

53.Cooke AR and Clark ED. Effect of first part of the duodenum on gastric emptying in dogs: response to acid, fat, glucose and neural blockade. *Gastroenterology* 70: 550-555, 1976.

54.Cooper HS, Murthy SN, Shah RS, and Sedergran DJ. Clinicopathologic study of dextran sulfate sodium experimental murine colitis. *Lab Invest* 69: 238-249, 1993.

55.Cordier-Bussat M, Bernard C, Haouche S, Roche C, Abello J, Chayvialle JA, and Cuber JC. Peptones stimulate cholecystokinin secretion and gene transcription in intestinal cell line STC-1. *Endocrinology* 138: 1137-1144, 1997.

56.Cordier-Bussat M, Bernard C, Levenez F, Klages N, Laser-Ritz B, Philippe J, Chayvialle JA, and Cuber JC. Peptones stimulate both the secretion of the incretin hormone glucagon-like peptide 1 and the transcription of the proglucagon gene. *Diabetes* 47: 1038-1045, 1998.

57.Corvilain B, Abramowicz M, Fery F, Schoutens A, Verlinden M, Balasse E, and Horowitz M. Effect of short-term starvation on gastric emptying in humans: relationship to oral glucose tolerance. *Am J Physiol* 269: G512-517, 1995.

58.Cotroneo P, Grattagliano A, Rapaccini GL, Manto A, Mancini L, Magnani P, Pompili M, Vccioli L, Greco AV, and Ghirlanda G. Gastric emptying rate and hormonal response in type 2 diabetes. *Diabetes Res* 17: 99-104, 1991.

59.Cottrell DF and Iggo A. Mucosal enteroceptors with vagal afferent fibres in the proximal duodenum of sheep. *J Physiol* 354: 497-522, 1984.

60.Cottrell DF and Iggo A. The responses of duodenal tension receptors in sheep to pentagastrin, cholecystokinin and some other drugs. *J Physiol* 353: 477-495, 1984.

61.Cottrell DF and Iggo A. Tension receptors with vagal afferent fibres in the proximal duodenum and pyloric sphincter of sheep. *J Physiol* 354: 457-475, 1984.

62.Cunningham KM, Daly J, Horowitz M, and Read NW. Gastrointestinal adaptation to diets of differing fat composition in human volunteers. *Gut* 32: 483-486, 1991.

63.Cunningham KM, Horowitz M, and Read NW. The effect of short-term dietary supplementation with glucose on gastric emptying in humans. *Br J Nutr* 65: 15-19, 1991.

64.D'Alessio D, Lu W, Sun W, Zheng S, Yang Q, Seeley R, Woods SC, and Tso P. Fasting and postprandial concentrations of GLP-1 in intestinal lymph and portal plasma: evidence for selective release of GLP-1 in the lymph system. *Am J Physiol Regul Integr Comp Physiol* 293: R2163-2169, 2007.

65.Damak S, Rong M, Yasumatsu K, Kokrashvili Z, Varadarajan V, Zou S, Jiang P, Ninomiya Y, and Margolskee RF. Detection of sweet and umami taste in the absence of taste receptor T1r3. *Science* 301: 850-853, 2003.

66.Danilova V, Damak S, Margolskee RF, and Hellekant G. Taste responses to sweet stimuli in alpha-gustducin knockout and wild-type mice. *Chem Senses* 31: 573-580, 2006.

67. Danilova V and Hellekant G. Comparison of the responses of the chorda tympani and glossopharyngeal nerves to taste stimuli in C57BL/6J mice *BMC Neuroscience* 4, 2003.

68.Date Y, Kojima M, Hosoda H, Sawaguchi A, Mondal MS, Suganuma T, Matsukura S, Kangawa K, and Nakazato M. Ghrelin, a novel growth hormone-releasing acylated peptide, is synthesized in a distinct endocrine cell type in the gastrointestinal tracts of rats and humans. *Endocrinology* 141: 4255-4261, 2000.

69.Davison JS. Response of single vagal afferent fibres to mechanical and chemical stimulation of the gastric and duodenal mucosa in cats. *Q J Exp Physiol Cogn Med Sci* 57: 405-416, 1972.

70.De Boer SY, Masclee AA, Lam WF, Jansen JB, and Lamers CB. Effect of intravenous glucose on intravenous amino acid-induced gallbladder contraction and CCK secretion. *Dig Dis Sci* 39: 268-274, 1994.

71.Deacon CF, Nauck MA, Toft-Nielsen M, Pridal L, Willms B, and Holst JJ. Both subcutaneously and intravenously administered glucagon-like peptide 1 are rapidly degraded from the NH2-terminus in type II diabetic patients and in healthy subjects. *Diabetes* 44: 1126-1131, 1995.

72.Deacon CF, Pridal L, Klarskov L, Olsen M, and Holst JJ. Glucagon-like peptide 1 undergoes differential tissue-specific metabolism in the anesthetized pig. *Am J Physiol Endocrinol Metab* 271: E458-464, 1996.

73.DeFazio RA, Dvoryanchikov G, Maruyama M, Kim JW, Pereira E, Roper SD, and Chaudhari N. Separate populations of receptor cells and presynaptic cells in mouse taste buds. *J Neurosci* 26: 3971-3980, 2006.

74.Dhanvantari S, Seidah NG, and Brubaker PL. Role of prohormone convertases in the tissue-specific processing of proglucagon. *Mol Endocrinol* 10: 342-355, 1996.

75.Diamond JM, Karasov WH, Cary C, Enders D, and Yung R. Effect of dietary carbohydrate on monosaccaride uptake by mouse small intestine *in vitro*. *J Physiol* 349: 419-440, 1984.

76.Diez-Sampedro A, Hirayama BA, Osswald C, Gorboulev V, Baumgarter K, Volk C, Wright EM, and Koepsell H. A glucose sensor hiding in a family of transporters. *PNAS* 100: 11753-11758, 2003.

77.Dockray GJ. Luminal sensing in the gut: an overview. *J Physiol Pharmacol* 54 Suppl 4: 9-17, 2003.

78. Drucker DJ. Minireview: the glucagon-like peptides. *Endocrinology* 142: 521-527, 2001.

79.Dubois A, Gross HA, Ebert MH, and Castell DO. Altered gastric emptying and secretion in primary anorexia nervosa. *Gastroenterology* 77: 319-323, 1979.

80.Dumoulin V, Dakka T, Plaisancie P, Chayvialle JA, and Cuber JC. Regulation of glucagon-like peptide-1-(7-36) amide, peptide YY and neurotensin secretion by neurotransmitters and guthormones in the isolated vascularly perfused rat ileum. *Endocrinology* 136: 5182-5188, 1995.

81.Dyer J, Salmon KS, Zibrik L, and Shirazi-Beechey SP. Expression of sweet taste receptors of the T1R family in the intestinal tract and enteroendocrine cells. *Biochem Soc Trans* 33: 302-305, 2005.

82.Dyer J, Vayro S, King TP, and Shirazi-Beechey SP. Glucose sensing in the intestinal epithelium. *Eur J Biochem* 270: 3377-3388, 2003.

83.Dyer J, Wood IS, Palejwala A, Ellis A, and Shirazi-Beechey SP. Expression of monosaccharide transporters in intestine of diabetic humans. *Am J Physiol Gastrointest Liver Physiol* 282: G241-248, 2002.

84.Eissele R, Goke R, Willemer S, Harthus HP, Vermeer H, Arnold R, and Goke B. Glucagon-like peptide-1 cells in the gastrointestinal tract and pancreas of rat, pig and man. *Eur J Clin Invest* 22: 283-291, 1992.

85.El-Salhy M, Zachrisson S, and Spangeus A. Abnormalities of small intestinal endocrine cells in non-obese diabetic mice. *J Diabetes Complications* 12: 215-223, 1998.

86.Elias E, Gibson GJ, Greenwood LF, Hunt JN, and Tripp JH. The slowing of gastric emptying by monosaccharides and disaccharides in test meals. *J Physiol* 194: 317-326, 1968.

87.Esjskaer NT, Bradley JL, Buxton-Thomas MS, Edmonds ME, Howard ER, Purewal T, Thomas PK, and Watkins PJ. Novel surgical treatment and gastric pathology in diabetic gastroparesis. *Diabet Med* 16: 488-495, 1999.

88.Feinle C and Read NW. Ondansetron reduces nausea induced by gastroduodenal stimulation without changing gastric motility. *Am J Physiol* 271: G591-597, 1996.

89.Ferraris RP. Dietary and developmental regulation of intestinal sugar transport. *Biochem J* 360: 265-276, 2001.

90.Ferraris RP and Diamond J. Crypt-villus site of glucose transporter induction by dietary carbohydrate in mouse intestine. *Am J Physiol* 262: G1069-G1073, 1992.

91.Ferraris RP and Diamond JM. Use of phloridzin binding to demonstrate induction of intestinal glucose transporters. *J Membr Biol* 94: 77-82, 1986.

92.Finger TE, Bottger B, Hansen A, Anderson KT, Alimohammadi H, and Silver WL. Solitary chemoreceptor cells in the nasal cavity serve as sentinels of respiration. *PNAS* 100: 8981-8986, 2003.

93.Finger TE, Danilova V, Barrows J, Bartel DL, Vigers AJ, Stone L, Hellekant G, and Kinnamon SC. ATP signaling is crucial for communication from taste buds to gustatory nerves. *Science* 310: 1495-1499, 2005.

94.Flint A, Raben A, Astrup A, and Holst JJ. Glucagon-like peptide-1 promotes satiety and suppresses energy intake in humans. *J Clin Invest* 101: 515-520, 1998.

95.Fox EA, Phillips RJ, Martinson FA, Baronowsky EA, and Powley TL. Vagal afferent innervation of smooth muscle in the stomach and duodenum of the mouse: morphology and topography. *J Comp Neurol* 428: 558-576, 2000.

96.Fraser R, Fone D, Horowitz M, and Dent J. Hyperglycaemia stimulates pyloric motility in normal subjects. *Gut* 32: 475-478, 1991.

97.Fraser RJ, Horowitz M, Maddox AF, Harding PE, Chatterton BE, and Dent J. Hyperglycaemia slows gastric emptying in type 1 (insulin dependent) diabetes mellitus. *Diabetologia* 33: 675-680, 1990.

98.Freeman SL, Bohan DC, Darcel N, and Raybould HE. Luminal glucose sensing in the rat intestine has characteristics of a sodium-glucose co-transporter. *Am J Physiol Gastrointest Liver Physiol* 291: G439-G445, 2006.

99.Fregonesi CE, Miranda-Neto MH, Molinari SL, and Zanoni JN. Quantitative study of the myenteric plexus of the stomcah of rats with streptozotocin-induced diabetes. *Arq Neuropsiquiatr* 59: 50-53, 2001.

100.Fujita T. Taste cells in the gut and on the tongue. Their common, paraneuronal features. *Physiol Behav* 49: 883-885, 1991.

101.Furness JB, Kunze WA, and Clerc N. Nutrient tasting and signaling mechanisms in the gut. II. The intestine as a sensory organ: neural, endocrine, and immune responses. *Am J Physiol* 277: G922-928, 1999.

102.Gebert A, al-Samir K, Werner K, Fassbender S, and Gebhard A. The apical membrane of intestinal brush cells possesses a specialised, but species-specific, composition of glycoconjugates--on-section and in vivo lectin labelling in rats, guinea-pigs and mice. *Histochem Cell Biol* 113: 389-399, 2000.

103.Gebert A and Cetin Y. Expression of fucose residues in entero-endocrine cells. *Histochem Cell Biol* 109: 161-165, 1998.

104.Gebhard A and Gebert A. Brush cells of the mouse intestine possess a specialized glycocalyx as revealed by quantitative lectin histochemistry. Further evidence for a sensory function. *J Histochem Cytochem* 47: 799-808, 1999.

105.Gershon MD and Tack J. The serotonin signaling system: from basic understanding to drug development for functional GI disorders. *Gastroenterology* 132: 397-414, 2007.

106.Gibbs J, Maddison SP, and Rolls ET. Satiety role of the small intestine examined in sham-feeding rhesus monkeys. *J Comp Physiol Psychol* 95: 1003-1015, 1981.

107.Gilbertson TA. Gustatory mechanisms for the detection of fat. *Curr Opin Neurobiol* 8: 447-452, 1998.

108.Gilbertson TA, Damak S, and Margolskee RF. The molecular physiology of taste transduction. *Curr Opin Neurobiol* 10: 519-527, 2000.

109.Glendinning JI, Bloom LD, Onishi M, Zheng KH, Damak S, Margolskee RF, and Spector AC. Contribution of alpha-gustducin to taste-guided licking responses of mice. *Chem Senses* 30: 299-316, 2005.

110.Gouyon F, Caillaud L, Carriere V, Klein C, Dalet V, Citadelle D, Kellet GL, Thorens B, Leturque A, and Brot-Laroche E. Simple-sugar meals target GLUT2 at enterocyte apical membranes to improve sugar absorption: a study in GLUT2-null mice. *J Physiol* 552: 823-832, 2003.

111.Gribble FM, Williams L, Simpson AK, and Reimann F. A novel glucose-sensing mechanism contributing to glucagon-like peptide-1 secretion from the GLUTag cell line. *Diabetes* 52: 1147-1154, 2003.

112.Grundy D. Signalling the state of the digestive tract. *Auton Neurosci*, 2006.

113.Grundy D. Vagal afferent mechanisms of mechano- and chemoreception. In: *Neuroanatomy and physiology of abdominal vagal afferents*, edited by Ritter S, Ritter RC and Barnes CD: CRC Press Inc., 1992, p. 181-191.

114.Gygi SP, Rochon Y, Franza BR, and Aebersold R. Correlation between protein and mRNA abundance in yeast. *Mol Cell Biol* 19: 1720-1730, 1999.

115.Hansen L, Deacon CF, Orskov C, and Holst JJ. Glucagon-like peptide-1-(7-36)amide is transformed to glucagon-like peptide-1-(9-36)amide by dipeptidyl peptidase IV in the capillaries supplying the L cells of the porcine intestine. *Endocrinology* 140: 5356-5363, 1999.

116.Hardcastle J, Hardcastle PT, and Sanford PA. Effect of actively transported hexoses on afferent nerve discharge from rat small intestine. *J Physiol* 285: 71-84, 1978.

117.Hass N, Schwarzenbacher K, and Breer H. A cluster of gustducin-expressing cells in the mouse stomach associated with two distinct populations of enteroendocrine cells. *Histochem Cell Biol* 128: 457-471, 2007.

118.He CL, Soffer EE, Ferris CD, Walsh RM, Szurszewski JH, and Farrugia G. Loss of interstitial cells of Cajal and inhibitory innervation in insulin-dependent diabetes. *Gastroenterology* 121: 427-434, 2001.

119.He W, Danilova V, Zou S, Hellekant G, Max M, Margolskee RF, and Damak S. Partial rescue of taste responses of alpha-gustducin null mice by transgenic expression of alpha-transducin. *Chem Senses* 27: 719-727, 2002.

120.He W, Yasumatsu K, Varadarajan V, Yamada A, Lem J, Ninomiya Y, Margolskee RF, and Damak S. Umami taste responses are mediated by alpha-transducin and alpha-gustducin. *J Neurosci* 24: 7674-7680, 2004.

121.Hebbard GS, Samsom M, Sun WM, Dent J, and Horowitz M. Hyperglycemia affects proximal gastric motor and sensory function during small intestinal triglyceride infusion. *Am J Physiol* 271: G814-819, 1996.

122.Hebbard GS, Samson M, Andrews JM, Carman D, Tansell B, Sun WM, Dent J, and Horowitz M. Hyperglycemia affects gastric electrical rhythm and nausea during intraduodenal triglyceride infusion. *Dig Dis Sci* 42: 568-575, 1997.

123.Hebbard GS, Sun W, Dent J, and Horowitz M. Hyperglycaemia affects proximal gastric motor and sensory function in normal subjects. *Eur J Gastroenterol Hepatol* 8: 211-217, 1996.

124.Heddle R, Fone D, Dent J, and Horowitz M. Stimulation of pyloric motility by intraduodenal dextrose in normal subjects. *Gut* 29: 1349-1357, 1988.

125.Hellstrom PM and Naslund E. Interactions between gastric emptying and satiety, with special reference to glucagon-like peptide-1. *Physiol Behav* 74: 735-741, 2001.

126.Herman RH. Hydrolysis and absorption of carbohydrates, and adaptive responses of the jejunum. In: *Sugars in nutrition*, edited by Sipple HL and McNutt KW. New York: Acadmic Press, 1974.

127.Herness MS and Gilbertson TA. Cellular mechanisms of taste transduction. *Annu Rev Physiol* 61: 873-900, 1999.

128.Herness S, Zhao FL, Kaya N, Shen T, Lu SG, and Cao Y. Communication Routes within the Taste Bud by Neurotransmitters and Neuropeptides. *Chem Senses* 30 Suppl 1: i37-i38, 2005.

129.Herness S, Zhao FL, Lu SG, Kaya N, and Shen T. Expression and physiological actions of cholecystokinin in rat taste receptor cells. *J Neurosci* 22: 10018-10029, 2002.

130.Hicks GA, Coldwell JR, Schindler M, Ward PA, Jenkins D, Lynn PA, Humphrey PP, and Blackshaw LA. Excitation of rat colonic afferent fibres by 5-HT_3 receptors. *J Physiol* 544: 861-869, 2002.

131.Hines OJ, Whang EE, Bilchik AJ, Zinner MJ, Welton ML, Lane J, McFadden DW, and Ashley SW. Role of Na+-glucose cotransport in jejunal meal-induced absorption. *Dig Dis Sci* 45: 1-6, 2000.

132.Hisatsune C, Yasumatsu K, Takahashi-Iwanaga H, Ogawa N, and HKuroda Y. Abnormal taste perception in mice lacking the Type 3 Inositol 1, 4, 5-trisphosphate receptor. *J Biol Chem* Epub ahead of print, 2007.

133.Hofer D, Asan E, and Drenckhahn D. Chemosensory Perception in the Gut. *News Physiol Sci* 14: 18-23, 1999.

134.Hofer D and Drenckhahn D. Cytoskeletal markers allowing discrimination between brush cells and other epithelial cells of the gut including enteroendocrine cells. *Histochem Cell Biol* 105: 405-412, 1996.

135.Hofer D and Drenckhahn D. Identification of the taste cell G-protein, alpha-gustducin, in brush cells of the rat pancreatic duct system. *Histochem Cell Biol* 110: 303-309, 1998.

136.Hofer D, Jons T, Kraemer J, and Drenckhahn D. From cytoskeleton to polarity and chemoreception in the gut epithelium. *Ann N Y Acad Sci* 859: 75-84, 1998.

137.Hofer D, Puschel B, and Drenckhahn D. Taste receptor-like cells in the rat gut identified by expression of alpha-gustducin. *Proc Natl Acad Sci U S A* 93: 6631-6634, 1996.

138.Holsbeeks I, Lagatie O, Van Nuland A, Van de Velde S, and Thevelein JM. The eukaryotic plasma membrane as a nutrient-sensing device. *Trends Biochem Sci* 29: 556-564, 2004.

139.Holt S, Ford MJ, Grant S, and Heading RC. Abnormal gastric emptying in primary anorexia nervosa. *British Journal of Psychiatry* 139: 550-552, 1981.

140.Holzer HH, Turkelson CM, Solomon TE, and Raybould HE. Intestinal lipid inhibits gastric emptying via CCK and a vagal capsaicin-sensitive afferent pathway in rats. *Am J Physiol Gastrointest Liver Physiol* 267: G625-G629, 1994.

141.Holzer P, Michl T, Danzer M, Jocic M, Schicho R, and Lippe IT. Surveillance of the gastrointestinal mucosa by sensory neurons. *J Physiol Pharmacol* 52: 505-521, 2001.

142.Hoon MA, Adler E, Lindemeier J, Battey JF, Ryba NJ, and Zuker CS. Putative mammalian taste receptors: a class of taste-specific GPCRs with distinct topographic selectivity. *Cell* 96: 541-551, 1999.

143.Horowitz M, Cunningham KM, Wishart JM, Jones KL, and Read NW. The effect of short-term dietary supplementation with glucose on gastric emptying of glucose and fructose and oral glucose tolerance in normal subjects. *Diabetologia* 39: 481-486, 1996.

144.Horowitz M, Edelbrock M, Fraser R, Maddox AF, and Wishart JM. Disordered gastric motor function in diabetes mellitus: recent insights into prevalence, pathophysiology, clinical relevance and treatment. *Scand J Gastroenterol* 26: 673-684, 1991.

145.Horowitz M, Edelbrock M, Wishart JM, and Straathof JW. Relationship between oral glucose torlerance and gastric emptying in normal healthy subjects. *Diabetologia* 36: 857-862, 1993.

146.Horowitz M, Harding PE, Maddox AF, Akkermans LM, Chatterton BE, and Shearman DJ. Gastric and oesophageal emptying in patients with type 2 (non-insulin-dependent) diabetes mellitus. *Diabetologia* 32: 151-159, 1989.

147.Horowitz M, Maddox AF, Wishart JM, Harding PE, Chatterton BE, and Shearman DJC. Relationships between oesophageal transit and solid and liquid gastric emptying in diabetes mellitus. *Eur J Nucl Med* 18: 229-234, 1991.

148.Horowitz M and Nauck MA. To be or not to be - an incretin or enterogastrone? *Gut* 55: 148-150, 2006.

149.Horowitz M, O'Donovan D, Jones KL, Feinle C, Rayner CK, and Samsom M. Gastric emptying in diabetes: clinical significance and treatment. *Diabet Med* 19: 177-194, 2002.

150.Houghton LA, Atkinson W, Whitaker RP, Whorwell PJ, and Rimmer MJ. Increased platelet depleted plasma 5-hydroxytryptamine concentration following meal ingestion in symptomatic female subjects with diarrhoea predominant irritable bowel syndrome *Gut* 52: 663-670, 2003.

151.Hoyt EC, Lund PK, Winesett DE, Fuller CR, Ghatei MA, Bloom SR, and Ulshen MH. Effects of fasting, refeeding, and intraluminal triglyceride on proglucagon expression in jejunum and ileum. *Diabetes* 45: 434-439, 1996.

152.Huang L, Shanker YG, Dubauskaite J, Zheng JZ, Yan W, Rosenzweig S, Spielman AI, Max M, and Margolskee RF. Ggamma13 colocalizes with gustducin in taste receptor cells and mediates IP3 responses to bitter denatonium. *Nat Neurosci* 2: 1055-1062, 1999.

153.Huang YJ, Maruyama Y, Dvoryanchikov G, Pereira E, Chaudhari N, and Roper SD. The role of pannexin 1 hemichannels in ATP release and cell-cell communication in mouse taste buds. *Proc Natl Acad Sci U S A* 104: 6436-6441, 2007.

154.Hughes PA, Brierley SM, Young RL, and Blackshaw LA. Localization and comparative analysis of acid-sensing ion channel (ASIC1, 2 and 3) mRNA expression in mouse colonic sensory neurons within thoracolumbar dorsal root gangia. *J Comp Neurol* 500: 863-875, 2007.

155.Imeryuz N, Yegen BC, Bozkurt A, Coskun T, Villanueva-Penacarrillo ML, and Ulusoy NB. Glucagon-like peptide-1 inhibits gastric emptying via vagal afferent-mediated central mechanisms. *Am J Physiol* 273: G920-927, 1997.

156.Inagaki E, Natori Y, Ohgishi Y, Hayashi H, and Suzuki Y. Segmental differences of mucosal damage along the length of a mouse small intestine in an Ussing chamber. *J Nutr Sci Vitamol (Tokyo)* 51: 406-412, 2005.

157.Itoh Y, Kawamata Y, Harada M, Kobayashi M, Fujii R, Fukusumi S, Ogi K, Hosoya M, Tanaka Y, Uejima H, Tanaka H, Maruyama M, Satoh R, Okubo S, Kizawa H, Komatsu H, Matsumura F, Noguchi

Y, Shinohara T, Hinuma S, Fujisawa Y, and Fujino M. Free fatty acids regulate insulin secretion from pancreatic beta cells through GPR40. *Nature* 422: 173-176, 2003.

158. Iwasaki H, Kajimura M, Osawa S, Kanaoka S, Furuta T, Ikuma M, and Hishida A. A deficiency of gastric interstitial cells of Cajal accompanied by decreased expression of neuronal nitric oxide synthase and substance P in patients with type 2 diabetes mellitus. *J Gastroenterol* 41: 1076-1087, 2006.

159. Jang HJ, Kokrashvili Z, Theodorakis MJ, Carlson OD, Kim BJ, Zhou J, Kim HH, Xu X, Chan SL, Juhaszova M, Bernier M, Mosinger B, Margolskee RF, and Egan JM. Gut-expressed gustducin and taste receptors regulate secretion of glucagon-like peptide-1. *Proc Natl Acad Sci U S A* 104: 15069-15074, 2007.

160. Jang HJ, Kokrashvili Z, Theodorakis MJ, Carslon OD, Kim BJ, Zhou JY, Kim HH, Xu X, Chan SL, Juhaszova M, Bernier M, Mosinger B, Margolskee RF, and Egan JM. Gut-expressed gustducin and taste receptors regulate secretion of glucagon-like peptide-1. *PNAS*: 1-6, 2007.

161. Jin SLC, Han VKM, Simmons JG, Towle AC, Lauder JM, and Lund PK. Distribution of glucagon-like peptide-1 (GLP-1), glucagon, and glicentin in the rat brain. *J Comp Neurol* 271: 519-532, 1988.

162. Johansson C. Studies of gastrointestinal interactions. VII. Characteristics of the absorption pattern of sugar, fat and protein from composite meals in man. A quantitative study. *Scand J Gastroenterol* 10: 33-42, 1975.

163. Jones KL, Horowitz M, Carney BI, Wishart JM, Guha S, and Green L. Gastric emptying in early non insulin-dependent diabetes mellitus. *J Nucl Med* 37: 1643-1648, 1996.

164. Kastin AJ, Akerstrom V, and Pan W. Interactions of GLP-1 with the blood-brain barrier. *J Mol Neurosci* 18: 7-14, 2002.

165. Kataoka S, Toyono T, Seta Y, and Toyoshima K. Expression of ATP-gated $P2X_3$ receptors in rat gustatory papillae and taste buds. *Arch Histol Cytol* 69: 281-288, 2006.

166. Kellet GL and Brot-Laroche E. Apical GLUT2: a major pathway of intestinal sugar absorption. *Diabetes* 54: 3056-3062, 2005.

167. Kellet GL and Helliwell PA. The diffusive component of intestinal glucose absorption is mediated by the glucose-induced recruitment of GLUT2 to the brush-border membrane. *Biochem J* 350: 155-162, 2000.

168. Keshavarzian A, Iber FL, and Vaeth J. Gastric emptying in patients with insulin-requiring diabetes mellitus. *Am J Gastroenterol* 82: 29-35, 1987.

169. Kieffer TJ, McIntosh CHS, and Pederson RA. Degradation of glucose-dependent insulinotropic polypeptide and truncated glucagon-like peptide 1 in vitro and in vivo by dipeptidyl peptidase IV. *Endocrinology* 136: 3585-3596, 1995.

170. Kim M, Cooke HJ, Javed NH, Carey HV, Christofi F, and Raybould HE. D-glucose releases 5-hydroxytryptamine from human BON cells as a model of enterochromaffin cells. *Gastroenterology* 121: 1400-1406, 2001.

171. Kim M, Javed NH, Yu JG, Christofi F, and Cooke HJ. Mechanical stimulation activates Galphaq signaling pathways and 5-hydroxytrptamine release from human carcinoid BON cells. *J Clin Invest* 108: 1051-1059, 2001.

172. Kim MR, Kusakabe Y, Miura H, Shindo Y, Ninomiya Y, and Hino A. Regional expression patterns of taste receptors and gustducin in the mouse tongue. *Biochem Biophys Res Commun* 312: 500-506, 2003.

173. Kinnamon SC and Margolskee RF. Mechanisms of taste transduction. *Curr Opin Neurobiol* 6: 506-513, 1996.

174. Kirkup AJ, Brunsden AM, and Grundy D. Receptors and transmission in the brain-gut axis: potential for novel therapies. I. Receptors on visceral afferents. *Am J Physiol Gastrointest Liver Physiol* 280: G787-794, 2001.

175. Kitagawa M, Kusakabe Y, Miura H, Ninomiya Y, and Hino A. Molecular genetic identification of a candidate receptor gene for sweet taste. *Biochem Biophys Res Commun* 283: 236-242, 2001.

176. Koch KL. Diabetic gastropathy: gastric neuromuscular dysfunction in diabetes mellitus: a review of symptoms, pathophysiology, and treatment. *Dig Dis Sci* 44: 1061-1075, 1999.

177.Kojima M, Hosoda H, Date Y, Nakazato M, Matsuo H, and Kangawa K. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. *Nature* 402: 656-660, 1999.

178.Kreymann B, Ghatei MA, Burnet P, Williams G, Kanse S, Diani AR, and Bloom SR. Characterisation of glucagon-like peptide-1 (7-36) amide in the hypothalamus. *Brain Res* 502: 325-331, 1989.

179.Kugler P, Hofer D, Mayer B, and Drenckhahn D. Nitric oxide synthase and NADP-linked glucose-6-phosphate dehydrogenase are co-localized in brush cells of rat stomach and pancreas. *J Histochem Cytochem* 42: 1317-1321, 1994.

180.Kusakabe Y, Yasuoka A, Asano-Miyoshi M, Iwabuchi K, Matsumoto I, Arai S, Emori Y, and Abe K. Comprehensive study on G protein alpha-subunits in taste bud cells, with special reference to the occurrence of Galphai2 as a major Galpha species. *Chem Senses* 25: 525-531, 2000.

181.Lal S, Kirkup AJ, Brunsden AM, Thompson DG, and Grundy D. Vagal afferent responses to fatty acids of different chain length in the rat. *Am J Physiol Gastrointest Liver Physiol* 281: G907-G915, 2001.

182.Larsen PJ and Holst JJ. Glucagon-related peptide 1 (GLP-1): Hormone and neurotransmitter. *Regul Pept* 128: 97-107, 2005.

183.Lavin JH, Wittert G, and Sun WM. Appetite regulation by carbohydrate: role of blood glucose and gastrointestinal hormones. *Am J Physiol* 271: E209-214, 1996.

184.Leek BF. Abdominal visceral receptors. In: *Handbook of sensory physiology*, edited by Neil E. New York: Springer-Verlag, 1972, p. 113-160.

185.Li X, Staszewski L, Xu H, Durick K, Zoller M, and Adler E. Human receptors for sweet and umami taste. *Proc Natl Acad Sci U S A* 99: 4692-4696, 2002.

186. Liman E. TRPM5 and taste transduction. *Handb Exp Pharmacol* 179: 287-298, 2007.

187.Lin HC. Abnormal intestinal feedback in disorders of gastric emptying. *Dig Dis Sci* 39: 54S-55S, 1994.

188.Lin HC, Doty JE, Reedy TJ, and Meyer JH. Inhibition of gastric emptying by glucose depends on length of intestine exposed to nutrient. *Am J Physiol* 256: G404-411, 1989.

189.Lin HC, Elashoff JD, Gu YG, and Meyer JH. Nutrient feedback inhibition of gastric emptying plays a larger role than osmotically dependent duodenal resistance. *Am J Physiol* 265: G672-676, 1993.

190.Lindemann B. Receptors and transduction in taste. *Nature* 413: 219-225, 2001.

191.Lindemann B. Taste reception. *Physiol Rev* 76: 718-766, 1996.

192.Lingenfelser T, Sun W, Hebbard GS, Dent J, and Horowitz M. Effects of duodenal distension on antropyloroduodenal pressures and perception are modified by hyperglycemia. *Am J Physiol* 276: G711-718, 1999.

193.Little TJ, Doran S, Meyer JH, Smout AJPM, O'Donovan D, Wu K, Jones KL, Wishart JM, Rayner CK, Horowitz M, and Feinle-Bisset C. The release of GLP-1 and ghrelin, but not GIP and CCK, by glucose is dependent upon the length of small intestine exposed. *Am J Physiol Endocrinol Metab* 291: E647-E655, 2006.

194.Liu D and Liman ER. Intracellular Ca2+ and the phospholipid PIP2 regulate the taste transduction ion channel TRPM5. *Proc Natl Acad Sci U S A* 100: 15160-15165, 2003.

195.Liu M, Seino S, and Kirchgessner AL. Identification and characterization of glucoresponsive neurons in the enteric nervous system. *J Neurosci* 19: 10305-10317, 1999.

196.Livak KJ and Schmittgen TD. Analysis of relative gene expression data using real-time quantitative PCR and the 2(-Delta Delta C(T)) Method. *Methods* 25: 402-408, 2001.

197.Lovshin J and Drucker DJ. Synthesis, secretion and biological actions of the glucagon-like peptides. *Pediatric Diabetes* 1: 49-57, 2000.

198.Lu WJ, Yang Q, Sun W, Woods SC, D'Alessio D, and Tso P. The regulation of the lymphatic secretion of glucagon-like peptide-1 (GLP-1) by intestinal absorption of fat and carbohydrate. *Am J Physiol Gastrointest Liver Physiol* 293: G963-971, 2007.

199.Lundgren O. Interface between the intestinal environment and the nervous system. *Gut* 53 Suppl 2: ii16-18, 2004.

200.Lynn PA and Blackshaw LA. In vitro recordings of afferent fibres with receptive fields in the serosa, muscle and mucosa of rat colon. *J Physiol* 518: 271-282, 1999.

201.Mace OJ, Affleck J, Patel N, and Kellet GL. Sweet taste receptors in rat small intestine stimulate glucose absorption through apical GLUT2. *J Physiol* 582: 379-392, 2007.

202.MacGregor IL, Gueller R, Watts HD, and Meyer JH. The effect of acute hyperglycaemia on gastric emptying in man. *Gastroenterology* 70: 190-196, 1976.

203.Margolskee RF, Dyer J, Kokrashvili Z, Salmon KS, Ilegems E, Daly K, Maillet EL, Ninomiya Y, Mosinger B, and Shirazi-Beechey SP. T1R3 and gustducin in gut sense sugars to regulate expression of Na^+-glucose cotransporter 1. *Proc Natl Acad Sci U S A*, 2007.

204.Martin DC, Magnant AD, and Kellum JM, Jr. Luminal hypertonic solutions stimulate concentration-dependent duodenal serotonin release. *Surgery* 106: 325-331, 1989.

205.Matsumura S, Mizushige T, Yoneda T, Iwanaga T, Tsuzuki S, Inoue K, and Fushiki T. GPR expression in the rat taste bud relating to fatty acid sensing. *Biomed Res* 28: 49-55, 2007.

206.Max M, Shanker YG, Huang L, Rong M, Liu Z, Campagne F, Weinstein H, Damak S, and Margolskee RF. Tas1r3, encoding a new candidate taste receptor, is allelic to the sweet responsiveness locus Sac. *Nat Genet* 28: 58-63, 2001.

207.McCallum R, Mittal R, and Sluss J. Effect of ICS 205-125, a potential prokinetic agent on upper gastrointestinal motility in normal subjects (Abstract). *Gastroenterology* 96: A332, 1989.

208.McLaughlin SK, McKinnon PJ, and Margolskee RF. Gustducin is a taste-cell-specific G protein closely related to the transducins. *Nature* 357: 563-569, 1992.

209.Mei N. Vagal glucoreceptors in the small intestine of the cat. *J Physiol* 282: 485-506, 1978.

210.Meier JJ, Gallwitz B, Scmidt WE, and Nauck MA. Glucagon-like peptide 1 (GLP-1) as a regulator of food intake and body weight: therapeutic perspectives. *Eur J Pharmacol* 440: 531-544, 2002.

211.Meier JJ and Nauck MA. Glucagon-like peptide 1 (GLP-1) in biology and pathology. *Diabetes Metab Res Rev* 21: 91-117, 2005.

212.Mentlein R. Dipeptidyl-peptidase IV (CD26)-role in the inactivation of regulatory peptides. *Regul Pept* 85: 9-24, 1999.

213.Mentlein R, Gallwitz B, and Schmidt WE. Dipeptidyl-peptidase IV hydrolyses gastric inhibitory polypeptide, glucagon-like peptide-1(7-36)amide, peptide histidine methionine an is responsible for their degredation in human serum. *Eur J Biochem* 214: 829-835, 1993.

214.Meyer JH. Feedback regulation and sensation. *Dig Dis Sci* 39: 56S-59S, 1994.

215.Meyer JH, Hlinka M, Tabrizi Y, DiMaso N, and Raybould HE. Chemical specificities and intestinal distributions of nutrient-driven satiety. *Am J Physiol Regul Integr Comp Physiol* 275: R1293-R1307, 1998.

216.Meyer JH, Tabrizi Y, DiMaso N, Hlinka M, and Raybould HE. Length of intestinal contact on nutrient-driven satiety. *Am J Physiol Regul Integr Comp Physiol* 275: R1308-R1319, 1998.

217.Miki T, Nagashima K, and Seino S. The structure and function of the ATP-sensitive K^+ channel in insulin-secreting pancreatic β-cells. *J Mol Endocrinol* 22: 113-123, 1999.

218.Miller LJ, Malagelada JR, Taylor WF, and Go VL. Intestinal control of human postprandial gastric function: the role of components of jejunoileal chyme in regulating gastric secretion and gastric emptying. *Gastroenterology* 80: 763-769, 1981.

219.Miyamoto Y, Yoneda M, Morikawa A, Itoh H, and Makino I. Gastric neuropeptides and gastric motor abnormality in streptozotocin-induced diabetic rats: observation for four weeks after streptozotocin. *Dig Dis Sci* 46: 1596-1603, 2001.

220.Miyoshi MA, Abe K, and Emori Y. IP(3) receptor type 3 and PLCbeta2 are co-expressed with taste receptors T1R and T2R in rat taste bud cells. *Chem Senses* 26: 259-265, 2001.

221.Mizushige T, Inoue K, and Fushiki T. Why is fat so tasty? Chemical reception of fatty acid on the tongue. *J Nutr Sci Vitaminol (Tokyo)* 53: 1-4, 2007.

222.Montmayeur JP, Liberles SD, Matsunami H, and Buck LB. A candidate taste receptor gene near a sweet taste locus. *Nat Neurosci* 4: 492-498, 2001.

223.Montmayeur JP and Matsunami H. Receptors for bitter and sweet taste. *Curr Opin Neurobiol* 12: 366-371, 2002.

224.Moran TH, Knipp S, and Schwartz GJ. Gastric and duodenal features of meals mediate controls of liquid gastric emptying during fill in rhesus monkeys. *Am J Physiol Regul Integr Comp Physiol* 277: R1282-R1290, 1999.

225.Moran TH, Ladenheim EE, and Schwartz GJ. Within-meal gut feedback signaling. *International Journal of Obesity* 25: S39-41, 2001.

226.Moran TH and McHugh PR. Distinctions among three sugars in their effects on gastric emptying and satiety. *Am J Physiol Regul Integr Comp Physiol* 241: R25-R30, 1981.

227.Moriarty P, Dimaline R, Thompson DG, and Dockray GJ. Characterization of cholecystokinin A and B receptors expressed by vagal afferent neurons. *Neuroscience* 79: 905-913, 1997.

228.Morroni M, Cangiotti AM, and Cinti S. Brush cells in the human duodenojejunal junction: an ultrastructural study. *J Anat* 211: 125-131, 2007.

229.Mortensen K, Christensen LL, Holst JJ, and Orskov C. GLP-1 and GIP are colocalized in a subset of endocrine cells in the small intestine. *Regul Pept* 114: 189-196, 2003.

230.Nagata K, Fujimiya M, Sugiura H, and Uehara M. Intracellular localization of serotonin in mast cells of the colon in normal and colitis rats. *Histochem J* 33: 550-568, 2001.

231.Nakabayashi H, Nishizawa M, Nakagawa A, Takeda R, and Niijima A. Vagal hepatopancreatic reflex effect evoked by introportal appearance of tGLP-1. *Am J Physiol Endocrinol Metab* 34: E808-E813, 1996.

232.Nakade Y, Tsukamoto K, Iwa M, Pappas TN, and Takahashi T. Glucagon like peptide-1 accelerates colonic transit via central CRF and peripheral vagal pathways in conscious rats. *Auton Neurosci* 131: 50-56, 2007.

233.Nakade Y, Tsukamoto K, Pappas TN, and Takahashi T. Central glucagon like peptide-1 delays solid gastric emptying via central CRF and peripheral sympathetic pathway in rats. *Brain Res* 1111: 117-121, 2006.

234.Nakagawa A, Satake H, Nakabayashi H, Nishizawa M, Furuya K, Nakano S, Kigoshi T, Nakayama K, and Uchida K. Receptor gene expression of glucagon-like peptide-1, but not glucose-dependent insulinotropic polypeptide, in rat nodose ganglion cells. *Auton Neurosci* 110: 36-43, 2004.

235.Nauck MA, Niedereichholz U, Ettler R, Holst JJ, Orskov C, Ritzel U, and Schmiegel WH. Glucagon-like peptide 1 inhibition of gastric empyting outweighs its insulinotropic effects in healthy humans. *Am J Physiol Endocrinol Metab* 273: E981-E988, 1997.

236.Nelson G, Chandrashekar J, Hoon MA, Feng L, Zhao G, Ryba NJ, and Zuker CS. An amino-acid taste receptor. *Nature* 416: 199-202, 2002.

237.Nelson G, Hoon MA, Chandrashekar J, Zhang Y, Ryba NJ, and Zuker CS. Mammalian sweet taste receptors. *Cell* 106: 381-390, 2001.

238.Netzer P, Gaia C, Lourens ST, Reber P, Wildi S, Noelpp U, Ritter EP, Ledermann H, Luscher D, Varga L, Kinser JA, Buchler MW, and Scheurer U. Does intravenous ondansetron affect gastric emptying of a solid meal, gastric electrical activity or blood hormone levels in healthy volunteers? *Aliment Pharmacol Ther* 16: 119-127, 2002.

239.Newson B, Ahlman H, Dahlstrom A, and Nyhus LM. Ultrastructural observations in the rat ileal mucosa of possible epithelial "taste cells" and submucosal sensory neurons. *Acta Physiol Scand* 114: 161-164, 1982.

240.Niijima A. The effect of D-glucose on the firing rate of glucose-sensitive vagal afferents inthe liver in comparison with the effect of 2-deoxy-D-glucose. *J Auton Nerve Syst* 10: 255-260, 1984.

241.Niijima A. Glucose-sensitive afferent nerve fibres inthe hepatic branch of the vagus nerve in the guinea-pig. *J Physiol* 332: 315-323, 1982.

242.Nishizawa M, Nakabayashi H, Kawai K, Ito T, Kawakami S, Nakagawa A, Niijima A, and Uchida K. The hepatic vagal reception of intraportal GLP-1 is via receptor different from the panceratic GLP-1 receptor. *J Auton Nerve Syst* 80: 14-21, 2000.

243.Nishizawa M, Nakabayashi H, Uchida K, Nakagawa A, and Niijima A. The hepatic vagal nerve is receptive to incretin hormone glucagon-like peptide-1, but not to glucose-dependent insulinotropic polypeptide, in the portal vein. *J Auton Nerve Syst* 61: 149-154, 1996.

244.Ohtani N, Sasaki I, Naito H, Shibata C, and Matsuno S. Mediators for fat-induced ileal break are different between stomach and proximal intestine in conscious dogs. *J Gastrointest Surg* 5: 377-382, 2001.

245.Okayasu I, Hatakeyama S, Yamada M, Ohkusa T, Inagaki Y, and Nakaya R. A novel method in the induction of reliable experimental acute and chronic ulcerative colitis in mice. *Gastroenterology* 98: 694-702, 1990.

246.Ordog T, Takayama I, Cheung WKT, Ward SM, and Sanders KM. Remodeling of networks of interstitial cells of Cajal in a murine model of diabetic gastroparesis. *Diabetes* 49: 1731-1739, 2000

247.Orihata M and Sarna SK. Nitric oxide mediates mechano- and chemoreceptor-activated intestinal feedback control of gastric emptying. *Dig Dis Sci* 41: 1303-1309, 1996.

248.Orskov C, Poulsen SS, Moller M, and Holst JJ. Glucagon-like peptide I receptors in the subfornical organ and the area postrema are accessible to circulating glucagon-like peptide I. *Diabetes* 45: 832-835, 1996.

249.Oshima S, Fujimura M, and Fukimiya M. Changes in number of serotonin-containing cells and serotonin levels in the intestinal mucosa of rats with colitis induced by dextran sodium sulfate. *Histochem Cell Biol* 112: 257-263, 1999.

250.Ozeck M, Brust P, Xu H, and Servant G. Receptors for bitter, sweet and umami taste couple to inhibitory G protein signaling pathways. *Eur J Pharmacol* 489: 139-149, 2004.

251.Page AJ and Blackshaw LA. An *in vitro* study of the properties of vagal afferent fibres innervating the ferret oesophagus and stomach. *J Physiol* 512: 907-916, 1998.

252.Page AJ, Martin CM, and Blackshaw LA. Vagal mechanoreceptors and chemoreceptors in mouse stomach and esophagus. *J Neurophysiol* 87: 2095-2103, 2002.

253.Page AJ, Slattery JA, Milte C, Laker R, O'Donnell T, Dorian C, Brierley SM, and Blackshaw LA. Ghrelin selectively reduces mechanosensitivity of upper gastrointestinal vagal afferents. *Am J Physiol Gastrointest Liver Physiol* 292: G1376-1384, 2007.

254.Page AJ, Slattery JA, O'Donnell TA, Cooper NJ, Young RL, and Blackshaw LA. Modulation of gastro-oesophageal vagal afferents by galanin in mouse and ferret. *J Physiol* 563: 809-819, 2005.

255.Page AJ, Young RL, Martin CM, Umaerus M, O'Donnell TA, Cooper NJ, Coldwell JR, Hulander M, Mattsson JP, Lehmann A, and Blackshaw LA. Metabotropic glutamate receptors inhibit mechanosensitivity in vagal sensory neurons. *Gastroenterology* 128: 402-410, 2005.

256.Pappenheimer JR. Intestinal absorption of hexoses and amino acids: from apical cytosol to villus capillaries. *J Membr Biol* 184: 233-239, 2001.

257.Perez CA, Huang L, Rong M, Kozak JA, Preuss AK, Zhang H, Max M, and Margolskee RF. A transient receptor potential channel expressed in taste receptor cells. *Nat Neurosci* 5: 1169-1176, 2002.

258.Pezos N, Sutherland K, Brierley SM, Horowitz M, Blackshaw LA, and Young RL. Vagal afferents do not directly detect intestinal glucose via a sweet taste mechanism. *Gastroenterology* 132: T1937, 2007.

259.Phillips RJ, Baronowsky EA, and Powley TL. Afferent innervation of gastrointestinal tract smooth muscle by the hepatic branch of the vagus. *J Comp Neurol* 384: 248-270, 1997.

260.Prawitt D, Monteilh-Zoller MK, Brixel L, Spangenberg C, Zabel B, Fleig A, and Penner R. TRPM5 is a transient Ca2+-activated cation channel responding to rapid changes in [Ca2+]i. *Proc Natl Acad Sci U S A* 100: 15166-15171, 2003.

261.Pumplin DW, Yu C, and Smith DS. Light and dark cells of rat vallate taste buds are morphologically distinct cell types. *J Comp Neurol* 378: 389-410, 1997.

262.Putney JWJ and McKay RR. Capacitative calcium entry channels. *Bioessays* 21: 38-46, 1999.

263.Racke K and Schworer H. Regulation of serotonin release from the intestinal mucosa. *Pharmacol Res* 23: 13-25, 1991.

264.Randich A, Tyler WJ, Cox JE, Meller ST, Kelm GR, and Bharaj SS. Responses of celiac and cervical vagal afferents to infusions of lipids in the jejunum or ileum of the rat. *Am J Physiol Regul Integr Comp Physiol* 278: R34-R43, 2000.

265.Raybould H. Primary afferent response to signals in the intestinal lumen. *J Physiol* 530: 343, 2001.

266.Raybould HE. Does Your Gut Taste? Sensory Transduction in the Gastrointestinal Tract. *News Physiol Sci* 13: 275-280, 1998.

267.Raybould HE. Visceral perception: sensory transduction in visceral afferents and nutrients. *Gut* 51 Suppl 1: i11-14, 2002.

268.Raybould HE, Glatzle J, Freeman SL, Whited K, Darcel N, Liou A, and Bohan D. Detection of macronutrients in the intestinal wall. *Auton Neurosci*, 2006.

269.Raybould HE, Glatzle J, Robin C, Meyer JH, Phan T, Wong H, and Sternini C. Expression of 5-HT3 receptors by extrinsic duodenal afferents contribute to intestinal inhibition of gastric emptying. *Am J Physiol Gastrointest Liver Physiol* 284: G367-372, 2003.

270.Raybould HE and Holzer H. Dual capsaicin-sensitive afferent pathways mediate inhibition of gastric emptying in rat induced by intestinal carbohydrate. *Neurosci Lett* 141: 236-238, 1992.

271.Raybould HE and Zittel TT. Inhibition of gastric motility induced by intestinal glucose in awake rats: role of Na(+)-glucose co-transporter. *Neurogastroenterol Motil* 7: 9-14, 1995.

272.Rayner CK and Horowitz M. Gastrointestinal motility and glycemic control in diabetes: the chicken and the egg revisited? *J Clin Invest* 116: 299-302, 2006.

273.Rayner CK, Park HS, Doran SM, Chapman IM, and Horowitz M. Effects of cholecystokinin on appetite and pyloric motility during physiological hyperglycemia. *Am J Physiol Gastrointest Liver Physiol* 278: G98-G104, 2000.

274.Rayner CK, Park HS, Wishart JM, Kong M, Doran SM, and Horowitz M. Effects of intraduodenal glucose and fructose on antropyloric motility and appetite in healthy humans. *Am J Physiol Regul Integr Comp Physiol* 278: R360-366, 2000.

275.Rayner CK, Samsom M, Jones KL, and Horowitz M. Relationships of upper gastrointestinal motor and sensory function with glycemic control. *Diabetes Care* 24: 371-381, 2001.

276.Rayner CK, Schwartz MP, van Dam PS, Renooij W, de Smet M, Horowitz M, Smout AJ, and Samsom M. Small intestinal glucose absorption and duodenal motility in type 1 diabetes mellitus. *Am J Gastroenterol* 97: 3123-3130, 2002.

277.Rayner CK, Schwartz MP, van Dam PS, Renooij W, de Smet M, Horowitz M, Wishart JM, Smout AJ, and Samsom M. Upper gastrointestinal responses to intraduodenal nutrient in type 1 diabetes mellitus. *Eur J Gastroenterol Hepatol* 16: 183-189, 2004.

278.Rayner CK, Verhagen MA, Hebbard GS, DiMatteo AC, Doran SM, and Horowitz M. Proximal gastric compliance and perception of distension in type 1 diabetes mellitus: effects of hyperglycemia. *Am J Gastroenterol* 95: 1175-1183, 2000.

279.Reid L, Meyrick B, Antony VB, Chang LY, Crapo JD, and Reynolds HY. The mysterious pulmonary brush cell, a cell in search of a function. *Am J Respir Crit Care Med* 172: 136-139, 2005.

280.Reimann F and Gribble FM. Glucose-sensing in glucagon-like peptide-1-secreting cells. *Diabetes* 51: 2757-2763, 2002.

281.Rigaud D, Bedig G, Marrouche M, Vulpillat M, Bonfils S, and Apelbaum M. Delayed gastric emptying in anorexia nervosa is improved by completion of a renutrition program. *Dig Dis Sci* 33: 919-925, 1988.

282.Rindi G, Leiter AB, Kopin AS, Bordi C, and Solcia E. The "normal" endocrine cell of the gut: changing concepts and new evidences. *Ann N Y Acad Sci* 1014: 1-12, 2004.

283.Ritzel U, Fromme A, Ottleben M, Leonhardt U, and Ramadori G. Release of glucagon-like peptide-1 (GLP-1) by carbohydrates in the perfused rat ileum. *Acta Diabetol* 34: 18-21, 1997.

284.Rocca AS and Brubaker PL. Role of the vagus nerve in mediating proximal nutrient-induced glucagon-like peptide-1 secretion. *Endocrinology* 140: 1687-1694, 1999.

285.Rogers RC, McTigue DM, and Hermann GE. Vagovagal reflex control of digestion: afferent moudulation by neural and 'endoneurocrine' factors. *Am J Physiol Gastrointest Liver Physiol* 31: G1-G10, 1995.

286.Rolland F, Winderickx J, and Thevelein JM. Glucose-sensing mechanisms in eukaryotic cells. *Trends Biochem Sci* 26: 310-317, 2001.

287. Roper SD. Cell communication in taste buds. *Cell Mol Life Sci* 63: 1494-1500, 2006.

288.Roper SD. Signal transduction and information processing in mammalian taste buds. *Pflugers Arch* 454: 759-776, 2007.

289.Rossler P, Kroner C, Freitag J, Noe J, and Breer H. Identification of a phospholipase C beta subtype in rat taste cells. *Eur J Cell Biol* 77: 253-261, 1998.

290.Roth KA, Hertz JM, and Gordon JI. Mapping enteroendocrine cell populations in transgenic mice reveals an unexpected degree of complexity in cellular differentiation within the gastrointestinal tract. *J Cell Biol* 110: 1791-1801, 1990.

291.Roth KA, Kim S, and Gordon JI. Immunocytochemical studies suggest two pathways for enteroendocrine cell differentiation in the colon. *Am J Physiol Gastrointest Liver Physiol* 263: G172-G180, 1992.

292.Roze C, Couturier D, Chariot J, and Debray C. Inhibition of gastric electrical and mechanical activity by intraduodenal agents in pigs and the effects of vagotomy. *Digestion* 15: 526-539, 1977.

293.Rozengurt E. Bitter taste receptors and alpha-gustducin in the mammalian gut. *Am J Physiol Gastrointest Liver Physiol* 291: G171-G177, 2006.

294.Rozengurt N, Wu S, Chen MC, Huang C, Sternini C, and Rozengurt E. Co-localization of the {alpha} subunit of gustducin with PYY and GLP-1 in L cells of human colon. *Am J Physiol Gastrointest Liver Physiol*, 2006.

295.Ruiz-Avila L, McLaughlin SK, Wildman D, McKinnon PJ, Robichon A, Spickofsky N, and Margolskee RF. Coupling of bitter receptor to phosphodiesterase through transduction in taste receptor cells. *Nature* 376: 80-85, 1995.

296.Ruiz-Avila L, Wong GT, Damak S, and Margolskee RF. Dominant loss of responsiveness to sweet and bitter compounds caused by a single mutation in alpha -gustducin. *Proc Natl Acad Sci U S A* 98: 8868-8873, 2001.

297.Sainz E, Cavenagh MM, LopezJimenez ND, Gutierrez JC, Battey JF, Northup JK, and Sullivan SL. The G-protein coupling properties of the human sweet and amino acid taste receptors. *Dev Neurobiol* 67: 948-959, 2007.

298.Sainz E, Korley JN, Battey JF, and Sullivan SL. Identification of a novel member of the T1R family of putative taste receptors. *J Neurochem* 77: 896-903, 2001.

299.Sakaguchi T, Ohtake M, and Yamazaki M. D-glucose anomers in the nucleus of the vagus nerve can depress gastric motility of rats. *Brain Res* 332: 390-393, 1985.

300.Samsom M, Vermeijden JR, Smout AJ, Van Doorn E, Roelofs J, Van Dam PS, Martens EP, Eelkman-Rooda SJ, and Van Berge-Henegouwen GP. Prevalence of delayed gastric emptying in diabetic patients and relationship to dyspeptic symptoms: a prospective study in unselected diabetic patients. *Diabetes Care* 26: 3116-3122, 2003.

301.Savastano D, Carelle M, and Covasa M. Serotonin-type 3 receptors mediate intestinal Polycose- and glucose-induced suppresssion of intake. *Am J Physiol Regul Integr Comp Physiol* 288: R1499-1508, 2005.

302.Savastano D and Covasa M. Intestinal nutrients elicit satiation through concomitant activation of CCK_1 and 5-HT_3 receptors. *Physiol Behav* 92: 434-442, 2007.

303.Sayegh AI, Covasa M, and Ritter RC. Intestinal infusions of oleate and glucose activate distinct enteric neurons in the rat. *Auton Neurosci* 115: 54-63, 2004.

304.Sbarbati A and Osculati F. A new fate for old cells: brush cells and related elements. *J Anat* 206: 349-358, 2005.

305.Schick RR, Zimmermann JP, vorm Walde T, Schusdziarra V, and Classen M. Glucagon-like-peptide (GLP)-1-(7-36)-amide: a central suppressor of food intake in rats. *Gastroenterology* 102: A756, 1992.

306.Schirra J and Goke B. The physiological role of GLP-1 in human: incretin, ileal brake or more? *Regul Pept* 128: 109-115, 2005.

307.Schirra J, Katchinski M, Weidmann C, Schafer T, Wank U, Arnold R, and Goke B. Gastric emptying and release of incretin hormones after glucose ingestion in humans. *J Clin Invest* 97: 92-103, 1996.

308.Schirra J, Nicolaus M, Roggel R, Katchinski M, Storr m, Woerle HJ, and Goke B. Endogenous GLP-1 controls endocrine pancreatic secretion and antro-pyloro-duodenal motility in humans. *Gut*, 2005.

309.Schmidt RE. Neuropathology and pathogenesis of diabetic autonomic neuropathy. *Int Rev Neurobiol* 50: 257-292, 2002.

310.Schuit FC, Huypens P, Heimberg H, and Pipeleers DG. Glucose sensing in pancreatic B-cells: A model for the studyof other glucose-regulated cells in gut, pancreas, and hypothalamus. *Diabetes* 50: 1-11, 2001.

311.Schvarcz E, Palmer M, Aman J, and Berne C. Hypoglycaemia increases the rate of gastric emptying in healthy subjects. *Diabetes Care* 18: 674-676, 1995.

312.Schvarcz E, Palmer M, Aman J, Horowitz M, Stridsberg M, and Berne C. Physiological hyperglycemia slows gastric emptying in normal subjects and patients with insulin-dependent diabetes mellitus. *Gastroenterology* 113: 60-66, 1997.

313.Schvarcz E, Palmer M, Ingberg CM, Aman J, and Berne C. Increased prevalence of upper intestinal symptoms in long-term type 1 diabetes mellitus. *Diabet Med* 13: 478-481, 1996.

314.Schwartz GJ, Berkow G, McHugh PR, and Moran TH. Gastric branch vagotomy blocks nutrient and cholecystokinin-induced suppression of gastric emptying. *Am J Physiol* 264: R630-637, 1993.

315.Schwartz GJ and Moran TH. Duodenal nutrient exposure elicits nutrient-specific gut motility and vagal afferent signals in rat. *Am J Physiol* 274: R1236-1242, 1998.

316.Schwartz MP, Samsom M, and Smout AJ. Chemospecific alterations in duodenal perception and motor response in functional dyspepsia. *Am J Gastroenterol* 96: 2596-2602, 2001.

317.Schwiebert EM and Zsembery A. Extracellular ATP as a signaling molecule for epithelial cells. *Biochim Biophys Acta* 1615: 7-32, 2003.

318. Scott K. Taste recognition: food for thought. *Neuron* 48: 455-464, 2005.

319.Seino S and Miki T. Physiological and pathophysiological roles of ATP-sensitive K^+ channels. *Progress in Biophysics & Molecular Biology* 81: 133-176, 2003.

320.Sharp PA, Debnam ES, and Srai SK. Rapid enhancement of brush border glucose uptake after exposure of rat jejunal mucosa to glucose. *Gut* 39: 545-550, 1996.

321.Shen T, Kaya N, Zhao FL, Lu SG, Cao Y, and Herness S. Co-expression patterns of the neuropeptides vasoactive intestinal peptide and cholecystokinin with the transduction molecules alpha-gustducin and T1R2 in rat taste receptor cells. *Neuroscience* 130: 229-238, 2005.

322.Shi G, Leray V, Scarpignato C, Bentouimou N, Bruley des Varannes S, Cherbut C, and Galmiche JP. Specific adaptation of gastric emptying to diets with differing protein content in the rat: is endogenous cholecystokinin implicated? *Gut* 41: 612-618, 1997.

323.Shi M, Jones AR, Niedringhaus MS, Pearson RJ, Biehl AM, Ferreira M, Jr., Sahibzada N, Verbalis JG, and Gillis RA. Glucose acts in the CNS to regulate gastric motility during hypoglycemia. *Am J Physiol Regul Integr Comp Physiol* 285: R1192-1202, 2003.

324.Shima K, Suda T, Nishimoto K, and Yoshimoto S. Relationship between molecular structures of sugars and their ability to stimulate the release of glucagon-like peptide-1 from canine ileal loops. *Acta Endocrinol (Copenh)* 123: 464-470, 1990.

325.Shimizu I, Hirota M, Ohboshi C, and Shima K. Identification and localization of the glucagon-like peptide-1 and its receptor in rat brain. *Endocrinology* 121: 1076-1082, 1987.

326.Slattery JA, Page AJ, Dorian CL, Brierley SM, and Blackshaw LA. Potentiation of mouse vagal afferent mechanosensitivity by ionotropic and metapotropic glutamate receptors. *J Physiol* 577: 295-306, 2006.

327. Smith DV and Margolskee RF. Making sense of taste. *Sci Am* 284: 32-39, 2001.

328.Spangeus A, Kand M, and El-Salhy M. Gastrointestinal endocrine cells in an animal model for human Type 2 diabetes. *dig Dis Sci* 44: 979-985, 1999.

329.Spiller RC, Trotman IF, Adrian TE, Bloom SR, Misiewicz JJ, and Silk DB. Further characterisation of the 'ileal brake' relfex in man - effect of ileal infusion of partial digests of fat, protein, and starch on jejunal motility and release of neurotensin, enteroglucagon, and peptide YY. *Gut* 29: 1042-1051, 1988.

330.Spiller RC, Trotman IF, Higgins BE, Ghatei MA, Grimble GK, Lee YC, Bloom SR, Misiewicz JJ, and Silk DB. The ileal brake - inhibition of jejunal motility after ileal fat perfusion in man. *Gut* 25: 365-374, 1984.

331.Stacher G, Bergmann H, Granser-Vacariu GV, Wiesnagrotzki S, Wenzelabatzi TA, Gaupmann G, Kugi A, Steinringer H, Schneider C, and Hobart J. Lack of systematic effects of the 5-hydroxytryptamine 3 receptor antagonist ICS 205-930 on gastric emptying and antral motor activity in patients with primary anorexia nervosa. *Br J Clin Pharmacol* 32: 685-689, 1991.

332.Stead RH, Tomioka M, Quinonez G, Simon GT, Felten SY, and Bienenstock J. Intestinal mucosal mast cells in normal and nematode-infected rat intestines are in intimate contact with peptidergic nerves. *Proc Natl Acad Sci U S A* 84: 2875-2979, 1987.

333.Sternini C. Taste receptors in the gastrointestinal tract. IV. functional implications of bitter taste receptors in gastrointestinal chemosensing. *Am J Physiol Gastrointest Liver Physiol* 292: G457-G461, 2007.

334.Suominen AH, Glimm DR, Tedesco D, Okine EK, McBurney MI, and Kennelly JJ. Intestinal nutrient-gene interaction: the effect of feed deprivation and refeeding on cholecystokinin and proglucagon gene expression. *J Anim Sci* 76: 3104-3113, 1998.

335.Sykes S, Morgan LM, English J, and Marks V. Evidence for preferential stimulation of gastric inhibitory polypeptide secretion in the rat by actively transported carbohydrates and their analogues. *J Endocrinol* 85: 201-207, 1980.

336.Symonds E, Butler R, and Omari T. Noninvasive breath tests can detect alterations in gastric emptying in the mouse. *Eur J Clin Invest* 32: 341-344, 2002.

337.Symonds EL, Butler RN, and Omari TI. Assessment of gastric emptying in the mouse using the [13C]-octanoic acid breath test. *Clin Exp Pharmacol Physiol* 27: 671-675, 2000.

338.Takahara H, Fujimura M, Taniguchi S, Hayashi N, Nakamura T, and Fujimiya M. Changes in serotonin levels and 5-HT receptor activity in duodenum of streptozotocin-diabetic rats. *Am J Physiol Gastrointest Liver Physiol* 281: G798-808, 2001.

339.Takahashi T, Kojima Y, Tsunoda Y, Beyer LA, Kamijo M, Sima AA, and Owyang C. Impaired intracellular signal transduction in gastric smooth muscle of diabetic BB/W rats. *Am J Physiol Gastrointest Liver Physiol* 270: G411-G417, 1996.

340.Takahashi T, Matsuda K, Kono T, and Pappas TN. Inhibitory effects of hyperglycemia on neural activity of the vagus in rats. *Intensive Care Med* 29: 309-311, 2003.

341.Takahashi T, Nakamura K, Itoh H, Sima AA, and Owyang C. Impaired expression of nitric oxide synthase in the gastric myenteric plexus of spontaneously diabetic rats. *Gastroenterology* 113: 1535-1544, 1997.

342.Takami S, Getchell ML, and Getchell TV. Lectin histochemical localization of galactose, N-acetylgalactosamine, and N-acetylglucosamine in glycoconjugates of the rat vomeronasal organ, with comparison to the olfactory and septal mucosae. *Cell Tissue Res* 277: 211-230, 1994.

343.Takeda N, Hasegawa S, Morita M, and Matsunaga T. Pica in rats is analogous to emesis: an animal model in emesis research. *Pharmacol Biochem Behav* 45: 817-821, 1993.

344.Tang-Christensen M, Larsen PJ, Goke R, Fink-Jensen A, Jessop DS, Moller M, and Sheikh SP. Central administration of GLP-1-(7-36) amide inhibits food and water intake in rats. *Am J Physiol Regul Integr Comp Physiol* 271, 1996.

345.Theodorakis MJ, Carlson O, Michopoulos S, Doyle ME, Juhaszova M, Petraki K, and Egan JM. Human duodenal enteroendocrine cells: source of both incretin peptides, GLP-1 and GIP. *Am J Physiol Endocrinol Metab* 290: E550-E559, 2006.

346.Thorens B. GLUT2 in pancreatic and extra-pancreatic gluco-detection. *Molecular Membrane Biology* 18: 265-273, 2001.

347.Tomchik SM, Berg S, Kim JW, Chaudhari N, and Roper SD. Breadth of tuning and taste coding in mammalian taste buds. *J Neurosci* 27: 10840-10848, 2007.

348.Tran VS, Marion-Audibert AM, Karatekin E, Huet S, Cribier S, Guillaumie K, Chapuis C, Desnos C, Darchen F, and Henry JP. Serotonin secretion by human carcinoid BON cells. *Ann N Y Acad Sci* 1014: 179-188, 2004.

349.Tricarico C, Pinzani P, Bianchi S, Paglierani M, Distante V, Pazzagli M, Bustin SA, and Orlando C. Quantitative real-time reverse transcription polymerase chain reaction: normalization to rRNA or single housekeeping genes is inappropriate for human tissue biopsies. *Analytical Biochemistry* 309: 293-300, 2002.

350.Turton MD, O'Shea D, Gunn I, Beak SA, Edwards CMB, Meeran K, Choi SJ, Taylor GM, Heath MM, Lambert PD, Wilding JPH, Smith DM, Ghatei MA, Herbert J, and Bloom SR. A role for glucagon-like peptide-1 in the central regulation of feeding. *Nature* 379: 69-72, 1996.

351.Vahl TP, Tauchi M, Durler TS, Elfers EE, Fernandes TM, Bitner RD, Ellis KS, Woods SC, Seeley RJ, Herman JP, and D'Alession DA. GLP-1 receptors expressed on nerve terminals in the portal vein mediate the effects of endogenous GLP-1 on glucose tolerance in rats. *Endocrinology* 148: 4865-73, 2007.

352.Van Citters GW and Lin HC. The ileal brake: a fifteen-year progress report. *Curr Gastroenterol Rep* 5: 404-409, 1999.

353.Van Citters GW and Lin HC. Ileal brake: neuropeptidergic control of intestinal transit. *Curr Gastroenterol Rep* 8: 367-373, 2006.

354.Vidon N, Pfeiffer A, Chayvialle JA, Merite F, Maurel M, Franchisseur C, Huchet B, and Bernier JJ. Effect of jejunal infusion of nutrients on gastrointestinal transit and hormonal response in man. *Gastroenterol Clin Biol* 13: 1042-1049, 1989.

355.Wade PR and Westfall JA. Ultrastructure of enterochromaffin cells and associated neural and vascular elements in the mouse duodenum. *Cell Tissue Res* 241: 557-563, 1985.

356.Wang FB and Powley TL. Topographic inventories of vagal afferents in gastrointestinal muscle. *J Comp Neurol* 421: 302-324, 2000.

357.Wang S, Liu J, Li L, and Wice BM. Individual subtypes of enteroendocrine cells in the mouse small intestine exhibit unique patterns of inositol 1,4,5-trisphosphate receptor expression. *J Histochem Cytochem* 52: 53-63, 2004.

358.Wei JY and Wang YH. Effect of CCK pretreatment on the CCK sensitivity of rat polymodal gastric vagal afferent in vitro. *Am J Physiol Endocrinol Metab* 280: E695-E706, 2000.

359.Weiser MM and Quill H. Intestinal villus and crypt cell responses to cholera toxin. *Gastroenterology* 69: 472-482, 1975.

360.Welch IM, Cunningham KM, and Read NW. Regulation of gastric emptying by ileal nutrients in humans. *Gastroenterology* 94: 401-404, 1988.

361.Welch IM, Sepple CP, and Read NW. Comparisons of the effects on satiety and eating behaviour of infusion of lipid into the different regions of the small intestine. *Gut* 29: 306-311, 1988.

362.Whited KL, Thao D, Kent Lloyd KC, Kopin AS, and Raybould HE. Targeted disruption of the murine CCK_1 receptor gene reduces intestinal lipid-induced feedback inhibition of gastrin function. *Am J Physiol Gastrointest Liver Physiol* 291: G156-G162, 2006.

363.Witt M and Miller IJ, Jr. Comparative lectin histochemistry on taste buds in foliate, circumvallate and fungiform papillae of the rabbit tongue. *Histochemistry* 98: 173-182, 1992.

364.Wong GT, Gannon KS, and Margolskee RF. Transduction of bitter and sweet taste by gustducin. *Nature* 381: 796-800, 1996.

365.Wright EM, Martin MG, and Turk E. Intestinal absorption in health and disease - sugars. *Best Practise and Reseach Clinical Gastroenterology* 17: 943-956, 2003.

366.Wu SV, Rozengurt N, Yang M, Young SH, Sinnett-Smith J, and Rozengurt E. Expression of bitter taste receptors of the T2R family in the gastrointestinal tract and enteroendocrine STC-1 cells. *Proc Natl Acad Sci U S A* 99: 2392-2397, 2002.

367.Yang H, Soderholm J, Larsson J, Perment J, Olaison G, Lindgren J, and Wiren M. Glutamine effects on permeability and ATP content of jejunal mucosa in starved rats. *Clin Nutr* 18: 301-306, 1999.

368.Yang H, Soderholm JD, Larsson J, Perment J, Lindgren J, and Wiren M. Bidirectional supply of glutamine maintains enterocyte ATP content in the in vitro Ussing chamber model. *Int J Colorectal Dis* 15: 291-296, 2000.

369.Yang R, Tabata S, Crowley HH, Margolskee RF, and Kinnamon JC. Ultrastructural localization of gustducin immunoreactivity in microvilli of type II taste cells in the rat. *J Comp Neurol* 425: 139-151, 2000.

370.Yang X, Kow L, Funabashi T, and Mobbs C. Hypothalamic Glucose Sensor: Similarites to and differences from pancreatic B-cell mechanisms. *Diabetes* 48: 1763-1772, 1999.

371.Yeap BB, Russo A, Fraser RJ, Wittert GA, and Horowitz M. Hyperglycemia affects cardiovascular autonomic nerve function in normal subjects. *Diabetes Care* 19: 880-882, 1996.

372.Yee CL, Yang R, Bottger B, Finger TE, and Kinnamon JC. "Type III" cells of rat taste buds: immunohistochemical and ultrastructural studies of neuron-specific enolase, protein gene product 9.5, and serotonin. *J Comp Neurol* 440: 97-108, 2001.

373.Yoshida MM, Schuffler MD, and Sumi SM. There are morphological abnormalities of the gastric wall or abdominal vagus in patients with diabetic gastroparesis. *Gastroenterology* 94: 907-914, 1988.

374.Young RL, Cooper NJ, and Blackshaw LA. Chemical coding and central projections of gastric vagal afferent neurons. *Neurogastroenterol Motil* 20: 708-718, 2008.

375.Yu P, Fujimura M, Okumiya K, Kinoshita M, Hasegawa H, and Fujimiya M. Immunohistochemical localisation of tryptophan hydroxylase in the human and rat gastrointestinal tracts. *J Comp Neurol* 411: 654-665, 1999.

376.Zeitz KP, Guy N, Malmberg AB, Dirajlal S, Martin WJ, Sun L, Bonhaus DW, Stucky CL, Julius D, and Basbaum AI. The 5-HT_3 subtype of serotonin receptor contributes to nociceptive processing via a novel subset of myelinated and unmyelingated nociceptors. *J Neurosci* 22: 1010-1019, 2002.

377.Zhang Y, Hoon MA, Chandrashekar J, Mueller KL, Cook B, Wu D, Zuker CS, and Ryba NJ. Coding of sweet, bitter, and umami tastes: different receptor cells sharing similar signaling pathways. *Cell* 112: 293-301, 2003.

378.Zhang Z, Zhao Z, Margolskee RF, and Liman E. The transduction channel TRPM5 is gated by intracellular calcium in taste cells. *J Neurosci* 27: 5777-5786, 2007.

379.Zhao FL, Shen T, Kaya N, Lu SG, Cao Y, and Herness S. Expression, physiological action, and coexpression patterns of neuropeptide Y in rat taste-bud cells. *Proc Natl Acad Sci U S A* 102: 11100-11105, 2005.

380.Zhao GQ, Zhang Y, Hoon MA, Chandrashekar J, Erlenbach I, Ryba NJ, and Zuker CS. The receptors for mammalian sweet and umami taste. *Cell* 115: 255-266, 2003.

381.Zhu JX, Zhu XY, Owyang C, and Li Y. Intestinal serotonin acts as a paracrine substance to mediate vagal signal transmission evoked by luminal factors in the rat. *J Physiol* 530: 431-442, 2001.

382.Zittel TT, Rothenhofer I, Meyer JH, and Raybould HE. Small intestinal capsaicin-sensitive afferents mediate feedback inhibition of gastric emptying in rats. *Am J Physiol* 267: G1142-1145, 1994.