ELSEVIER

Journal of Nutritional Biochemistry 13 (2002) 190–199

THE JOURNAL OF Nutritional Biochemistry

Regulation mechanisms of intestinal secretion: implications in nutrient absorption

Raul A. Wapnir[a,*], Saul Teichberg[a,b]

[a]*Department of Pediatrics, North Shore-Long Island Jewish Health System and Research Institute, New York University School of Medicine, Manhasset, New York 11030, USA*

[b]*Department of Laboratories, North Shore-Long Island Jewish Health System and Research Institute, New York University School of Medicine, Manhasset, New York 11030, USA*

Received 29 October 2001; received in revised form 28 January 2002; accepted 13 February 2002

Abstract

Intestinal secretion is a normal phenomenon, indispensible to solubilize and dilute nutrients and to maintain fluidity in the intestinal lumen. Enterotoxins and certain drugs may disrupt the proabsorptive status maintained by the small intestine under physiologic conditions. Hormones found in nervous and specialized intestinal enterochromaffin cells are responsible, in part, for secretion of fluid into the lumen. Afferent vagal nerve impulses mediated by 5-hydroxytryptamine (serotonin; 5-HT), vasoactive intestinal peptide (VIP) and substance P are the major agents of secretory stimulation. Toxins from pathogenic bacteria, especially some strains of *E. coli* and *V. cholerae,* trigger a secretory response and a chain of events involving cGMP and cAMP which result in chloride secretion, coupled to sodium and fluid efflux into the lumen. If secretion is unchecked by natural mechanisms or medications, the consequences are diarrhea, with potential dehydration, hyponatremia and ultimately death. Introduction of absorbable nutrients in the intestinal lumen has a major antisecretory action, both by a nutrient-gene interaction and by proabsorptive hormone expression. In additon, during the absorptive process water is carried into the enterocyte together with solutes. Hydrolysis-resistant peptides of dietary origin and ingested soluble fiber may also have a proabsorptive effect. The gastrointestinal system has a variety of antisecretory or proabsorptive hormonal and protein agonists that balance the outflow of fluid and electrolytes. The more extensively studied are neuropeptide Y/peptide YY (NPY/PYY) and the antisecretory factor (AF). Nitric oxide (NO), a short-lived second messenger, has a major role in secretion by activating cGMP. The intracellular concentration of NO may regulate the absorptive/secretory status of the small intestine, either stimulating absorption or inducing secretion. Specifically targeted 5-HT receptor antagonist drugs and other pharmacologic agents have been clinically tried for the treatment of severe diarrhea, drug-induced malabsorption and reversal of cellular damage.

Keywords: Intestinal secretion; Cyclic guanosine monophosphate (cGMP); Nitric oxide; Diarrhea; Serotonin; Enterotoxins

1. Introduction

Although under normal conditions the mammalian small intestine is in a net absorptive mode, secretion is a concurrent physiologic process. Together with movement from the lumen into the enterocyte, via the apical membrane and through intercellular tight junctions, there is simultaneous recirculation of water and electrolytes, exiting from the crypts into the lumen. Water influx occurs by diffusion driven by osmotic gradients generated during sodium-proton exchange, and by hydration of solutes which enter absorptive cells utilizing glucose and amino acid transporters [1,2]. These fluid exchanges drive the concentration of luminal contents close to isotonicity prior to absorption [3]. In adult humans, water reaching the jejunum is rapidly absorbed in a matter of minutes. However, the rate of lumen-to-blood fluid influx is several-fold greater than actual net absorption [4], reflecting considerable blood-to-lumen fluid efflux. When water efflux outpaces water inflow a net secretory condition ensues, resulting in malabsorption or diarrhea.

The distance between the two hydrogen atoms of water is less than 2 Å, small enough to allow for the crossing of

* Corresponding author. Tel.: +1-516-562-3889; fax: +1-516-562-1170.

E-mail address: rwapnir@nshs.edu (R.A. Wapnir).

0955-2863/02/$ – see front matter
PII: S0955-2863(02)00181-X

membrane channels, or intermolecular spaces between hydrophobic chains, even under conditions that would require a single file movement of water molecules. Immediately contiguous to the apical membrane there is an unstirred layer where fluid movement is laminar and which limits diffusion of solutes and accompanying water from the areas of turbulent movement in the center of the small intestinal lumen. This physiologic barrier slows access of water and electrolytes to the apical membrane or to the tight junctions where absorption occurs [5]. Water moves into the intercellular spaces between enterocytes via transcellular and paracellular routes in response to an osmotic gradient between the lumen and the cytosol of the enterocyte, and between the latter and the extracellular space, eventually reaching the circulation [1,2,6].

Intestinal secretion is vital to obtain a chyme with appropriate characteristics to serve as a substrate for digestion and absorption. Attaining an adequate pH, progressive solubilization of absorbable solid nutrients and combining with pancreatic and biliary secretions are all phenomena that take place in the duodenum and upper jejunum. Osmotic and neural stimuli trigger hormonal release and make possible normal absorption, as large molecules of macronutrients are progressively hydrolyzed either to single glucose (or other monosaccharides), di- and tripeptides, or monoglycerides and fatty acids. The successful interplay of regulatory mechanisms is consistent with normal gastrointestinal function, while pathological events lead to malabsorption. Only virulent pathogens, cytostatic drugs or hormone receptor agonists can overcome the natural balancing capacity of the system.

2. Hormonal regulation of secretion

A complex array of hormonal mechanisms controls entry and exit of fluid into the gastrointestinal tract. Synthesis of these hormones occurs both in neural and specialized intestinal enterochromaffin cells, and receptors for these hormones exist in both systems [7]. These two sets of hormonal secretory and absorptive regulators combine to produce a finely tuned control of secretory and absorptive mechanisms. In this section we describe the roles of some hormones responsible for controlling fluid secretion into the intestinal lumen. Antisecretory hormones and their agonists will be discussed in a subsequent section.

The most intensely studied secretory agents are 5-hydroxytryptamine (5-HT; serotonin) [8] and vasoactive intestinal peptide (VIP) [9,10]. VIP mediates some of the secretory effects of 5-HT as shown by inhibition of the secretory effect elicited in vitro by a 5-HT_3 receptor agonist with a VIP receptor antagonist [11]. A series of 5-HT receptors have been identified by radioligand binding studies in various areas of the gastrointestinal system, from the duodenum to the colon [12]. Specific antagonists to each receptor and its subtypes have been used to discriminate particular drug effects tested in clinical intervention trials for conditions such as carcinoid and irritable bowel syndrome to reduce the frequency of bowel movements [13]. In addition to the stimulation of cyclic nucleotide synthesis, 5-HT also inhibits sodium influx into the enterocyte via the Na^+/H^+ exchanger, as demonstrated by fluid accumulation in the lumen of ligated intestinal loops [14,15].

VIP is a 20-amino acid peptide, structurally related to another gastrointestinal hormone, secretin. VIP has substantial homology with a pituitary adenylate cyclase-activating peptide (PACAP). PACAP-27 has a 27-amino acid chain and predominates in the intestine. A longer peptide, PACAP-38, is found in neural tissues [16]. Both VIP and PACAP induce relaxation of precontracted rat ileal longitudinal muscle [9]. This action may explain the prosecretory activity of these peptides.

Substance P (SP), also known as P-glycoprotein [17], has been recognized for its secretory properties since the 1930's [18]. SP belongs to the tachykinin family (also described as neurokinins) and is a short peptide with 11 amino acids. It is widely distributed in the gastrointestinal tract, primarily in the small intestine. SP alters blood flow, water exchanges and intestinal motility. Secretion occurring in carcinoid syndrome has been attributed to SP overproduction, as much as that of 5-HT [18]. Kinins, in general, act on the basolateral membrane Na^+/K^+-ATPase and the apical cystic fibrosis transmembrane conductance regulator (CFRT) chloride channel, and secondarily on the K^+ channel of both apical and basolateral membranes [19,20]. CFRT is responsible for chloride transport in most epithelial tissues. Furthermore, neurokinins have been shown to mediate, at least partly, the secretory effects of cholera toxin-induced secretion in rat jejunum, as demonstrated by receptor antagonists of neurokinins 1 and 2, which inhibited cholera toxin secretory effects [21]. Neurokinins also regulate bicarbonate secretion in the duodenum, an action possibly mediated by prostanoids [22]. Other gastrointestinal hormones and peptides, such as cholecystokinin (CCK), galanin and guanylin/uroguanylin also play roles directly or indirectly on intestinal secretion [20,23,24].

Regulation of secretion by neurohormones is altered during gastrointestinal infections, especially due to *V. cholerae*, enterotoxigenic *E. coli* and *S. flexneri.* Cholera toxin induces 5-HT release from enterochromaffin cells [25], as well as increased production of cAMP [26]. Furthermore, *V. cholera* may produce a toxin which transiently opens the tight junctional barrier (zonula occludens) allowing paracellular efflux of water and sodium [27]. The other cyclic nucleotide, cGMP, perhaps the key molecule of the secretory process, is also similarly involved, as will be discussed later [28]. It is clear that cholera toxin inflicts a multipronged attack on secretory controls. Sensitivity to bacterial endotoxins decreases with age in experimental animals [29, 30]; this may explain why susceptibility to diarrheal disease is greater in infancy.

The biochemical precursor of 5-HT, L-tryptophan (Trp), also has secretory and/or antiabsorptive effects when presented to the luminal compartment of the small intestine [31,32], presumably by production of 5-HT via the 5-hydroxylation pathway, a minor, but physiologically important metabolic route of amino acid catabolism. Histamine, derived from histidine, extensively studied for its gastric effects, has been shown to affect H_2 receptors in the small intestine, which are also involved in regulating secretion [33,34].

Secretory gastrointestinal hormones may act through the modulation of intracellular Ca^{2+} concentration, probably more significantly in the colon than in the small intestine. Ca^{2+} is released from its stores by inositol triphosphate (IP_3) and increases the conductance of basolateral K^+ channels with exit of this ion to the circulation and chloride release into the lumen [35,36]. Chloride secretion induced by histamine is Ca^{2+}-dependent, as demonstrated *in vitro* by removal of serosal Ca^{2+} or by calcium channel blockers [33], a class of drugs with strong antisecretory effects. Calcium channels are also affected by 5-HT and cholera toxin [37]. It has been suggested that Ca^{2+} signaling takes place via sigma receptors [38]. There are at least two subtypes of sigma receptors, denominated 1 and 2. The latter, when activated, produce an increase of intracellular Ca^{2+} [39], and offer a potential antidiarrheal approach, since sigma receptors are concentrated in the small intestine. This class of agonists may offer therapeutic advantages over calcium channel blockers, which have multiorgan, and often undesirable, side effects [40].

An indirect hormonal regulation of secretion may be due to dietary bioactive peptides [41]. Some of these substances escape or are impervious to luminal and intracellular peptidases and hydrolases; they can reach the circulation from where they return to the gastrointestinal system or other organs. Arguably the most important substance in this category is carnosine (β-alanyl-L-histidine), a dipeptide with vasodilatory action mediated by enhancement of cGMP production [42], with additional effects on cardiac contractility and intracellular calcium concentration [43].

3. Antisecretory regulation

Physiologic proabsortive mechanisms are vital to assure the normal functioning of the intestine and to counterbalance fluid outflow. Introduction of digestible foods into the gastrointestinal tract is an important part of the proabsorptive/antisecretory capacity of the organism. The use of agonists and antagonist ligands of certain hormone receptors has also deserved attention as possible treatment of diarrheal disease.

3.1. Nutrients

Absorbable nutrients have clear antisecretory effects due to the physiology of the absorptive process itself. Such nutrients act by presenting to apical mucosa transporters, which bind and translocate substrates across the luminal membrane creating a lumen-to-serosa movement of small molecules into the enterocyte. Assimilated nutrients enter the cell surrounded by water molecules, thus effectively producing a hydrating action simultaneously with the uptake of nutrients.

Normal small intestinal absorption centers on the activity of two major mechanisms: the sodium-dependent SGLT1 glucose transporter [44], and the uptake of protein-derived substrates, namely oligopeptides and amino acids, by another group of transporters, which may entail sodium requirements in certain cases [45]. Absorption of lipids has a lesser impact on fluid exchanges. Micronutrients in the diet have a minor role in terms of hydration. The major sources of sodium in the intestinal lumen required for transport include all types of gastrointestinal secretions and, to a minor extent, the diet. An adult may ingest 1000 kCal or more per day from carbohydrates, which would represent at least 250 g of glucose, that is, no less of 1.5 moles. If sodium were not secreted and reabsorbed, that amount of carbohydrate would require 3 moles of sodium, or more, or a minimum of 175 g of sodium chloride, since the SGLT1 transporter couples two atoms of sodium for each glucose molecule. Clearly, this amount far exceeds physiologic tolerance.

Glucose absorption entails net water influx into the enterocyte, since each glucose molecule in solution is surrounded by water molecules which are carried over during membrane translocation [46]. Solutes in the lumen also trigger physicochemical phenomena linked to osmolality changes [47], which can contribute to diminish secretory effects due to enterotoxins, rotavirus, inflammation and other causes of gastrointestinal disease. In addition, osmotic stimuli release 5-HT from enterochromaffin cells, thus activating 5-HT_3 receptors which send vagal afferent information to the brainstem [48]. The presence of nutrients in the gastrointestinal tract influence the expression of gastrointestinal neuropeptides, such as CCK and the glucagon-like peptides (GLP-1 and GLP-2) [49]. GLP-2 increases nutrient absorption with consequent improvement of lean body mass and total body weight in patients without terminal ileum and colon, who had functional short-bowel syndrome [50]. It has also been shown that peptones, a soluble protein hydrolysis product, activate CCK gene transcription in enteroendocrine cells, thus establishing a direct link between nutrient and hormone secretion [51].

Certain natural peptides derived from casein, such as β-casomorphins, elicit opioid effects and act as “food hormones” [52]. They appear to be absorbed intact by the apical mucosa and reach the serosal side where opiate receptors are located [53]. These considerations have in-

creased the relevance of peptide-based enteral formulas, as means to improve nitrogen absorption, especially in critically ill and hypoalbuminemic patients [54].

A related aspect of potential proabsorptive/antisecretory action is the introduction of non-absorbable soluble fiber in the intestinal lumen. Some products, such as soy fiber, gum arabic and partially hydrolyzed guar gum have shown effectiveness in clinical trials [55,56], as well as in animal models of gastrointestinal disease [57]. It is still unclear what mechanisms may be involved in the putative proabsorptive effects of this kind of substances. Studies with gum arabic in rats suggest that a physicochemical modification of the fluid phase, altering paracellular transport, may provide a tentative explanation [58]. Experiments with dogs revealed that fermentable fiber increased release of GLP-1 and insulin, while poorly fermentable wood cellulose was much less effective [59]. The greater relevance of fiber in the diet has paralleled the growing recognition of their potential beneficial role in formulas as proabsorptive agents [60].

Mucins and at least one type of immunoglobulin (IgA) are also secreted by the small intestine, as early as in the fetal stage [61,62]. Both have enteroprotective roles and at variance with smaller molecules are not recirculated intact. Simultaneously with IgA a secretory component related to the poly-IgA receptor is secreted into the lumen by exocytosis after having crossed the enterocyte by a transcytotic process [63]. These macromolecules bind to dietary indigestible material and possibly to lectins and intestinal bacteria [64].

3.2. Hormones

Neuropeptide Y (NPY), also described as peptide YY (PYY), is a hormone present in neural and gastrointestinal tissues. PYY is the denomination more frequently used for the gastrointestinal hormone. NPY/PYY is a 36 amino acid peptide, and in the gut PYY is predominantly found in crypt and neuroendocrine L cells. It is considered to be the major proabsorptive hormone of the small intestine [65–67]. The antisecretory action of CCK in the colon has also been attributed to its eliciting PYY release [68]. The proabsorptive effects of PYY have been clearly demonstrated by its administration to humans [69], and PYY has been proposed as a potential treatment for syndromes involving malabsorption [70]. PYY is a powerful inhibitor of gastrointestinal motility, pancreatic, gastric and chloride secretions [15]. Its function has been equated with earlier descriptive concepts of 'ileal brake', or 'colonic brake', because PYY lengthens the mucosal contact time of luminal nutrients in the ileum and the colon, counterbalancing gastric emptying impulses and intestinal peristalsis [71,72]. Receptors for PYY are expressed in human and rodent gastrointestinal epithelia and are coupled to G-proteins on the membranes. PYY induces a specific type of protein kinase C (PKCϵ) [73], which may play a role in the activation of transport mechanisms. In addition to being neuroregulated, PYY is induced by nutrients in the gut [74,75], although studies in a monogastric animal model showed it made no difference whether feedings were continuous or intermittent [76]. Fats appear to be potent activators of PYY release in the distal segments of the gut [77]. Long-chain, but especially medium-chain triglycerides (MCT) stimulate PYY secretion. Although rapidly absorbed in the proximal gut, however, MCT exert their effects in a distal part of the gastrointestinal tract, but do not stimulate CCK release, as was considered earlier [78]. PYY action as a proabsorptive hormone and food intake stimulant may also involve a histaminergic mechanism [79].

In the last two decades, proteins with antisecretory properties have been identified and generically denominated 'antisecretory factor' (AF) [80,81]. They have been largely studied by Swedish investigators who confirmed the effects of AF on cholera toxin-induced hypersecretion [80,82,83]. AF proteins have a pituitary origin [84], and have been cloned and sequenced from a human pituitary library [85]. Animal studies indicate that AF can be induced by certain types of foods. This has led to the testing of hydrothermally processed cereals (partially hydrolyzed complex carbohydrates) for the relief of symptoms of patients with inflammatory bowel disease (ulcerative colitis and Crohn's disease). The results confirmed induction of AF synthesis and subjective improvement of the gastrointestinal symptoms in the majority of subjects [86].

3.3. Antisecretory drugs

A number of 5-HT_3 receptor antagonists in the 'setron' group: granisetron, ondansetron, dolasetron and tropisetron, as well as thioperamide, have been used to diminish secretion or treat certain types of diarrhea [79,87]. These agents are already extensively used for chemotherapy- and motion-induced nausea and vomiting. European investigators [88] have pioneered in the study of antisecretory drugs to counter the effects of *V. cholerae* and *E. coli* toxins. The most extensively tried have been granisetron [89], substance P and kinin antagonists [90], as well as the sigma ligand igmesine [91,92]. Another type of drug for the same purpose is racecadotril (acetorphan), an enkephalinase inhibitor, which has proven to be effective and with less side effects than the widely used μ-opiate receptor agonist, loperamide [93,94], including intervention in infantile diarrhea of viral or bacterial origin [95]. Although certain ciclooxygenase (COX) inhibitors, such as indomethacin, increase duodenal secretion and paracellular permeability [96], selective inhibitors of COX-2 suppress cholera toxin-induced prostaglandin E2 biosynthesis and decrease fluid secretion in a dose-dependent fashion [97].

A diagrammatic summary of secretory agonists and antagonists is depicted in Fig. 1.

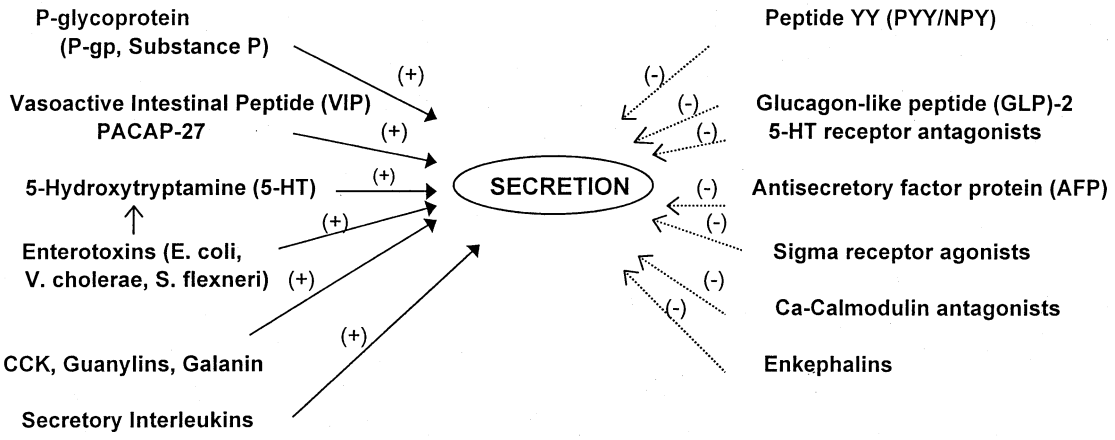

Fig. 1. Schematic depiction of major hormones and agents that induce intestinal secretion, marked with filled arrows and (+). Significant antisecretory and proabsorptive factors, or sites for receptor antagonists used to counteract secretion are indicated with dashed arrows and (−).

4. Role of nitric oxide in secretory regulation

Since the importance of nitric oxide (NO) as a second messenger became better understood in the last several years, new connections between gastrointestinal disease, inflammation and tissue damage by free radicals have been mapped. NO plays an important role in the control of secretion and in many conditions associated with pathologic changes of the gut. NO has the chemical characteristics of a free radical, and since the half-life of NO molecules in tissues is in the order of seconds, they can be considered an ideal regulatory mechanism to rapidly respond to hormonal or exogenous stimuli, as well as to cease its action within a short interval. Arguably, NO control is the point where several cell signaling pathways converge, including neurohormones, such as VIP, inteleukins and cyclic nucleotides [98–100].

NO modulates inflammation and can act both as a pro-inflammatory and as an anti-inflammatory agent depending on whether there is excess or limited synthesis [101]. The nuclear transcription factor, NF-κB, a central regulator of gene activation involved in cell adhesion, immune and inflammatory responses, may determine the expression of inducible NO synthase (iNOS), the key mechanism in the control of tissue NO concentration. NF-κB also regulates the synthesis of pro-inflammatory cytokines. The latter can also upregulate iNOS and perpetuate pathologic conditions (Fig. 2) [102–104]. The effects of NO in experimental colitis were shown to be mediated by proinflammatory cytokines [105]. The NF-κB/iNOS axis may be activated in sepsis and in localized infections. Conversely, a sharp reduction of NO synthesis in endothelia may lead to cell contraction, increased vascular protein leakage and tissue damage. There is evidence that in the small intestine the normal proabsorptive status entails a delicate balance in the modulation of NO synthesis. Severe inhibition of NO synthesis is deleterious, since insufficient generation of NO may be detrimental to the integrity of the mucosal epithelium and produce a dysfunctional epithelial barrier. This may be translated into partial loss of protection against

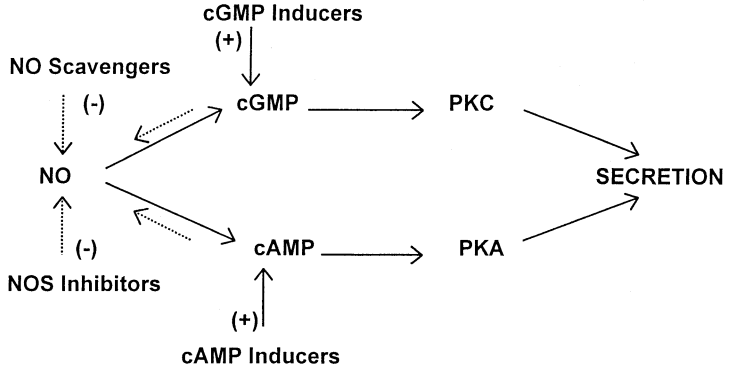

Fig. 2. Diagrammatic pathways leading to secretion via cyclic nucleotides cGMP and cAMP. NO in excess, as well as other inducers, will result in an intracellular elevation of cGMP and cAMP concentrations. The synthesis of NO, in turn, is downregulated by cyclic nucleotides.

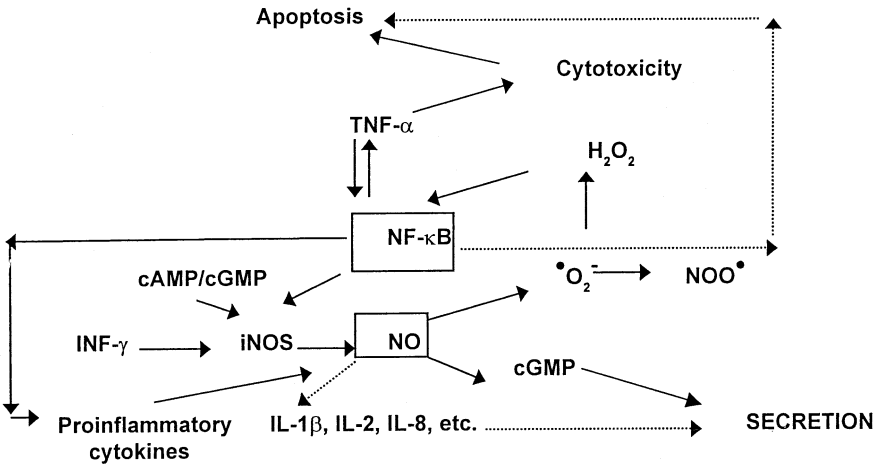

Fig. 3. Interactions operating in the synthesis of NO via stimulation of iNOS. An increase of nuclear factor NF-κB expression upregulates iNOS, and consequently accelerates NO synthesis and increases secretion. Other concurrent effects attributable to NF-κB that may affect cellular integrity are depicted as well. NF-κB regulates the expression of proinflammatory cytokines. NO is also linked to the release of cytokines with strong secretory action. The interactions described in the text are indicated with full arrows; other metabolic consequences are marked with dotted arrows.

transcellular passage of potentially deleterious antigens, allowing the translocation of pathogenic bacteria [106–109]. Infection by a toxigenic organism, such as *V. cholerae*, and probably other enteric pathogens, is associated with an increased NO production [110].

Experiments with iNOS inhibitors and the NO biochemical precursor, L-arginine, have been the key to understanding the role of NO in secretion [107,111–113]. Luminal low concentrations of L-arginine (1–2 mM) were found to enhance absorption of water, electrolytes and glucose, while a higher concentration (20 mM) reduced fluid exchanges. Laxatives, such as phenolphthalein, biscacodyl, castor oil and magnesium sulfate elicit an increase of small intestinal NO synthesis, in addition to the osmotic effect caused by sulfates and magnesium salts [114,115]. Removal of NO from the intestinal lumen by scavenging or trapping may be partially responsible for the antisecretory action of a soluble fiber such as gum arabic [57,116], poorly soluble fibers like psyllium, calcium carbophil or wheat bran [117], and presumably solids such as bismuth subsalicylate, kaolin, tannins, activated charcoal and anionic resins [118–120].

There is a close link between NO and cyclic nucleotide metabolism. NO forms a Fe-nitrosyl complex in guanylate cyclase, which becomes activated and upregulates the synthesis of cGMP (Fig. 3). In turn, cGMP activates a cGMP-dependent protein kinase C [121–124]. Following kinase phosphorylation, and dephosphorylation of the light chain of myosin, cell contraction and relaxation of the interepithelial junctions takes place, together with an increase of permeability of the membrane barrier with the consequences mentioned above [125]. In addition, protein kinase C acts on the CFRT precipitating an outflow of chloride, ionically balanced by loss of sodium and, to a lesser extent, potassium. If unchecked or not compensated, the secretory condition may end in diarrhea. A similar phenomenon is produced via formation of cAMP [126]. There is crosstalk between the cAMP and cGMP pathways, not only in the gastrointestinal system, but in many other physiologic and cellular processes as well [122].

5. Conclusions

Gastrointestinal hormones and NO interplay in response to neural and external physiologic and pathologic stimuli. Under normal conditions the brain-gut axis functions through a strong array of counterbalancing mechanisms maintaining equilibrium between absorption and secretion that responds to the precise needs of the organism. Under certain circumstances, such as toxigenic bacterial infection, as side effects of chemotherapy, or membrane targeting drugs, antisecretory defenses may be overcome leading to secretion and diarrhea. In higher organisms, the main exchange of water and solids between the body and the environment is protected by coordinated checks and balances, which have served well throughout evolution.

Nuclear factors, peptide hormones and intracellular messengers constitute the signaling system that operates to provide the necessary fluid milieu to achieve optimal absorption. Mono- and multigastric organisms possess the mechanisms to solubilize foodstuffs and render them ready for absorption. Secretion is also the process that allows the body to create the environment to free itself of microscopic pathogens and indigestible material. After weaning, alimentation would be impossible if secretory mechanisms would not be in place. It may also be considered an Achilles' heel, since loss of its regulation may open the doors to dehydration and its consequences.

References

[1] D.W. Powell, Ion and water transport in the intestine, in: Andreoli, Hoffman, Fanestil, Schultz (Eds.), Physiology of Membrane Disorders, 2nd ed., Plenum, Inc., New York, NY, 1986, pp. 559–596.

[2] J.A. Schafer, T.E. Andreoli, Principles of water and nonelectrolyte transport across membranes, in: Andreoli, Hoffman, Fanestil, Schultz (Eds.), Physiology of Membrane Disorders, 2nd ed., Plenum, Inc., New York, NY, 1986, pp. 177–190.

[3] J.R. Pappenheimer, K.Z. Reiss, Contribution of solvent drag through intercellular junctions to absorption of nutrients by the small intestine of the rat, J. Membr. Biol. 100 (1987) 123–136.

[4] H.W. Davenport, Physiology of the Digestive Tract, 4th ed., Year Book, Chicago, 1977, pp. 198–213.

[5] K.W. Smithson, D.B. Millar, L.R. Jacobs, G.M. Gray, Intestinal diffusion barrier: unstirred water layer or membrane surface mucous coat?, Science 214 (1981) 1241–1244.

[6] J.L. Madara, J.R. Pappenheimer, Structural basis for physiologic regulation of paracellular pathways in intestinal epithelia, J. Membr. Biol. 100 (1987) 149–164.

[7] H.J. Cooke, Neuroimmune signaling in regulation of intestinal ion transport, Am. J. Physiol. 266 (1994) G167–G178.

[8] S. Graf, S.K. Sarna, 5-HT-induced colonic contractions: enteric locus of action and receptor subtypes, Am. J. Physiol. 273 (1997) G68–G74.

[9] E. Ekblad, F. Sundler, Distinct receptors mediate pituitary adnylate cyclase-activating peptide- and vasoactive intestinal peptide-induced relaxation of rat ileal longitudinal muscle, Eur. J. Pharmacol. 334 (1997) 61–66.

[10] H.J. Cooke, Neurotransmitters in neuronal reflexes regulating intestinal secretion, Ann. N. Y. Acad. Sci. 915 (2000) 77–80.

[11] J.C. Arcuni, M.C. Stoner, J.M. Kellum, Vasoactive intestinal peptide is a neuropeptide mediator of the secretory response to serotonin in rat, J. Surg. Res. 91 (2000) 118–122.

[12] D. Hoyer, D.E. Clarke, J.R. Fozard, P.R. Hartig, G.R. Martin, E.J. Myecharane, P.R. Saxena, P.P.A. Humphrey, International Union of Pharmacology classification of receptors for 5-hydroxytryptamine (serotonin), J. Pharmacol. Exp. Ther. 46 (1994) 157–203.

[13] C.J. Steadman, N.J. Talley, S.F. Phillips, A.R. Zinsmeister, Selective 5-hydroxytryptamine type 3 receptor antagonism with ondansetron as treatment for diarrhea-predominant irritable bowel syndrome: a pilot study, Mayo Clin. Proc. 67 (1992) 732–738.

[14] O. Grishina, K. Volant, F. Marquet, D. Pansu, M. Descroix-Vagne, Effect of serotonin on unidirectional fluxes in rat intestine in vivo, Gastroenterol. Clin. Biol. 22 (1998) 792–800.

[15] R.C. Spiller, Effects of serotonin on intestinal secretion and motility, Curr. Opin.Gastroenterol. 17 (2001) 99–103.

[16] L.J. Miller, Gastrointestinal hormones and receptors, in: Yamada (Ed.), Textbook of Gastroenterology, Lippincott Williams Wilkins, Philadelphia, PA (1999) Vol. 1, pp. 35–66.

[17] A. Hanafy, P. Langguth, H. Spahn-Langguth, Pretreatment with potent P-glycoprotein ligands may increase intestinal secretion in rats, Eur. J. Pharm. Sci. 12 (2001) 405–415.

[18] D. McFadden, M.J. Zinner, B.M. Jaffe, Substance P-induced intestinal secretion of water and electrolytes, Gut 27 (1986) 267–272.

[19] T.S. Gaginella, J.F. Kachur, Kinins as mediators of intestinal secretion, Am. J. Physiol. 256 (1989) G1–G15.

[20] A.W. Cuthbert, Kinins and epithelial ion transport in the alimentary tract, Biol. Chem. 382 (2001) 57–60.

[21] J.L. Turvill, P. Connor, M.J.G. Farthing, Neurokinin 1 and 2 receptors mediate cholera toxin secretion in rat jejunum, Gastroenterology 119 (2000) 1037–1044.

[22] A. Hallgren, G. Flenstrom, O. Nylander, Interaction between neurokinin A, VIP, prostanoids, and enteric nerves in regulation of duodenal function, Am. J. Physiol. 275 (1998) G95–103.

[23] K. Bedecs, M. Berthold, T. Bartfai, Galanin—10 years with a neuroendocrine peptide, Int. J. Biochem. Cell Biol. 27 (1995) 337–349.

[24] L.R. Forte, F.K. Hamra, Guanylin and uroguanylin: intestinal peptide hormones that regulate epithelial transport, News Physiol. Sci. 11 (1996) 17–24.

[25] C.P. Bearcroft, D. Perrett, M.J.G. Farthing, 5-hydroxytryptamine release into human jejunum by cholera toxin, Gut 39 (1996) 528–531.

[26] D.W. Powell, R.K. Farris, S.T. Carbonetto, Theophylline, cyclic AMP, choleragen and electrolyte transport by rabbit ileum, Am. J. Physiol. 243 (1975) G117–G126.

[27] A. Fasano, S. Uzzau, C. Fiore, K. Margaretten, The enterotoxic effect of zonula occludens toxin on rabbit small intestine involves the paracellular pathway, Gastroenterology 112 (1997) 839–846.

[28] M.J.G. Farthing, Enterotoxins and the enteric nervous system—a fatal attraction, Int. J. Med. Microbiol. 290 (2000) 491–496.

[29] M.B. Cohen, M.S. Moyer, M. Luttrell, R.A. Gianella, The immature rat small intestine exhibits an increased sensitivity and response to *Escherichia coli* heat-stable enterotoxin, Pediatr. Res. 20 (1986) 555–560.

[30] G.T. McEwan, B. Schousboe, C.G. Nielsen, E. Skadhauge, Effect of age on the secretory capacity of pig small intestine in vivo and in vitro, Am. J. Physiol. 259 (1990) G474–G480.

[31] H.J. Cooke, A.R. Cooke, Effect of tryptophan on transport properties of newborn rabbit jejunum, Am. J. Physiol. 242 (1982) G308–G318.

[32] S. Teichberg, R.A. Wapnir, M. Zdanowicz, B. Roberts, H.C. Ribeiro, F. Lifshitz, Morphologic and functional alterations in absorptive epithelial cells during L-tryptophan induced inhibition of net sodium and fluid absorption in the rat ileum, Lab. Invest. 60 (1989) 88–101.

[33] J. Hardcastle, P.T. Hardcastle, The secretory actions of histamine in rat small intestine, J. Physiol. 388 (1987) 521–532.

[34] J. Del Valle, I. Gantz, Novel insights into histamine H2 receptor biology, Am. J. Physiol. 273 (1997) G987–G996.

[35] M. Donowitz, Ca^{++} in the control of active intestinal Na and Cl transport: involvement in neurohumoral action, Am. J. Physiol. 245 (1983) G165–G177.

[36] R. Greger, M. Bleich, J. Leipziger, D. Ecke, M. Mall, K. Kunzelmann, Regulation of ion transport in colonic crypts, News Physiol. Sci. 12 (1997) 62–66.

[37] A.T. Peregrin, H. Ahlman, M. Jodal, O. Lundgren, Involvement of serotonin and calcium channels in the intestinal fluid secretion evoked by bile salt and cholera toxin, Br. J. Pharmacol. 127 (1999) 887–894.

[38] T. Hayashi, T. Maurice, T.P. Su, Ca^{2+} signaling via sigma(1)-receptors: novel regulatory mechanism affecting intracellular Ca^{2+} concentration, J. Pharmacol. Exp. Ther. 293 (2000) 788–798.

[39] W.D. Bowen, Sigma receptors: recent advances and new clinical potentials, Pharm. Acta Helv. 74 (2000) 211–218.

[40] M.J.G. Farthing, Diarrhoea: a significant worldwide problem, Int. J. Antimicrob. Agents 14 (2000) 65–69.

[41] P.R. Roberts, G.P. Zaloga, Dietary bioactive peptides, New Horiz. 2 (1994) 237–243.

[42] D.G. Ririe, P.R. Roberts, M.N. Shouse, G.P. Zaloga, Vasodilatory actions of the dietary peptide carnosine, Nutrition 16 (2000) 168–172.

[43] G.P. Zaloga, P.R. Roberts, K.W. Black, M. Lin, G. Zapata-Sudo, R.T. Sudo, T.E. Nelson, Carnosine is a novel peptide modulator of intracellular calcium and contractility in cardiac cells, Am. J. Physiol. 272 (1997) H462–H468.

[44] S.P. Shirazi-Beechey, Molecular biology of intestinal glucose transport, Nutr. Res. Rev. 8 (1995) 27–41.
[45] S.G. Schultz, Ion-coupled transport of organic solutes across biological membranes, in: Andreoli, Hoffman, Fanestil, Schultz (Eds.), Physiology of Membrane Disorders, 2nd ed., Plenum, Inc., New York, NY, 1986, pp. 283–294.
[46] D.D.F. Loo, T. Zeuthen, G. Chandy, E.M. Wright, Cotransport of water by the Na^+-glucose cotransporter, Proc. Natl. Acad. Sci. USA 93 (1996) 13367–13370.
[47] R.A. Wapnir, F. Lifshitz, Osmolality and solute concentration—their relationship with oral hydration solution effectiveness: an experimental assessment, Pediatr. Res. 19 (1985) 894–898.
[48] J.X. Zhu, X.Y. Zhu, C. Owyang, Y. Li, Intestinal serotonin acts as a paracrine substance to mediate vagal signal transmission evoked by luminal factors in the rat, J. Physiol. 530 (2001) 431–442.
[49] A.H Suominen, D.R. Glimm, D. Tedesco, E.K. Okine, M.I. McBurney, J.J. Kennelly, Intestinal nutrient-gene interaction: the effect of feed deprivation and refeeding on cholecystokinin and proglucagon gene expression, J. Anim. Sci. 76 (1998) 3104–3113.
[50] P.B. Jeppesen, B. Hartmann, J. Thulesen, J. Graff, J. Lohmann, B.S. Hansen, F. Tofteng, S.S. Poulsen, J.L. Madsen, J.J. Holst, P.B. Martensen, Glucagon-like peptide 2 improves nutrient absorption and nutritional status in short-bowel patients with no colon, Gastroenterology 120 (2001) 1041–1043.
[51] C. Bernard, A. Sutter, C. Vinson, C. Ratineau, J. Chayvialle, M. Cordier-Bussat, Peptones stimulate intestinal cholecystokinin gene transcription via cyclic adenosine monophosphate response element-binding factors, Endocrinology 142 (2001) 721–729.
[52] H. Teschemacher, G. Koch, V. Brantl, Milk protein-derived receptor ligands, Biopolymers 43 (1997) 99–107.
[53] M. Hautefeuille, V. Brantl, A.M. Dumontier, J.F. Desjieux, In vitro effects of beta-casomorphins on ion transport in rabbit ileum, Am. J. Physiol. 250 (1986) G92–G97.
[54] R.R. Brinson, S.K. Hanumanthu, W.M. Pitts, A reappraisal of the peptide-based enteral formulas: clinical applications, Nutr. Clin. Pract. 4 (1989) 211–217.
[55] J.A. Vanderhoof, N.D. Murray, C.L. Paule, K.M. Ostrom, Use of soy fiber in acute diarrhea in infants and toddlers, Clin. Pediatr. 36 (1997) 135–139.
[56] N.H. Alam, R. Meier, H. Schneider, S.A. Sarker, P.K. Bardhan, D. Mahalanabis, G.J. Fuchs, N. Gyr, Partially hydrolyzed guar gum-supplemented oral rehydration solution in the treatment of acute diarrhea in children, J. Pediatr. Gastro. Nutr. 31 (2000) 503–507.
[57] R.A. Wapnir, M.A. Wingertzahn, J. Moyse, S. Teichberg, Gum arabic promotes rat jejunal sodium and water absorption from oral rehydration solutions in two models of diarrhea, Gastroenterology 112 (1997) 1979–1985.
[58] M. Wingertzahn, S. Teichberg, R.A. Wapnir, Stimulation of non-sodium dependent water, electrolyte, and glucose transport in rat small intestine by gum arabic, Dig. Dis. Sci. 46 (2001) 1105–1112.
[59] S.P. Massimino, M.I. McBurney, C.J. Field, A.B. Thomson, M. Keelan, M.G. Hayek, G.D. Sunvold, Fermentable dietary fiber increases GLP-1 secretion and improves glucose homeostasis despite increased intestinal glucose transport capacity in healthy dogs, J. Nutr. 128 (1998) 1786–1793.
[60] R.R. Brinson, Fiber-containing enteral formulas: clinical importance, Nutr. Clin. Pract. 5 (1990) 97.
[61] M.P. Buisine, L. Devisme, T.C. Savidge, C. Gespach, B. Gosselin, N. Porchet, J.P. Aubert, Mucin gene expression in human embryonic and fetal intestine, Gut 43 (1998) 519–524.
[62] A. Stauffer, A. Lallemand, D. Gaillard, Mucin histochemistry of the digestive tract in the human fetus, Gastroenterol. Clin. Biol. 14 (1990) 561–566.
[63] J.P. Kraehenbuhl, M.R. Neutra, Molecular and cellular basis of immune protection of mucosal surfaces, Physiol. Rev. 72 (1992) 853–879.
[64] J. Pacha, Development of intestinal transport function in mammals, Physiol. Rev. 80 (2000) 1633–1667.
[65] T.E. Adrian, G.L. Ferri, A.J. Bacarese-Hamilton, H.S. Fuessl, J.M. Polak, S.R. Bloom, Human distribution and release of a putative new gut hormone, peptide YY, Gastroenterology 89 (1985) 1070–1077.
[66] G.J. Anthone, M.S. Orandle, Z.V. Macrophilipos, B.H. Wang, C.J. Yeo, Neuropeptide Y is a proabsorptive agent in the small intestine, J. Surg. Res. 50 (1991) 589–594.
[67] A.J. Bilchik, O.J. Hines, M.J. Zinner, T.E. Adrian, J.J. Berger, S.W. Ashley, D.W. McFadden, Peptide YY (PYY) augments postprandial small intestinal absorption *in vivo*. Am. J. Surg. 167 (1994) 570–574.
[68] C.D. Liu, O.J. Hines, T.R. Newton, T.E. Adrian, M.J. Zinner, S.W. Ashley, D.W. McFadden, Cholecystokinin mediation of colonic absorption via peptide YY: foregut-hindgut axis, World J. Surg. 20 (1996) 221–227.
[69] U. Holzer-Petsche, W. Petritsch, T. Hinterleitner, A. Eherer, G. Sperk, G.J. Krejs, Effect of neuropeptide Y on jejunal water and ion transport in humans, Gastroenterology 101 (1991) 325–330.
[70] C.D. Liu, T. Aloia, T.E. Adrian, T.R. Newton, A.J. Bilchik, M.J. Zinner, S.W. Ashley, D.W. McFadden, Peptide YY: a potential proabsorptive hormone for the treatment of malabsorptive disorders, Am. Surg. 62 (1996) 232–236.
[71] J.M. Nightingale, M.A. Kamm, J.R. van der Sijp, M.A. Ghatei, S.R. Bloom, J.E. Lennard-Jones, Gastrointestinal hormones in short bowel syndrome. Peptide YY may be the "colonic brake" to gastric emptying, Gut 39 (1996) 267–272.
[72] J. Chariot, A. Tsocas, A. Souli, O. Presset, C. Roze, Neural mechanism of the antisecretory effect of peptide YY in the rat colon in vivo, Peptides 21 (2000) 59–63.
[73] P.J. Mannon, J.M. Mele, Peptide YY Y1 receptor activates mitogen-activated protein kinase and proliferation in gut epithelial cells via the epidermal growth factor receptor, Biochem. J. 350 (2000) 655–661.
[74] X. Fu-Cheng, Y. Anini, J. Chariot, T. Voisin, J.P. Galmiche, C. Roze, Peptide YY release after intraduodenal, intraileal, and intracolonic administration of nutrients in rats, Pflugers Arch. 431 (1995) 66–75.
[75] X. Fu-Cheng, A. Souli, J. Chariot, C. Roze, Antisecretory effect of peptide YY through neural receptors in the rat jejunum in vitro, Peptides 20 (1999) 987–993.
[76] J.B. van Goudoever, B. Stoll, B. Hartmann, J.J. Holst, P.J. Reeds, D.G. Burrin, Secretion of trophic gut peptides is not different in bolus- and continuously fed piglets, J. Nutr. 131 (2001) 729–732.
[77] H.C. Lin, W.Y. Chey, X. Zhao, Release of distal gut peptide YY (PYY) by fat in proximal gut depends on CCK, Peptides 21 (2000) 1561–1563.
[78] M.K. Vu, M. Verkijk, E.S. Muller, I. Biemond, C.B. Lamers, A.A. Masclee, Medium chain triglycerides activate distal but not proximal gut hormones, Clin. Nutr. 18 (1999) 359–363.
[79] E. Itoh, M. Fujimiya, A. Inui, Thioperamide, a histamine H3 receptor antagonist, powerfully suppresses peptide YY-induced food intake in rats, Biol. Psychiatry 45 (1999) 475–481.
[80] I. Lonnroth, S. Lange, Purification and characterization of the antisecretory factor: a protein in the central nervous system and in the gut which inhibits intestinal hypersecretion induced by cholera toxin, Biochim. Biophys. Acta 883 (1986) 138–144.

[81] I. Lonnroth, S. Lange, E. Skadhauge, The antisecretory factors: inducible proteins which modulate secretion in the small intestine, Comp. Biochem. Physiol. A 90 (1988) 611–617.
[82] E. Johansson, E. Jennische, S. Lange, I. Lonnroth, Antisecretory factor suppresses intestinal inflammation and hypersecretion, Gut 41 (1997) 642–645.
[83] S. Lange, D.S. Delbro, E. Jennische, E. Johansson, I. Lonnroth, Recombinant or plasma-derived antisecretory factor inhibits cholera toxin-induced increase in Evans blue permeation of rat intestinal capillaries, Dig. Dis. Sci. 43 (1998) 2061–2070.
[84] K. Tateishi, Y. Misumi, Y. Ikehara, K. Miyasaka, A. Funakoshi, Molecular cloning and expression of rat antisecretory factor and its intracellular localization, Biochem. Cell Biol. 77 (1999) 223–228.
[85] S. Lange, E. Jennische, E. Johansson, I. Lonnroth, The antisecretory factor: synthesis and intracellular localization in porcine tissues, Cell Tissue Res. 296 (1999) 607–617.
[86] S. Bjorck, I. Bosaeus, E. Jennische, I. Lonnroth, E. Johansson, S. Lange, Food induced stimulation of the antisecretory factor can improve symptoms in human inflammatory bowel disease: a study of a concept, Gut 46 (2000) 824–829.
[87] S.M. Walton, Advances in the use of the 5-HT3 receptor antagonists, Exper. Opin. Pharmacother. 1 (2000) 207–223.
[88] M.J.G. Farthing, Novel targets for the pharmacotherapy of diarrhoea: a view for the millennium, J. Gastroenterol. Hepatol. 15 (2000) G38–G45.
[89] J.L. Turvill, P. Connor, M.J.G. Farthing, The inhibition of cholera toxin-induced 5-HT release by the 5-HT(3) receptor antagonist, granisetron, in the rat, Br. J. Pharmacol. 130 (2000) 946–951.
[90] J.L. Turvill, P. Connor, M.J.G. Farthing, Neurokinin 1 and 2 receptors mediate cholera toxin secretion in rat jejunum, Gastroenterology 119 (2000) 1037–1044.
[91] C. Roze, S, Bruley Des Varannes, G. Sh, J. Geneve, J.P. Galmiche, Inhibition of prostaglandin-induced intestinal secretion by igmesine in healthy volunteers, Gastroenterology 115 (1998) 591–596.
[92] J.L. Turvill, P. Kasapidis, M.J.G. Farthing, The sigma ligand, igmesine, inhibits cholera toxin and Escherichia coli enterotoxin induced jejunal secretion in the rat, Gut 45 (1999) 564–569.
[93] J. Roge, P. Baumer, H. Berard, J.C. Schwartz, J.M. Lecomte, Scand. J. Gastroenterol. 28 (1993) 352–354.
[94] M.P. Primi, L. Bueno, P. Baumer, H. Berard, J.M. Lecomte, Racecadotril demonstrates intestinal antisecretory activity in vivo, Aliment. Pharmacol. Ther. 13 (Suppl 6) (1999) 3–7.
[95] E. Salazar-Lindo, J. Santisteban-Ponce, E. Chea-Woo, M. Gutierrez, Racecadotril in the treatment of acute watery diarrhea in children, N. Engl. J. Med. 343 (2000) 463–467.
[96] O. Nylander, A. Hallgren, M. Sababi, COX inhibition excites enteric nerves that affect motility, alkaline secretion, and permeability in rat duodenum, Am. J. Physiol. 281 (2001) G1169–G1178.
[97] E. Beubler, R. Schuligoi, Mechanisms of cholera toxin-induced diarrhea, Ann. N. Y. Acad. Sci. 915 (2000) 339–346.
[98] J.S. Stamler, D.J. Singel, J. Loscalzo, Biochemistry of nitric oxide and its redox-activated forms, Science 258 (1992) 1898–1902.
[99] K.S. Murthy, J.R. Grider, J.G. Jin, G.M. Makhlouf, Interplay of VIP and nitric oxide in the regulation of neuromuscular activity in the gut, Arch. Int. Pharmacodyn. Ther. 329 (1995) 27–38.
[100] M.C. Stoner, A.M. Scherr, J.A. Lee, L.G. Wolfe, J.M. Kellum, Nitric oxide is a neurotransmitter in the chloride secretory response to serotonin in rat colon, Surgery 128 (2000) 240–245.
[101] R.M. Clancy, S.B. Abramson, Nitric oxide: a novel mediator of inflammation, Proc. Soc. Exp. Biol. Med. 210 (1995) 93–101.
[102] T.A. Pritts, Q. Wang, X. Sun, M.R. Moon, D.R. Fischer, J.E. Fischer, H.R. Wong, P.O. Hasselgren, Induction of the stress response in vivo decreases NF-κB activity in jejunal mucosa of endotoxemic mice, Arch. Surg. 135 (2000) 860–866.
[103] C. Jobin, R.B. Sartor, The IκB/NF-κB system: a key determinant of mucosal inflammation and protection, Am. J. Physiol. Cell Physiol. 278 (2000) C451–C462.
[104] A.S. Baldwin Jr., The transcription factor NF-κB and human disease, J. Clin. Invest. 107 (2001) 3–6.
[105] A. Southey, S. Tanaka, T. Murakami, H. Miyoshi, T. Ishizuka, M. Sugiura, K. Kawashima, T. Sugita, Pathophysiological role of nitric oxide in rat experimental colitis, Int. J. Immunopharmacol. 19 (1997) 669–676.
[106] M.K. Barry, J.D. Aloisi, S.P. Pickering, C.J. Yeo, Nitric oxide modulates water and electrolyte transport in the ileum, Ann. Surg. 219 (1994) 382–388.
[107] F.H. Mourad, L.J. O'Donnell, E.A. Andre, C.P. Bearcroft, R.A. Owen, M.L. Clark, M.J.G. Farthing, L-arginine, nitric oxide, and intestinal secretion: studies in rat jejunum in vivo, Gut 39 (1996) 539–544.
[108] A. Fasano, Nitric oxide and intestinal water and electrolyte transport: in, out, or both?, J. Pediatr. Gastro. Nutr. 32 (2001) 527–528.
[109] I. Alican, P. Kubes, A critical role for nitric oxide in intestinal barrier functions and dysfunction, Am. J. Physiol. 270 (1996) G225–G237.
[110] E.N. Janoff, H. Hayakawa, D.N. Taylor, C.E. Fasching, J.R. Kenner, E. Jaimes, L. Raij, Nitric oxide production during *Vibrio cholerae* infection, Am. J. Physiol. 273 (1997) G1160–1167.
[111] A. Schirgi-Degen, E. Beubler, Significance of nitric oxide in the stimulation of intestinal fluid absorption in the rat jejunum in vivo, Br. J. Pharmacol. 114 (1995) 13–18.
[112] E. Beubler, A. Schirgi-Degen, Nitric oxide counteracts 5-hydroxytryptamine- and cholera-induced fluid secretion and enhances the effect of oral rehydration solution, Eur. J. Pharmacol. 326 (1997) 223–228.
[113] R.A. Wapnir, M.A. Wingertzahn, S. Teichberg, L-arginine in low concentration improves rat intestinal water and sodium absorption from oral rehydration solutions, Gut 40 (1997) 602–607.
[114] T.S. Gaginella, N. Mascolo, A.A. Izzo, G. Autore, F. Capasso, Nitric oxide as a mediator of biscacodyl and phenolphthalein laxative action: induction of nitric oxide synthase, J. Pharmacol. Exp. Ther. 270 (1994) 1239–1245.
[115] A.A. Izzo, T.S. Gaginella, N. Mascolo, F. Capasso, Nitric oxide as a mediator of the laxative action of magnesium sulfate, Br. J. Pharmacol. 113 (1994) 228–232.
[116] K. Rehman, M.A. Wingertzahn, R.G. Harper, R.A. Wapnir, Proabsorptive action of gum arabic: regulation of nitric oxide metabolism in the basolateral potassium channel of the small intestine, J. Pediatr. Gastro. Nutr. 32 (2001) 529–533.
[117] A.J. Eherer, C.A. Santa Ana, J. Porter, J.S. Fordtran, Effect of psyllium, calcium polycarbophil, and wheat bran on secretory diarrhea induced by phenolphthalein, Gastroenterology 104 (1993) 1007–1012.
[118] V. Burke, M. Gracey, Studies with enterotoxigenic microorganisms: effects of candidate antidiarrhoeal in experimental animals *in vivo*, J. Pediatr. Gastro. Nutr. 3 (1984) 585–592.
[119] H. Loeb, Y. Vandenplas, P. Würsch, P. Guesry, Tannin-rich carob pod for the treatment of acute-onset diarrhea, J. Pediatr. Gastro. Nutr. 8 (1989) 480–485.
[120] R. Steffen, Worldwide efficacy of bismuth subsalicylate in the treatment of travelers' diarrhea, Rev. Inf. Dis. 12 (Suppl 1) (1990) S80–S86.
[121] H.H.H.W. Schmidt, S.M. Lohmann, U. Walter, The nitric oxide and cGMP signal transduction system: regulation and mechanism of action, Biochim. Biophys. Acta 1178 (1993) 153–175.
[122] F. Murad, Regulation of cytosolic guanylyl cyclase by nitric oxide: the NO cyclic GMP signal transduction system, Adv. Pharmacol. 26 (1994) 19–33.

[123] T.M. Lincoln, P. Komalavilas, N.J. Boerth, L.A. MacMillan-Crow, T.L. Cornwell, cGMP signaling through cAMP- and cGMP-dependent protein kinases, Adv. Pharmacol. 34 (1995) 305–322.

[124] L.J. McDonald, F. Murad, Nitric oxide and cGMP signaling, Adv. Pharmacol. 34 (1995) 263–275.

[125] S.M. Lohmann, A.B. Vaandrager, A. Smolenski, U. Walter, H.R. de Jonge, Distinct and specific functions of cGMP-dependent protein kinases, Trans. Biol. Sci. (TIBS) 22 (1997) 307–312.

[126] T. Imai, K. Irata, F. Marumo, Induction of nitric oxide synthase by cyclic AMP in rat vascular smooth muscle cells, J. Clin. Invest. 93 (1994) 543–549.