Blood flowing through an artery, air flowing through the airways, transit of a meal through the intestine: what have they in common? The artery, airway, and intestine are tubular structures exposed to a changing mechanical environment consisting of forces that govern physiological responses (5, 6, 8). Release of nucleotides, ATP and UTP, occurs in response to physical forces, and this is also a response in common among the artery, airway, and intestine. An increasing number of studies have extended these fundamental observations to reach the astounding conclusion that most cells are mechanosensitive and release nucleotides. ATP or other nucleotides are not only released from neural or nonneuronal cells by mechanical stimulation but also by receptor activation, hypoxia, osmotic shock, acidosis, and others.

How do these unassuming cells detect physical forces due to mechanical activation and convert them into biological responses in the intestine? This is the quest for the “Holy Grail” of mechanosensory transduction. What is the mechanosensor? What is the mechanotransducer? Is ATP the common chemical mediator involved? These questions will be the subject of this review as they relate to secretory reflexes in response to mechanical activation of the intestinal mucosa. We will pay special attention to the role of ATP in mechanosensory transduction.

Nucleotides

ATP is the most fundamental of biological molecules because it is an energy source for all cells. It is generated from catabolism of glucose to lactic acid during the citric cycle. In its capacity as a fuel, it is found in high concentrations (2–5 mM) within cells where it was thought to be trapped by its size and ionic charge. When cells are in a static state, there is a steady resting level of nucleotides outside the cell that is dependent on the rate of basal or constitutive release and the rate of hydrolysis by scavenger enzymes, called 5’-ectonucleotidases. Most cells appear to be sensitive to mechanical forces and respond by releasing ~0.5–10% of the intracellular pool of nucleotides (9). Larger amounts of ATP are released into the extracellular compartment during cell damage, cytosis, or apoptosis. ATP transporters, exocytosis, hemi-gap junctions, or ATP-conducting ion channels are possible mechanisms by which ATP may be released from nonneural cells. In neural cells, ATP is often stored in vesicles with other mediators or neurotransmitters and released by exocytosis, a process of vesicle fusion with the plasma membrane. The products of nucleotide hydrolysis of ATP and UTP are ADP, AMP, adenosine, UDP, UMP, and uracil.

A complex metabolic pathway for extracellular nucleotides (ectonucleoside diphosphokinases, ectonucleotidases) and dinucleotides (ectonucleotidase pyrophosphatases) makes it difficult to know with certainty the true levels of nucleotides available to activate extracellular receptors (9). Nucleotide release from epithelia lining the airway lumen provides a mechanism for mucociliary clearance in resting cells. Mechanical activation stimulates bilateral nucleotide release, which provides autocrine and paracrine signals at the same cell or adjacent cells (8). Although differences exist between cells lining the airway or gut lumen, both are exquisitely sensitive to mechanical stimulation.

When nucleotides are released from the cell into the extracellular compartment, they bind to receptors on the surface of the cell where they influence the function of that cell (autocrine regulation). Adenine (ATP, ADP) or uracil (UDP and UTP) nucleotides are important extracellular signaling molecules that act at cell surface receptors. Burnstock and Williams (2) proposed a classification scheme for distinguishing two classes of purinoceptors: P1, which includes adenosine A1, A2a, A2b, and A3, and the nucleotide P2 receptors (for ATP, ADP, UTP etc.), which are subclassified as P2X/ligand-gated ion channels P2X1–P2X7 and as P2Y receptors P2Y1, P2Y2, P2Y4, P2Y6, P2Y11, P2Y12, or P2Y13, which are coupled to GTP-binding proteins called G proteins. Because ATP is ubiquitous, there is bound to be a very complex scheme of physiological regulation of gut function.
Mechanotransduction and gut neural reflexes

In the colon of the guinea pig, a common model for studying the enteric nervous system, brush stroking the mucosa stimulates enterochromaffin cells, epithelial cells, and neurons, culminating in a neural reflex regulating chloride secretion. Brush stroking the mucosa is an attempt to mimic in vitro some of the physical/mechanical forces involved in activation of the reflex. Normally, physiological activation is provided by remains of a meal in the colonic lumen that serve to dimple or deform the cell surface and impart touch, pressure, and stretch forces. Flow of luminal contents during mixing or propulsive movements impacts pressure and shear stress, a frictional force that acts at the interface between the gut wall and the flowing contents and produces tangential distortion of enteroendocrine, enterochromaffin, and epithelial cells lining the lumen of the gut. In addition, complex gradients of shear stress occur and may produce uneven stretch forces.

As described for other cells, physical forces applied to the plasma membrane generate tension in the lipid bilayer that behaves like an elastic solid, resisting compression, expansion, bending, and extension (5). The lipid bilayer is supported by the cytoskeleton, which is composed of microtubules, intermediate filaments, and actin microfilaments and is linked to the extracellular matrix through focal adhesion complexes. In addition to tension affecting the bilayer directly, tension may be distributed through the cytoskeleton and the extracellular matrix.

The submucous and myenteric plexuses, which comprise the enteric nervous system, are the brains behind the secretory and contractile operation of the gut. The stroking reflex (Fig. 1) through the submucous plexus consists of release of 5-HT and ATP from enterochromaffin cells, paracrine activation of intrinsic primary afferent neurons (IPANs), synaptic transmission to vasoactive intestinal peptide (VIP) and cholinergic secretomotor neurons, release of VIP and acetylcholine (which bind to receptors on chloride-secreting crypt epithelial cells) and stimulation of chloride secretion with sodium and water following (4). Appropriate control of chloride secretion is a necessity to provide hydration of viscous mucins and to participate in host defense mechanisms to prevent microbial penetration of the gut.

Whereas chloride secretion is regulated mainly by reflex pathways through the submucosal plexus, less frequently regulation can occur via longer reflex pathways through the myenteric plexus. Connections between the submucous plexus and myenteric plexus provide the hardwiring for reflexes that coordinate chloride secretion with muscle contraction. Distention of the gut wall also evokes reflexes regulating chloride secretion in the mammalian colon, possibly through stretch-sensitive subsets of submucous and myenteric neurons. The integrated response is an appropriate rate of secretion to match the digestive state. All of the cells in the gut reflex may respond to different mechanical forces (5). Each component of the response in the reflex will be described in terms of the role of ATP or nucleotides in mechanotransduction.

Mechanosensors

Mechanosensors in enterochromaffin, epithelial, or neural cells in the gut wall detect changes in tension from touch, stretch, pressure, and shear stress and convert it into a membrane or intracellular event. The mechanosensor must be able to recognize the membrane property or intracellular event. Given that several mechanical forces may be applied simultaneously, more than one type of mechanosensor may be operational at any one time. In general, mechanosensitivity may be conferred by 1) the opened or closed state of a mechanically gated ion channel; 2) a receptor such as P2Y1 or an enzyme; 3) an intracellular second messenger like calcium, cAMP, or even reactive oxygen species; 4) mechanically evoked vesicular fusion and transmitter release; 5) mechanosensitive release of a neurotransmitter such as ATP and activation of receptor-gated calcium channel; 6) mechanically gated potassium channels such as the two-pore domain arachidonic acid channel (TRAAK); 7) integrins; 8) receptor tyrosine kinases; 9) caveolae; and 10) G proteins (5). That membrane or intracellular event is exclusively referred to as the “mechanoresponse,” whether it is the opening of an ion channel, release of a mediator, or direct activation of a membrane protein. It triggers a physiological response via a process called mechanotransduction.

Are P2Y receptors the mechanotransducers in enterochromaffin cells?

Previous studies in tissue preparations have suggested a
complex regulation of 5-HT release from enterochromaffin cells via stimulatory and inhibitory receptors (14). The complications associated with interpretation of in vivo results were overcome by using a cell model system to study how mechanical forces are detected and transduced by enteroendocrine cells. Human BON cells derived from a metastasis of a pancreatic carcinoid tumor of enterochromaffin origin have been used as a model of enterochromaffin cells. Rotational shaking was used to simulate a changing mechanical environment of the gut and to generate changes in hydrostatic pressure, cyclical shear stress, and possibly other forces that lead to an increase in 5-HT release.

Studies indicated that shaking mobilized calcium from intracellular stores and that this was mediated by a G protein, G<sub>q</sub>α (6). The G<sub>q</sub>α signaling pathway includes an endogenous ligand that binds to a receptor coupled to G<sub>q</sub>α, activation of phospholipase C, mobilization of calcium from internal stores, and release of 5-HT. Blockade of G<sub>q</sub>α and other G proteins by GDPβS completely abolished the response to shaking and ruled out the direct effect of the applied force on phospholipase C (6). Use of a synthetic peptide disguised as the truncated COOH-terminal tail of G<sub>q</sub>α, which interferes with receptor-G protein coupling, prevented mechanically evoked 5-HT release from BON cells. These and other observations ruled out direct activation of G<sub>q</sub>α by physical forces, and they reinforced the belief that receptor-G protein coupling was necessary for 5-HT release. P2Y receptors that signal through G<sub>q</sub>α were implicated, because mechanical stimulation releases ATP and UTP, both endogenous ligands for P2Y receptors (20). These findings suggest that a nucleotide is the principal autocrine mediator of 5-HT release during rotational shaking.

Initial findings point to P2Y receptors as potential mechanotransducers in BON cells. The ectoenzyme apyrase that breaks down ATP or other nucleotides prevents 5-HT release from BON cells in response to rotational shaking and prevents the response to ATP on 5-HT release. The preferred nucleotide for the receptor in BON cells based on its agonist activity is ATP (20); UTP, UDP, ADP, and AMP are inactive or partial agonists. This potency profile may vary depending on the species (14). The question of which purinoceptor (P2Y1, P2Y2, P2Y4, P2Y6, P2Y11, and P2Y12 receptor transcripts are expressed in BON cells) that signals through G<sub>q</sub>α is involved in mechanosensory transduction in BON cells is unanswered; however, there are hints that P2Y1 receptors are implicated in mechanosensory transduction and signaling in other cells, in particular dorsal root ganglion neurons.

For P2Y receptors to be activated, ATP must be released into the extracellular compartment. How is this accomplished? New evidence in oocytes made mechanosensitive by transfecting them with a cDNA encoding a P2Y1 receptor from sensory neurons suggests that ATP does not exit the cell via an ATP-permeable ion channel (11). Other alternatives include permeation through hemi-gap junctions, ATP transporters, and exocytosis fusion of vesicle with the plasma membrane. A strong case for exocytosis of ATP by fusion of trafficking vesicles with the plasma membrane occurs in this oocyte model of light touch. This may also be the case in enterochromaffin cells of the gut. Vesicles that are used to traffic proteins to and from the plasma membrane and the Golgi apparatus may also contain ATP or 5-HT. The corelease of ATP with 5-HT from enterochromaffin cells may provide a secondary amplification mechanism of the initial nucleotide response to mechanical activation.

5-HT can also be released from enterochromaffin cells by calcium influx through L-type voltage-sensitive calcium channels. This mechanism is not involved in mechanotransduction in BON cells, and as such it would be useful to explore the role of ATP corelease in autocrine regulation of 5-HT release. Therefore, 5-HT release occurs via either a mechanosensitive P2Y/G<sub>q</sub>α-calcium signaling pathway or a nonmechanosensitive L-type calcium channel pathway (4, 10).

The emerging picture is a complex interplay of paracrine and autocrine mediators released from enterochromaffin cells and epithelial cells. The expected net effect is a dramatic stimulation of 5-HT release from enterochromaffin cells to activate the secretory reflex. It is likely that the P2Y receptor/G<sub>q</sub>α signaling pathway is the primary transduction pathway involved in converting physical forces generated by rotational shaking to a physiological response of 5-HT release. However, Schumacker (16) cautions, one of the difficulties in identifying the most upstream event in mechanotransduction is not knowing whether one event is the sensor or a downstream target of the mechanotransducer. A P2Y receptor coupled to G<sub>q</sub>α is likely to be the mechanotransducer in the plasma membrane of BON cells. An illustration of purinergic signaling pathways for 5-HT release in human BON cells used as a model of enterochromaffin cells is illustrated in Fig. 2.

Epithelial cells

As described earlier, physical forces evoke release of nucleotides from enterochromaffin cells, leading to release of 5-HT that triggers a neural reflex response. The crypt epithelial cell is the target of neurotransmitters released from secretomotor neurons in the purinergic reflex. Epithelial cells respond to VIP and acetylcholine (Fig. 1) by augmenting chloride secretion via cAMP-dependent cystic fibrosis transmembrane conductance regulator (CFTR) chloride channels and calcium-dependent chloride channels.

Stroking or mechanical activation of the mucosa evokes release of ATP from epithelium as well as enterochromaffin cells (Fig. 2). The mechanism for ATP release from epithelium is unknown. Basal ATP release occurs across the apical side of the cell, whereas hypotonicity and cell swelling trigger ATP release from both apical and basolateral sides, a process that is associated with gadolinium-sensitive, stretch-activated ion channels (18). In cystic fibrosis, airway epithelial cells lose their ability to release ATP via the apical membrane, and this defect may contribute to the pathology of the disease that is...
characterized by deficient secretion of fluid and mucociliary clearance. In the airways, epithelial cells release ATP when mechanically simulated regardless of the expression of CFTR chloride channels. Thus ATP release is independent of the CFTR channel in this model (18). In a colonic epithelial HT29-Cll.16F cells, ATP stimulates a chloride conductance that is not mediated by an increase in intracellular calcium (2), raising the possibility that another signaling pathway is involved such as the adenylyl cyclase/Gs pathway or alternatively that purinergic receptors directly activate chloride channels.

Once ATP is released it acts as an autocrine mediator, binding to receptors on epithelial cells to stimulate chloride and fluid secretion, or as a paracrine messenger and regulator of enterochromaffin cells. When colonic tissues are "denerivated" with tetrodotoxin, chloride secretion is augmented by inhibitors of ATP hydrolysis, indicating that endogenous nucleotides can affect epithelial cells directly. Although not all of the receptors for nucleotides have been identified on epithelial cells, messenger RNA transcripts for P2Y2, P2Y4, and P2Y6 receptors are present in human Caco-2 cells. P2Y2 and P2Y4 receptors have been identified in human Caco-2 or T84 colonic cells, and P2Y1 and P2Y2 receptors have been identified in rat colonic mucosa (2).

Role of purines on integrated neural reflex responses

Sensory signals regarding the digestive state of the colon are transmitted from gut mucosa to the enteric ganglia by IPANs or to the spinal cord via extrinsic primary afferent neurons (EPANs) where motor and secretory function is modified through reflexes (15). An IPAN is identified by having afterhyperpolarizing (AH)/type 2 electrophysiological behavior. 5-HT acting at 5-HT1P4 receptors activates the primary afferent process by evoking a nerve impulse leading to depolarization of submucosal IPANs and activation of the secretory reflex. Thus 5-HT released from mechanosensitive enterochromaffin cells acts as a paracrine regulator of IPANs. The stimulus for 5-HT release can be pressure, puffs of nitrogen, touch, or mucosal stroking. The mechanosensors that detect force must reside in the enterochromaffin cell, but their identities are unknown.

Some submucous neurons in the secretory reflex are modulated indirectly by mediators from remote mechanosensitive cells. For example, distention causes reflex muscle contraction. Contraction stretches and activates nerve terminals of EPANs in dorsal root ganglia that have processes projecting to the mucosa. Stretch of the mucosal process of EPANs releases substance P and causes chloride secretion by stimulating secretomotor neurons (19). If EPANs are blocked with capsaicin, distension-evoked chloride secretion is only partially reduced, suggesting that submucous and myenteric IPANs may be activated directly by stretch. Stretch-induced chloride secretion is a mechanism that becomes significant during pathological states such as intestinal obstruction.

IPANs whose cell bodies are in the myenteric ganglia respond indirectly to stretch as already indicated, and a small subset may respond directly to stretch. In contrast to indirect activation of neurites of myenteric IPANs, deformation of the cell somas increases the opening of potassium channels, which inhibits the gut, perhaps protecting the gut from over-
activity of reflexes.

The low rate of basal chloride secretion in the guinea pig distal colon is a composite of stimulatory and inhibitory mediators that are constitutively produced, including release of 5-HT, prostaglandins, and now nucleotides. Resting release of ATP and its activation of P2Y receptors determines the set-point of signal transduction pathways and second messenger systems in a variety of cell types at rest or during mechanical stimulation (13). The fact that nucleotides may sensitize or desensitize signaling pathways implies that they may serve as modulators of cell responsivity to other endogenous substances like hormones or neurotransmitters. In enterochromaffin cells, nucleotides modulate intracellular free calcium and cAMP levels involved in 5-HT release, whereas in submucous neurons nucleotides primarily elevate calcium levels (1).

During the stroking reflex, endogenous release of ATP likely mediates 5-HT release from the enterochromaffin cells. ATP is the preferred agonist at P2Y receptors in stimulating 5-HT release, elevating 5-HT release by >1,000% in BON cells, whereas UTP, UDP, and the selective P2Y1/ADP agonist are virtually inactive up to a 1 mM concentration. In contrast, in submucous neurons, the preferred agonist may be ADP and ATP. Potency profiles for nucleotides suggest that neural P2Y1 receptors, which are ADP-prefering receptors, mediate chloride secretion in the guinea pig colon in response to mucosal stroking. However, some caution must be used in interpreting results across species. Although there is evidence for P2Y1 receptors in secretory reflexes, the expression of other P2Y receptor subtypes in enteric neurons implies that we have seen only the “tip of the iceberg.” Determining the functional significance of all of these P2Y receptors will be challenging.

Purines released by mechanical stimulation may evoke action potentials in afferent fibers directly. The molecular basis of sensory signaling in the gut elsewhere is not understood, although some evidence exists to support the participation of nucleotides through activation of both P2X2/3 and P2Y1 receptors. Burnstock and Williams (2) proposed that purinergic mechanosensory transduction occurs in hollow viscera such as sacs (i.e., gut, gallbladder) or tubes (i.e., bile ducts, ureter). Accordingly, distension releases ATP from epithelial cells lining the visera, which then acts on P2X3 or P2X2/3 receptors on subepithelial sensory nerves to transmit nociceptive signals to the central nervous system. Supporting evidence exists for this hypothesis in the bladder epithelium for the P2X3 knockout mouse and by the expression of P2X2/3 receptors on capsaicin-resistant sensory neurons. Although this concept is still speculative, the findings imply that P2X receptors could be expressed on primary afferent processes of IPANs in the enteric nervous system as well.

It is also possible that ATP or other nucleotides released from enterochromaffin or epithelial cells has a paracrine effect on primary afferents of IPANs by activating P2Y/putative P2Y1 receptors shown to exist on EPANs. Therefore, in addition to ATP acting at P2X2/3 receptors on EPANs, P2Y1 receptors have been implicated in the generation of sensory action potentials by light touch. It is known that P2Y1 mRNA is concentrated in large-fiber EPANs in dorsal root ganglia. A single complimentary RNA encoding a P2Y1 receptor derived from sensory neurons of the dorsal root ganglion renders *Xenopus laevis* oocytes mechanosensitive to touch, and exogenous ATP releases calcium from internal stores. The evidence suggests that the P2Y1 receptor in sensory neurons may induce mechanosensitivity in oocytes by providing a missing link in the signaling pathway (12). Is the P2Y1 receptor the mechanotransducer of light touch? The jury is still out on that question, because other steps may also be involved in mechanotransduction.

An important consideration relates to the mechanical stimuli and the types of forces they generate. It is conceivable that different stimuli might be detected by different mechanosensory-mechanotransduction pathways leading to 5-HT release. The P2 receptor subtype involved in mechanotransduction in human BON cells (enterochromaffin cell model) remains unknown.

In mucosal stroking reflexes in guinea pig colon, P2 antagonists or apyrase reduce the secretory response to brush stroking by 30–50%, indicating that endogenous nucleotides participate in the neural secretory reflex. Neural P2Y1 receptors are clearly involved in the chloride secretory response to stroking, since the P2Y1 receptor antagonist MRS-2179 reduces the reflex response. 2-Methylthio-ADP, a P2Y1 agonist, is the most potent nucleotide, having a low-nanomolar potency on neurons to stimulate chloride secretion. Similarly, in the rat distal colon, mucosal touch evokes an increase in calcium in submucous neurons that is prevented by the P2Y1 antagonist by blocking nerve conduction with tetrodotoxin by removing the mucosa, which effectively eliminates the mechanosensory mechanism. Immunofluorescent studies provide support for P2Y1, P2Y2, and P2Y4 receptors at presynaptic sites on submucous neurons, and RT-PCR analysis provided evidence for mRNA transcripts for P2Y1, P2Y2, P2Y4, P2Y6, and P2Y12 receptors in submucous ganglia/submucosa. In the stroking reflex, the functional identity of neurons with P2Y receptors or whether these receptors contribute to mechanosensitivity directly is unknown.

In addition to P2Y receptors, the stroking reflex also involves neural P2X receptors. Desensitization of P2X receptors with αβ-methylene-ATP reduces the stroking reflex response by 30% but does not affect the neural secretory response to the P2Y1 agonist. Therefore, both P2X and P2Y1 receptors are involved in neural secretion. This is in keeping with electrophysiological studies showing that exogenous nucleotides have a dual excitatory effect on submucous S-type 1 secretomotor neurons. ATP causes a fast depolarizing response that is mediated by P2X receptors and a slow depolarization that is mediated by P2Y receptors. Both responses are coupled to a rise in intracellular free calcium (1).

Studies on neural reflexes through the myenteric plexus...
indicate that mechanical stimulation of the mucosa releases acetylcholine and ATP in both ascending and descending excitatory pathways that provide synaptic inputs to excitatory motoneurons to the circular and longitudinal muscles (17). In initial studies, P2 antagonists pyrodoxyl phosphatase-6-azophenyl-2′,4′-disulfonic acid (PPADS) and MRS-2179 (selective for P2Y1 receptors) reduce the coordinated secretory and tension responses in the rodent colon. P2Y1, P2Y2, and P2Y4 receptor immunoreactivity was localized to specific subsets of enteric neurons at pre- or postsynaptic sites. Therefore, mucosal stimulation releases ATP from myenteric and submucous neurons in the reflex. ATP then has far-reaching effects, and it is also involved in the purinergic component of the reflex that coordinates muscle contraction and epithelial secretion. Figure 3 illustrates a working model of purinergic mechanosensory signaling in gut neural reflexes involved in the coordination of motility and secretion in the distal colon.

It is quite interesting that IPANs with their cell somas in the myenteric plexus are detectors of neurite distortion and compression of the soma; neurite distortion increases and soma distortion inhibits action potential firing and cell excitability (7). ATP causes slow membrane hyperpolarization associated with a reduction in excitability in these AH neurons. The response to ATP is more potent and of greater magnitude than that of adenosine, suggesting that a genuine nucleotide P2Y response is involved. As is the case in EPANs in dorsal root ganglia, P2Y receptors on IPANs of the gut could display the same characteristics (7), but this remains to be proven.

A significant body of evidence supports the hypothesis that the metabolite of ATP, adenosine, provides a physiological inhibitory brake on secretory reflexes in the guinea pig colon. Adenosine acts at neural P1 (A1 subtype) receptors to suppress both the serotonergic and prostaglandin-mediated arms of the secretory reflex pathways. The role of adenosine in gut neural reflexes was recently reviewed (3). Adenosine inhibitory P1 receptors are present at cell somas of both myenteric and submucous IPANs and therefore serve to gate incoming sensory information. It has been speculated that putative P1 receptors could be present on primary afferent processes of IPANs as well.

Little or no information exists on the contribution of ATP to adenosinergic responses via its metabolic degradation. It is likely that important interactions exist between ATP acting at P2 receptors and adenosine interacting at adenosine P1 receptors following mucosal stimulation. These interactions provide additive or synergistic effects or antagonistic responses; the net impact and duration of the response is...
consequence of such interactions. The interactions are relevant to the mechanotransducing cell, in the nervous system, and at the effector system. The nature of these interactions at each step of the reflex require further clarification. More important is the effect of adenosine and ATP in diseases involving the gut (i.e., chronic inflammation, intestinal ischemia, irritable bowel syndrome, or diabetes) in which there is a shift in the balance between ATP and adenosine in gut cells. This should be a focus of future studies, because it likely holds important clues to our understanding of dysfunctions in the diseased gut.

Do nucleotides or nucleosides have a role in the diseased gut?

Purinergic pathways are slowly emerging as therapeutic targets for alleviating gut dysfunction in such diverse diseases as Chagas disease, Hirschsprung's disease, inflammatory bowel disease, colitis, intestinal ischemia, diabetes, colonic tumors, and irritable bowel syndrome. Purinergic signaling appears to be impaired in Chagas disease, caused by a parasitic protozoan that requires a human host to synthesize adenosine. The disorder is characterized by loss of enteric ganglia, motility disturbances, and inflammatory changes. Enzymes that break down nucleotides are found in the parasite, and enhancement of cell permeability occurs during the acute phase of the disease that is mediated by P2X/P2Y receptors. In Hirschsprung's disease, in which ganglia are absent in the nervous system (i.e., aganglionic segment), inhibitory junction potentials in smooth muscle that are partly mediated by ATP are absent, whereas excitatory purinergic responses are present in the contrasted aganglionic segment. ATP-MgCl₂ or Mg-ATP compounds have been suggested to be of therapeutic value in intestinal ischemia or shock, although this is still controversial. P2Y6 receptors have been implicated in human T cells, where they play a putative role in the pathology of intestinal inflammation. ATP may be a neuroimmunomodulator with anticancer activity that may be relevant to suppressing colonic tumors. Its metabolite adenosine may be of potential therapeutic value in the postischemic intestine and in colitis because of its anti-inflammatory and cyto- and neuroprotective effects. In particular, an adenosine kinase inhibitor that elevates endogenous adenosine levels was shown to attenuate experimental colitis in vivo. Further studies on the roles of purines in the immune, neural, secretory, and absorptive functions in the diseased gut are clearly suggested. A better understanding of the role of purines in mechanosensory transduction and neural reflexes is critical if we are to understand their role in the diseased gut.

We are grateful to Iveta Grants, Jun Ge Yu, Yu-Zhong Wang, and Jianjing Xue for their contributions to P2Y receptor studies.

Jacqueline Wunderlich is a visiting medical scientist from Germany.

Support for some of the studies described in this review was provided by National Institutes of Health Grants R01-DK-44179, DK-37240, DK-57016, National Center for Research Resources Grant 1S10-RR-11434, DK-44179-07S1 Fellowship, and a Samuel J. Roessler Scholarship to Jorge Guzman.

References