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Purinergic mechanisms in the control of gastrointestinal motility

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Abstract For many years, ATP and adenosine have been implicated in movement regulation of the gastrointestinal tract. They act through three major receptor subtypes: adenosine or P1 receptors, P2X receptors and P2Y receptors. Each of these major receptor types can be subdivided into several different classes and is widely distributed amongst various neurons, muscle types, glia and interstitial cells that regulate intestinal functions. Several key roles for the different receptors and their endogenous ligands have been identified in physiological and pharmacological studies. For example, adenosine acting at A_1 receptors appears to inhibit intestinal motility in various pathological conditions. Similarly, ATP acting at P2Y receptors is an important component of inhibitory neuromuscular transmission, acting as a cotransmitter with nitric oxide. ATP acting at P2X and $P2Y_1$ receptors is important for synaptic transmission in simple descending excitatory and inhibitory reflex pathways. Some P2Y receptor subtypes prefer uridine nucleotides over purine nucleotides. Thus, roles for UTP and UDP as enteric transmitters in place of ATP cannot be excluded. ATP also appears to be important for sensory transduction, especially in chemosensitive pathways that initiate local inhibitory reflexes. Despite this evidence, data are lacking about the roles of either adenosine or ATP in more complex motility patterns such as segmentation or the interdigestive migrating motor complex. Clarification of roles for purinergic transmission in these common, but understudied, motility patterns will depend on the use of subtype-specific antagonists that in some cases have not yet been developed.

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Introduction

Purine nucleosides and nucleotides have long been thought to play important roles as signalling molecules in the complex interactions between neurons and muscle that regulate intestinal movements (motility). The evidence for this is compelling, and various studies have implicated purine compounds and their receptors as important at virtually every point in the pathways regulating motility, from sensory transduction to neuromuscular transmission.

Despite this evidence, however, identifying the specific sites within the gastrointestinal tract where purine compounds act to regulate motility has been more difficult than might be expected. There are many reasons for this. Purine receptors are found on many different types of cells within the gut. They can be broadly divided into two classes: P1 receptors, for which adenosine is the endogenous ligand, and P2 receptors, which are sensitive to ATP and other nucleotides [1]. Many cells express both P1 and P2 receptors (e.g. compare [2] and [3]), which makes it difficult to discern the parts played by each receptor type. Furthermore, species and regional differences in roles are common, making it difficult to generalise between preparations. This problem is rendered more complex by the presence of ectonucleotidases that can rapidly break down ATP to ADP, AMP or adenosine [1]. Thus, although there is abundant evidence that ATP and adenosine are released from intestinal (enteric) nerve terminals or smooth muscle by a variety of stimuli (for examples [4–12]), the exact mix of ATP, ADP, AMP and adenosine seen by specific

receptors is almost impossible to determine. This makes the use of subtype-specific antagonists indispensable in order to discriminate the contributions of different receptors and their endogenous ligands. Unfortunately, specific antagonists for many P2 receptors are either unavailable or have only recently come into use.

Several P2Y receptor subtypes have a higher affinity for either UTP or UDP than for either ATP or ADP [1]. Thus, whereas release of uridine nucleotides within the gastrointestinal tract has not been the subject of detailed investigation, it is possible that either UTP or UDP is the endogenous ligand for some P2Y receptors. Although ATP is used throughout this review to designate the probable transmitter as enteric synapses and junctions, the possibility that a uridine nucleotide acts in its place should be kept in mind.

A key issue for considering regulation of intestinal behaviour is the definition of motility itself. Commonly used measures of motility, such as intestinal (or colonic) transit, are the end product of several different motility patterns, making such measures too imprecise to identify the site of action of a drug. Most studies record smooth-muscle contractions in strips or segments but ignore the role of the neural circuitry. However, motility is the end product of the interactions of a complex nervous system (both extrinsic and intrinsic) with myogenic pacemakers [the interstitial cells of Cajal (ICC)] and the two major muscle coats. This review seeks to put the available data into a physiological context to identify current knowledge about the roles of purine nucleosides and purine nucleotides in motility regulation.

Purine receptor subtypes

The basic properties of purine receptors, their signal transduction mechanisms and their division into P1 (adenosine receptors), P2X and P2Y receptors, have been extensively reviewed elsewhere [1, 13, 14]. P1 and P2Y receptors are members of the G-protein-coupled receptor family, and multiple subtypes of each have been cloned. Four subtypes of P1 receptor have been cloned (A_1, A_{2A}, A_{2B}, A_3), and specific antagonists are now available for all subtypes [15]. To date, eight subtypes of mammalian P2Y receptors ($P2Y_1$, $P2Y_2$, $P2Y_4$, $P2Y_6$, $P2Y_{11}$, $P2Y_{12}$, $P2Y_{13}$, $P2Y_{14}$) have been cloned [13]. Specific antagonists are available for only about half of these receptors [15], which makes analysis of their functions difficult. The P2Y receptors differ in rank order of potency of different nucleotides so that $P2Y_1$ receptors are more sensitive to ADP than they are to ATP, whereas $P2Y_6$ receptors are most potently activated by UDP, and ATP is either ineffective or an antagonist at other P2Y receptors (e.g. $P2Y_4$, $P2Y_6$, $P2Y_{14}$) [13]. However, knowing the efficacy of exogenous agonists often does not help in understanding the physiological roles of receptors intermingled in a complex system. P2X receptors are ligand-gated cation channels that respond to ATP, although they differ in sensitivity to ATP analogues [1]. Seven different P2X receptor molecules have been cloned ($P2X_1$, $P2X_2$, ..., $P2X_7$) [1, 14], but some of these can be present as heteromers [14]. Specific antagonists are available for only three of these receptors [15], so they are usually studied using the relatively nonspecific antagonists suramin and pyridoxal phosphate-6-azopheyl-2′,4′-disulphonic acid (PPADS), which also act at some P2Y receptors and can interact with ectonucleotidases [1]. The different receptor subtypes are differentially expressed within the intestinal wall, which is important for consideration of their functions.

Motility patterns

The end point of gastrointestinal motility is movement of intestinal contents from stomach to anus, but transit is only part of the story and occurs via the interaction of several distinct motility patterns (for reviews see [16–18]). In the small intestine after a meal, these include receptive relaxation [19, 20], segmentation [21, 22], peristalsis (oral to anal propulsion) and retropulsion [23]. The rate of content transit along the intestine is set by the relative contribution of each pattern [24]. Receptive relaxation occurs when intestinal contents enter a previously empty section of intestine and allows this segment to accommodate the distending material. It limits the distance over which propulsive motor activity can move the intestinal contents. Segmentation makes up more than 90% of the small intestine contractile activity during digestion and absorption of a meal, with the exact proportion depending on the nutrient content of the meal [22]. It consists of rhythmic localised constrictions that alternate with relaxations [21] and divide and redivide the intestinal contents, mixing luminal content with intestinal secretions (water, bicarbonate, enzymes, bile and mucin), facilitating digestion and nutrient absorption. Although segmentation slowly moves the contents of the lumen anally, about 10% of contractile activity in the small intestine after a meal involves rapid propulsive contractions that propagate anally over significant distances (peristalsis). In the upper small intestine, orally propagating constrictions that propel content within the duodenum towards the stomach (retrograde peristalsis) are also prominent immediately after a meal [23].

Once digestion is complete, animals enter a fasted state in which a distinctively different motor activity is seen [16, 18]. This interdigestive migrating motor complex (MMC) has three distinct phases that migrate slowly along the

small intestine from the pylorus to the ileocolonic junction (4 cm/min upper jejunum, 0.6 cm/min distal ileum of humans). Phase I is a period of quiescence that takes up 40–60% of the complex in humans. This gives way to phase II, a period of irregular contractions that increase in magnitude over 20–30% of the complex. Phase III is the most prominent component of the MMC and gives it its name. It is a period (5–10% of the complex) of very strong rhythmic contractions that propagate slowly along the intestine. Phase III contractions are initiated in either the gastric antrum or the proximal duodenum at about the time that the previous phase III contraction reaches the end of the ileum, a cycle duration of 84–112 min in humans.

Motor activity in the colon is largely independent of that in the small intestine and reflects its three primary functions: storage, water recovery and excretion [18]. Receptive relaxation is important for the first; peristalsis or mass-movement contractions or both are the mechanisms for the last. Haustral contractions clearly are relevant in some species (e.g. humans), and retrograde peristalsis is also seen.

These motor patterns are not always readily observed in vitro. However, detailed analyses require such studies. In vitro preparations include isolated segments of otherwise intact small or large intestine; opened segments dissected to expose the mucosa, muscle or enteric neurons; and muscle strips cut either longitudinally or circumferentially. Intact segments are used to study propulsive motor activity, receptive relaxation, propagating contractile complexes such as models of the MMC and, very recently, segmentation. Opened and dissected preparations are used to study simple motility reflexes—ascending excitation, descending inhibition [25] and descending excitation [26]. They are also used to study individual enteric neurons and the locations of functionally identified receptors. Muscle-strip preparations are the most studied and provide information about effects of agonists and antagonists, but this can be hard to translate meaningfully to complex motor patterns.

Neural circuits mediating motility

The basic control of intestinal motility depends on the activity of the enteric nervous system (ENS), a network of neurons contained entirely within the gastrointestinal wall [16]. Although the ENS is modulated by the central nervous system (CNS), the sympathetic nervous system and hormonal factors, each motor pattern identified above is programmed within the enteric neural circuitry. There have been extensive studies directed at identifying the elements of the enteric circuits, largely focusing on the guinea-pig ileum (for reviews see [17, 27, 28]) and recently

Table 1 Functional types of enteric neuron that can be deduced from physiological and anatomical studies

Basic Function	Plexus	Subtypes in guinea-pig ileum
Intrinsic sensory neuron	SMP	AH/Dogiel type II, ChAT/TK-IR, mucosal mechanoreceptor
	MP	AH/Dogiel type II, ChAT/calbindin/TK-IR, muscle mechanosensory, chemosensitive
	MP	AH/Dogiel type II, ChAT/calbindin/TK-IR, anal projection, distension sensitive
Ascending interneuron	MP	MP, ChAT/calretinin/TK/ENK
Descending interneuron	MP	NOS/VIP/GRP/±ChAT
	MP	ChAT/5-HT, targets myenteric and/or submucosal ganglia
	MP	ChAT/SOM, targets myenteric and/or submucosal ganglia
Excitatory longitudinal muscle motor neuron	MP	ChAT/calretinin/TK
Inhibitory longitudinal muscle motor neuron	MP	NOS/VIP/GABA, rare in guinea-pig ileum
Excitatory circular-muscle motor neuron	MP	ChAT/TK, short oral projection
	MP	ChAT/TK, long oral projection
Inhibitory circular-muscle motor neuron	MP	NOS/VIP/PACAP/ENK, short anal projection
	MP	NOS/VIP/PACAP/GRP, long anal projection
Cholinergic secretomotor neuron	SMP	ChAT/NPY
	MP	ChAT/NPY
Noncholinergic secretomotor neuron	SMP	VIP
	MP	VIP
Vasodilator neuron	SMP	ChAT/calretinin, cholinergic
Intestinofugal neuron	MP	ChAT/VIP/

The subtypes identified come from the guinea-pig ileum, as does the elementary chemical code [17, 27, 28].
SMP submucosal plexus, *MP* myenteric plexus, *ChAT* choline acetyltransferase, *TK* tachykinin, *IR* immunoreactive, *ENK* enkephalin, *NOS* nitric oxide synthase, *VIP* vasoactive intestine peptide, *5-HT* 5-hydroxytryptamine (serotonin), *SOM* somatostatin, *GABA* γ-aminobutyric acid, *PACAP* pituitary adenylyl-cyclase-activating peptide, *NPY* neuropeptide Y

branching out to guinea-pig and mouse colon. At least 11 functionally distinct types of enteric neurons can be identified, and many can be further subdivided according to their neurochemistry, projections or functional specificity (Table 1). For a general review of transmission between functionally identified enteric neurons, see [29]. Studies of ascending excitation and descending inhibition have allowed construction of a basic circuit that accounts for these reflexes (Fig. 1, for review see [17]). Features include feed-forward circuits of orally directed (ascending) interneurons that activate excitatory motor neurons and anally directed (descending) interneurons that activate inhibitory motor neurons. Another key element is a circumferentially organised recurrent network of intrinsic sensory neurons that excite each other [30–32] and have outputs to the ascending and descending feed-forward pathways and to local excitatory and inhibitory motor neurons [33, 34]. The intrinsic sensory neurons respond to changes in length and tension within the intestinal wall, to mucosal deformation and to mucosal chemical stimulation [33, 34]. A less characterised component of the circuit is an anally directed network that ultimately activates excitatory motor neurons to produce descending excitation [26, 35]. Although there are differences in the details of this circuit between species and regions [36–40], it provides a broad template for identifying the sites of purine nucleoside and purine nucleotide action in motility regulation.

Four broadly defined targets for adenosine or ATP can be identified within this circuit: sensory transduction, the recurrent network of intrinsic sensory neurons, transmission within the feed-forward pathways and neuromuscular transmission. There is evidence for purinergic involvement in each.

P1 (adenosine) receptors

Exogenous adenosine and related agonists generally inhibit intestinal motility, depressing peristaltic reflexes and transit in the small and large intestines of rats and guinea pigs [5, 41–46]. This is largely due to actions on A_1 receptors. Thus, it might be suggested that endogenous adenosine regulates motility in control intestine. Indeed, A_1 receptor blockade increases defecation in normal rats [47, 48]. However, neither small intestinal peristalsis nor colonic transit is altered by A_1 receptor antagonists [45–47], unless the system has been perturbed by a pathological insult. Similarly, peristaltic reflexes in the rat jejunum in vitro, are unaffected by blockade of A_1 receptors, although they are markedly depressed by activation of these receptors [41–43]. On the other hand, blockade of A_1 receptors restores normal transit in the rat colon in vivo when it has been depressed by either transient ischaemia [45] or as a result of postoperative ileus [46]. How these observations relate to the increased defecation produced by A_1 blockade is unclear. Furthermore, the roles of adenosine in the major motor activities of the small intestine, segmentation and MMC have not been studied.

Studies of of A_1 agonist action sites reveal several mechanisms that can account for their propulsion inhibition. The most obvious is that A_1 receptor activation inhibits release of the excitatory transmitter acetylcholine

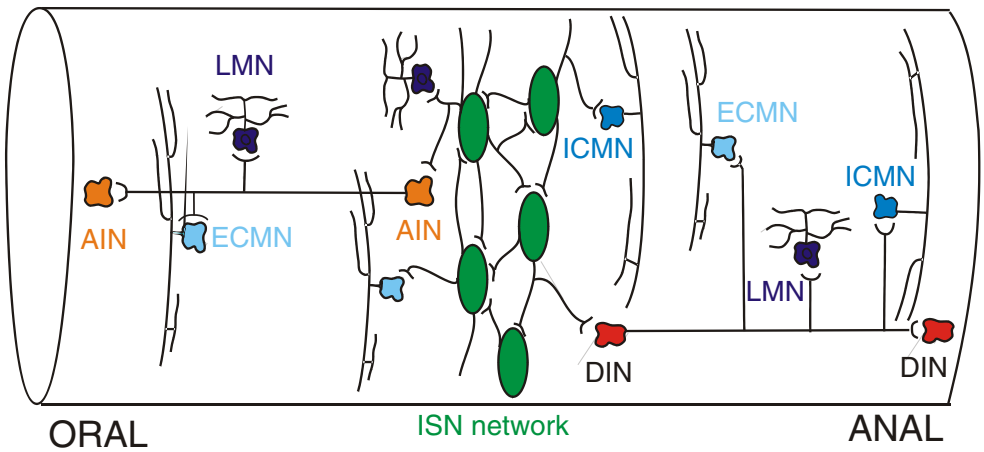

Fig. 1 A basic circuit that accounts for what is known about the mechanisms that produce ascending excitatory and descending inhibitory reflexes in the guinea-pig ileum. Intrinsic sensory neurons (ISN) are shown in *green*, ascending interneurons (AIN) in *orange*, excitatory circular-muscle motor neurons (ECMN) in *pale blue*, longitudinal muscle motor neurons (LMN) in *purple*, descending interneurons (DIN) in *red* and inhibitory circular-muscle motor neurons (ICMN) in *blue*. Inhibitory longitudinal muscle motor neurons are not illustrated, as these are very rare in the guinea-pig ileum. The various populations of descending interneurons are shown as a single population for simplicity

(ACh) from motor neurons innervating the circular and longitudinal muscles [49–52]. This is supported by a large body of indirect evidence for A_1-receptor-mediated inhibition of release from excitatory motor nerve terminals [43, 53–56]. This can clearly account for the abolition of propulsive motor activity by adenosine and A_1 agonists. However, other mechanisms are also likely to be important.

Functional studies of A_1 receptor locations in pathways that regulate motility (for secretion studies see [57]) have focused on the myenteric plexus intrinsic sensory neurons, neurons with distinctive electrophysiological and morphological properties. Unlike other myenteric neurons, action potentials in these neurons are followed by prolonged afterhyperpolarisations (AHPs), and they usually lack fast excitatory synaptic potentials (EPSPs) but have prominent slow EPSPs (for reviews see [33, 34]). They all have a similar shape; a large, smooth soma with several axons known as Dogiel type II, so they are termed AH/Dogiel type II neurons. Other characteristic features are that axons usually project circumferentially [58] and make synapses with other AH/Dogiel type II neurons [59, 60]. These neurons express both P1 and P2 receptors (Fig. 2). Transmission between them is via slow EPSPs, mediated by tachykinins [61–63]. Importantly, they respond directly to mechanical myenteric plexus deformation [64, 65], to increased tension within the intestinal muscle [66, 67] and to chemical stimulation of the mucosa [29, 68, 69], indicating that they can act as mechanoreceptive and/or chemoreceptive intrinsic sensory neurons. Because they project circumferentially [58] and excite each other [60], the intrinsic sensory neurons form a recurrent excitatory network. This network can encode ongoing sensory stimuli, with its output depending on neuron excitability, slow EPSP amplitude and AHP magnitude [30, 31]. A_1 receptor agonists modify all these parameters. Most AH/Dogiel type II neurons (about 85%) are hyperpolarised by adenosine, largely through A_1 receptors [70], so A_1 activation will markedly depress the network's output. Furthermore, A_1 receptor agonists abolish slow EPSPs evoked in these neurons by electrical stimulation via presynaptic receptors that inhibit transmitter release (Fig. 2) [54]. This would also depress the network's output. Finally, A_1 receptor activation enhances AHPs in these neurons [70], which would also suppress firing in the sensory neuron network [30, 31]. These effects would be most prominent under conditions in which the stimulus was slow in onset; for example, during the distensions typically used to evoke propulsive motor activity in isolated intestinal segments. Thus, in addition to reductions in ACh release from excitatory motor neurons, A_1 agonists probably depress activity evoked by sensory stimuli in the enteric neural circuitry.

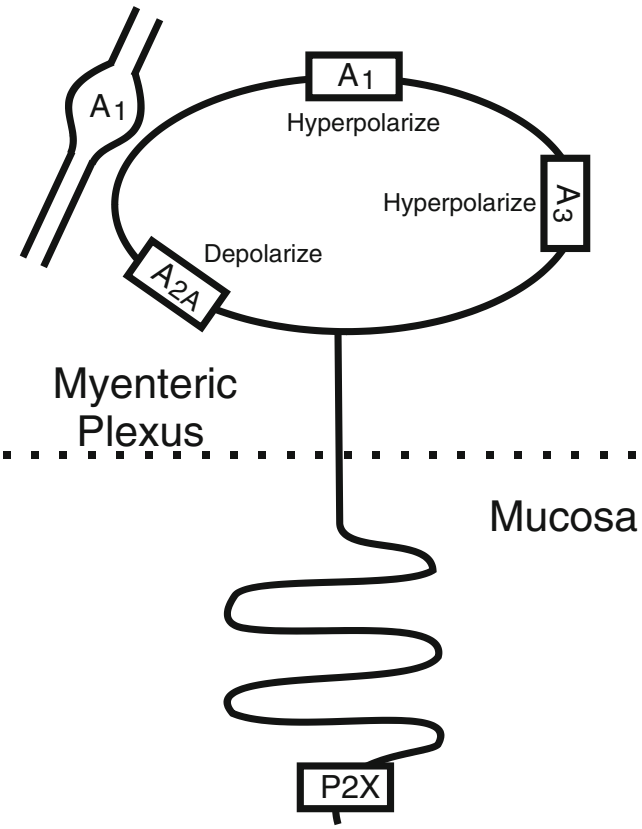

Fig. 2 Functionally identified purinergic receptors in myenteric intrinsic sensory neurons. A_1, A_{2A} and A_3 receptors are all found on the soma, A_1 receptors are present on many presynaptic terminals and P2X receptors appear to be expressed by the mucosal terminals of these neurons. There is also evidence for P2Y receptors on the soma, but the significance of these is unknown

Presynaptic A_1 receptors are widely distributed within the ENS. A_1 agonists depress fast EPSPs mediated by ACh in many myenteric neurons other than AH/Dogiel type II neurons but do not depress responses to ACh in these neurons [54]. This indicates that adenosine has a fourth site of action within enteric pathways that modulate motility. Furthermore, A_1 receptor activation depresses tachykinin release from enteric synaptosomes [71] and more intact myenteric networks [72, 73], indicating that presynaptic A_1 receptors inhibit release of transmitters other than ACh. However, presynaptic A_1 receptors are not ubiquitous, as A_1 receptor blockade reveals inhibitory synaptic potentials (IPSPs) in many AH/Dogiel type II neurons [54]. The IPSPs are normally obscured by slow EPSPs [54]. The IPSPs may be mediated by 5-HT_{1A} receptors, because they are blocked by a 5-HT_{1A} antagonist [62]. Thus, whereas many cholinergic nerve terminals in the myenteric plexus have A_1 receptors, the terminals of serotonin-containing interneurons do not. Nevertheless, that ability of A_1 agonists to reveal IPSPs in the intrinsic sensory neurons indicates another site at which adenosine can act to depress motility.

Thus, there are many sites within the enteric neural circuitry where A_1 receptors and endogenous adenosine may act to modulate motility. However, there is also evidence that A_1 receptors may be located on some intestinal smooth muscles [74–77], where they can act to directly inhibit or relax the muscle.

The roles of A_2 and A_3 receptors are much less clearly defined that those of A_1 receptors. Virtually all studies of A_2 receptor function indicate that activation of these receptors can relax or inhibit contractions of intestinal smooth muscle, largely, if not exclusively, through A_{2B} receptors. Activation of these receptors relaxes smooth muscle from guinea-pig distal colon [56]; rat duodenum [78], ileum [43] and colon [77]; and mouse distal colon [79]. Various sites of action have been described, including receptors on the smooth muscle [56] and facilitation of the release of NO from inhibitory motor neurons [79]. By contrast, adenosine-mediated relaxation of possum duodenum appears to be via A_{2A} receptors on the smooth muscle [80]. However, results for A_{2A} receptors are inconsistent with other data, indicating that they act to facilitate ACh release in the guinea-pig ileum [53].

There have been no studies of the effects of A_2 agonists and antagonists on complex motor patterns. Depolarisations mediated by A_{2A} receptors have been identified electrophysiologically in a subpopulation of myenteric AH/Dogiel type II neurons from the guinea pig, suggesting that A_{2A} receptors may act to enhance the output of intrinsic sensory neuron networks [2]. The functions of this subpopulation of sensory neurons have not been identified as yet. A_3 receptor activation hyperpolarises some AH/Dogiel type II neurons [2], but again, the exact function of these neurons is unknown. Functional roles for the A_2 subtypes and the A_3 subtype will only be determined when the cellular locations and effects on complex motor patterns have been fully investigated. As yet, the only real evidence is that A_3 receptors have been localised to neurons immunoreactive for substance P in the human submucosal plexus [81], which suggests that these receptors may be important in enteric sensory pathways. However, no data are available about a similar localisation in equivalent myenteric neurons.

P2 receptors

The literature on the roles of P1 receptors in the gastrointestinal tract is relatively limited, but the literature on P2 receptors is vast. This is largely because of the many studies testing whether ATP or a related purine nucleotide mediates inhibitory neuromuscular transmission in the gut (for review see [82]). There is also substantial literature directed at identifying the roles of P2 receptors in transmission between enteric neurons (reviewed by [14, 83, 84] and elsewhere in this issue). However, whereas recent immunohistochemical studies show that P2 receptors are found at many sites within the gut, the roles of these receptors in motility regulation are enigmatic. This section will focus on the various functional roles for P2 receptors and hence for purine nucleotides highlighting P2X and P2Y receptors as necessary.

Inhibitory neuromuscular transmission

It is widely accepted that ATP is important for transmission from enteric inhibitory motor neurons to the intestinal smooth muscle [82, 85, 86]. Activation of these neurons produces a rapid hyperpolarisation of the smooth-muscle membrane, an inhibitory junction potential (IJP), often followed by a smaller, but more prolonged, hyperpolarisation (for some representative papers see [87–93]). Inhibitory motor neuron activation relaxes intestinal smooth muscle [86, 92, 94], and this relaxation is markedly reduced IJP blockade in some preparations (for examples see [95–98]). The inhibitory motor neurons contain nitric oxide synthase (NOS) [99], and blockade of this enzyme prevents the prolonged hyperpolarisations and depresses smooth-muscle relaxation, but not the IJPs, evoked by their activity [87, 90, 93, 98, 100]. The IJPs are blocked by the bee venom toxin apamin, an antagonist of the SK form of calcium-dependent potassium channels [95, 96, 101].

Evidence that ATP mediates IJPs in intestinal smooth muscle is extensive and includes observations that ATP hyperpolarises intestinal smooth muscle [102, 103], an effect blocked by apamin [95, 96] and by the broad-spectrum P2 receptor antagonist suramin [104, 105]. However, this evidence has been fraught with problems. For example, in the guinea-pig taenia caeci, hyperpolarisation evoked by pituitary adenylyl-cyclase-activating peptide, which is contained in many inhibitory motor neurons, is blocked by apamin and depressed by suramin [106–108]. In the dog colon, both the IJP and the slow hyperpolarisation evoked by inhibitory nerve stimulation are abolished by inhibition of NOS [109–111], leaving no place for an ATP-mediated component of inhibitory transmission. Similarly, studies of inhibitory neuromuscular transmission that measure relaxation often lead to the conclusion that either NO or vasoactive intestinal peptide (VIP) (see [82, 85]), each of which is released by inhibitory motor neurons, are the major mediators. NO can produce relaxation independently of changes in membrane potential [112], so measures of membrane potential and relaxation may not produce equivalent results. The problem is compounded because the commonly used broad spectrum antagonist PPADS is not very effective at blocking electrically evoked IJPs in circular muscle of either guinea-pig ileum or colon [39, 113]. Nevertheless, recent data obtained using specific

antagonists for and structural localisation of $P2Y_1$ receptors place this hypothesis on a more secure footing (for review see [114]). In human and mouse intestine, IJPs and the associated relaxations are blocked by the $P2Y_1$ receptor antagonist MRS 2179 [92, 98]. Furthermore, immunoreactivity for the $P2Y_1$ receptor protein is located on the smooth muscle in both species [92, 115]. Together with the knowledge that enteric nerve stimulation releases ATP and its metabolites (see above), these data are compelling evidence that ATP acting at $P2Y_1$ receptors mediates IJPs evoked by activity in intrinsic inhibitory motor neurons.

Whereas IJPs are probably mediated by $P2Y_1$ receptors, the cellular location of these receptors is less clear. Neuromuscular transmission in the intestine appears to be an indirect process, with neurotransmitters acting on ICC, which then couple to the smooth muscle via gap junctions. The evidence for this is compelling for both ACh and NO (reviewed by [116]). But it is less clear that purinergic neuromuscular transmission requires ICC as intermediates [117]. For example, $P2Y_1$ receptor immunoreactivity has been localised to human smooth-muscle cells [92], whereas $P2Y_1$ mRNA is seen in ICC of small intestine from mice and humans [118]. Furthermore, whereas NO-mediated responses of murine intestine disappear when ICC are absent, IJPs can still be recorded in the same tissues [119]. Perhaps IJPs are mediated by both direct action of ATP on smooth-muscle P2Y receptors and via ICC.

Functional roles of purinergic IJPs

IJPs are the most prominent electrophysiological response to inhibitory nerve activity, so they would be expected to play a major role in intestinal motility regulation. However, studies of the purinergic component of inhibitory neuromuscular transmission and regulation of the major intestinal motor patterns have been ambiguous. These studies have used apamin to block IJPs, because most precede the availability of specific $P2Y_1$ antagonists and because broad-spectrum blockers of P2 receptors can act within the enteric circuits themselves (see below and [120]). Indeed, both suramin and PPADS can block ectonucleotidases [121], making interpretation of results more difficult.

Receptive relaxation of the ileum depends on activity in inhibitory motor neurons but is unaffected by concentrations of apamin that abolish IJPs [19, 122]. By contrast, NOS blockade abolishes receptive relaxation [19, 122]. Thus, although IJPs must have been evoked by the inhibitory neural activity underlying receptive relaxation, they play little role in the behaviour itself.

Studies with apamin on roles for IJPs in propulsive contraction generation and propagation triggered by saline distension have yielded contrasting results, with reports that the threshold for propulsion initiation is either reduced [123] or unaffected by apamin [124]. By contrast, threshold is clearly reduced when NOS activity is inhibited [123, 124]. However, apamin increases the pressure produced during propulsive contractions and reveals localised circular-muscle contractions that do not propagate along the intestine [124]. When apamin is combined with NOS inhibition, the anally propagating contractions are converted to apparently uncoordinated contractions at many sites along the segment [122–124]. Saline distension is a distributed stimulus activating intrinsic sensory neurons all along the intestinal segment. Thus, the muscle would receive converging excitatory and inhibitory input from ascending and descending pathways, and blocking IJPs would allow the excitation to predominate, thereby leading to the uncoordinated activity.

Localised distension or mucosal deformation also leads to anally propagating contractions of the longitudinal and circular muscle in guinea-pig ileum [26, 35, 125, 126] and colon, descending excitation [127]. In the colon, the descending excitation is preceded by a descending relaxation that is depressed by apamin, indicating that it depends, in part, on IJPs, presumably resulting from ATP release [127]. The apamin-resistant component is abolished by NOS inhibition, so the relaxation depends on both purinergic and nitrergic transmission [127]. In contrast, no descending relaxation is seen in the ileum [26], but apamin increases the amplitude and rate of rise of the descending contractions [26]. Electrophysiological studies of guinea-pig ileum in which contractile activity is blocked show that distension and mucosal stimulation evoke prominent apamin-sensitive IJPs, but not excitatory junction potentials (EJPs), in the circular-muscle anal to the stimulus [128–130]. It appears that purinergic IJPs slow and limit the size of descending contractions but do not relax the muscle itself. Similar results have recently been obtained by combining extracellular recording from the circular smooth muscle with video-imaging contractile activity during anally propagating propulsive contractions [131]. EJP/action potential complexes associated with propulsive contractions were not preceded by IJPs, although small, spontaneous IJPs were readily detected. Thus, the roles of IJPs in the ileum and colon are distinctively different. Purinergic neuromuscular transmission in the ileum limits the excitation resulting from EJPs, whereas in the colon, it also helps set the muscle tension, even in the absence of excitatory input.

There have been very few studies of the effects of inhibiting IJPs on the two most prominent motor behaviours of the intestine: MMCs and segmentation. Each has been difficult to characterise in vitro. However, recent developments allow some conclusions to be drawn. Isolated mouse intestine and colon exhibit periodic strong contraction complexes that propagate along the segment in a

manner analogous to phase III contractions of interdigestive MMCs [132–135]. This similarity is so strong that the colonic propagating contraction complexes are usually termed colonic MMCs, although they may actually be analogues of mass-movement contractions involved in defecation. Whereas IJPs are seen in the mouse colon, apamin does not affect colonic MMC cycling frequency or propagation speeds and has inconsistent effects on contraction amplitude [132, 136, 137].

Development of methods for constructing contractile activity maps as functions of time and length along the intestine from video recordings of isolated intestinal segments [138] has allowed analysis of nutrient-induced segmentation in guinea-pig small intestine [131]. This manifests as episodes of contractile activity evoked by either fatty acids or amino acids in the intestinal lumen. Several motility patterns are seen, but the most prominent consists of rhythmic stationary contractions confined to narrow regions: segmentation. Large numbers of small apamin-sensitive IJPs are recorded between contraction episodes [131], indicating ongoing activity of inhibitory motor neurons along the length of the segment. Interestingly, large apamin-sensitive IJPs are time-locked to the stationary contractions on both the oral and anal sides outside the contracting region during episodes [131]. This suggests that IJPs limit the spread of contractions, perhaps by preventing propagation of smooth-muscle action potentials from the excited region.

Nutrient-induced motor activity also includes circular-muscle constrictions that propagate slowly for short distances orally or anally [139]. Like the stationary contractions, these short-length propagating contractions may be limited by large apamin-sensitive IJPs that are seen just beyond the point at which the contraction disappears [131]. It seems IJPs also limit the propagation speed of these contractions, as blocking IJPs converts much of the contractile activity induced by luminal nutrients to constrictions that propagate rapidly along the entire segment [131].

Overall, IJPs mediated by ATP in the ileum appear to limit the spread and efficacy of excitatory input to the muscle rather than to relax it, as in the colon. Relaxation is the province of NO released from the same neurons.

P2X receptors within the muscle

Both $P2X_2$ and $P2X_5$ receptors have been identified immunohistochemically on ICC from mouse and guinea pig [140], which raises a question as to their roles. Intestinal smooth muscle is often excited by P2X receptor activation [115], so receptors on ICC may be important. Furthermore, some ICCs are pacemakers for the smooth muscle, driving slow waves that set the underlying rhythm for motor activity (for review see [141]). P2X receptor activation modifies pacemaker activity in some ICCs [142], so these receptors may regulate intestinal pacemakers. However, P2X receptors are also found in both canine and murine colonic smooth-muscle cells [115, 143], which are contracted by P2X stimulation. There has been no analysis of muscle or ICC P2X receptor involvement in intestinal motor patterns.

P2 receptors within enteric neural circuits

There is excellent evidence that P2 receptors play important roles within the ENS. Fast EPSPs mediated by P2X receptors are seen in both myenteric and submucosal neurons (see [120]), and there is strong evidence for synaptic potentials mediated by $P2Y_1$ receptors in submucosal neurons [144, 145]. This section deals with myenteric receptor location and how they fit into the neural circuits mediating different motor reflexes.

In guinea-pig ileum, P2X receptors have been identified immunohistochemically in three classes of myenteric neurons, each with its own distinct set of functions. The AH/Dogiel type II neurons express immunoreactivity for $P2X_2$ [3] and $P2X_7$ receptors [146]. Ascending interneurons express immunoreactivity for $P2X_3$ receptors [147, 148]. Most NOS neurons express immunoreactivity for $P2X_2$ receptors [3], and a subset also express $P2X_3$ receptors [147, 148]. NOS neurons are either inhibitory motor neurons or descending interneurons [99]. Analysis of P2X receptor distribution amongst functionally identified classes of neurons in other species is more limited, because knowledge of the functions of immunohistochemically identified neuronal subtypes is less complete. Nevertheless, some information is available. A key point is that $P2X_1$ receptors have not been identified in enteric neurons in any species studied. On the other hand, $P2X_2$ receptors are expressed in some mouse myenteric neurons [115, 149], although their neurochemistry has not been identified. $P2X_2$ receptors are also found in a minority of rat calretinin immunoreactive myenteric neurons and in a subset of calbindin immunoreactive neurons in the same preparation [150]. In the rat, many calretinin neurons have Dogiel type II morphology, and neurons with this morphology have the electrophysiological properties of AH neurons [151], as they do in both guinea pig and mouse [64, 152]. Thus, some AH/Dogiel type II neurons in the rat myenteric plexus probably express $P2X_2$ receptors. Many more apparently express $P2X_3$ receptors, as about 80% of calretinin neurons in the rat ileal myenteric plexus are $P2X_3$ receptor immunoreactive [150]. The functions of P2X receptors in AH/Dogiel type II neurons are discussed below. $P2X_5$ receptors are widespread in submucosal neurons of mouse but are largely localised to axons in the myenteric plexus [153].

P2Y receptors have also been found immunohistochemically on neurochemically identified enteric neurons. In guinea pig, virtually all calbindin, and thus AH/Dogiel type II, myenteric neurons express $P2Y_{12}$ but not $P2Y_6$ or $P2Y_2$ receptors [154]. On the other hand, some calretinin neurons express $P2Y_2$ receptors and/or $P2Y_6$ receptors, and a subpopulation of NOS neurons express $P2Y_6$ receptors [154]. The functions of these receptors are unclear, as the only evidence about roles for P2Y receptors in motility regulation suggests that $P2Y_1$ receptors are the major contributors (see below). Whereas reverse transcriptase polymerase chain reaction (RT-PCR) shows that $P2Y_1$ receptors are expressed in the guinea-pig submucosa [155], the available antisera against this receptor subtype have yet to reveal neurons in either the myenteric or submucosal plexuses of guinea pigs.

By contrast, $P2Y_1$ receptors have been identified in myenteric neurons in both human and mouse [92, 115] and submucous neurons in mouse and rat [115, 156]. In mice, $P2Y_1$ receptors are seen in many but not all myenteric neurons immunoreactive for NOS, although these neurons do not account for all $P2Y_1$ immunoreactive myenteric neurons.

Neural P2X receptors and motility

P2X receptors mediate fast EPSPs in some myenteric neurons (see [84, 120, 157]). To identify their physiological roles, it has been necessary to control for effects of broader-spectrum antagonists on inhibitory neuromuscular transmission. Two strategies have evolved to identify at least some roles of neural P2X receptors. First, PPADS has been used as the antagonist in several studies of motility reflexes and motor patterns. PPADS depresses IJPs in guinea-pig circular muscle [39, 113] but only at concentrations higher than needed to block purinergic fast EPSPs in myenteric neurons [158]. This may be because PPADS is relatively ineffective in blocking $P2Y_1$ receptors negatively coupled to adenylyl cyclase [1]. Second, these studies have used divided organ baths that allow separate superfusion of different parts of reflex pathways running along the intestine [113, 159]. The results show that in guinea-pig ileum, P2X receptors mediate transmission from descending interneurons to inhibitory motor neurons (Fig. 3) but not transmission between interneurons or from intrinsic sensory neurons to interneurons [113]. Inhibitory motor neurons are all immunoreactive for NOS [99], and 90% of all NOS neurons in this preparation express $P2X_2$ receptors [3], indicating that this receptor subtype mediates this form of transmission. However, some NOS neurons express $P2X_3$ receptors [147, 148], so a $P2X_{2.3}$ heteromer may be involved.

P2X receptors may also play a role in transmission between descending interneurons in the descending excitatory reflex pathway (Fig. 4). PPADS depresses descending excitation of both longitudinal and circular muscle, but blocking 5-HT_3 receptors depresses descending excitation in circular muscle only [35]. Blockade of nicotinic receptors has no effect on these reflexes in either muscle layer. Combined blockade of P2X and 5-HT_3 receptors has no greater effect on descending excitation of the circular muscle than blockade of either receptor alone, suggesting that the two are acting in series. Anatomical studies indicate that excitatory circular-muscle motor neurons but not longitudinal muscle motor neurons receive synaptic input

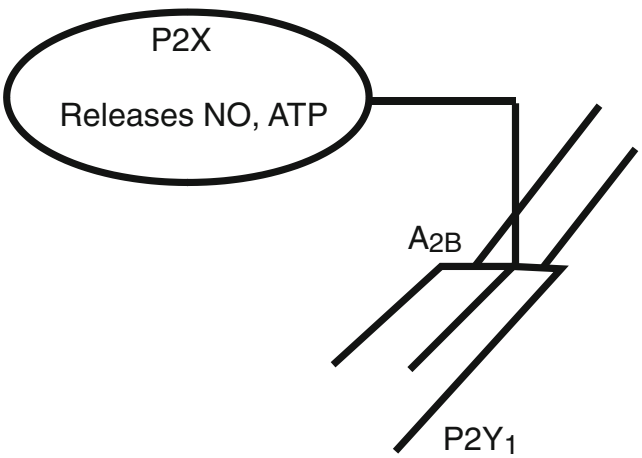

Fig. 3 Purinergic receptors and their relationships to inhibitory motor neurons supplying the circular muscle. These neurons are excited by descending interneurons via P2X receptors, release ATP to act on $P2Y_1$ receptors within the circular muscle and also release nitric oxide (NO). NO release is facilitated by A_{2B} receptors

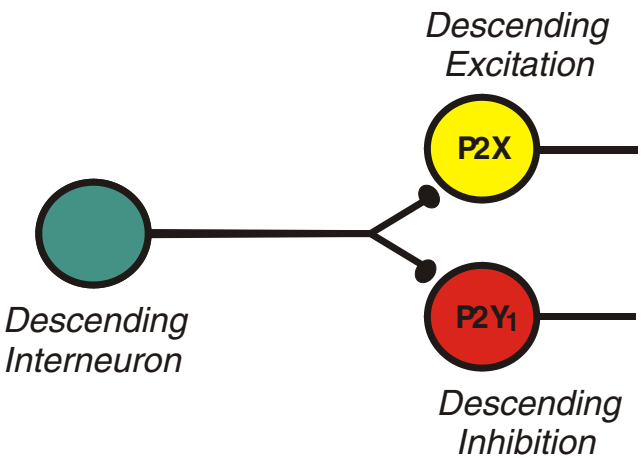

Fig. 4 Different P2 receptors have independent roles in transmission between interneurons in two descending reflex pathways. P2X receptors are important for transmission to interneurons of the descending excitatory pathway (*yellow*), whereas $P2Y_1$ receptors are important for transmission between interneurons of the descending inhibitory pathway (*red*)

from 5-HT-containing descending interneurons [160], suggesting that this is where the 5-HT_3 receptors act. Thus, the simplest explanation for the data is that PPADS blocks transmission from descending interneurons to two types of interneurons, including 5-HT-containing interneurons (Fig. 4). This is supported by a divided organ bath study, which found that PPADS depressed descending excitatory reflexes when in a chamber where it would act on synapses between interneurons but not on the muscle [125].

A surprising conclusion from these studies is that P2X receptors have no major role in ascending reflex pathways [159, 161] or in transmission to longitudinal muscle motor neurons [35]. This is despite the fact that $P2X_3$ receptors are found in calretinin-immunoreactive neurons of guinea-pig ileum [147, 148], which are either ascending interneurons or longitudinal muscle motor neurons [99].

Whereas these studies of simple reflexes indicate that P2X receptors are important, studies of more complex motor patterns using PPADS to identify P2X involvement have been disappointing. PPADS does not alter the threshold of propulsive reflex activation by saline distension [35], nor does it change the motor activity induced by luminal nutrients in the guinea-pig small intestine [139]. A reduction in threshold for initiation of propulsion by PPADS that was antagonised by suramin has also been reported [162]. This may have been due to the interactions with ectonucleotidases of these antagonists [121] rather than effects on P2 receptors. Thus, it is not yet clear how the involvement of P2X receptors in simple reflexes is translated into more complex behaviours.

Two studies have addressed the role of the P2X receptors in complex behaviours using mice in which either $P2X_2$ or $P2X_3$ receptors were knocked out. Knockout of the $P2X_2$ receptor depressed propulsive reflexes evoked by saline distension and eliminated P2-mediated fast EPSPs in myenteric neurons, although responses to ATP and α,β-methylene ATP (an agonist at $P2X_3$ receptors) were preserved in AH/Dogiel type II neurons [149]. On the other hand, intestinal transit of a radioactive marker was normal in the knockout mice. Knockout of the $P2X_3$ receptor also depressed propulsive reflexes evoked by saline distension, with no effect on intestinal transit, and this was associated with depressed sensitivity of AH/Dogiel type II neurons to α,β-methylene ATP [163]. These results highlight two significant issues for interpreting the available data. First, although AH/Dogiel type II neurons in guinea pig and mouse appear functionally identical [164], they may express different P2X receptor subtypes with $P2X_2$ in the former and $P2X_3$ in the latter. Thus, species differences may be critical. Second, different measures of motility can give very different results, even when they appear to be measuring the same thing—in this case, the mechanisms that propel content along the gut. As yet, there have been no studies of either segmentation or the MMC using P2X receptor knockouts.

Whereas there is strong evidence for a role for P2X receptors in descending reflexes in guinea-pig ileum, identical experiments in guinea-pig and rat colon provide no evidence for such a role [39, 40]. This is despite electrophysiological evidence for P2X-receptor-mediated EPSPs in the guinea-pig colon at least [158, 165].

Neural P2Y receptors and motility

There have been almost no studies of the roles of neural P2Y receptors in motility reflexes, although more is known about the involvement of such receptors in reflex control of secretion. However, distension evokes slow EPSPs that trigger action potentials in NOS descending interneurons but not in other myenteric neurons [166]. The distension-evoked slow EPSPs arise from descending interneurons and are blocked by PPADS at higher concentrations than needed to abolish P2X-mediated fast EPSPs [167]. This higher concentration of PPADS depresses transmission along the descending inhibitory pathway when added to the interneuron chamber of a divided organ bath, but lower concentrations of PPADS that block fast EPSPs have no effect [167]. Descending inhibition depression is mimicked by a $P2Y_1$ receptor antagonist (McMillan & Gwynne, unpublished). Thus, $P2Y_1$ receptors may mediate transmission between interneurons in the descending inhibitory pathway via slow EPSPs. As yet, roles for other P2Y receptors located on enteric neurons have not been identified, and there are no published studies of neural P2Y receptors on complex motility patterns.

Sensory transduction

The presence of P2X receptors within intrinsic sensory neurons suggests they are involved in sensory transduction [168], and recent data support this idea. ATP applied to mucosal villi of the guinea-pig ileum evokes bursts of action potentials in nearby myenteric AH/Dogiel type II neurons [169]. The ATP-evoked bursts of action potentials mimic the effect of mucosally applied 5-HT and low pH. Some amino acids have a similar effect, and this is depressed by PPADS [29]. Both mucosal application of amino acids and mucosal application of ATP evoke local inhibitory reflexes in the circular muscle, and each is depressed by PPADS [170]. The wider physiological significance of these observations for motility regulation has not been tested, but chemical stimuli, such as nutrients, may act in part by the release of ATP from intestinal epithelial cells.

There is also evidence suggesting a role for $P2Y_1$ receptors in sensory transduction within the intestinal wall. A subepithelial layer of fibroblasts in the rat intestinal

mucosa expresses $P2Y_1$ receptors and releases ATP to act back on these receptors in response to mechanical deformation [171]. There is evidence indicating that mechanical deformation of the mucosa releases 5-HT [172–174] and that this is the primary mechanism of sensory transduction for this stimulus. However, the possibility of a significant role for $P2Y_1$ receptors remains to be tested.

Roles of enteric glial cells

Whereas the roles of P1 and P2 receptors on neurons and in the muscle layers are the focus of this review, P2X and P2Y receptors have been identified on enteric glial cells [175–177]. Roles of glia in neural signalling elsewhere in the nervous system have become topics of major interest and are the subject of many studies in the CNS (for recent reviews see [178–180]). Thus, it is reasonable to assume that enteric glia play a role in purinergic signalling within the ENS. Indeed, there is evidence that networks of enteric glia can generate propagating waves of intracellular Ca^{2+} that pass via gap junctions throughout the networks and that this depends on ATP release [181]. Furthermore, enteric glia express an extracellular surface-bound ectonucleotidase [182], so that they will be important in the regulation of ATP levels following release from nerve terminals or other glia. Also, reductions in enteric glia have been correlated with some motility disturbances [183, 184]. However, how glial P2 receptors, Ca^{2+} waves or glial ectonucleotidases fit into the regulation of intestinal motility is unclear, and there is no evidence as to the part they play in the circuitry responsible for any given motor pattern. This can be expected to be an important issue for investigation as mechanisms of glial signalling to neurons are clarified.

Where to from here?

There is no doubt that ATP and its metabolites play signalling roles within the gastrointestinal tract and hence in motility regulation. The difficulty has been in defining the physiological and pathophysiological conditions under which they act. This problem has been similar for many other compounds found to act as either neurotransmitters or modulators within the intestine. For example, although tachykinin-mediated slow EPSPs are prominent in many enteric neurons [61, 62] and simple motility reflexes are altered by specific tachykinin antagonists [185, 186], it has been very difficult to show a role for neural tachykinin receptors in normal motility patterns. It seems likely that many of the effects of these relatively enigmatic transmitters and modulators will be seen only in pathological circumstances, as with the A_1 receptor involvement in the postoperative ileus. If so, then identifying appropriate model systems will be crucial for understanding the roles of these compounds. An important issue here is to examine the actions of specific antagonists for the different P1 and P2 receptor subclasses on motility patterns other than propulsive reflexes. The major motor activities of the small intestine are segmentation in the fed state and the MMC in the fasted state, but neither has been studied in sufficient detail to identify roles for either P1 or P2 receptors. In vitro model systems for both behaviours are now becoming available, and analysing the roles of ATP and adenosine, in particular, in these models should finally begin to identify their significance for intestinal behaviour.

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