Unlocking Mysteries of Gut Sensory Transmission: Is Adenosine the Key?

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Endogenous adenosine acts at pre- or postsynaptic A1, A2, or A3 receptors to inhibit synaptic transmission in intrinsic primary afferent/AH neurons, S neurons, and mucosal and motility reflexes. Adenosine provides dual modulation of adenylyl cyclases. Its modulation of sensory transmission may be of therapeutic potential in gut inflammation, ischemia, and constipation.

Adenosine interacts with A1, A2a, A2b, and A3 receptors to produce a wide variety of physiological effects in both central and peripheral tissues. All four receptors have been cloned from a variety of mammalian species. Several comprehensive reviews have been written in recent years on adenosine’s broad effects on gastrointestinal function (4, 18). A primary site of action of adenosine in the enteric nervous system (ENS) is the afterhyperpolarizing (AH) neuron. This review will discuss evidence in support of the hypothesis that endogenous adenosine is a key modulator of sensory transmission, present a current model of adenosine's dual modulation of intracellular signaling, discuss the implications of ganglionic adenosine release during gut ischemia or inflammation, and identify key areas of future research.

Physiology of IPANs/AH neurons

The ENS is programmed to respond to mechanical and chemical stimuli by activating networks of neurons that control muscle contraction and motility, secretion, or blood flow. An important player is the intrinsic primary afferent neuron(s) (IPANs), which constitutes an afferent limb of a gut neural reflex. A distinguishing electrophysiological feature of IPANs is the long-lasting afterhyperpolarizing potential (AHP), which limits the frequency for firing action potentials repetitively. IPANs detect, process, and relay sensory information, although some IPANs may be mechanosensitive and respond to stretch and glucose (9). Those located in the myenteric plexus are AH neurons with multipolar, Dogiel type II morphology, having one axon that projects to the mucosa and one or more axons projecting to other neurons within the ENS. Activation of IPANs is often indirect via the release of 5-HT from enterochromaffin cells in the epithelial layer (12). In the myenteric plexus, IPANs synapse with each other and transmit via slow excitatory postsynaptic potentials (sEPSPs) to form self-reinforcing networks around the circumference of the intestine (20). They also synapse with and activate interneurons and motoneurons in the myenteric plexus via fast excitatory postsynaptic potentials (fEPSPs) and sEPSPs. In contrast to extrinsic afferent neurons, IPANs are multipolar neurons and their excitability is modulated by slow synaptic transmission. Not all AH neurons are IPANs; some likely function strictly as interneurons. A small minority of S neurons with uniaxial morphology could also function as IPANs (9).

Sensitivity of “activated AH cells” to adenosine

The main effect of adenosine on AH neurons is suppression of excitability associated with a reduction in cell input resistance, slow membrane hyperpolarization, a higher threshold for action potential discharge, and an increase in the amplitude and duration of the AHP (3, 5, 6). About 85% of AH neurons are hyperpolarized by adenosine. The residual 15% may not express inhibitory adenosine receptors.

Several technical considerations provide insight into the actions of adenosine and mechanosensitive IPANs/AH neurons. Tissue stretch during the dissection likely causes activation of IPANs/AH neurons. In electrophysiological experiments, intracellular microelectrodes are used to record electrical activity in individual neurons in enteric ganglia. It is critical to prevent movement of the underlying muscle so that the electrode is not dislodged. Two methods have been used to immobilize muscle: one is by using muscle relaxants and the other by applying metal pressure feet to stretch and immobilize the ganglia (3–6, 20). The latter method undoubtedly stretches and activates some IPANs/AH neurons. Activated AH neurons have more depolarized membrane potentials, higher cell input resistance, lower threshold for action potential discharge, and decreased amplitude and duration of the AHP compared with the resting state.

The excitability of activated AH neurons is particularly sensitive to inhibition by adenosine receptor agonists. In fact, a linear 1:1 inverse relationship exists between the resting membrane potential and adenosine-induced slow hyperpolarization of the resting membrane potential of IPANs/AH neurons (4, 6). Studies on mechanosensitive responses in AH neurons can provide direct proof for the ability of endogenous adenosine to modulate stretch activation of IPANs/AH neurons.

Whereas adenosine is most effective in suppressing the excitability of activated AH neurons, adenosine antagonists are most effective in increasing excitability in AH neurons that are in a resting state and not activated (relatively unexcitable with lower cell input resistance and membrane potentials in the 60- to 70-mV range). This implies that endogenous adenosine must be keeping those IPANs/AH neurons suppressed, i.e., at a lower state of excitability. Appropriate levels of muscle stretch and sEPSPs would be expected to overcome the inhibitory effect of adenosine and permit spread of the incoming sensory information. Adenosine can interact with A1 and A2b receptors.
expressed on smooth muscle (15) and thereby also indirectly modulate IPAN/AH cell excitability during distension reflexes.

Endogenous adenosine and IPANs/AH neurons

Interstitial adenosine levels in myenteric ganglia are sufficient for tonic inhibition of neuronal excitability, synaptic transmission, or neurotransmitter release (2, 4–7). Therefore, inactivating endogenous adenosine with the enzyme adenosine deaminase enhances the excitability of AH neurons, whereas blocking the nucleoside/adenosine uptake mechanism with dipyridamole elevates extracellular levels of endogenous adenosine and decreases AH neuron excitability. Adenosine receptor antagonists elevate AH cell excitability by competing with adenosine for A1 receptors. Adenosine A1 receptor antagonists alone enhance synaptic transmission via EPSPs in 70% of myenteric neurons that include AH, S, and nonspiking neurons (5). In AH neurons, A1 receptor antagonists increase repetitive spike discharge, amplitude of depolarization, and duration of slow EPSPs. A1 receptor antagonists reverse the inhibitory effect of A1 receptor agonists on slow EPSPs and further enhance it. An A1 receptor antagonist was able to unmask existing fast and slow excitatory synaptic inputs to nonspiking neurons that are relatively unexcitable cells with membrane potentials of about −70 mV and input resistances of 10–30 MΩ, indicating that their excitability and sEPSPs are gated by endogenous adenosine acting at A1 sites. IPANs synapse with each other and also synapse with and activate motor neurons (S type) and interneurons (S or AH type). It may be inferred, then, that endogenous adenosine provides an ongoing inhibition of such neural communication. In S neurons, antagonists increased the amplitude of fEPSPs by >50% and in some cases also unmasked a sEPSP in the same cell. Therefore, endogenous adenosine provides an ongoing inhibitory mechanism that “gates” (20) excitatory synaptic inputs and/or somal excitability in AH and S neurons. Accumulation of endogenous adenosine could occur under physiological conditions such as intense contracture of the musculature or pathophysiological states such as ischemia or hypoxia (see below). The sources and mechanisms of adenosine release are complex (18). The net amount of adenosine released involves an intricate balance between ATP utilization and increase in adenosine with increased energy demand, ATP release as a neurotransmitter and its further breakdown to adenosine, or adenosine release from neurons or nonneuronal cells (8).

Exogenous adenosine and neurotransmission

Figure 1 is our current model of adenosinergic modulation of the activity of IPANs/AH neurons and their transmission to first-order neurons (3–7, 20). In AH neurons, adenosine likely acts at both presynaptic and postsynaptic receptors to inhibit sEPSPs. The postsynaptic actions of adenosine have already been described. Indirect evidence also suggests presynaptic involvement in the inhibition of sEPSPs in the AH neurons. Supporting evidence includes the following: Adenosine suppresses all sEPSPs in AH neurons. Substance P, 5-HT, and calcitonin gene-related peptide (CGRP) are the most likely mediators of the sEPSPs. Adenosine, however, does not inhibit, but rather enhances excitatory responses to these neurotransmitters (20). If these neurotransmitters are indeed the mediators of sEPSPs, then only presynaptic inhibition by adenosine could explain its inhibitory action on all sEPSPs. Also, adenosine is known to suppress substance P release from isolated varicose nerve endings (4) or ganglion networks from the myenteric plexus (8) as well as release of 5-HT from central neurons. Inhibition in IPANs/AH neurons is analogous to adenosinergic inhibition in the central nervous system where both presynaptic and postsynaptic A1 receptors are involved. In S neurons or nonspiking neurons, adenosine exclusively inhibits sEPSPs at presynaptic sites, since adenosine does not inhibit the release or excitability characteristics in most of those neurons. Adenosine’s predominant actions at pre- and postsynaptic sites to suppress sEPSPs and excitability in AH neurons would ensure that neuronal excitability remains below the firing threshold and it would make it more difficult for incoming sensory stimuli to elicit action potentials in IPANs. Adenosine is expected to block incoming sensory inputs to IPANs from the gut lumen or mechanosensitive reflex responses conveyed to first-order neurons in ascending or descending reflex pathways. However, it is possible that, under conditions favoring feedforward excitation between AH cells via sEPSPs that are mediated by either Substance P, 5-HT, or CGRP, slow synaptic transmission will not be interrupted by adenosine. In fact, such excitatory feedforward transmission could be facilitated by adenosine’s actions at excitatory A2a receptors on some AH neurons.

Adenosine suppresses nicotinic cholinergic fEPSPs mediated by ACh in gastric antrum, small intestine myenteric plexus, and small intestine submucous plexus.

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Synaptic inhibition plays an important role in the integrated functions of the enteric neural circuits. Yet robust slow inhibitory postsynaptic potentials (sIPSPs) are not frequently observed in myenteric neurons controlling motility, unlike submucous neurons controlling secretion and blood flow. Selective blockade of the predominant sEPSP with adenosine A1 receptor agonists unmasks robust sIPSPs in myenteric AH neurons (5). Further application of an A1 receptor antagonist offsets the unmasking action of the agonist, confirming the A1 receptor interaction. Apparently, the neural circuits in the myenteric plexus are organized for adenosine to suppress excitatory transmission without interfering with inhibitory transmission. The ability of adenosine to shut down excitatory neural circuits would be complemented by its ability to reveal inhibitory transmission (5). In hippocampal neurons, adenosine similarly inhibits excitatory transmission without interfering with inhibitory transmission. In contrast, adenosine acts differently in the submucous plexus by suppressing sIPSPs.

**Multiplicity of adenosine receptors that modulate IPAN/AH neuron activity**

Inhibitory effects of adenosine on the excitability of IPANs/AH neurons are mediated by A1 receptors [linked to adenylyl cyclase (AC)/cAMP signaling] and lower affinity non-A1 receptors (linked to a steady-state membrane hyperpolarization) (3, 6). Previously described inhibitory non-A1 receptors on AH neurons likely represent A3 receptors, since it is now known that A3 receptor-immunoreactive myenteric neurons include multipolar Dogiel type II neurons, which are known to have AH-type electrophysiology. Recent RT-PCR studies provided definitive proof for widespread expression of A3 receptor mRNA in the intestines of several mammalian species, including humans. A unique feature of the A3 receptor is that it shows a species-specific distribution, pharmacology, and diversity of structure. This suggests that any electrophysiological or other types of data on A3 receptors obtained from the gut of guinea pigs or rats may not be easily extrapolated to other species, including humans. This poses an added difficulty in the study of the neurophysiological role of A3 receptors in the gut. Exogenous or endogenous adenosine alone never excites AH neurons or stimulates neurotransmitter release (4–6, 20), but A2 receptor agonists elevate excitability and depolarize 40% of AH neurons (3). In the remainder, the agonists depress excitability and hyperpolarize the neurons. In 13% of neurons, A2 receptor agonists cause a biphasic depolarization followed by hyperpolarization at higher concentrations. It appears that the activity of some AH neurons with predominant A1/A3 receptor inhibitory responses is modulated by the excitatory A2a receptor. Adenosine A2a, A1, and A3 receptors coexist on some AH neurons. The signaling pathways activated by these receptors will be discussed later. RT-PCR analysis revealed differential expression of adenosine receptor subtypes in the rat digestive tract, but it remains unknown whether A1, A2a, A2b, or A3 receptor mRNAs and proteins are expressed in specific subsets of gut neurons, including IPANs, in these regions.
Adenosine provides a dual modulation of AC/cAMP signaling in IPANs/AH neurons

In the late 1980s, Drs. Jackie Wood, Jeff Palmer, and co-workers proposed the hypothesis that slow synaptic excitation (sEPSPs) in AH neurons occurs via activation of AC and the consequent elevation of intraneuronal cAMP levels leading to inhibition of Ca-dependent K conductance (gKca) (20). That work, along with more recent studies, revealed that adenosine suppressed sEPSPs, slow excitatory responses to forskolin, cholecystokinin (CCK), vasoactive intestinal peptide (VIP), gastrin-releasing peptide (GRP), pituitary adenyl cyclase-activating peptide (PACAP), and histamine (Hist). In AH neurons, slow excitatory responses to CGRP, substance P, or 5-HT were enhanced by 10−50 μM adenosine or priming doses (10−50 nM) of the AC activator forskolin. A related study showed that A2 receptor agonists cause potentiation of the response to priming doses of AC activators like forskolin. A2 receptor agonists potentiate the cAMP response in myenteric ganglia to submaximal doses of forskolin. A2 receptor agonists alone also elicit slow excitatory responses in a minority of AH neurons (3). Biphasic dose-response curves to adenosine A2 receptor agonists on membrane potential on some neurons indicates that both inhibitory and excitatory adenosine receptors are coexpressed on a subset of AH neurons. Both the transmitters with responses enhanced by adenosine, forskolin, or A2 receptor agonists and those inhibited by adenosine or A1 receptor agonists increase the production of cAMP in myenteric ganglia. These data support the hypothesis of dual modulation of AC/cAMP levels by A1/A3 and A2a receptors. Inhibitory A1 (and perhaps A3) receptors are linked to one type of AC isoform that is activated by PACAP, GRP, CCK, VIP, or Hist. Excitatory A2a receptors are linked to another type of AC isoform on the same or a different subset of AH neurons that is activated by CGRP, substance P, or 5-HT. Figure 2 summarizes a working hypothesis for dual modulation of AC/cAMP signaling in myenteric neurons.

The distribution of AC in the intestine has been studied with BODIPY forskolin binding (14) or AC immunoreactivity (13). In the guinea pig ileum, AC I, III, and IV immunoreactivities were respectively expressed in 26, 58, and 89% of calbindin-D28-calabeled myenteric neurons of the ileum. AH neurons exclusively express calbindin-D28 in this region. No immunoreactivity was detected for AC II, AC V/VI, AC VII, or AC VIII. AC isoforms were expressed in the order of AC IV > III > I. In neurons loaded with the cAMP-dependent protein kinase A (PKA) fluorosensor FlCRhR, forskolin or PACAP caused an increase in cAMP/FlCRhR fluorescence levels in the cell somas and neurites of myenteric neurons. This study provided direct evidence for activation of PKA in myenteric neurons. The data support that AC I, AC III, and AC IV are differentially expressed in distinct subsets of calbindin-D28 neurons that are IPANs/AH neurons (13). However, it is not known which of the three AC isoenzymes are linked to A1, A2, or A3 receptors on AH neurons.

The nine mammalian AC isoforms exhibit type-specific inhibitory or stimulatory modulation by Ca-calmodulin (CaM), G protein βγ-subunits, and protein kinase C (PKC) phosphorylation. PKC stimulates AC I and AC IV isoforms. AC I and AC II are activated by Ca-CaM. AC I is inhibited by Gβγ, AC III is activated by Ca-CaM. AC I is inhibited by Gβγ, AC III is activated by Ca-CaM.
Is interstitial adenosine in enteric ganglia important in the neuropa-thophysiology of the gut?

Recent studies in Dr. Michael Cook's laboratory showed that endogenous interstitial adenosine in myenteric neural networks varies inversely with prevailing PO\textsubscript{2}, (8). The adenosine released during hypoxia, in part from neurons, is sufficient to cause considerable A1 receptor inhibition of the release of substance P. Adenosine release during ischemia acting at A1 receptors may provide neuroprotection in the gut. For instance, oxidative stress resulting from ischemia-reperfusion increases A1 receptor expression that could provide neuroprotection in the gut by shutting down neural activity. In the brain, enhancing adenosine A1 receptor binding with PD 81-273 decreases hypoxic brain damage.(11). Direct studies are needed to prove that IPANs/ AH neurons are particularly sensitive to elevated interstitial adenosine in hypoxic or ischemic gut.

Studies are also warranted to explore the therapeutic potential of endogenous adenosine in a variety of clinical conditions related to ischemia-reperfusion injury. These include nonocclusive mesenteric ischemia-reperfusion leading to dysfunction of enteric motility patterns, acute ischemic colitis in long-distance runners, or small bowel transplantation that involves ischemia-reperfusion injury. During ischemia or hypoxia (or traumatic injury), adenosine, ATP, and GTP are known to be elevated at the site of injury. These substances are believed to play a crucial role in limiting damage and further promoting repair and restoration of physiological function. Overall, adenosine provides neuroprotection against ischemic injury by inhibiting excessive transmitter release, blocking neuronal Ca influx, reducing the formation of reactive oxygen species that limit reperfusion injury, and causing vasodilation to supply more oxygen and nutrients.

Dr. Jeff Palmer has shown that acute jejunal inflammation in *Trichinella spiralis*-infected guinea pigs has several important effects in IPANs/AH neurons. It leads to an increase in electrical excitability and enhancement of excitatory synaptic potentials, increase in metabolic activity, and increase in transcriptional-translational activity (16). Such excitability changes in IPANs/AH neurons may be attributed to changes in receptor/AC-cAMP signaling pathways. Alterations in adenosine A1, A3, or A2a receptors or in the concentration of endogenous adenosine that is released would affect both the resting and activated states of AH neurons and is expected to have important consequences on enteric neural reflexes governing motility and secretion. Some evidence also suggests that serine proteases that are released in the inflamed intestine would interfere with normal purinergic and nonpurinergic neurotransmission and motility in the gut. The upregulation of adenosine receptors has been described in various disease states. Adenosine kinase inhibitors have strong anti-inflammatory and neuroprotective properties due to their ability to elevate endogenous adenosine levels in vivo. In the gut, adenosine kinase inhibitors are expected to shut down IPAN/AH cell excitability and synaptic transmission. An added benefit is that they do not cause systemic side effects as adenosine analogs would (10). Regulators of endogenous adenosine levels show promise as therapeutic agents in the treatment of gut inflammation and ischemia. The general protective and neuroprotective roles of nucleosides/adenosine and ATP in inflammation and ischemia were discussed in detail in a recent review on pathophysiological roles of purines (1). The neuroprotective role of endogenous adenosine in the gut in conditions like acute inflammation (i.e., *T. spiralis* infection), chronic inflammation (i.e., Crohn’s disease), or gut ischemia deserves serious consideration.

Adenosine may protect the enteric nervous system in a variety of ways, as shown in other systems: adenosine is elevated in extracellular fluids during ischemia, reduces metabolic demand on neurons and inhibits cell firing, inhibits chemotaxis and activation of neutrophils as well as release of superoxide anions, has antioxidant properties and may prevent lipid peroxidation, inhibits production of proinflammatory cytokines, causes vasodilation and increase in blood supply (9), may inhibit release of vasoconstrictive monoamines, and may have a preconditioning effect by activating A1 receptors.

Adenosine A1 receptor antagonists may also be of therapeutic potential in constipation (19). Endogenous adenosine provides an ongoing inhibition of intestinal contraction and propulsion. Thus adenosine A1 receptor antagonists increase giant migrating contractions induced by glycerol enema, whereas A1 receptor agonists abolish the contractions in the rat colon. A1 receptor antagonists increase colonic propulsion without diarrhea or any effects on gastric emptying. Therefore, A1 receptor antagonists are expected to have fewer abdominal adverse effects in the treatment of constipation than treatments such as laxatives, which are associated with symptoms of bloating and nausea. The therapeutic potential of A1 receptor antagonists in motility disorders is evident but requires more rigorous investigation. It is also not known whether the thera-

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peutic effect is through blockade of the actions of endogenous adenosine at neural sites, including IPANs/AH neurons, EPSPs, and transmitter release sites or smooth muscle adenosine receptors.

Actions of endogenous adenosine on mucosal reflexes

The role of neural A1 receptors in the physiological regulation of mucosal reflexes was explored with treatments that either limit or increase the availability of endogenous adenosine at A1 receptors (7). The results of these experiments established that endogenous and exogenous adenosine modulate stroking-induced short-circuit current responses indicative of Cl secretion.

Figure 3 is a working model by Dr. Helen Cooke of the possible sites of action of endogenous adenosine at neural A1 receptors to modulate Cl secretion in the guinea pig colon. Stroking releases prostaglandins (PG) from unknown sources and causes Cl secretion by acting directly and indirectly on secretomotor neurons. Stroking the luminal or mucosal surface releases 5-HT from enterochromaffin cells (EC), 5-HT activates 5-HT₁₆/5-HT₄ receptors on submucosal IPANs containing substance P, ACh, glutamate, or CGRP. Release of these transmitters activates secretomotor neurons that release ACh or VIP and cause Cl secretion. Submucosal IPANs project to VIP- or ACh-containing secretomotor neurons via SP, but it is not clear if this also occurs indirectly via interneurons (?). ACh via M₃ muscarinic receptors (M-R) and VIP via VIP receptors (VIP-R) stimulate chloride secretion by colonic crypt cells. Endogenous adenosine interacts with A1 receptors on submucosal neurons to inhibit both the PG and 5-HT limbs of the mucosal reflex. A1 receptors are presumed to be located at both presynaptic (2, 3) and postsynaptic (1) sites in the neural reflex. This model is a revision and extension of the basic model presented by Cooke et al. (7); reproduced with permission.

The subtype of adenosine A2 receptors involved in depolarization of S submucous neurons has not been identified. However, the potency profile of selective A1 and A2 receptor agonists at this A2 receptor is clearly different from that obtained for the A2a receptor on a subset of myenteric AH neurons/IPANs (2, 3). The A2 receptor on submucosal neurons likely represents
an excitatory A2b receptor. This can easily be resolved by immunohistochemistry using an anti-A2b receptor antiserum. In submucosal S neurons, adenosine is believed to activate PKA, resulting in a reduction of the gKca and membrane depolarization. Whole cell recordings showed that activation of somal A1 receptors inhibits N-type voltage-activated Ca currents via pertussis toxin-sensitive G proteins in the submucosal neurons. Presynaptic A1 receptor inhibition of cholinergic transmission involves the activation of a pertussis toxin-insensitive G proteins.

Recent experiments in Dr. Helen Cooke’s laboratory indicate that adenosine receptors are also involved in the regulation of 5-HT release from Bon cells, which represent a model of human enterochromaffin cells. Therefore, at least in the human cells, adenosine also exerts direct effects on the release of the sensory mediator 5-HT.

Concluding remarks

We propose that endogenous adenosine is a key modulator of sensory transmission in the gut. Endogenous adenosine provides significant inhibitory modulation of IPANs/AH neurons that may be relevant in both normal and pathophysiological states of the gut, such as ischemia and inflammation. Adenosinergic inhibition is produced by A1 receptors and possibly A3 receptors located on the somas of IPANs/AH neurons. Inhibition of somal excitability is associated with a reduction in cell input resistance and cell membrane hyperpolarization. Slow synaptic transmission to and from IPANs/AH neurons is blocked by activation of A1/A3 receptors that are located at presynaptic or postsynaptic membranes. Adenosinergic A1/A3 receptor inhibition is presumed to be the predominant effect in feedforward activation of AH neurons via sEPSPs in the enteric microcircuits. However, in a minority of AH neurons with excitatory A2a receptor and under ill-defined circumstances, adenosine could facilitate feedforward excitation of AH neurons. In IPANs/AH neurons, adenosine provides a dual modulation of AC/cAMP signaling via two or more distinct AC isoforms that include AC I, III, and IV, which are known to exist in subsets of IPANs/AH neurons. Presynaptic A1 receptors are involved in inhibition of both fast cholinergic synaptic transmission in S neurons from IPANs/AH neurons and excitatory neuromuscular transmission to smooth muscle. The role for endogenous adenosine in the modulation of mucosal and submucosal reflexes in normal and disease states deserves serious consideration. A key unresolved question is the physiological identity of the gut neurons expressing A1, A2, and A3 receptors. Future investigations must also explore the therapeutic potential of adenosine compounds in constipation, gut inflammation, and ischemic bowel disorders.

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