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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 mechano- or chemosensitive 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 electrophysiological 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 stretched and activates some IPANs/AH neurons. Activated AH neurons have more depolarized membrane potentials, higher membrane 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 dipryidamole 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 resting 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, which 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 would 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....
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 adenylyl 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 transmitter 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-labeled 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 soma and neurites of myenteric neurons. This study provided direct evidence for activation of PKA in myenteric neurons. The data suggest that AC I, AC III, and AC IV are differentially expressed in distinct subsets of calbindin-D28 neurons that are IPANs/AH neurons (3). 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 subunits, and protein kinase C (PKC) phosphorylation. PKC stimulates AC I and AC IV isoforms. AC I and AC III are activated by Ca-CaM. AC I is inhibited by Gs/Ga, AC III is not.
affected by Gβγ, and AC IV is stimulated by Gβγ. This provides
more insights for further investigation of how neuromodulators
(adenosine) or neurotransmitters (CCK, PACAP, GRP, SP, VIP,
Hist, CGRP, 5-HT) may exert their discrete actions through
activation of AC I, III, or IV. The signaling mechanisms coupled
to the slow 5-HT1P/5-HT4 response in AH neurons were stud-
ied in greater detail by Michael Gershon’s group (12, 17). They
found that 5-HT activates both PKC and PKA via a Go protein,
leading to inhibition of gKcα. 5-HT activates a Go/PKC-phos-
phodiesterase pathway that leads to inhibition of gKca without liberating inositol 1,4,5-trisphosphate that
would also elevate Ca in the cells. As suggested, Ca elevation
in the cell would be counterproductive, since 5-HT inhibits

gKca. Collectively, the data suggest that 5-HT and perhaps sub-
stance P, CGRP, and adenosine (A2 effect) activate AC IV that
is stimulated by PKC and not affected by Ca-CaM. It is tempt-
ing to suggest that AC I or III would be linked to receptors for
A1, A3, CCK, Hist, GRP, VIP, and PACAP. However, it is dif-
cult then to explain the antagonistic effect of Ca on responses
to the excitatory neurotransmitters.

Is interstitial adenosine in enteric ganglia important in the
neuropathophysiology of the gut?

Recent studies in Dr. Michael Cook’s laboratory showed that
endogenous interstitial adenosine in myenteric neural net-
works varies inversely with prevailing Po2 (8). The adenosine
released during hypoxia, in part from neurons, is sufficient to
cause considerable A1 receptor inhibition of the release of sub-
stance 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, enhanc-
ing 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.

Studios are also warranted to explore the therapeutic poten-
tial of endogenous adenosine in a variety of conditions related
to ischemia-reperfusion injury. These include noncol-
clusive mesenteric ischemia-reperfusion leading to dysfunc-
tional 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 cru-
cial role in limiting damage and further promoting repair and
restoration of physiological function. Overall, adenosine pro-
vides 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 elec-
trical excitability and enhancement of excitatory synaptic poten-
tials, increase in metabolic activity, and increase in transcrip-
tional-translational activity (16). Such excitability changes in
IPANs/AH neurons may be attributed to changes in recep-
tor/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 impor-
tant consequences on enteric neural reflexes governing motil-
ity and secretion. Some evidence also suggests that serine pro-
teases that are released in the inflamed intestine would inte-
fer with normal purinergic and nonpurinergic neurotransmis-
sion and motility in the gut. The upregulation of adenosine
receptors has been described in various disease states. Adeno-
sine kinase inhibitors have strong anti-inflammatory and neu-
roprotective properties due to their ability to elevate endoge-
 nous adenosine levels in vivo. In the gut, adenosine kinase
inhibitors are expected to shut down IPAN/AH cell excitation
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 pathophysio-
logical roles of purines (1). The neuroprotective role of endoge-
nous adenosine in the gut in conditions like acute inflamma-
tion (i.e., T. spiralis infection), chronic inflammation (i.e.,
Crohn’s disease), or gut ischemia deserves serious considera-
tion.

Adenosine may protect the enteric nervous system in a vari-
ety 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 chemotax-
sis and activation of neutrophils as well as release of super-
oxide anions, has antioxidant properties and may prevent lip-
peroxidation, inhibits production of proinflammatory cyto-
kines, causes vasodilation and increase in blood supply
(9), may inhibit release of vasoconstrictive monoamines, and
may have a preconditioning effect by activating A1 receptors
in the gut. Adenosine A1 receptor antagonists may also be of therapeu-
tic potential in constipation (19). Endogenous adenosine pro-
vides 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 abdomi-
al adverse effects in the treatment of constipation than treat-
ments such as laxatives, which are associated with symptoms of
bloating and nausea. The therapeutic potential of A1 receptor
agonists in motility disorders is evident but requires more
rigorous investigation. It is also not known whether the thera-

“Adenosine may protect the enteric nervous system in a variety of ways...”

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The therapeutic 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 secretory reflexes. Nanomolar doses of A1 receptor antagonists enhance reflex-evoked Cl secretion. Preventing adenosine reuptake by blocking adenosine transport with dipyridamole decreases reflex-evoked responses. Increasing the degradation of adenosine by adenosine deaminase enhances the reflex response. After cyclooxygenase blockade or after bypassing the enterochromaffin cell by a pulse of 5-HT, nanomolar doses of A1 receptor agonists still suppress the reflex response. When the 5-HT limb of the reflex is blocked by the 5-HT<sub>1p</sub> antagonist, the residual response is still sensitive to adenosine. Therefore, A1 receptors provide dual modulation of the 5-HT and prostaglandin-activated neural pathways stimulating secretion. A1 receptor agonists nearly abolish the reflex response to a pulse of 5-HT but do not affect the tetrodotoxin-insensitive responses to forskolin or carbamol. The efficacy of A1 receptor agonists to reduce the short-circuit current response is highly correlated with the degree of ongoing neural activity in the basal state. A1 receptor immunoreactivity was identified in submucous neurons and in presynaptic varicose nerve endings surrounding the cell somas. Overall, the data indicate that endogenous adenosine provides a physiological break to suppress reflex-evoked Cl secretion acting at the level of the neurons.

The types of neurons expressing A1 receptors in submucosal plexus of the colon are unknown. Our knowledge is based on electrophysiological and patch-clamp recordings from the small intestine carried out by Dr. Barajas-Lopez and co-workers (2). Activation of adenosine A1 and A2 receptors leads to presynaptic inhibition and postsynaptic excitation in guinea pig submucosal neurons of the ileum (2). Adenosine activates presynaptic A1 sites to inhibit the release of ACh from intramural nerves and noradrenaline from sympathetic nerves. A1 receptors are also expressed on AH neurons of the submucous plexus, which are presumed to be IPANs like their counterparts in the myenteric plexus (9). If A2 receptors also exist on colonic neurons, only inhibitory A1 receptors are activated by release of endogenous adenosine. Also, it is unresolved as to whether adenosine can inhibit 5-HT release from enterochromaffin cells to suppress the mucosal reflex. Studies are needed to clarify the neural targets for endogenous adenosine in modulating submucosal reflexes. It is also of interest to know whether adenosine preferentially inhibits ascending cholinergic or descending VIPergic motor pathways leading to Cl secretion.

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 distension 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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