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Mechanisms of Excitatory Synaptic Transmissiom in the Enteric Nervous System

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The enteric nervous system can control gastrointestinal function independent of direct connections with the central nervous system. Enteric nerves can perform this task as there are multiple mechanisms of excitatory neurotransmission in enteric ganglia. There are two broad types of excitatory synaptic transmission, fast and slow excitatory synaptic responses. Fast excitatory postsynaptic potentials (fEPSPs) are recorded from "S" type neurons and some AH type neurons. S neurons are interneurons and motorneurons while AH neurons are intrinsic sensory neurons. Slow excitatory postsynaptic potentials (sEPSPs) can be recorded from some S neurons and also from AH type neurons. The fEPSPs recorded from S neurons are mediated largely by acetylcholine acting at nicotinic cholinergic receptors (nAChRs). However, ATP acting at P2X purine receptors contributes to the fEPSP in many S neurons. The fEPSPs recorded from AH neurons are also mediated largely by nAChRs but glutamate acting at AMPA receptors contributes to fEPSPs in some AH neurons. The sEPSPs in AH neurons are mediated by one or more neuropeptides and 5-hydroxytryptamine. The sEPSPs in AH neurons are due to inhibition of two types of resting potassium channels and activation of a chloride channel or a nonspecific cation channel. The multiple mechanisms of excitatory synaptic transmission in the enteric nervous system contribute to its capacity to regulate complex gastrointestinal functions.

(Key words: enteric nervous system, electrophysiology, ion channels, synaptic transmission)

Introduction

The enteric nervous system (ENS) is the collection of neurons and support cells that reside within the wall of the gastrointestinal tract. The ENS controls most gastrointestinal functions including motility, blood flow and absorption and secretion of water and electrolytes. While connections with the central nervous system (CNS) integrate digestive behaviors with other behaviors, the ENS can maintain essentially normal gastrointestinal function independent of direct connections with the CNS (12). Enteric nerves are neurochemically diverse as they contain more than thirty different neuroactive substances. As there are many potential neurotransmitters and/or chemical messengers, there are also likely to be many different receptors and cellular mechanisms by which these substances can act on enteric nerves. This review will focus on the cellular mechanisms of excitatory synaptic transmission in the ENS.

The enteric nervous system

The ENS consists of two ganglionated plexuses, the submucosal plexus and the myenteric plexus. The submucosal plexus is embedded in the submucosal layer between the mucosa and circula muscle layers. The submucosal plexus is primarily responsible for regulating water and electrolyte secretion by the mucosal epithelium and for regulating local blood flow. Individual submucosal ganglia contain 8-12 neurons and these ganglia are dispersed in an irregular arrangement throughout the submucosal. The myenteric plexus resides between the circular and longitudinal muscle layers and is primarily responsible for controlling contractions and relaxations of these muscle layer. Myenteric ganglia contain anywhere from 60 - 100

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neurons and the ganglia are arranged in rows oriented in the circular axis of the gastrointestinal tract (12).

There are two types of neurons in the submucosal and myenteric plexuses that can be distinguished based on their electrophysiological properties when these neurons are studied using conventional intracellular microelectrodes. These cell types are designated "S" neurons and "AH" neurons (7, 36). Single electrical stimuli applied to interganglionic connectives elicit fast excitatory postsynaptic potentials (fEPSPs) in S type neurons. Short trains of electrical stimuli elicit slow excitatory postsynaptic potentials (sEPSPs) in most S neurons. The action potential recorded from the soma of S neurons is completely blocked by the sodium channel blocker, tetrodotoxin and most S neurons fire continuously when depolarized with a current pulse applied through the recording microelectrode (7).

Single electrical stimuli fail to elicit a synaptic response in most AH neurons, however, trains of stimuli elicit sEPSPs from all AH neurons (7, 13, 36). The action potential in AH neurons has a prominent shoulder that is due to a calcium current contribution to the action potential (13). As a result the somal action potential in AH neurons is only partly blocked by TTX. The action potential in AH neurons is followed by an afterhyperpolarization that lasts from 1-20 seconds (25). The afterhyperpolarization is mediated by a calcium-dependent potassium channel activated by calcium entering the neuron during the action potential (14, 25-27). Under resting conditions, AH neurons usually only fire one or two action potentials when depolarized by an intracellular current pulse as the spike afterhyperpolarization limits the firing rate. Data from functional and neuroanatomical studies indicate that AH neurons are likely to be intrinsic sensory neurons in both the myenteric plexus and submucosal plexus (13).

Fast excitatory postsynaptic potentials (fEPSPs)

Responses mediated at nicotinic acetylcholine receptors (nAChRs)

The predominant mechanism of excitatory neurotransmission in the autonomic nervous system which includes the ENS is *via* nerve released acetylcholine acting at nAChRs. As nAChRs are ligand gated ion channels they mediate short latency (>2 ms) and short-lived (<50 ms) synaptic responses (14). There are multiple nicotinic receptor subtypes whose properties are determined by the subunit composition of the receptor heteromer (20). There are no functional studies examining the specific nAChRs expressed by enteric nerves however, recent immunohistochemical studies have revealed that some enteric nerves and nerves fibers express immunoreactivity for the $\alpha 7$ subunit while most enteric nerves are recognized by a monoclonal antibody, mAb35, which binds the α_3, α_5 and β_4 subunits (17). The fEPSPs in myenteric neurons have a reversal potential near 0 mV suggesting that the fEPSPs are due to an increase in a nonspecific cation conductance including calcium ions (14, 32).

Studies done in myenteric neurons maintained in primary culture have characterized some of the pharmacological and kinetic properties of nAChRs (38). Agonists for the nAChR were applied using a method for rapid drug application to minimize receptor desensitization. The rank order potency for activation of myenteric nAChRs was nicotine > ACh > dimethylphenyl-piperazinium >> cytisine. Inward currents elicited by nAChR agonists are blocked completely by hexamethonium but are unaffected by prior incubation of the cells with α-bungarotoxin. These data indicate that myenteric nAChRs do not contain $\alpha 7$ (α-bungarotoxin-sensitive) subunits (20). Inward currents caused by activation of nAChRs have a reversal potential of 0 mV and the whole cell current/voltage relationship show marked inward rectification. Steady state application of maximum ACh concentrations (1 mM) causes myenteric neuronal nAChRs desensitize by more than 80% in less than 300 ms. Application of ACh to outside-out patches of myenteric neurons showed that nAChRs have a single channel conductance of approximately 20 pS. Unlike whole cell currents, the current/voltage relationship for the single channel current was linear in the range of potentials between -90 and $+40$ mV but channel open probability decreased at less negative patch potentials.

Responses mediated at P2X purine receptors

Exogenously applied ATP causes a fast depolarization in myenteric and submucosal neurons that is similar to that caused by ACh acting at nicotinic receptors (4, 9, 14). In submucosal neurons, all fEPSPs are completely blocked by nicotinic cholinergic receptor antagonists (9). However, fEPSPs recorded from myenteric neurons are not all purely cholinergic (14, 19). In these studies it was shown that in 60-70% of myenteric neurons, fEPSPs were only partly inhibited by the nicotinic cholinergic receptor antagonist, hexamethonium. The hexamethonium-resistant fEPSPs were reduced in a concentration dependent manner by suramin or PPADS or by desensitization with α, β-methylene ATP (14, 19).

Fast excitatory postsynaptic currents (fEPSCs) can be recorded using whole cell patch clamp methods from myenteric neurons maintained in primary culture (37). The fEPSCs are completely blocked by hexamethonium in most neurons. However in a subpopulation of cells, complete inhibition of fEPSCs requires the combined application of hexamethonium and PPADS. In 90% of neurons studied, ATP elicited an inward current that desensitized by more than 80% in 7 seconds. In 10% of the neurons studied, ATP elicited a rapidly developing inward current (10-90% rise time <50 ms) that desensitized in less than 200 ms. The pharmacological properties of the slowly desensitizing response suggest they are mediated at P2X2 receptors while the rapidly desensitizing response had the pharmacological properties of the P2X3 receptor (8, 10). The whole cell current-voltage relationship reveals a reversal potential near 0 mV and shows marked inward rectification. P2X receptors are nonspecific cation channels that are permeable to sodium, potassium and calcium ions (7, 38). Single channels activated by ATP in outside-out patches have a conductance of 25 pS and the current/voltage relationship of the single channel current was linear between -80 and $+40$ mV while the open probability decreased at less negative to positive patch potentials. Rectification of the whole cell current appears to be due to voltage dependence of the gating of the P2X receptor (11).

Responses mediated at inotropic glutamate receptors

Not all fEPSPs recorded from the intact myenteric plexus are blocked by the combined application of nicotinic and P2X receptor antagonists. These non-cholinergic, non-purinergic fEPSPs may be due to the action of nerve-released glutamate (21). Immunohistochemical studies showed that myenteric neurons express ionotropic glutamate receptors and the neuronal glutamate transporter. Furthermore, application of exogenous glutamate elicited a biphasic depolarization. The early fast phase mimicked by AMPA while the late slower depolarization was mimicked by NMDA. Finally, some fEPSPs recorded from myenteric AH neurons were inhibited by DNQX, an antagonist of AMPA type glutamate receptors. These data indicate that glutamate contributes to fast excitatory transmission in the myenteric plexus (21). The signaling mechanisms for fast excitatory synaptic transmission in the ENS are summarized in Figs. 1 and 2.

Mechanisms of slow synaptic excitation

Nerve stimulation elicits sEPSPs in S and AH neurons. There are many substances contained in and released from enteric nerves that when applied to individual neurons cause responses that mimic the sEPSP (15, 33, 34). However, there are only a few of these substances for which there are sufficient data to indicate that they are mediators of synaptic responses. ACh acting at muscarinic M_1 type receptor mediates sEPSPs in myenteric S neurons (24). Substance P (SP) acting at NK-3 receptors (6, 15, 33) and 5-hydroxytryptamine (5-HT) acting at 5-HT_{1P} receptors (22, 23, 35), are mediators of sEPSPs in AH neurons (Figs. 1 and 2).

Ionic mechanisms of sEPSPs

Most sEPSPs are associated with a net decrease in membrane conductance and have a reversal potential at -90 mV with normal extacellular potassium concentrations. When the extracellular potassium concentrations are altered, the reversal potential for the sEPSP changes with the predicted change in the potassium equilibrium potential. These studies indicate that most sEPSPs are due in large part to a decrease in resting potassium conductance (15, 16). In AH neu-

rons there are two potassium conductances inhibited during the sEPSP. The first is a background or "leak" conductance. The second is a persistent calcium-dependent potassium conductance that is the same conductance mediating the spike afterhyperpolarization (1, 27).

The sEPSP in most AH neurons is due to inhibition of the leak potassium conductance and the calcium-activated potassium conductance. However, single electrode voltage clamp recordings from myenteric and submucosal neurons showed that not all sEPSPs reverse at the potassium equilibrium potential or are associated with a net conductance change. Pharmacological and electrophysiological analysis showed that these "non-reversing" sEPSPs were due to a simultaneous decrease in potassium conductance and increase in a non-specific cation conductance in submucous neurons (31) and a decrease in potassium conductance and increase in a chloride conductance in myenteric neurons (6).

Signaling mechanisms for sEPSPs

The sEPSPs in enteric S and AH neurons have a long latency to onset (200 ms to several seconds) and long duration (seconds to minutes). These observations indicate that there are likely to be several signaling steps between neurotransmitter binding to its receptor and alterations in ion channel activity. Substances which mimic the sEPSP increase intracellular cyclic AMP in myenteric ganglia and activation of adenylate cyclase is one intracellular pathway involved in slow synaptic excitation in the myenteric plexus (28, 29).

Biochemical studies have shown that NK-3 receptors, which mediate some sEPSPs, couple to phospholipase C (17). The contribution of this NK-3 coupled pathway to the generation of sEPSPs in myenteric AH neurons has been studied using inhibitors of these pathways (5).

In myenteric AH neurons, sEPSPs and responses caused by the NK-3 selective agonist, senktide are potentiated and prolonged following intracellular injections of the non-hydrolyzable GTP analog GTPγS but persist in pertussis toxin (PTX)-treated preparations. These data indicate that the G-proteins participating in this signaling pathway are PTX-insensitive. Phorbol dibutyrate (PDBu) which activates protein kinase C (PKC) causes a concentration-dependent inward current that was due only to inhibition of a potassium conductance. PDBu also inhibits the spike afterhyperpolarization in AH neurons. Staurosporine, a drug somewhat selective for inhibition of PKC, reduced the amplitude of inward currents caused by PDBu and reduced the amplitude of the sEPSP. It was also found that D600, an inhibitor of phosphotidyl choline-dependent phospholipace C (PC-PLC) reduced the amplitude of the sEPSP and senktide response. These data indicate that sEPSPs mediated via activation of NK-3 receptors are due to activation of PC-PLC and activation of PKC. The background and calcium activated potassium channels may be targets for PKC-induced phosphorylation which would cause them to close. The signaling mechanism activating the chloride conductance that contributes to the sEPSP in some myenteric AH neurons is unknown. However, it was shown that neither forskolin, an activator of adenylate cyclase, or PDBu could activate the chloride conductance. However, in submucous neurons the cation conductance that contributes to the sEPSP could be activated by forskolin suggesting that a cAMP-dependent pathway is involved in activation of these non specific cation channels (5) (Fig. 2A).

5-HT, acting at 5-HT_{1P} receptors, inhibits the spike afterhyperpolarization in AH neurons and causes a slow depolarization associated with an increase in input resistance (16, 36). Further-more, some sEPSPs recorded from AH neurons are blocked by 5-HT_{1P} receptor antagonists suggesting that 5-HT is a slow synaptic transmitter in the myenteric plexus (22, 23). The signaling mechanisms coupled to the 5-HT_{1P} receptor are complex. The structure of the 5-HT_{1P} receptor has not been established, however, slow depolarizations caused by 5-HT are inhibited and prolonged by intracellular injections of GDPβS and GTPγS, respectively (30). Furthermore, intracellular injections of Fab fragments of antibodies raised against Gαo or pretreatment of tissues with PTX also inhibited some sEPSPs and the 5-HT_{1P}-mediated slow depolarizations caused by local application of 5-HT. Finally, slow depolarizations caused by 5-HT and sEPSPs are inhibited by the separate application of PKC and protein kinase (PKA) inhibitors and are completely blocked

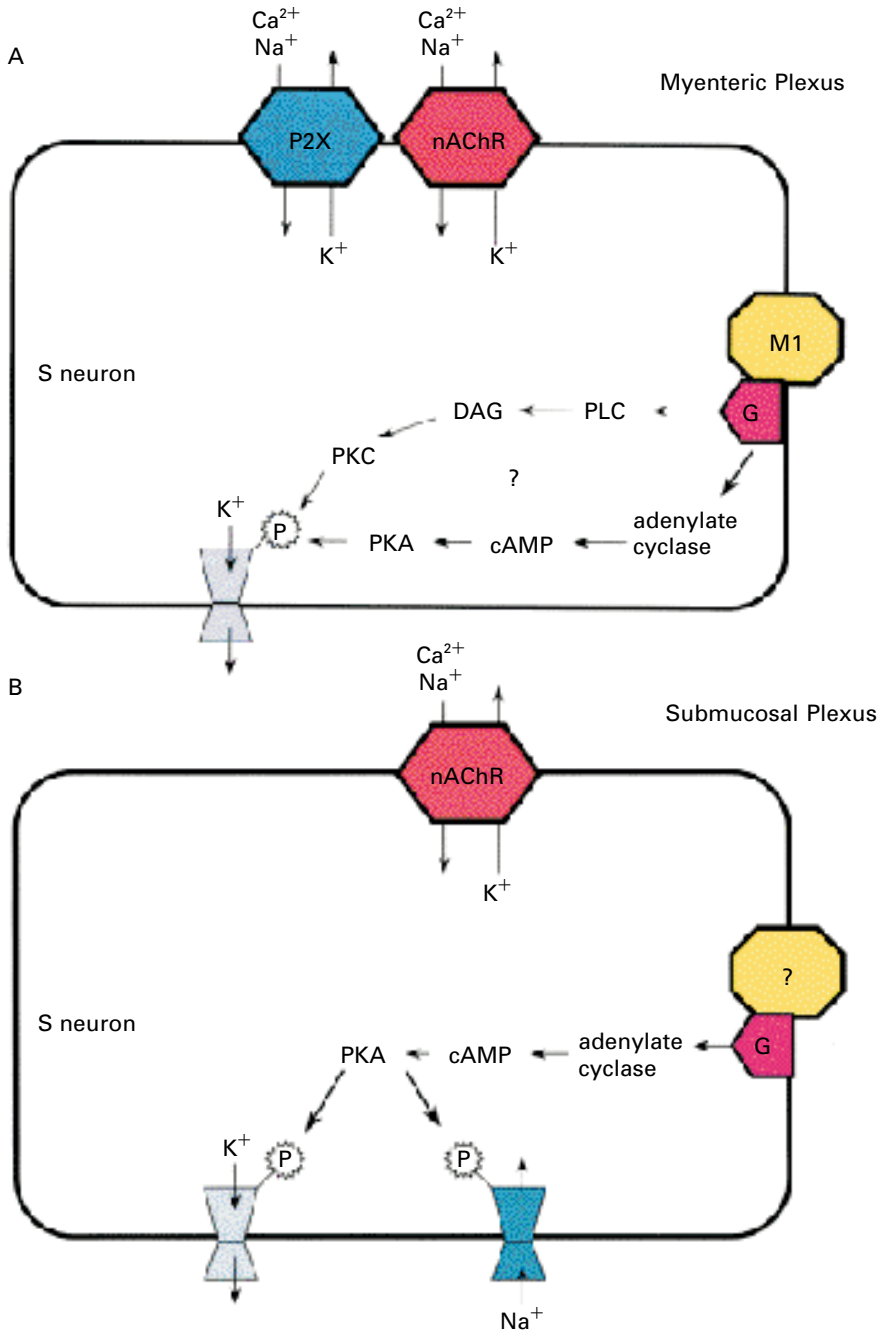

Fig. 1 Mechanisms of excitatory synaptic transmission in enteric S neurons. A: Fast and slow excitatory synaptic transmission in myenteric S neurons. M_1 muscarinic receptors mediate sEPSPs in S neurons. The signaling pathways coupled to M_1 receptors in these neurons has not been established. However, activators of PKC and an adenylate cyclase mimic the sEPSP in these cells. A background potassium channel is a possible target for PKC or PKA induced phosphorylation. P2X purine receptors and nAChRs mediate fEPSPs in S neurons. These ligand gated cation channels permeable to sodium potassium and calcium ions. B: Fast and slow synaptic transmission in submucosal S neurons. The mediator(s) of the sEPSP in submucous neurons has not been established but the sEPSP can be mimicked by activators of adenylate cyclase. The targets of PKA induced phosphorylation are likely to be a background potassium channel and a non-specific cation channel that is primarily sodium permeant.

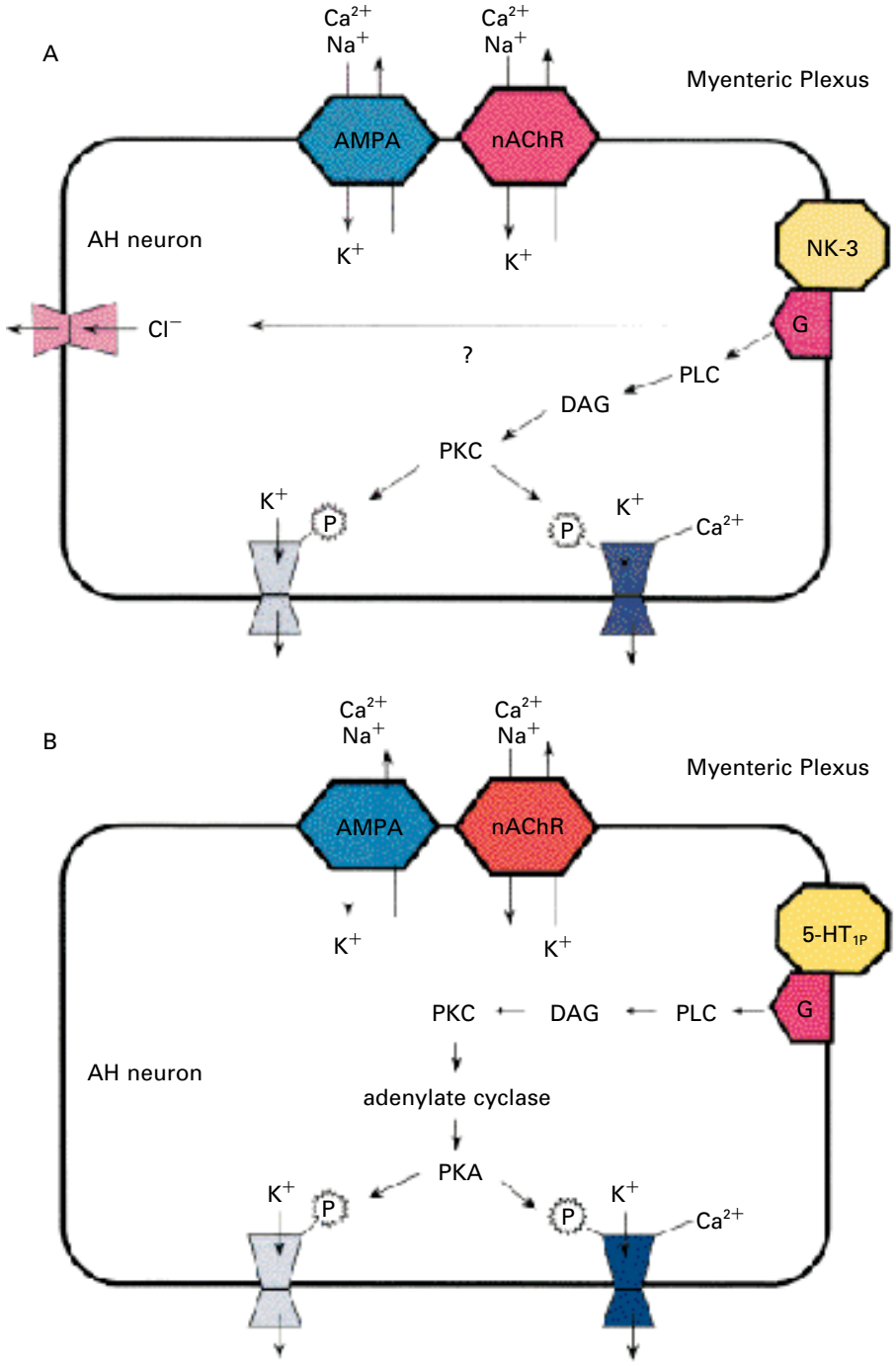

Fig. 2 Mechanisms of excitatory transmission in myenteric AH neurons. AMPA receptors and nAChRs mediate the fEPSPs that can be recorded from some AH neurons. 5-HT and SP are mediators of the sEPSP in AH neurons. 5-HT acting at 5-HT_{1P} receptors activates a sequential signaling pathway involving PKC and PKA resulting in the likely phosphorylation of a background potassium channel and a calcium-dependent potassium channel. In other AH neurons, substance P acts at NK-3 receptors to activate PKC which likely phosphorylates the background and calcium-dependent potassium channels. NK-3 receptors also couple to activation of chloride conductance via an unknown signaling pathway.

by co-application of inhibitors of these enzymes. These data indicate that the leak and calcium-activated potassium channels are substrates for both PKC and PKA and that the signaling mechanism coupled to the 5-HT_{1P} receptor may involve a sequential activation of Gαo, PKC, adenylate cyclase and PKA (30) (Fig. 2B).

Summary and conclusions

The neurochemistry and synaptic connections of enteric neurons are complex with several different mechanisms for fast and slow synaptic excitation. There are three different mechanisms of fast excitatory synaptic transmission including ACh acting at nAChRs, ATP acting at P2X receptors and glutamate acting at AMPA receptors. Each receptor is a ligand-gated ion channel mediating short latency, short duration synaptic excitation. Slow synaptic excitation is also an important mechanism of neurotransmission in the ENS. Slow EPSPs are mediated by ACh acting at M_1 muscarinic receptor, substance P acting at NK-3 receptors and 5-HT acting at 5-HT_{1P} receptors. The sEPSPs are due to transmitter induced inhibition of two resting potassium conductances and activation of a chloride (myenteric neurons) or a non-specific cation conductance (submucous neurons).

Normal gastrointestinal function requires a complex interaction between intrinsic and extrinsic gastrointestinal nerves, circulating and locally acting hormones and effector cells (smooth muscle, epithelial cells etc.). The complexity of the neural mechanisms of excitation in the gut wall permit a high degree of flexibility in the intensity and duration of neural activity. This allows for marked alterations in or subtle modifications of gastrointestinal behavior. The multiple mechanisms of synaptic excitation also provide an opportunity for the development of new and novel drugs which could modify excitatory neurotransmission in the gastrointestinal tract and therefore treat some disorders of gastrointestinal function.

REFERENCES

1) Akasu T and Tokimasa T: Potassium currents in submucous neurones of guinea-pig caecum and their synaptic modification. J Physiol 416: 571-588, 1989.
2) Barajas-Lopez C: Adenosine reduces the potassium conductance of guinea pig submucosal plexus neurons by activating protein kinase A. Pfluegers Arch 424: 410-495, 1993.
3) Barajas-Lopez C, Huzinga JD, Collins SM, Gerzanich V, Espinosa-Luna R and Peres AL: P2X-purinoceptors of myenteric neurones from the guinea pig ileum and their unusual pharmacological properties. Br J Pharmacol 119: 1541-1548, 1996.
4) Barajas-Lopez C, Espinosa-Luna R and Gerzanich V: ATP closes a potassium and opens a cationic conductance throuth different receptors in neurons of guinea pig submucosal plexus. J Pharmacol Exp Ther 268: 1397-1402, 1994.
5) Bertrand PP and Galligan JJ: Signal transduction pathways causing slow synaptic excitation in guinea pig myenteric AH neurons. Am. J. Physiol. 269: G710-G720, 1995.
6) Bertrand PP and Galligan JJ: Contribution of a chloride conductance increase to slow EPSC and tachykinin current in guinea pig myenteric neurones. J. Physiol. 481: 47-60, 1994.
7) Bornstein, JC, Furness JB, and Kunze WAA: Electrophysiological characterization of myenteric neurons: how do classification schemes relate? J Auton Nerv Syst 48: 1-15, 1994.
8) Collo G, North RA, Kawashima E, Merlo-Pich E, Neidhart S, Surprenant A and Buell G: Cloning of $P2X_5$ and $P2X_6$ receptors and the distribution and properties of an extended family of ATP-gated ion channels. J Neurosci 16: 2495-2507.
9) Evans RJ and Surprenant A: Vasoconstriction of guinea pig submucosal arterioles following sympathetic nerve stimulation is mediated by the release of ATP. Br J Pharmacol 106: 242-249, 1992.
10) Evans RJ, Lewis C, Buell G, Valera S, North RA and Surprenant A: Pharmacological characterization of heterologously expressed ATP-gated cation channels (P2X purinoceptors). Mol Pharmacol 48: 178-183, 1995.
11) Fieber LA and Adams DJ: Adenosine triphosphate-evoked currents in cultured neurones dissociated from rat parasympathetic cardiac ganglia. J Physiol 434: 239-256, 1991.
12) Furness JB and Costa M: The enteric nervous system, Churchill Livingstone, Edinburgh, 1987.
13) Furness JB, Kunze WAA, Bertrand PP, Clerc N and Bornstein JC: Intrinsic primary afferent neurons of the intestine. Prog Neurobiology 54: 1-18, 1998.
14) Galligan JJ and Bertrand PP: ATP mediates fast synaptic potentials in enteric neurons. J. Neuroscience 14: 7563-7571, 1994.
15) Galligan JJ, Peptides and enteric neural activity. In Handbook of Experimental Pharmacology, V. 106, Gastrointestinal Regulatory Peptides. D. R. Brown, Ed. Springer Verlag, Berlin, pp. 253-276, 1993.
16) Grafe P, Mayer CJ and Wood JD: Synaptic modulation of calcium dependent potassium conductance in myenteric neurones in the guinea pig. J. Physiol. 305: 235-248, 1980.
17) Guard S, Watling KJ and Watson SP: Neurokinin 3 receptors are linked to inositol phospholipid hydrolysis in the guinea pig ileum longitudinal muscle myenteric plexus preparation. Br J Pharmacol 94: 148-154, 1988.
18) Kirchgessner A and Liu M: Immunohisto-chemical

localization of nicotinic acetylcholine receptors in the guinea pig bowel and pancreas. J Comp Neurol (in press), 1998.
19) LePard KJ, Messori E and Galligan JJ: Purinergic postsynaptic potentials in myenteric neurons of guinea pig: distribution and pharmacology. Gastroenterology 113: 1522-1534, 1997.
20) Lindstrom J, Anand R, Gerzanich V, Peng X, Wang F and Wells G: Structure and function of neuronal nicotinic acetylcholine receptors. Prog Brain Res 109: 125-137, 1996.
21) Liu MT, Rothstein JD, Gershon MD and Kirchgessner AL: Glutamatergic enteric neurons. J Neuroscience 17: 4764-4784, 1997.
22) Mawe, G. M., Branchek, T., and Gershon, M. D. Peripheral neural sertonin receptors: Identification of characterization with specific antagonists and agonists. Proc. Natl. Acad. Sci. USA 83: 9799-9803, 1986.
23) Mawe, G. M., Branchek, T., and Gershon, M. D. Blockade of 5-HT-mediated enteric slow EPSPs by BRL 24924: gastrokinetic effects. *Am. J. Physiol.* 257: G386-G396, 1989.
24) North, R. A. and Tokimasa, T. Muscarinic synaptic potentials in guinea-pig myenteric plexus neurones. J Physiol 333: 151-156, 1982.
25) North, R. A., Morita, K., and Tokimasa, T. Muscarinic agonists inactive potassium conductance of guinea-pig myenteric neurones. J. Physiol. 333: 125-139, 1982.
26) North RA and Tokimasa T: Depression of calcium-dependent potassium conductance of guinea pig myenteric neurones by muscarinic agonists. J. Physiol. 342: 253-266, 1983.
27) North RA and Tokimasa T: Persistent calcium-sensitive potassium current and the resting properties of myenteric neurones. J. Physiol. 386: 333-353, 1987.
28) Palmer JM, Wood JD and Zafirov DH: Transduction of aminergic and peptidergic signals in enteric neurones of the guinea pig. J. Physiol. 387: 371-383, 1987.
29) Palmer JM, Wood JD and Zafirov DH: Elevation of adenosine 3'-5' phosphate mimics slow synaptic excitation in myenteric neurones of the guinea pig. J. Physiol. 376: 451-460, 1987.
30) Pan H, Wang H-Y, Friedman E, and Gershon MD: Mediation by protein kinases C and A of G_0-linked slow responses of enteric neurons to 5-HT. J Neuroscience 17: 1011-1024, 1977.
31) Shen K-Z, and Surprenant A: Common ionic mechanisms of excitation by substance P and other transmitters in guinea pig submucosal neurones. J Physiol 462: 483-501, 1993.
32) Trouslard J, Mirsky R, Jesson KR, Burnstock G, and Brown DA: Intracellular calcium changes associated with cholinergic nicotinic receptor activation in cultured myenteric plexus neurones. Brain Research 624: 103-108, 1993.
33) Willard AL: Substance P mediates synaptic transmission between rat myenteric neurones in cell culture. J. Physiol. 426: 453-471, 1990.
34) Willard AL: A vasoactive intestinal peptide-like cotransmitter at cholinergic synapses between rat myenteric neurons in cell culture. J. Neuroscience 10: 1025-1034, 1990.
35) Wood, JD and Mayer, CJ: Serotonergic activation of tonic-type enteric neurons in guinea pig small bowel. J. Neurophysiol 42: 582-593, 1979.
36) Wood, JD: Application of classification schemes to the enteric nervous system. J Autonomic Nerv Syst 48: 17-19, 1994.
37) Zhou X and Galligan JJ: Purinoceptors in cultured myenteric neurons of guinea pig small intestine. J Physiol 496: 719-729, 1996.
38) Zhou X and Galligan JJ: Functional interactions between nicotinic cholinergic and P2X purine receptors in myenteric neurons of guinea pig small intestine. J Physiol (submitted), 1998.