NANC transmission in intestines and its pharmacological modulation

Viktor Bauer

Institute of Experimental Pharmacology, Slovak Academy of Sciences, 9 Dúbravská St., 842 16 Bratislava, Republic of Slovakia

Abstract. Non-adrenergic, non-cholinergic (NANC) nerve stimulation results in excitation (e.g., rebound depolarization, contractions) or inhibition (i.e., afterhyperpolarization, relaxations) of the gut. NANC neuronal mechanisms participate in the maintenance of the basal tone and spontaneous activity of the gut. There are however species differences, i.e., both NANC excitation and inhibition are present in the guinea pig and only NANC inhibition in the rat intestine. Substance P-like neuropeptides are suggested to be mediators released from excitatory NANC and sensory nerves. The latter are activated by histamine and degenerated by capsaicin. There is evidence in favor of a nitric oxide-like substance rather than ATP, dopamine, GABA and neuropeptides (e.g., VIP, PHI/PHM) as the inhibitory NANC mediator in the gut. TTX, high Mg$^{2+}$-low Ca$^{2+}$ media, 3,4-diaminopyridine, dipyridamol and adenosine deaminase modulate NANC excitation and inhibition. The NANC excitation is more sensitive than the NANC inhibition to the action of catecholamines, reserpine, 6-hydroxydopamine, chymotrypsin, prednisolone, bacitracin, opioids, free oxygen species and low concentration of local anesthetics.

Key words: mediators, modulators, nonadrenergic-noncholinergic transmission, intestine, guinea-pig, rat
INTRODUCTION

The complex neural control of the intestinal smooth muscles involves inhibitory and excitatory nerves present in the myenteric and submucosus plexuses (Burnstock et al. 1963, Kosterlitz and Watt 1963, Kuriyama et al. 1967, Ambache and Freeman 1968, Burnstock et al. 1972, Bauer et al. 1982a). Multiple nerve fibers containing a variety of inhibitory and excitatory transmitters which affect intestinal smooth muscles by different mechanisms were described (Bauer and Kuriyama 1982a,b, Furness and Costa 1982a, Niel et al. 1983, Hoyle and Burnstock 1989). Until the sixties it was believed that the autonomic nervous system consists of two components, namely the cholinergic and the adrenergic. First evidence of autonomic nerves other than adrenergic and cholinergic dates back to the end of the 19th century (Langley 1898, Bayliss and Starling 1899). In the last decades along with the cholinergic and adrenergic control mechanisms, neurally mediated contractile and relaxatory pathways which are neither cholinergic nor adrenergic in nature have been demonstrated in the course of pre- and/or postsynaptic blockade of adrenergic and cholinergic mechanisms.

Excitatory (e-NANC) and inhibitory (i-NANC) NANC responses in the gut of different animal species were described both in vivo and in vitro (Burnstock et al. 1972, Holzer et al. 1989). The NANC responses are suggested to be mediated by the release of different neurotransmitters. A number of putative neuropeptides (e.g. VIP, SP) and non-peptidergic (e.g. ATP, NO) neuromediators or neuromodulators have been found to be present in the intramural nerves (Burnstock et al. 1970, Franco et al. 1979, Furness and Costa 1982b, Bredt et al. 1990). They were either co-localized with classical autonomic neurotransmitters or in discrete nerve fibers with close apposition to classical autonomic nerves and smooth muscle cells. From substances present and released from the intramural nerve fibers, some do while others do not mimic the action of NANC nerve stimulation in a given tissue and animal species.

The aim of the present study was therefore to provide further evidence in favor of the existence of NANC transmission, on the nature of its neurotransmitters and possibilities of its pharmacological modulation.

METHODS

Guinea-pigs and rats of either sex (250-500 g) were stunned and bled. Segments of the small (duodenum, jejunum, proximal and terminal ileum) and large (colon and taenia caeci) intestine were dissected. Segments of the whole intestine, or its longitudinal muscle layer with attached myenteric plexus were used. The experiments were carried out in modified Krebs solution (Na+ 136.6, K+ 5.9, Ca2+ 2.5, Mg2+ 1.2, Cl- 133.3, HCO3- 15.4, H2PO4- 1.2 and glucose 11.5 mmol/l) gassed with 95% O2 and 5% CO2 and the pH was maintained at 7.2-7.4.

Recording of muscle tension and membrane potential

For mechanical recording the tissues were put under 25-30 mN tension during the initial 30 min of equilibration and the experiments were carried out under the basal tension of about 10 mN. Changes of the muscle tension elicited by transmural or field stimulation were recorded isometrically using a strain gauge transducer (Matušák and Bauer 1986a).

Membrane potential and junction potentials (e.j.p. and i.j.p.) of single cells were recorded by using conventional glass capillary micro-electrodes (Bauer and Kuriyama 1982a) and of the tissue strips by using double sucrose gap method (Bauer and Zakhari 1977).

Substances

Atropine sulphate, isoprenaline hydrochloride, lysenyl, morphine sulphate, noradrenaline hydrochloride, procaine hydrochloride, trimecaine hydrochloride (Spofa), ATP: adenosine-5’-triphosphate (Reanal), adenosine deaminase, neurotensin, D-Pro2,D-Lys2-SP, SP: substance P (Sigma), adenosine purum (Loba Chemie), bradykinin triacetate
(Fluka), D-Arg, D-Trp, Leu, (Bachem Feinchemikalien), des-arg-bradykinin, GABA: 7-aminobutyric acid (Serva), diprydamol (Germab), D-Pro, D-Phe, D-Trp-SP (Inst. Biomed. Res. Univ. Texas, Austin), capsaicin (Merck), chymotrypsin (Medika), guanethidine sulphate, phentolamine hydrochloride (Ciba), HC-3: hemicholinium-3 (EGA Chemie), histamine hydrochloride (Merck), 5-HT: serotonin creatinine sulphate (Calbiochem), propranolol hydrochloride (Galenika), TTX: tetrodotoxin (Sankyo), VIP: vasoactive intestinal polypeptide (PRF, Osaka), BK-141: N-[2-(1-methoxymethyl)-2-(2-propoxyphenyl-carbamoyloxy)-ethyl]-pyrrolidium oxalate, heptacaine: N-[2-(2-heptyloxyphenylcarbamoyloxy)-ethyl]-piperidinium chloride (Faculty of Pharmacy, Comenius University, Bratislava). D-600 hydrochloride (Knoll AG), sodium nitroprusside (Lachema), verapamil hydrochloride (Läiketehdas Orion).

**RESULTS**

**Basic features of excitatory and inhibitory NANC responses**

In the course of pre- or postsynaptic blockade of adrenergic (10 μmol/l guanethidine or 0.5 μmol/l phentolamine and 3 μmol/l propranolol) and cholinergic (0.5 mmol/l hemicholinium-3 or 1-2 μmol/l atropine) transmission, transmural stimulation of

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**Fig. 1.** Mechanical and membrane potential changes elicited by stimulation of intramural NANC nerves of the guinea-pig intestine. Atropine (1 μmol/l) and guanethidine (10 μmol/l) were included in the Krebs solution for at least 20 min. A, longitudinal muscle of the ileum (a, b, d, e) and colon (c); B, circular muscle of the ileum (a, b). PR, primary relaxation; PC, primary contraction; RC, rebound contraction; RR, rebound relaxation; AH, after hyperpolarization; RD, rebound depolarization; e.j.p., excitatory junction potential; i.j.p., inhibitory junction potential. Frequency of stimulation, number of applied pulses and calibrations are given.
the guinea-pig small and large intestine or field stimulation of their myenteric plexus - longitudinal muscle strips with single pulse or trains of pulses induced a complex NANC response. This was composed of an initial relaxation (primary relaxation, PR) upon which at the frequencies higher than 2 Hz (train duration 5-10 s), contraction (primary contraction, PC) appeared. To elicit an e-NANC response in the whole intestine higher frequencies of stimulation were necessary than for the i-NANC one. The relationship between amplitude of both components of the primary response depended on the spontaneous tension of the preparations. At the basal tension of the longitudinal muscles of small intestine the NANC PC was predominant even at the low frequency stimulation (2 Hz for 10 s). In the large intestine and circular muscle layers the NANC PC was apparent only at high stimulation frequencies (20-30 Hz for 10 s). On termination of NANC nerve stimulation the smooth muscle generated rebound contraction (RC) either with or without a preceding transient relaxation (rebound relaxation, RR) (Fig. 1). If the basal tension of longitudinal muscles was increased by histamine (1 μmol/l, Fig. 5), KCl (50 mmol/l, n=5), ouabaine (10 μmol/l, n=7) or by potassium-free solution (n=4), the amplitudes of NANC PR and RR, if present, were enlarged and dominated above PC and RC. Correspondingly, stimulation of the NANC nerves in longitudinal smooth muscle cells of the guinea-pig ileum and the strips of taenia caecii evoked membrane hyperpolarization (i.j.p.), depolarization (e.j.p.) or both. At high stimulus strength the NANC membrane responses were followed by a poststimulus hyperpolarization (after hyperpolarization, AH) and rebound depolarization (RD) accompanied by spike discharge (Fig. 1). The amplitude of the NANC mechanical and membrane responses was dependent also on the intensity of stimulation, pulse duration and number of applied pulses as we showed...
Neurotransmission in intestines

TABLE I

Cross desensitization between the NANC response and putative NANC transmitters in the gut

<table>
<thead>
<tr>
<th></th>
<th>NANC</th>
<th>ATP</th>
<th>VIP</th>
<th>SP</th>
<th>BK</th>
<th>5-HT</th>
<th>NT</th>
<th>GABA</th>
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<tr>
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<td>no</td>
<td>no</td>
<td>yes</td>
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<tr>
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<tr>
<td>SP</td>
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<tr>
<td>BK</td>
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<td>n.t.</td>
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<tr>
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<td>n.t.</td>
<td>partial</td>
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earlier (Bauer et al. 1982a, Bauer and Kuriyama 1982a). There were quantitative differences in the distribution of NANC inhibitory and excitatory inputs among different regions of the intestine. The excitatory inputs were predominant in the terminal part of the ileum and the inhibitory ones in the colon and taenia caeci.

Stimulation of NANC nerves (0.1 - 20 Hz for 10 s) in the rat small intestine rapidly inhibited its spontaneous rhythmic activity and decreased its basal tension. In the rat tissue even prolongation of the NANC nerve stimulation (from 10 to 20 s) at high frequency (30 Hz) failed to evoke any primary excitatory response (n=25).

As indicative of the neuronal origin of NANC responses, they were abolished by tetrodotoxin (0.3 - 1 µmol/l)(Bauer and Kuriyama 1982a, Bauer and Matušák 1986) and by substitution of [Na⁺]₀ by sucrose, while the action of KCl (50 mmol/l) (Fig. 2), and isoprenaline (1 µmol/l, n=4) remained unaffected. The local anesthetics in concentrations which block conduction of nerve impulses, procaaine (2 mmol/l; n=9), trimecaine (1 mmol/l; n=7), heptacaine (0.5 mmol/l; n=9), BK-141 (0.1 mmol/l; n=7), abolished also the NANC responses. In 10-50 times lower concentrations than given above, however, they reduced the NANC PC (by 80-100%) and correspondingly enhanced the amplitude of the NANC PR (at least 7 trials with each). Attenuation of the NANC PC by 84 ± 9%, and RC 39 ± 7% (n=8) due to reduction of the extracellular concentration of Ca²⁺ from 2.7 to 0.3 mmol/l along with marginal enhancement of PR (by 13 ± 9%, n=8) and higher sensitivity of NANC contractile than relaxatory responses to the action of Ca²⁺ channel blockers (verapamil, D-600, sodium nitroprusside; 0.1-10 µmol/l, n=7) suggest higher requirements of [Ca²⁺]₀ for the e-NANC than i-NANC responses.

Putative NANC transmitters

A number of putative neuromediators were localized to the intestine and believed to function as NANC neurotransmitters. Some of them (ATP, 5-HT, GABA, NO, SP, bradykinin, VIP, somatostatin, neurotensin) were analyzed also in our study. As demonstrated earlier (Bauer and Kuriyama 1982b, Matušák and Bauer 1986a) ATP, 5-HT, SP and to a small extent GABA act, at least in part, independently of the intramural cholinergic and adrenergic neurons, since they affect directly the muscle tension and membrane potential.

Desensitization of the intestine to ATP, VIP, SP, bradykinin, 5-HT, neurotensin, GABA and the endogenous excitatory NANC transmitter is rather selective since the tissues rendered insensitive to these substances remained sensitive to histamine or isoprenaline. Analysis of cross desensitization between the endogenous e-NANC mediator and the above mentioned potential neurotransmitters (Table I) showed that SP, bradykinin, and 5-HT may be considered for the role of an e-NANC transmitter in the intestine. Against the transmitter role of bradykinin speak the facts that desensitization to
Fig. 3. Effects of SPA\textsubscript{A}; [D-Pro\textsuperscript{2}, D-Trp\textsuperscript{7,9}-SP] (lower traces) on the NANC responses of the guinea-pig ileum longitudinal muscle - myenteric plexus (control response - upper traces) to single stimuli (•) and field stimulation at the frequency of 4, 8 and 20 Hz for 10 s. The inserts are e.j.p.s elicited by the given number of pulses at 20 Hz stimulation frequency. Atropine (1 \textmu mol/l) and guanethidine (10 \textmu mol/l) were included in the Krebs solution for at least 20 min.

Fig. 4. Effects of two chymotrypsin (CTr) concentrations on the NANC responses of the guinea-pig duodenum to single stimuli (•) and transmural nerve stimulation at the frequency of 4 and 20 Hz for 10 s. Atropine (1 \textmu mol/l) and guanethidine (10 \textmu mol/l) were included in the Krebs solution for at least 20 min.
the endogenous NANC transmitter did not affect the action of bradykinin and NANC e.j.p. and i.j.p. remained unaffected on repolarization of the membrane to the initial level in the presence of bradykinin (Bauer and Kuriyama 1982b). The bradykinin antagonist des-arg<sup>9</sup>-bradykinin did not affect the NANC responses in the guinea-pig intestine (Matušák and Bauer 1986a). Although there was a partial cross desensitization between the 5-HT and e-NANC transmitter, lysenyl, a 5-HT receptor subtype unspecific antagonist (1-10 μmol/l, n=9), did not influence NANC contractions. Reduction of the e-NANC responses in the presence of histamine was suggested to result from its action on sensoric nerve fibres (Matušák and Bauer 1986b). Since the H<sub>1</sub>- and H<sub>2</sub>-antagonists mepyramine and cimetidine (0.1-10 μmol/l, n=5) did not influence the PC, participation of histamine on the e-NANC transmission might be excluded.

SP present in the sensory neurons and ubiquitously distributed in the body might participate in the e-NANC responses both in the presence and absence of histamine or capsaicin in bathing fluid. To verify participation of SP in the e-NANC responses of intestinal smooth muscles the e-NANC responses were analyzed also in the presence of SP antagonists (0.1-10 μmol/l of D-Pro<sup>2</sup>, D-Trp<sup>7,9</sup>-SP, (Fig. 3), (D-Pro<sup>2</sup>, D-Phe<sup>7</sup>, D-Trp<sup>9</sup>-SP and D-Arg<sup>1</sup>, D-Trp<sup>7,9</sup>, Leu<sup>11</sup>-SP, n=5-9). They attenuated the e.j.p.s and the spike generation superimposed on the e.j.p.s. Consequently the NANC PC was reduced with the same concentration dependent patterns as the contractions elicited by exogenous SP (1 nmol/l). In accordance with this the NANC PR was augmented and the posttetanic inhibition reduced. Effects of the peptidase inhibitor by bacitracin and of the activator prednisolon on NANC PC (Bauer 1988) and its reduction by chymotrypsin (0.04-0.8

![Fig. 5. Effects of two N-omega-nitro-L-arginine methylester (L-NONAME) concentrations on the NANC responses of the histamine (Hi, 1 μmol/l) precontracted longitudinal muscle-myenteric plexus of the guinea-pig proximal ileum to single stimuli and field stimulation at the frequency of 2, 8 and 20 Hz for 10s. Atropine (Atr, 1 μmol/l) and guanethidine (Gu, 10 μmol/l) were included in the Krebs solution for at least 20 min. The inserts are; j.p.s elicited by single pulse.](image)
mg/ml) (Fig. 4) are in support of the peptidergic nature of the NANC excitation.

Somatostatin was also suggested to be an NANC transmitter. Cysteamine (0.5-2 μmol/l) which affects somatostatin release did not influence \( n=12 \) the NANC PR and as we found in the case of other substances (ATP, VIP, neurotensin, bradykinin) earlier (Bauer and Kuriyama 1982b, Bauer and Matušák 1986, Matušák and Bauer 1986a) and in the present experiments, neither of them fulfill the criteria for an i-NANC transmitter.

Recently accumulating evidence suggests that NO should play the role of an inhibitory transmitter in different tissues. To study nitric oxide (NO) as a potential inhibitory NANC transmitter in the intestine we used NO synthase inhibitors (10-100 μmol/l of N-omega-nitro-L-arginine methylester and \( N^G \)-monomethyl- L-arginine). They had no effect on histamine induced elevation of the basal tension and on isoprenaline induced smooth muscle relaxation, failed to affect RC and RR \( n=5-15 \) but reduced the amplitude of the i.j.p.s as well as of the PR and unmasked the PC even under histamine induced elevation of muscle tension (Fig. 5). The effect of NO synthase inhibitors was more pronounced at high than at low frequencies of stimulation.

Modulation of NANC transmission

The NANC presynaptic mechanisms may be facilitated or attenuated. Thus high concentrations of \( Mg^{2+} \) (12 mmol/l), which reduce transmitter release, reduce the NANC e.j.p. and i.j.p. (Bauer and Kuriyama 1982a), 3,4-diaminopyridine (0.1-1 mmol/l), which potentiates transmitter release and antagonizes the presynaptic inhibitory modulation (Bauer 1985), augments the NANC PR, PC and RC (Bauer and Matušák 1986). From the other substances studied, noradrenaline (0.1-10 μmol/l), ATP (0.01-0.5 mmol/l), adenosine (1-100 μmol/l)

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**Fig. 6. Effect of in vivo reserpine and 6-hydroxydopamine (6-OHDA) pretreatment on the NANC responses of histamine precontracted guinea-pig proximal ileum to transmural nerve stimulation in vitro.** At each frequency (0.1, 4, 8 and 20 Hz, for 10 s) responses of the control, reserpine and 6-OHDA pretreated tissues are shown. PR, primary relaxation, PC, primary contraction and RC, rebound contraction.
Fig. 7. Effects of dipyridamol (Dip) on the NANC responses of guinea-pig proximal ileum to single stimuli (♂) and transmural nerve stimulation at the frequency of 4 and 20 Hz for 10 s. Control response (upper trace), administration of Dip (middle trace) and response in the presence of Dip for 15 min (lower trace). Atropine (Atr, 1 μmol/l) and guanethidine (Gu, 10 μmol/l) were included in the Krebs solution for at least 20 min.

Fig. 8. Effects of adenosine deaminase (ADA) on the NANC responses of guinea-pig proximal ileum to single stimuli (♂) and transmural nerve stimulation at the frequency of 4, 8 and 20 Hz for 10 s. Control response (upper trace), responses in the presence of ADA for 15 min (lower trace). Atropine (Atr, 1 μmol/l) and guanethidine (Gu, 10 μmol/l) were included in the Krebs solution for at least 20 min.
(Bauer et al. 1982a, Bauer and Matušák 1986, Matušák and Bauer 1986a), as well as morphine (1 μmol/l, n=7), H₂O₂ (0.02-0.2 mmol/l, n=15) and Fe²⁺/ascorbic acid (10 μmol/l, n=14) in the present experiments, reduced more effectively the NANC excitatory responses (by 60-100%) than the inhibitory ones (by 5-25%).

Depletion of catecholamines and probably also ATP from the presynaptic nerve terminals by reserpine (5 mg/kg, i.p.) or 6-hydroxydopamine (250 mg/kg, i.p.) pretreatment resulted in significant enhancement of NANC PC on basal tension and of both PR and PC on elevated basal tension (Fig. 6). Enhancement of adenosine local concentration by dipyridamol (0.1-1 μmol/l) and its reduction by adenosine deaminase (1-4 mg/ml) significantly reduced and enhanced the NANC PR and PC, respectively (Figs 7 and 8). In accordance with this dipyridamol enhanced and adenosine deaminase reduced the NANC posttetanic inhibition as well.

DISCUSSION

The first suggestion on the existence of an NANC inhibitory component in the vagal innervation of the stomach and esophagus was reported at the end of the last century (Langley 1898). Since the beginning of sixties when evidence in favor of NANC inhibitory and excitatory pathways in the intestine was given (Burnstock et al. 1963, Kosterlitz and Watt 1963), extensive studies of NANC transmission in different tissues were carried out (see reviews Burnstock 1979, 1985, Krell et al. 1981, Bauer and Matušák 1986, Hansen et al. 1986, Kubota et al. 1988, Stretton 1991).

At present the existence of NANC innervation of the small and large intestine of different animal species, in addition to their adrenergic and cholinergic innervation, seems to be generally accepted. Their mutual interactions, and pre- and postsynaptic modulatory processes may play an important role in physiological regulations and pathophysiology of the intestinal motility. The neuronal origin of the excitatory and inhibitory NANC responses of the intestine is beyond dispute, because they are fully prevented by TTX or reduction of the extracellular Na⁺, while these procedures do not affect the contraction or relaxation of the intestinal smooth muscles elicited by direct action of drugs. The dominance of the e-NANC or i-NANC primary mechanical response depends on the level of the spontaneous muscle tension. Their relationship is accordingly changed by pharmacological modifications of muscle tension, thus the primary mechanical NANC responses might be clearly differentiated. In contrast to the i-NANC innervation, the distribution of the e-NANC innervation is not homogenous. It is most pronounced close to the guinea-pig ileocecal valve and is reduced in direction to the duodenum. Moreover, it is smaller in the large than in the small intestine of the guinea-pig. In the small and large intestine of the rat we were unable to detect NANC excitation.

The different stimulation threshold, frequency dependence and distribution suggest that excitatory and inhibitory NANC responses are due to activation of nerve fibers possessing various features. Their differences are expressed also in their sensitivity to the reduction of [Ca²⁺]₀ and in the action of local anesthetics and Ca²⁺ channel blockers.

While Mg²⁺ and 3,4-diaminopyridine affect the excitatory and inhibitory NANC responses to the same degree, endogenous and exogenous catecholamines, purines, reactive oxygen species and opioids reduce more intensively the excitatory than the i-NANC responses, suggesting that they are due to activation of distinct nerve fibers.

In the gut a number of candidates have been postulated as putative neurotransmitters of NANC responses, including peptides and substances of non-peptidergic nature. Desensitization of the intestine to ATP, 5-HT, histamine, SP, bradykinin, GABA, VIP, neurotensin (Lembeck and Fischer 1967, Weston 1973, Costa and Furness 1979, Krantis et al. 1980, Butler et al. 1981,), and prolonged stimulation of the e-NANC nerves seem to be rather selective. Cross desensitization between the exogenous potenital neurotransmitters and the endogenous e-NANC mediator suggests that SP and partially histamine, 5-HT and bradykinin might be
Fig. 9. Adrenergic, cholinergic, NANC excitatory and inhibitory and sensoric nerves with stored and released neurotransmitters, which act on receptors present on the gut smooth muscles and on nerve varicosities. Activation of these receptors leads to a number of physiological responses, such as contraction and relaxation of the gut smooth muscles, maintenance of the basal tension and peristalsis. s.m., smooth muscle; receptors (P, purinergic; αβ, adrenergic; PG, prostaglandin; M, muscarinic; Pept, peptidergic; H, histaminergic; NO, nitric oxide); proposed transmitters (ATP, adenosine 5'-triphosphate; NA, noradrenaline; PGs, prostanoids; ACh, acetylcholine; VIP, vasoactive intestinal polypeptide; PHM, peptide histidine methionine; PHI, peptide histidine isoleucine; ENK, enkephalines; Hist, histamine; Sp, substance P; NK, neurokinines; NO, nitric oxide); n.v., nerve varicosities.

real candidates of the e-NANC transmitter. Specific receptors for these substances and their currently avaible antagonists, except those of SP, failed to affect significantly the NANC responses. SP is very potent in depolarizing longitudinal muscle cells (Bauer and Kuriyama 1982b) and contracting the longitudinal muscle of different segments of the guinea-pig intestine. Dense SP innervation of the intestinal smooth muscle (Franco et al. 1979), similarity in the action of SP and the e-NANC transmitter on membrane potential and muscle tension, cross desensitization, inhibition of the NANC PC by chymotrypsin, prednisolone and the action of SP antagonists as well as their augmentation by bacitracin support the proposed role of SP as an excitatory neuromediator in the guinea-pig intestine. SP originates in part from the sensoric C-fibers affected by histamine and capsaicin and in part from the actual excitatory NANC nerves. The subtype of the NK-receptors involved in the NANC excitation has not been characterized yet.

The nature of the NANC inhibitory transmitter remained controversial for a long time. As shown earlier (Bauer et al. 1982a, Bauer and Kuriyama 1982b, Bauer and Matušák 1986) as well as in the present paper, ATP, VIP, GABA, bradykinin, somatostatin and neurotensin did not fullfil the criteria of an NANC inhibitory transmitter. Attention has been drawn recently to the possible role of NO as a putative i-NANC transmitter in a number of tissues (Bult et al. 1990, Osthaus and Galligan 1992, Ward et al. 1992). Bredt et al. (1990) and Sanders and Ward (1992) showed that NO synthase, an enzyme which forms NO from L-arginine, is present also in the neuronal tissue and gut. Marked reduction of the NANC inhibitory responses, mainly those elicited
by high frequency stimulation, by compounds which act as inhibitors of NO synthase suggests that NO mediates NANC relaxation. The remaining portion of the inhibitory NANC response elicited by low frequency stimulation suggests that in addition to NO some other neurotransmitter (neuropeptide?) might also been released from the NANC inhibitory nerves of the intestine (Fig. 9). Our previous studies (Bauer et al. 1982b) demonstrated that prostaglandins do not participate in the generation of RC. Since NO synthase inhibitors did not affect the amplitude of RC and RR the present results do not support the proposed (Ward et al. 1992) involvement of NO in these poststimulus responses.

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Neurotransmission in intestines


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