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Properties of the inhibitory junction potential in smooth muscle of the guinea-pig gastric fundus

Naotomo Ohno, Lin Xue, Yoshimichi Yamamoto & [1]Hikaru Suzuki

Department of Physiology, Nagoya City University Medical School, Mizuho-ku, Nagoya 467, Japan

1 In circular smooth muscle of the guinea-pig gastric fundus, transmural nerve stimulation evoked a cholinergic excitatory junction potential (e.j.p.), and blockade of the e.j.p. by atropine revealed a non-adrenergic non-cholinergic (NANC) inhibitory junction potential (i.j.p.).

2 The amplitude of the e.j.p. was increased by apamin, suramin or N^Gnitro-L-arginine (L-NOARG), with no significant change in the membrane potential.

3 The i.j.p. consisted of two components (fast and slow); apamin inhibited the former, nitroarginine inhibited the latter, and suramin inhibited both components.

4 Apamin inhibited the hyperpolarization produced by adenosine 5'-triphosphate (ATP) but not by vasoactive intestinal polypeptide (VIP). Suramin inhibited the hyperpolarization produced by VIP but not by ATP. The sodium nitroprusside (SNP)-induced hyperpolarization was not blocked by apamin or suramin. L-NOARG or tetrodotoxin did not inhibit the hyperpolarization produced by ATP, VIP or SNP.

5 The data did not support the hypothesis that ATP, VIP or nitric oxide (NO) is the main transmitter responsible for generation of the NANC i.j.p. in the fundus.

6 Actions of L-NOARG suggest that endogenous NO may be involved in junctional transmission, mainly as an inhibitory modulator of cholinergic transmission.

Keywords: Smooth muscle; stomach; membrane potential; inhibitory junction potential; adenosine 5'-triphosphate; vasoactive intestinal polypeptide; nitric oxide; acetylcholine; prejunctional regulation

Introduction

The changes in membrane potential of gastrointestinal smooth muscle in response to transmural nerve stimulation consist of a complex mixture of excitatory and inhibitory potentials (Hoyle & Burnstock, 1989). The two potentials are likely to be generated by separate substances, since they show different electrical properties and sensitivities to pharmacological blocking drugs. The excitatory junction potential (e.j.p.) generated in the smooth muscle of most regions of the gastro-intestinal tract is sensitive to atropine, and thus this potential is likely to be generated by acetylcholine (ACh) (Hoyle & Burnstock, 1989). In the guinea-pig small intestine, an e.j.p. with two components (one fast and the other of slow time course) is generated by nerve stimulation. These are likely to be produced by ACh and substance P respectively, based on evidence that atropine inhibits the former, while desensitization with substance P inhibits the latter (Bywater & Taylor, 1986).

Inhibitory junction potentials (i.j.ps) are also present in many types of gastrointestinal smooth muscles, and most are non-adrenergic non-cholinergic (NANC) in nature. The candidate transmitter substances responsible involve adenosine 5'-triphosphate (ATP), vasoactive intestinal polypeptide (VIP), or nitric oxide (NO) (Hoyle & Burnstock, 1989; Sanders & Ward, 1992). In the guinea-pig small intestine, an i.j.p. with two components (fast and slow) has been identified (Niel *et al.*, 1983; Bywater & Taylor, 1986). It has been proposed that the fast component is generated by ATP and the slow component by NO; the latter is proposed to be generated in the tissue (site unknown) by neurally released VIP (Grider & Makhlouf, 1988; Crist *et al.*, 1992; He & Goyal, 1993; Makhlouf & Grider, 1993). These two components of i.j.p. are also noted in the guinea-pig taenia coli, but the slow component may be generated by an unidentified substance, since the potential is insensitive to NO synthase inhibitor (Bridgewater *et al.*, 1995).

Junction potentials evoked in gastric smooth muscle differ between species and also between regions in the stomach. In circular muscle of the guinea-pig stomach, the cholinergic e.j.p. is generated in muscle from the fundus, whereas the NANC i.j.p. is generated in muscle from the antrum and atropinized fundus (Komori & Suzuki, 1986). Although the NANC i.j.p. is reportedly generated by substances other than ATP (Frew & Lundy, 1982; Daniel *et al.*, 1983), the inhibition by a selective ATP-receptor antagonist, suramin (Inoue & Nakazawa, 1993) of the i.j.p. (Ohno *et al.*, 1993) may indicate an involvement of ATP. However, potent inhibition of the NANC i.j.p. by drugs which inhibit the synthesis of NO, such as N^G-nitro-L-arginine (L-NOARG) or N^G-nitro-L-arginine methylester (L-NAME) (Moncada *et al.*, 1991), suggests an important role of NO in the generation of the i.j.p. (Dalziel *et al.*, 1991; Sanders & Ward, 1992; Makhlouf & Grider, 1993). Contribution of NO to the generation of the i.j.p. has also been suggested for opossum oesophageal muscle (Du *et al.*, 1990; Chrisinck *et al.*, 1991; Tottrup *et al.*, 1991). VIP has been proposed as the transmitter of NANC inhibitory nerves in the rat stomach, because the electrical and mechanical responses elicited by nerve stimulation are similar to those produced by exogenously applied VIP (Ito *et al.*, 1990). Interestingly, Kitamura *et al.* (1993) using a different technique (electrophysiology) on the same tissue preparation (rat stomach), found a similarity in the properties of hyperpolarization underlying the i.j.p. and that produced by S-nitrocysteine, suggesting an involvement of nitro-compounds in the generation of the NANC i.j.p.

We examined the effects of inhibitors of the i.j.p. (particularly, apamin, suramin and L-NOARG) on hyperpolarizations produced by ATP, VIP or sodium nitroprusside (SNP) in smooth muscle of the guinea-pig fundus to investigate putative neurotransmitter(s) underlying the generation of NANC i.j.ps.

[1] Author for correspondence.

Our results showed that ATP, VIP and NO could not mimic the NANC i.j.p. in the fundus. However, NO appears to be produced during transmural nerve stimulation causing a slow hyperpolarization of the membrane and an inhibitory modulation of cholinergic transmission.

Methods

Albino guinea-pigs (male, weighing 200–250 g) were stunned and bled. The fundus region of the stomach was excised and opened by cutting the small curvature. The mucosal layer of the stomach was removed by scissors, in the Krebs solution. Circular muscle strips of 1.0–1.5 mm width and about 1.0 cm long were mounted on a rubber plate fixed at the bottom of the recording chamber (8 mm width, 3 cm long, 8 mm depth), with the mucosal layer upside, and immobilized with fine pins. The tissues were superfused with oxygenated warm (35°C) Krebs solution, at a constant flow rate of about 3 ml min^{-1}. The depth of the superfusate was kept at about 1 mm, so that the volume of the solution in the recording chamber was less than 1 ml.

Glass capillary microelectrodes were prepared from borosilicate glass tubing with glass filament inside (tube outer diameter, 1.2 mm, Hilgenberg, Germany), and filled with 3 M KCl (tip resistance, 40–80 MΩ). Transmural stimulation of the intramural nerves was achieved with a silver wire (diameter, 0.3 mm) coated with enamel, except at the tip, and located to just touch the tissue, and a second electrode (silver plate) placed in the bath (i.e., the point stimulating method). Brief current pulses (0.05–0.1 ms duration, 10–50 V intensity) were applied to the stimulating electrodes, by an electric stimulator (SEN-3303, Nihon Kohden, Japan).

The ionic composition of the Krebs solution was as follows (in mM): Na^+ 137.4, K^+ 5.9, Mg^{2+} 1.2, Ca^{2+} 2.5, HCO_3^- 15.5, $H_2PO_4^-$ 1.2, Cl^- 134 and glucose 11.5. The solution was aerated with O_2 containing 5% CO_2, and pH of the solution was about 7.3 throughout.

Drugs used were atropine sulphate, acetylcholine chloride (ACh), adenosine 1,4,5-triphosphate disodium salt (ATP), Na-nitroprusside (SNP), N^G-nitro-L-arginine (L-NOARG), tetrodotoxin (TTX), apamin (all from Sigma, St. Louise, MO, U.S.A.), vasoactive intestinal polypeptide (VIP, Peptide Institute, Osaka, Japan) and suramin (Behlinger, Germany).

The observed values were expressed as the mean ± standard deviation (s.d.). Statistical significances of the values were tested by Student's paired and unpaired t tests. Differences in potency of drugs on the enhancement of the e.j.p. were estimated by Mann-Whitney's U-test. In both cases probabilities of less than 5% ($P<0.05$) were considered significant.

Results

Electrophysiological properties of junction potentials

In circular smooth muscle of the guinea-pig fundus, the membrane potential ranged between −45 and −50 mV, and was either quiescent or spontaneously active with slow waves of small amplitude (up to 5 mV). Application of transmural electrical stimulation with a brief pulse generated a cholinergic excitatory junction potential (e.j.p.), and in the presence of atropine, a non-adrenergic non-cholinergic (NANC) inhibitory junction potential (i.j.p.) was observed. These properties of smooth muscle of the fundus agree with those reported by Komori & Suzuki (1986).

Figure 1 shows the effects of suramin on junction potentials recorded in a muscle from the fundus. The cell shown in Figure 1a generated slow waves with 3–4 mV in amplitude and application of transmural stimulation elicited an e.j.p. which was followed by a slow wave. In the presence of 10^{-4}M suramin, the amplitude of the e.j.p. was doubled (Figure 1b), with no significant change in the resting membrane potential (control, −49.5±2.2 mV, $n=15$; in suramin, −49.2±2.0 mV, $n=12$). In the presence of atropine (10^{-6} M), transmural stimulation elicited an i.j.p. which consisted of a fast and slow component (Figure 1c). Amplitude of both components of the i.j.p. increased in an intensity-dependent manner, and when stimuli with supramaximal intensity (50 V) were applied, the fast component of the i.j.p. ranged in amplitude between 3–10 mV (mean value, 6.0±1.2 mV, $n=22$), and reached a peak in 300–400 ms (mean value, 355±31 ms, $n=22$). The slow component was detectable at 700–800 ms (mean value, 755±51 ms, $n=22$) at the decay phase of the fast component of the i.j.p. (shown by arrow-head in Figure 1c). The amplitude of the slow component measured at the arrow-head in Figure 1c ranged from 1 to 5 mV (mean value, 2.4±0.8 mV, $n=22$). This component of the i.j.p. terminated at 3–7 s after the stimulation (mean value, 4.2±1.4 s, $n=22$). Suramin (10^{-4} M) reduced the amplitude of both components of the i.j.p., with no significant effects on the membrane potential (in atropine −49.5±2.1 mV, $n=16$; atropine + suramin, −49.2±1.8 mV, $n=10$) and slow waves (control, 3.8±0.8 mV, $n=12$; in suramin, 3.5±0.7 mV, $n=10$).

The effects of 10^{-4} M L-NOARG on junction potentials are shown in Figure 2. L-NOARG increased the amplitude of the

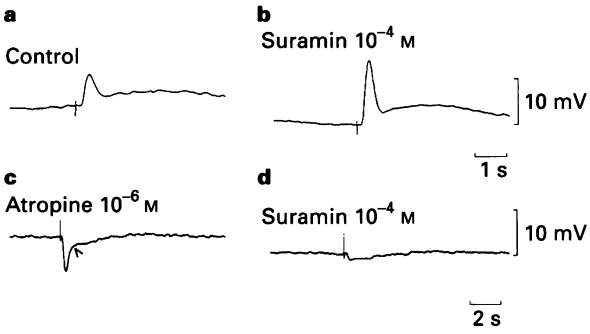

Figure 1 Effects of suramin on the e.j.p. (a and b) and i.j.p. (c and d) evoked in smooth muscle cells of the guinea-pig stomach fundus. Stimuli: (a and b) 10 V intensity, 0.05 ms duration; (c and d) 14.1 V intensity, 0.05 ms duration. (c) and (d) were recorded in the presence of 10^{-6} M atropine; (b) and (d) were recorded after application of suramin (10^{-4} M) for 16 and 18 min, respectively. (a–b) and (c–d) were recorded in single cells from different tissues. Amplitude of junction potentials: (a) 7.1±1.8 mV ($n=7$); (b) in the presence of suramin for 12–25 min, 13.8±2.1 mV ($n=6$); (c) 6.1±1.2 mV ($n=7$); (d) in the presence of suramin for 15–28 min, 0.8±0.5 mV ($n=7$).

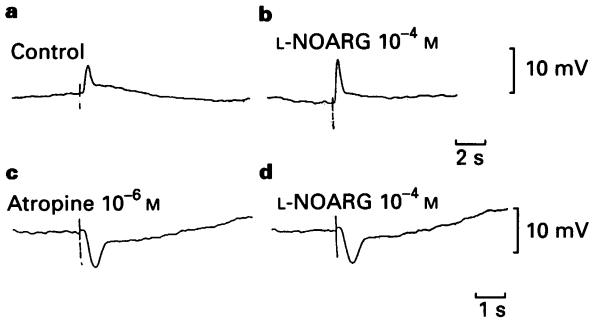

Figure 2 Effects of L-NOARG on junction potentials evoked in circular muscle of the guinea-pig fundus. The e.j.p. and i.j.p. were evoked before (a and c) and after application of 10^{-4} M L-NOARG for over 10 min (b and d), respectively. Atropine (10^{-6} M) was present in (c) and (d). Transmural nerve stimulation (0.05 ms duration, 50 V intensity, two pulses at 25 Hz frequency) was applied every 1 or 1.5 min. (a – b) and (c – d) were recorded from single cells in different tissues. Amplitude of junction potentials: (a) 6.6±1.5 mV ($n=8$); (b) 10.2±1.8 mV ($n=6$); (c) 8.0±1.6 mV ($n=9$); (d) 7.8±1.9 mV ($n=11$).

e.j.p., with no change in either the membrane potential (control, -49.8 ± 1.5 mV, $n=17$; in the presence of L-NOARG, -49.0 ± 2.5 mV, $n=12$) or amplitude of slow waves (control, 3.5 ± 0.6 mV, $n=10$; in L-NOARG, 3.6 ± 0.8 mV, $n=14$) (Figure 2a and b). In the presence of 10^{-6} M atropine (Figure 2c and d), L-NOARG reduced the amplitude of the slow component of the i.j.p. (control, 2.8 ± 0.8 mV, $n=5$; in nitroarginine, 1.5 ± 1.0 mV, $n=6$, $P<0.05$), with no significant change in the amplitude of the fast component of the i.j.p. (control, 8.0 ± 1.6 mV, $n=9$; in nitroarginine, 7.8 ± 1.9 mV, $n=11$, $P>0.1$).

The effects of apamin, suramin and L-NOARG on the amplitude of the e.j.p. and fast component of the i.j.p. obtained from 5–12 tissues are summarized in Figure 3. Both apamin and suramin caused an apparent increase in the amplitude of the e.j.p. (10^{-4} M suramin > 10^{-7} M apamin = 10^{-5} M suramin). These drugs reduced the amplitude of the fast component of the i.j.p. to a similar extent (10^{-7} M apamin = 10^{-4} M suramin), suggesting the possibility that the i.j.p. (and not the e.j.p.) was their primary site of action. However, L-NOARG increased the amplitude of the e.j.p., with no change in the i.j.p. amplitude. The e.j.p. was enhanced by L-NOARG (10^{-5} M) and suramin (10^{-4} M) to a similar extent, and apamin was less potent than these drugs.

The inhibitory actions of apamin and suramin on the i.j.p. were examined further in quiescent muscles from the atropinized fundus. As shown in Figure 4a and b, apamin inhibited only the fast component, with no significant change in the amplitude of slow component. Additional application of 10^{-5} M L-NOARG greatly reduced the slow component of the i.j.p. (Figure 4c). The effects of apamin and suramin on junction potentials tested in another 8 tissues were similar for all cases. In separate experiments, application of L-NOARG inhibited the slow component alone, and the remaining fast component was inhibited by additional application of apamin ($n=3$, data not shown). The slow component inhibited by L-NOARG was again generated, by addition of 10^{-3} M L-arginine for over 15 min ($n=2$, data not shown). Application of 10^{-4} M suramin reduced both components of the i.j.p. to a similar extent (to about 12% of control, Figure 4d and e), with the remainder largely inhibited by additional application of 10^{-7} M tetrodotoxin (TTX) (Figure 4f). The effects of suramin were confirmed in 5 different tissues.

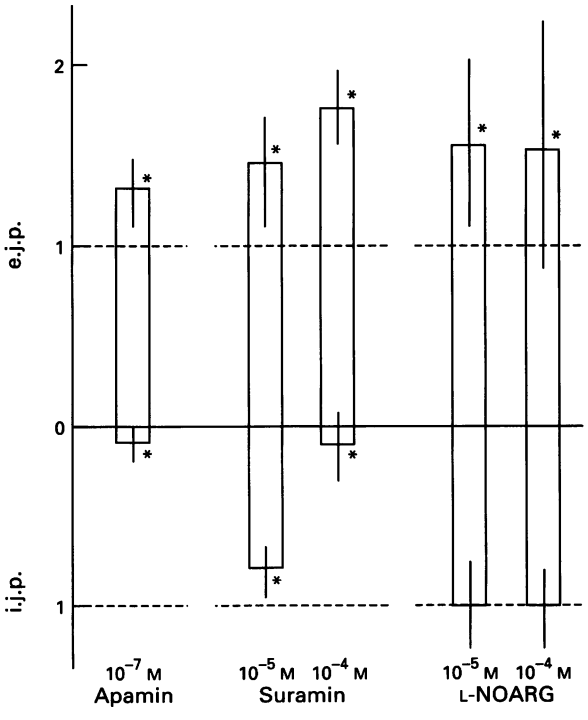

Figure 3 Summary of the effects of apamin (10^{-7} M), suramin (10^{-5} and 10^{-4} M) and L-NOARG (10^{-5} and 10^{-4} M) on junction potentials recorded from circular smooth muscles of the guinea-pig stomach fundus. The e.j.p. (upper graph) and i.j.p. (lower graph) were evoked by single or double stimuli, and their relative amplitudes were expressed by mean ± s.d. ($n=5-12$). Atropine (10^{-6} M) was present throughout. *Significant change in the paired test ($P<0.05$).

Hyperpolarization of the membrane by ATP, VIP or SNP

In muscles from the fundus, application of ATP (5×10^{-4} M), VIP (5×10^{-7} M) or SNP (10^{-5} M) hyperpolarized the membrane by about 7 mV. These hyperpolarizations were not sensitive to 3×10^{-7} M TTX (Table 1). As shown in Figure 5a and b, the hyperpolarization produced by VIP was inhibited by suramin, but curiously this was not the case for ATP (Figure 5c and d), a finding observed in 6 tissues. In the other 5 tissues, apamin inhibited the hyperpolarization produced by ATP but not by VIP.

The effects of apamin and suramin on hyperpolarization of the membrane in muscles from the fundus, in response to ATP, VIP or SNP are summarized in Figure 6. Apamin inhibited only the ATP-induced hyperpolarization, whereas suramin

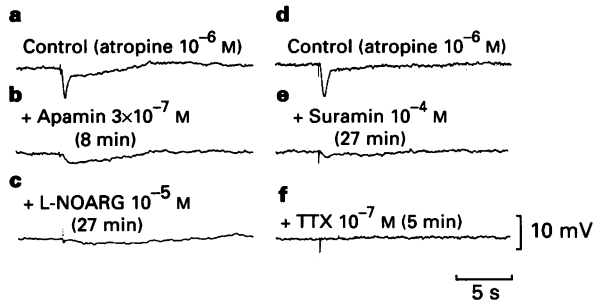

Figure 4 Effects of apamin, suramin or L-NOARG on the i.j.p. generated in circular smooth muscles of the guinea-pig stomach fundus. Atropine (10^{-6} M) was present throughout. The i.j.p. was evoked by single stimuli (0.05 ms duration, 50 V intensity), before (a) and after application of 3×10^{-7} M apamin for 8 min (b), and apamin plus 10^{-5} M L-NOARG for 27 min (c), or before (d) and after application of 10^{-4} M suramin for 27 min (e) and additional application of 10^{-7} M TTX for 5 min (f). The mean values (± s.d.) of the maximum amplitude of the hyperpolarization are shown below (n = number of observations). *Significant from the value in (a); **, significant from the value in (d).

	Fast i.j.p.	*Slow i.j.p.*
(a) Control	9.1 ± 0.5 mV ($n=15$)	2.0 ± 0.4 mV ($n=15$)
(b) Apamin	0 ± 0 mV ($n=10$)*	1.9 ± 0.4 mV ($n=10$)
(c) Nitroarginine	0 ± 0 mV ($n=8$)*	0.9 ± 0.4 mV ($n=10$)*
(d) Control	8.4 ± 0.6 mV ($n=11$)	1.6 ± 0.2 mV ($n=11$)
(e) Suramin	1.0 ± 1.0 mV ($n=11$)**	0.24 ± 0.3 mV ($n=11$)**
(f) TTX	0 ± 0 mV ($n=5$)**	0 ± 0 mV ($n=5$)**

Table 1 Effects of tetrodotoxin (TTX, 3×10^{-7} M) on membrane hyperpolarizations produced by ATP, VIP and SNP in circular smooth muscle cells of the guinea-pig fundus

	Control	*TTX*
ATP 5×10^{-4} M	6.6 ± 2.1 mV ($n=10$)	6.5 ± 2.0 mV ($n=5$)
VIP 5×10^{-7} M	7.0 ± 1.9 mV ($n=14$)	6.6 ± 1.5 mV ($n=5$)
SNP 10^{-5} M	6.3 ± 1.7 mV ($n=7$)	7.2 ± 1.2 mV ($n=5$)

Amplitude of the peak hyperpolarization was measured (mean ± s.d.).

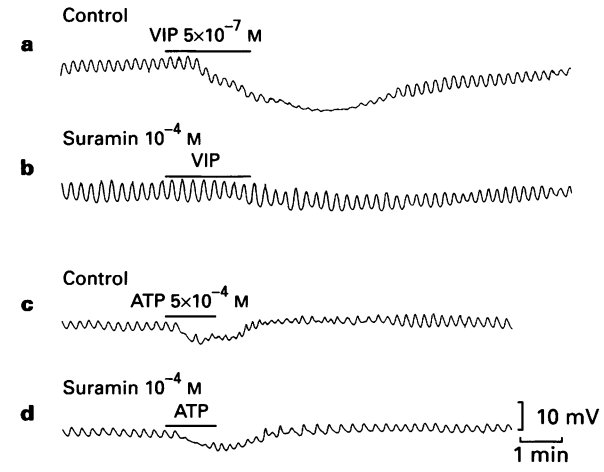

Figure 5 Effects of suramin on membrane hyperpolarizations produced by VIP or ATP in smooth muscle of the guinea-pig stomach fundus. VIP (5×10^{-7} M) was applied for 2 min before (a) and after application of 10^{-4} M suramin for 15 min (b). ATP (5×10^{-4} M) was applied for 70 s before (c) and after application of 10^{-4} M suramin for 18 min (d). a, b and c, d were recorded from different single cells in the same tissue. The membrane potential: (a – b), −48 mV; (c – d), −46 mV.

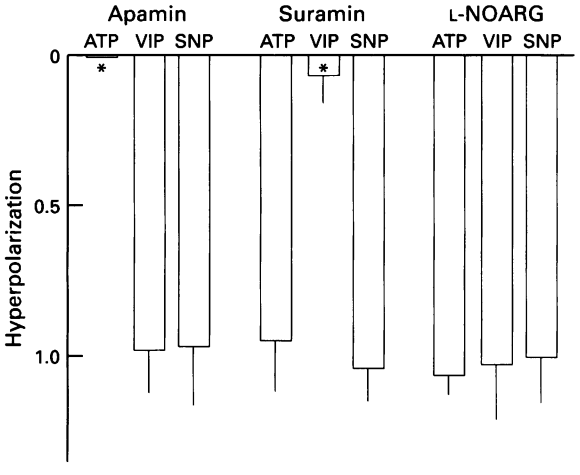

Figure 6 Summary of the effects of apamin, suramin and L-NOARG on hyperpolarizations produced by ATP (5×10^{-4} M), VIP (5×10^{-7} M) or SNP (10^{-6} M) in smooth muscle of the guinea-pig stomach fundus. Relative values are expressed by the mean ± s.d. ($n = 5-8$). *Significant inhibition.

selectively inhibited the VIP-induced hyperpolarization. The SNP-induced hyperpolarization was not inhibited by apamin or suramin. The hyperpolarizations produced by ATP, VIP or SNP were also not sensitive to L-NOARG.

Discussion

The NANC i.j.p. has been recorded in gastrointestinal smooth muscle of many laboratory animals, and the actions of many types of pharmacological agents suggest an involvement of ATP, VIP or NO in the generation of this potential (Hoyle & Burnstock, 1989; Sanders & Ward, 1992). The fast component of the i.j.p. recorded from circular muscle of the guinea-pig fundus is also generated by stimulation of NANC nerves, and this potential can be blocked by apamin (Komori & Suzuki, 1986) or suramin (Ohno *et al.*, 1993). Apamin is an inhibitor of Ca^{2+}-activated K^+-channels (Romey & Lazdunski, 1984), while suramin is an inhibitor of the ATP-receptor (Inoue & Nakazawa, 1992). Therefore, the NANC i.j.p. in the guinea-pig fundus may be generated by activation of Ca^{2+}-activated K^+-channels through stimulation of the ATP-receptor. If this is the case, the main substance responsible for generation of the fast i.j.p. is ATP, which differs from the transmitter proposed as the mediator of the i.j.p. in other animals (Frew *et al.*, 1982; Daniel *et al.*, 1983). However, the present experiments showed that the properties of the i.j.p. differ from those of the ATP-induced hyperpolarization, in that the former, but not the latter, is inhibited by suramin, confusing the interpretation that ATP is the main transmitter of the i.j.p. (traditionally suramin is used as an antagonist of ATP receptors).

In the guinea-pig small intestine, the i.j.p. consists of both fast and slow components, with the former proposed to be produced by ATP and the latter by NO produced endogenously (at sites unknown) by VIP released from nerves (Makhlouf & Grider, 1993; He & Goyal, 1993). The i.j.p. generated in the guinea-pig taenia caeci could also be separated into two components, but their slow component is insensitive to the inhibitor of NO synthase, suggesting a contribution of substances other than NO (Bridgewater *et al.*, 1995). We found that the i.j.p. generated in the atropinized fundus of the guinea-pig also consists of two components, an apamin-sensitive and insensitive component. The former component of the i.j.p. was fast in time course, this property being similar to the fast i.j.p. generated in the small intestine or taenia. The latter component was slow in time course with amplitude reduced by nitroarginine and antagonized by L-arginine. These observations are consistent with the idea that the slow component of the i.j.p. is produced by NO, as in the case of the guinea-pig small intestine (Crist *et al.*, 1992) or rat gastric fundus (Shimamura *et al.*, 1993).

Although the smooth muscle of the fundus was hyperpolarized by ATP, VIP or SNP, the properties of the resulting hyperpolarizations differed in sensitivity to apamin and suramin. Apamin inhibited only the ATP-response, whereas suramin inhibited only the VIP-induced hyperpolarization. By comparison, both apamin and suramin inhibited the fast component of the i.j.p. Thus, the results indicate that ATP, VIP or NO are not the transmitter underlying the fast component of the NANC i.j.p. in the guinea-pig stomach. In the guinea-pig taenia caeci, pituitary adenylyl cyclase activating peptide (PACAP) is considered to be involved in the NANC inhibitory transmission, since the relaxation produced by this peptide is sensitive to apamin and suramin (McConalogue *et al.*, 1995). Inhibition by suramin of the i.j.p. generated in this tissue (Den Hertog *et al.*, 1989) also supports this concept. However, the inhibition by suramin of the relaxation produced by electrical stimulation of inhibitory nerves is very weak, in comparison with that by apamin (McConalogue *et al.*, 1995). Thus, available results related to the transmitter substance of the NANC nerves are equivocal. Alternatively, it is also possible that there are different types of receptors in the subjunctional membrane which differ in their properties from the junctional receptors. This appears to be the case in the guinea-pig small intestine where distribution of two types of muscarinic receptors (intrajunctional and extrajunctional receptors) has been reported (Cousins *et al.*, 1993; 1995).

The present experiments showed that the amplitude of the e.j.p. was increased by apamin, suramin and L-NOARG. These actions of apamin or suramin are at least partly related to the reduced amplitude of the fast component of i.j.p. (Komori & Suzuki, 1986; Ohno *et al.*, 1993; Bridgewater *et al.*, 1995).However, the actions of L-NOARG on the e.j.p. seem to differ from that of apamin and suramin, in that the amplitude of the fast component of the i.j.p. was not modified by L-NOARG. The excitatory actions of L-NOARG on the e.j.p. may be, therefore, related to an increased release of ACh. Thus, in the guinea-pig fundus, one of the possible roles of endogenous NO is to inhibit the release of ACh. Although NO has been proposed as the transmitter substance of the NANC

i.j.p. in some tissues (Sanders & Ward, 1992), indirect release of NO from unidentified sources in response to VIP released from nerves has also been reported (Crist *et al.*, 1991; Grider *et al.*, 1992; Makhlouf & Grider, 1993). The present experiments did not determine the source of the endogenous NO.

However, the actions of endogenously produced NO on the prejunction in the small intestine seem to differ from those found in the present experiments; the former facilitates the release of VIP (Makhlouf & Grider, 1993), while the latter reduces the release of ACh. The membrane response of fundus smooth muscles to NO appears to be a hyperpolarization, since the exogenously applied NO producer, SNP, hyperpolarized the membrane. The fast component of the i.j.p. was little changed by L-NOARG suggesting that this potential was not generated/modulated by NO. Therefore, these results indicate that in this tissue, NO production is enhanced by nerve stimulation, which primarily acts on cholinergic nerves to inhibit the release of ACh, with no obvious effect on NANC inhibitory nerves. Thus, NO acts mainly as an inhibitory modulator of ACh release in the guinea-pig stomach.

In summary, the NANC i.j.p. generated in smooth muscle from the guinea-pig fundus consists of two components (fast and slow). Comparison of the electrical responses suggests that the fast component is not produced by ATP, VIP or NO, whereas the slow component may be produced by NO. Endogenous NO produced during nerve stimulation may have a role in modulating the release of transmitter from cholinergic nerves.

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