Inhibitory Actions of Indomethacin on Electrical and Mechanical Responses Produced by Nerve Stimulation in Circular Smooth Muscle of the Guinea-Pig Gastric Fundus

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Abstract

The effects of indomethacin on electrical and mechanical responses produced by transmural nerve stimulation (TNS) were investigated in isolated circular smooth muscle of the guinea-pig gastric fundus. TNS evoked a cholinergic excitatory junction potential (e.j.p.). The e.j.p.s were inhibited by 1–10 µM indomethacin, in a concentration-dependent manner, with no marked alteration of the resting membrane potential. Exogenously applied acetylcholine caused a depolarization of the membrane that was not altered by indomethacin. TNS evoked a cholinergic twitch contraction at low frequencies (0.1 Hz). A train of TNS’s at high frequency (1 Hz) produced a transient contraction with a subsequent sustained relaxation. Indomethacin reduced the resting tension and inhibited these TNS-induced contractions. Application of N-ω-nitro-L-arginine (NOLA), an inhibitor of nitric oxide (NO) synthesis, increased the amplitude of twitch contractions, and altered transient contractions to tetanic contractions during TNS at a frequency of 1 Hz, also with an increased amplitude. In the presence of NOLA, indomethacin (5 µM) again reduced the resting tension and inhibited TNS-induced contractions. This inhibition was greater for twitch contractions than for tetanic contractions. Nifedipine reduced the TNS-induced contractions, while addition of indomethacin further reduced the amplitude of contractions. Contraction produced by low concentrations of acetylcholine (0.1 µM) were inhibited by indomethacin, while those produced by 1 µM were not. These results indicate that the inhibitory actions of indomethacin on TNS-induced contractions do not involve enhanced production of NO or selective inhibition of voltage-gated Ca-channels. Prejunctional autoregulatory mechanisms may also not be altered by indomethacin. As indomethacin inhibits the enzyme cyclooxygenase, it is speculated that endogenously produced prostaglandins exert excitatory actions on gastric smooth muscle, and act mainly postjunctonally to facilitate spontaneous and neurogenic electrical and mechanical activity.

Key words: gastric muscle, indomethacin, excitatory junction potential, contraction, nerve stimulation

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Introduction

Indomethacin is clinically important as an anti-inflammatory drug (Lewis and Furst, 1987). This chemical is commonly used as an inhibitor of cyclooxygenase. The digestive dysfunction which occurs as a side effect following oral ingestion of indomethacin is mainly the result of impairment of the protective functions of the mucosa due to a reduced production of prostanoids (Insel, 1991). In isolated smooth muscle, the concentration of indomethacin required to inhibit production of prostanoids is in the order of 1–10 µM (Lewis and Furst, 1987). In vascular tissues, however, indomethacin is a Ca-antagonist at these concentrations due to inhibition of Ca\(^{2+}\) influx through voltage-gated Ca-channels (Northover, 1977). Thus indomethacin may have multiple actions on smooth muscle.

We have investigated the actions of indomethacin on electrical and mechanical responses produced by transmural nerve stimulation (TNS) in isolated circular smooth muscle of the guinea-pig gastric fundus. The circular smooth muscle of the guinea-pig gastric fundus is electrically and mechanically quiescent, or occasionally produces small rhythmic activity. Electrical responses of the circular muscle of the gastric fundus evoked by transmural nerve stimulation (TNS) are atropine-sensitive excitatory junction potentials (e.j.p.s) but after inhibition with atropine, apamin-sensitive inhibitory junction potentials (i.j.p.s) become evident (Komori and Suzuki, 1986; Ohno et al., 1996). The effects of indomethacin on cholinergic transmission were evaluated from junction potentials recorded using intracellular microelectrodes. TNS also produces contractions in fundus smooth muscle, and a single TNS or a train of TNS's at low frequency (<0.2 Hz) produces a twitch contraction in response to each TNS (Komori and Suzuki, 1988). TNS at high frequency (>1 Hz) produces a transient contraction, which is changed to a tetanic contraction after inhibiting the production of nitric oxide (NO) with nitroarginine (Yoneda and Suzuki, 2001b). Experiments were also carried out to investigate the effects of indomethacin on twitch or tetanic contractions produced by TNS. The results indicate that in circular smooth muscle of the guinea-pig gastric fundus, indomethacin inhibits TNS-induced electrical and mechanical responses, possibly by mechanisms other than an increased production of NO or selective inhibition of voltage-gated Ca-channels. A preliminary part of this work was reported to the 78th annual meeting of the Japanese Physiological Society (Yoneda and Suzuki, 2001a).

Methods

Albino male guinea pigs, weighing 200–250 g, were anesthetized with fluoromethyl 2,2,2-trifluoro-1-(trifluoromethyl) ethyl ether (sevoflurane; Maruishi Pharm., Osaka, Japan), and then decapitated. The animals were treated ethically according to the guidelines for the Care and Use of Animals approved by the Physiological Society of Japan. The fundus region of the stomach was isolated, and the mucosal layer removed using fine scissors. Small segments of circular smooth muscle tissue (1.0–1.5 mm wide, 2.5–3.0 mm long) were dissected together with the adherent longitudinal smooth muscle layer.

Isolated muscle strips were mounted on a silicone rubber plate fixed at the bottom of the
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recording chamber, with the mucosal layer uppermost, and immobilized by fine pins (diameter, 0.1 mm). The rectangular recording chamber, which was made from Lucite plate, measured 8.0 × 20.0 mm with a depth of 5.0 mm and a capacity of about 1.0 ml. The muscle strips were superfused with warmed (35°C) Krebs solution at a constant flow rate of about 3 ml/min. Electrical responses were recorded from circular smooth muscle cells using a conventional microelectrode technique, with a glass capillary microelectrode filled with 3 M KCl (tip resistance: 50–80 MΩ). Intramural nerves were electrically stimulated using the point stimulation method (Komori and Suzuki, 1986). Briefly, a silver wire (diameter, 0.5 mm) coated with enamel except at the tip, was attached gently to the end of the tissue, and brief electrical pulses (0.1–0.5 ms duration, 10–30 V intensity) were applied to the tissue. Selective excitation of intramural nerves during this transmural nerve stimulation (TNS) was confirmed by the reversible inhibition of the TNS-induced electrical responses by 0.1 µM tetrodotoxin.

Mechanical responses of the circular smooth muscle of the fundus were measured as follows. Both ends of the fundus circular smooth muscle strip (1.0–1.5 mm wide, 10–15 mm long) were tied with fine threads, and the strip mounted vertically in a cylindrical recording chamber (10.0 mm diameter, 20.0 mm high, capacity 2 ml). This was perfused with warmed (35°C) Krebs solution at a constant flow rate (3 ml/min). The lower end of the thread was fixed at the bottom, and the upper end was connected to a mechano-transducer (TB-612T, Nihon Kohden, Tokyo, Japan), and isometric mechanical responses measured in the direction of the circular muscle. A pair of silver plates (2.0 mm wide, 20.0 mm long) was fixed opposite each other to the inner wall of the recording chamber, and electric pulses applied to the muscle strip to transmurally stimulate intramural nerves. Selective excitation of intramural nerves by these pulses was confirmed by the reversible inhibition of the evoked responses (twitch contractions) by 0.1 µM tetrodotoxin.

The ionic composition of the Krebs solution was as follows (in mM): Na⁺ 137.4, K⁺ 5.9, Ca²⁺ 2.5, Mg²⁺ 1.6, HCO₃⁻ 15.5, H₂PO₄⁻ 1.2, Cl⁻ 134, glucose 11.5. The solution was aerated with O₂ containing 5% CO₂, and pH of the solution was 7.2–7.3.

Drugs used were atropine sulphate, indomethacin, Nω-nitro-L-arginine (NOLA) and tetrodotoxin (all purchased from Sigma Chem., MO, USA). Indomethacin was dissolved in a 5 mM Na₂CO₃ solution at a concentration of 5 mM as a stock solution, and diluted further with Krebs solution to prepare the desired concentration.

The values measured were expressed as the mean ± standard deviation (S.D.), and differences tested using the Student’s t-test. Probabilities of less than 5% (P<0.05) were considered to be significant.

Results

Effects of indomethacin on electrical responses

In isolated smooth muscle tissue of the fundus, the resting membrane potential of smooth muscle cells was −50.5 ± 2.5 mV (n=12), which was maintained in the presence of 10 µM indomethacin (−50.1 ± 2.8 mV, n=12, P>0.05). However, the excitatory junction potential (e.j.p.) evoked by transmural nerve stimulation (TNS) was inhibited by 1–10 µM indomethacin, in a
concentration-dependent manner (Fig. 1). In the presence of 10 µM indomethacin, the amplitude of an e.j.p. was reduced to about half (Fig. 1, E). The e.j.p.s were not altered (n=3, data not shown) by the addition of Na₂CO₃ solution to the Krebs solution in an amount equivalent to that required for the preparation of the 10 µM indomethacin-containing solution. This suggests that the inhibition was mainly due to the actions of indomethacin. The inhibition of the e.j.p. by indomethacin was reversible, but this required more than 30 min washing with indomethacin-free solution (n=5, data not shown).

Application of a train of TNS's at high frequencies (1–2 Hz) evoked e.j.p.s with successively decreasing amplitude (the depression phenomenon), confirming previously reported observations (Yoneda and Suzuki, 2001b). Figure 2 shows the effects of 3 µM indomethacin on the e.j.p.s evoked by a train of 10 TNSs at a frequency of 1 Hz. These TNS's elicited a weak depression phenomenon in the e.j.p.s, with indomethacin reducing the amplitude of all e.j.p.s to a similar extent (Fig. 2, A and B). When the amplitude of individual e.j.p.s was expressed relative to the first e.j.p. of the train of responses, indomethacin did not show a significant alteration of the depression phenomenon of e.j.p.s (Fig. 2, C).
Thus, indomethacin inhibits the amplitude of e.j.p.s without altering the depression phenomenon, suggesting that this inhibition was mainly a postjunctional event. If this is the case, it might be expected that the depolarization produced by exogenously applied acetylcholine (ACh) might be inhibited by indomethacin. Experiments were developed further to test the effects of indomethacin on the ACh-induced depolarization in the circular smooth muscle of the guinea-pig gastric fundus. ACh (0.1 and 1 µM) depolarized the membrane (0.1 µM, 4.0 ± 2.1 mV, n=11; 1 µM, 8.6 ± 1.6 mV, n=8). These values were not altered in the presence of 10 µM indomethacin (0.1 µM, 3.3 ± 2.1 mV, n=5, P>0.05; 1 µM, 7.8 ± 2.2 mV, n=10, P>0.05). Thus it does not appear that indomethacin inhibits postjunctational cholinergic mechanisms in fundus smooth muscle.
Effects of indomethacin on TNS-induced mechanical responses

In isolated fundus smooth muscle, single TNS produced a twitch contraction. A train of 3–10 TNS's at a frequency of 0.1 Hz elicited twitch contractions in response to individual TNSs, mostly with a successive decrease in amplitude. A train of TNS's with 1 Hz frequency for 30 s produced a transient contraction and a following relaxation. These TNS-induced contractions were either abolished or sometimes converted to relaxation responses by application of 1 µM atropine. The TNS-induced contractions were also abolished reversibly by tetrodotoxin (0.1 µM). This suggests that they were produced by ACh released in response to excitation of intramural cholinergic nerves. These properties of TNS-induced contractions supported previous observations (Komori and Suzuki, 1988; Yoneda and Suzuki, 2001b).

A single TNS evoked a twitch contraction followed by a transient relaxation. When indomethacin (3 µM) was applied while continuing single TNS every 5 min, the amplitude of the twitch contractions was successively reduced, with an associated reduction in the resting tension. The inhibition of twitch contractions reached a stable level within a period of 20 min of superfusion of the preparation with indomethacin-containing solution (Fig. 3). The reduction in amplitude of the twitch contraction was between 10 and 30% of control (mean, 14 ± 4%, n=8) during inhibition by indomethacin. This inhibition did not recover until preparations had been washed for up to 2 hr with an indomethacin-free solution (n=2).

In fundus smooth muscle, TNS causes the release of nitric oxide (NO) together with ACh and unidentified inhibitory transmitter substances (Yoneda and Suzuki, 2001b). Therefore, experiments were designed to test the effects of indomethacin in the presence of NOLA, an inhibitor of NO synthesis (Moncada et al., 1991). TNS was applied in trains at both 0.1 and 1 Hz frequencies, since these two frequencies of TNS could produce typical twitch and tetanic contractions in this preparation (Yoneda and Suzuki, 2001b). In the presence of 10 µM NOLA, the amplitude of the twitch contraction was increased to 159 ± 52% (n=14) of control (Fig. 4, Ab). Addition of 3 µM indomethacin in the presence of NOLA resulted in a reduction in the
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Amplitude of twitch contractions to between 1–20% of control (Fig. 5).

A train of TNS’s at a frequency of 1 Hz for 30 s produced a transient contraction (Fig. 4, Ba); the peak amplitude was 139 ± 52% (n=14) of the twitch contraction produced by a single TNS. Indomethacin inhibited the amplitude of these contractions by about a half (Fig. 5). In the presence of NOLA, the transient contraction was changed to a tetanic contraction (Fig. 4, Bb) with a peak amplitude which was increased to 263 ± 92% (n=14) of that of a twitch contraction evoked in the absence of NOLA. In the presence of NOLA, addition of 3 µM indomethacin again inhibited the contractions, but the inhibition was not as large as that seen with twitch contractions (Fig. 4, Bc). The summarized data (Fig. 5) indicated that the amplitude of tetanic contractions produced in the presence of NOLA and indomethacin was about two times larger than the twitch contractions elicited under control conditions. Indomethacin inhibited twitch

Fig. 4. Effects of inhibition of NO production on the actions of indomethacin. In isolated circular smooth muscle tissue of the guinea-pig fundus, TNS (1 ms duration, 100 V intensity) was applied for 4 trains of 0.1 Hz frequency (A) and for 30 trains of 1 Hz frequency (B), in the absence (a, Control), and in the presence of 10 µM NOLA (b) and NOLA + 3 µM indomethacin (c). All responses were recorded from the same tissue.
contractions much more strongly than it did for tetanic contractions.

The possible involvement of Ca-antagonistic actions of indomethacin in the inhibition of TNS-induced contractions was investigated by using nifedipine, a dihydropyridine derivative inhibitor of voltage-gated L-type Ca-channels (Mori et al., 1999). In the presence of NOLA, nifedipine (1 µM) reduced the amplitude of twitch and tetanic contractions to 50.2 ± 7.8% (n=5) and 75.4 ± 13.4% (n=5), respectively (Fig. 6, C). In the presence of nifedipine, together with NOLA, indomethacin further reduced the amplitude of twitch and tetanic contractions to 7.3 ± 6.0% (n=4) and 27.5 ± 10.6% (n=4) respectively of the contractions produced in the presence of NOLA alone (Fig. 6, D). These results collectively indicate that the inhibitory actions of indomethacin occur independently of the alteration of the activities of voltage-gated Ca-channels. An increased production of NO by indomethacin would also be unlikely.

The effects of indomethacin on contractions produced by exogenously applied ACh were observed. ACh was applied at both 0.1 and 1 µM concentrations. The lower concentration was considered to be comparable to that of nerve-derived ACh acting at the smooth muscle membrane (equal to 0.08 µM, Komori and Suzuki, 1988), while the higher concentration produced contractions similar to those produced by 1 Hz TNS in the presence of NOLA (105 ± 58%, n=5). The amplitudes of contraction produced by both concentrations of ACh were not significantly altered by NOLA. Indomethacin significantly inhibited the contractions produced by 0.1 µM ACh but not those elicited by 1 µM ACh (Fig. 7). The results support the idea that
Indomethacin has inhibitory actions on gastric smooth muscle. The inhibition of ACh-induced contraction by indomethacin appeared stronger for lower concentrations than for higher concentrations.

Fig. 6. Effects of NOLA and nifedipine on the actions of indomethacin. In isolated circular smooth muscle tissue of the guinea-pig gastric fundus, TNS (a, 0.1 Hz frequency, 10 times; b, 1 Hz frequency, 30 times) was applied in the absence (A, Control) and presence of 10 μM NOLA (B), NOLA + 1 μM nifedipine (C) and NOLA + nifedipine + 5 μM indomethacin (D). All responses were recorded from the same tissue. TNS: 0.5 ms duration, 100 V intensity.
Discussion

The present experiments showed that in isolated circular smooth muscle of the guinea-pig gastric fundus, indomethacin inhibits e.j.p.s produced by TNS, with no significant alteration of the depression phenomenon. The depression phenomenon of e.j.p.s is considered to be due to successive reduction of the supply of Ca2+ required for transmitter release (Katz and Miledi, 1968). Therefore, the unaltered depression phenomenon by indomethacin suggests that the Ca-mobilization processes at cholinergic nerve terminals may not be significantly attenuated by indomethacin. Prejunctional autoregulation mechanisms for the release of ACh are also one of the important factors which induce the depression phenomenon (Starke et al., 1989; Broadley, 1996). The lack of a significant alteration of the depression phenomenon by indomethacin suggests that the prejunctional cholinergic autoregulation mechanism may be not markedly altered. These results suggest that the inhibitory actions of indomethacin on the e.j.p. may be mainly postjunctional events. The depolarization of the membrane by exogenously applied ACh may be mainly a postjunctional event, and this was also not altered by indomethacin. Thus, consistent results were not obtained for the effects of indomethacin on the electrical responses of smooth muscle produced by TNS, and the mechanisms of inhibition of e.j.p.s. by indomethacin remain unclear.

Recently, it was proposed that the i.j.p.s recorded from smooth muscle cells in response to TNS are indirect via excitation of interstitial cells of Cajal (ICC) distributed in the gastric walls, through gap junctional transmissions (Publicover et al., 1993; Burns et al., 1996). Attenuation of
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The inhibitory actions of indomethacin are more marked on twitch contractions than on
tetanic contractions. The amount of ACh released in response to a single TNS may be smaller
than that released during a train of TNS's at a frequency of 1 Hz. This is consistent with the
differences noted with the indomethacin-induced inhibition of contractions produced by
exogenously applied ACh, i.e., contractions produced by lower concentration of ACh were
inhibited more than those produced by higher concentration of ACh. It is reasonable to
speculate that intracellular Ca²⁺ concentrations may be elevated more by a higher concentration
of ACh than by a lower concentration of ACh. This may be the reason for the difference in the
inhibition between twitch and tetanic contractions. These results could be reasonably explained
if the inhibitory actions of indomethacin were the result of a lowering the intracellular Ca²⁺
concentration in smooth muscle cells, due to a decreased level of excitatory prostaglandins.

It is concluded that in circular smooth muscle of the guinea-pig stomach fundus,
indomethacin inhibits TNS-induced electrical and mechanical responses. The inhibitory actions
of indomethacin do not involve the increased production of NO, activation of prejunctional
cholinergic autoregulation mechanisms, or the inhibition of L-type Ca-channels. Although the
present experiments could not clearly indicate the possible mechanisms of these actions of
indomethacin, a reduction in the level of endogenously produced excitatory prostaglandins is
considered. Clinically, gastrointestinal complaints such as anorexia, nausea and abdominal pain
appear as one of the side effects of indomethacin ingestion (Insel, 1991). The present
experiments suggest that the depression of the vagal control of gastric smooth muscle may be
also involved in these indomethacin-induced disorders.

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