EFFECTS OF PROSTAGLANDINS ON ELECTRICAL AND MECHANICAL ACTIVITIES OF THE GUINEA PIG STOMACH

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Abstract Effects of prostaglandin E₁, E₂, and F₂α (PGE₁, PGE₂, and PGF₂α) on the electrical and mechanical properties of the smooth muscle of various areas of the guinea pig stomach were investigated. PGE₁ and PGE₂ (10⁻⁸–10⁻⁶ g/ml) suppressed the spontaneously generated mechanical activity in circular muscle of the pylorus, but increased the activity of muscles in other areas of the stomach, while PGF₂α (10⁻⁹–10⁻⁶ g/ml) showed excitatory action on muscles in all the areas of the stomach. These PG actions on the stomach muscle were mainly myogenic responses, and were not affected in the presence of tetrodotoxin (10⁻⁷ g/ml). PGE₁ and PGE₂ (10⁻⁸–10⁻⁶ g/ml) hyperpolarized the membrane and suppressed the generation of slow potential change in the circular muscle of the pylorus, thus causing the cessation of spikes which were superimposed on the slow potential change. On the other hand, these agents depolarized the membrane and increased membrane activity in the longitudinal muscle of the pylorus and both layers of the corpus. When voltage-current relationships were observed before and during application of PGs in the circular muscle of the pylorus, PGE₁ and PGE₂ consistently reduced membrane resistance at any given membrane potential level when compared with that in Krebs solution. In other regions of the stomach, PGE₁ and PGE₂ depolarized the membrane, and reduced the membrane resistance at any given membrane potential level. The differences of PG action on the various regions of stomach were compared with those observed in the other visceral smooth muscles.

Stomach muscles of the guinea pig shows marked topical differences in electrical and mechanical properties, i.e. in Na-free solution the circular muscle of the pylorus relaxes but the longitudinal muscle of the fundus produces contracture. The former produces a small tonic response but the latter a large tonic response when contracture is induced by potassium. Moreover, the former generates a burst discharge on a slow potential change which is generated periodically, but the
latter is electrically quiescent (KURIYAMA et al., 1975).

In the present experiments, we intended to further elucidate the topical differences of the electrical and mechanical properties of the guinea pig stomach based on response to chemical substances, namely prostaglandins (PGs), since PGs shows marked differences in electrical and mechanical responses in longitudinal and circular muscles of the intestine (ISHIZAWA, 1967; BENNETT et al., 1968; ISHIZAWA and MIYAZAKI, 1973; SUZUKI and KURIYAMA, 1975). The results obtained in the present experiments showed that PGE₁ and PGE₂ suppressed the electrical activity and relaxed the circular muscle of the pylorus but increased the electrical and mechanical activities of other regions of the longitudinal and circular muscles. These observations suggested that the topical differences in muscle properties appeared not only in the electrical and mechanical events but also in the chemoreceptors.

METHODS

Guinea pigs, weighing 250–300 g, were stunned and bled. The stomach was excised and dissected starting along the greater curvature. The muscle layers were separated from the mucous layer with the aid of a binocular microscope, and longitudinal (circular muscle attached) and circular (longitudinal muscle attached) muscle strips were prepared. However, the circular muscle preparation of the pylorus was dissected solely as a circular muscle preparation.

To measure spontaneous mechanical activity, both longitudinal muscle and circular muscle preparations (15 mm in length and 2–3 mm in width) were perfused together in the same chamber (2.5 ml in capacity).

The microelectrode method was used to record electrical activity (SUZUKI and KURIYAMA, 1975). The glass capillary microelectrode (tip diameter, less than 0.2 μm) was filled with 3 M KCl by a conventional method.

A modified Krebs solution (hereafter referred to as Krebs) with the following composition was used (mm): Na⁺, 137.4; K⁺, 5.9; Mg²⁺, 1.2; Ca²⁺, 2.5; Cl⁻, 134.0; HCO₃⁻, 15.5; H₂PO₄⁻, 1.2 and glucose, 11.5: equilibrated with 97% O₂–3% CO₂. Isotonic K Krebs solution was prepared by replacing NaCl and NaHCO₃ with isomolar KCl and KHCO₃, respectively, and Na-free Krebs solution was prepared by replacing NaCl and NaHCO₃ with isomolar sucrose and 5.6 mM KHCO₃. The pH of the Na-free Krebs solution was adjusted to 7.2 with Tris buffer.

All experiments were carried out at 35±0.2°C. The drugs used in the experiments were prostaglandin E₁, E₂, and F₂₀ (Ono Pharm., Ltd. 511, 512, and 602, respectively) and tetrodotoxin (Sankyo Pharm., Ltd.). The concentrations of PGs are expressed in g/ml.

RESULTS

Effect of PGs on the mechanical activity

The upper areas of the corpus and fundus, in both the longitudinal and circular
muscle layers, were mechanically quiescent. However, in the lower areas of the corpus and antrum spontaneous contraction triggered by either slow potential change (basic electric rhythm; slow depolarization) or a spike which was superimposed on slow potential change could be observed.

The membrane potentials and the length constants of the tissue recorded in various areas of the stomach showed roughly the same value; in the range of \(-55\) mV and \(-58\) mV, and 1.1 and 1.4 mm, respectively (KURIYAMA et al., 1970; KURIYAMA et al., 1975).

Figure 1 shows the effects of PGE\(_1\) \((10^{-7} \text{ g/ml})\) on the mechanical activity of circular muscle of the pylorus and of the longitudinal muscle of fundus in the presence or absence of tetrodotoxin \((10^{-6} \text{ g/ml})\). The above two strips were selected as the typical examples of different regions of stomach, since they showed marked differences from each other in their mechanical responses when treated with isotonic K-Krebs solution or Na-free (sucrose) solution, as described in the introduction (KURIYAMA et al., 1975). PGE\(_1\) suppressed the generation of spontaneous contraction in the circular muscle, but generated contracture in the longitudinal muscle. These mechanical responses of the stomach muscles in response to PGE\(_1\) were not affected in the presence of tetrodotoxin (b). These results, therefore, suggest that PGE\(_1\) mainly affects the mechanical properties of both tissues without mediating the nervous activity.

Figure 2 shows the effects of PGE\(_1\), PGE\(_2\), and PGF\(_2\alpha\) on the mechanical

![Fig. 1](image)

**Fig. 1.** Effects of prostaglandin E\(_1\) (PGE\(_1\); \(10^{-7} \text{ g/ml}\)) on the mechanical activities of the circular muscle of the pylorus and longitudinal muscle of the fundus in the presence (b) and absence (a) of tetrodotoxin (TTX; \(10^{-6} \text{ g/ml}\)). Bars indicate the presence of drugs.
activity of the longitudinal and circular muscles of the pylorus. Both muscle tissues produced spontaneous contraction. PGs caused an increase in mechanical activity of the longitudinal muscle, but a decrease in mechanical activity of the circular muscle. The potencies of these chemicals on excitatory and inhibitory action were in order of $\text{PGE}_1 > \text{PGE}_2 > \text{PGF}_{2\alpha}$. From these results and the effect of PGs in other areas of the stomach, it was concluded that the PGs series used in the present experiments increased the mechanical response in all the areas of the stomach except for the circular muscle of the pylorus.

The effect of PGE$_1$, PGE$_2$, and PGF$_{2\alpha}$ ($10^{-6}$ g/ml) on contracture induced by isotonic K-Krebs solution and by Na-free (sucrose) Krebs solution of longitudinal muscle of fundus and circular muscle of pylorus were observed. Isotonic K-Krebs solution produced phasic and tonic contracture responses in both muscle layers; the tonic response was larger in the longitudinal muscle than in the circular muscle. During the generation of tonic response of K-induced contracture, PGE$_1$ and PGE$_2$ further enhanced the mechanical response without any noticeable change in the membrane potential of the longitudinal muscle, and slightly suppressed the mechanical response of the circular muscle. PGF$_{2\alpha}$ ($10^{-6}$ g/ml) showed weaker action than PGE$_1$ and PGE$_2$ on the mechanical responses of both tissues. On the other hand, PGE$_1$, PGE$_2$, and PGF$_{2\alpha}$ ($10^{-6}$ g/ml) generated neither further contraction of the Na-free induced contracture of the longitudinal muscle nor relaxation of the circular muscle.
The effect of PGE₁, PGE₂, and PGF₂α (10⁻⁷ g/ml) on mechanical activity recorded in the various areas of the stomach are summarized in Table 1.

**Effect of PGs on electrical activity**

The effect of PGE₁ (10⁻⁷ g/ml) and PGF₂α (10⁻⁶ g/ml) on membrane activity of the longitudinal and circular muscle of the pylorus was observed. As shown in Fig. 3, PGE₁ depolarized the membrane and increased the number and frequency of mechanical activity.

<table>
<thead>
<tr>
<th>Region</th>
<th>Layer</th>
<th>PGE₁</th>
<th>PGE₂</th>
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<tr>
<td>Pylorus</td>
<td>circ.</td>
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<td>long.</td>
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<td>Corpus</td>
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<td>long.</td>
<td>+</td>
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<tr>
<td>Fundus</td>
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<td></td>
<td>long.</td>
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+: contraction  -: relaxation

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**Guinea pig stomach pylorus**

- **Fig. 3.** Effects of prostaglandin E₁ (10⁻⁷ g/ml) and prostaglandin F₂α (10⁻⁸ g/ml) on the electrical activities of the circular and longitudinal muscles of the pylorus. a–b: longitudinal muscle (Long. M.). c–d: circular muscle (Cir. M.), inward current pulses (3 sec pulse) were successively applied. Durations between dots indicate application of drugs.
of the spikes superimposed on the slow potential change of the longitudinal muscle. The duration of the slow potential change was prolonged but its frequency appearance was not influenced. However, PGE₁ hyperpolarized the membrane and suppressed the generation of slow potential change with spike in the circular muscle. Even at a concentration ten times higher than that employed for PGE₁, PGF₂α showed much weaker action or nearly no action on the electrical activity in both tissues.

Figure 4 shows the effects of PGs (10⁻⁷ g/ml) on the electrical activity recorded in the circular muscle of the corpus region. In the upper region of the corpus, the amplitude of the slow potential change was small and spikes were usually not evoked by the slow potential. PGE₁, PGE₂, and PGF₂α depolarized the membrane and suppressed the generation of slow potential change.

These results confirmed the PG actions observed from the mechanical responses, i.e. electrical and mechanical activities were suppressed by PGs only in the circular muscle of the pylorus but not in the other areas of the stomach.

To measure the changes in membrane resistance in the presence of PGs, short inward current pulses of various intensities were applied to the membrane at a different membrane potential which was displaced by current injection before and during application of the PGs. Figure 5 shows the effect of PGE₂ (10⁻⁷ g/ml) on the amplitudes of the electrotonic potential of the circular muscle of the pylorus. In a, the membrane potential was displaced either to a hyperpolarized or to a depolarized direction by the injection of long current pulses; short inward current pulses (1 sec) with various intensities were then applied to the tissue. When a long inward current pulse was applied, the electrotonic potential was followed by a rebound slow depolarization which was often had a spike superimposed. The amplitude of the rebound depolarization depended on the intensity of the applied inward current pulse. In b, current-voltage relationship was recorded in the presence of PGE₂ (10⁻⁷ g/ml). By treatment with PGE₂, the amplitude of the electrotonic potential was smaller than that evoked in Krebs solution at any given

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**Fig. 4.** Effects of prostaglandin E₁, E₂, and F₂α (10⁻⁷ g/ml) on the membrane activity recorded in the circular muscle of corpus area.
Fig. 5. Effects of prostaglandin E₂ (10⁻⁷ g/ml) on the electrical properties of the circular muscle of the pylorus. a; control, b; during application of PGE₂. The membrane potential was displaced by dc current at various levels and short inward current pulses (3 sec) with various intensities were applied. Top records in a and b show the changes in the membrane potential and membrane activity, and low records in a and b show the applied electrical stimulation which was expressed as V/cm.

membrane potential level. The rebound slow depolarization produced by cessation of the inward current pulse was also suppressed.

Figure 6 shows the current-voltage relationships of the circular muscle cells of the fundus and pylorus observed before and during application of PGE₂ (10⁻⁷ g/ml). Throughout the experiments, the microelectrode was inserted into the same cell at a distance of 0.5 mm from the stimulating electrode. When PGE₂ was applied to the circular muscle of the fundus, the membrane was depolarized and the slope of the current-voltage relationship at any given potential level showed a consistently lower value than that measured in the Krebs solution. This means that the membrane resistance was smaller during the application of PGE₂ than that in the Krebs solution. On the other hand, in the circular muscle of the pylorus, PGE₂ hyperpolarized the membrane and reduced membrane resistance more than that in the Krebs solution at any given membrane potential level. In Na-free (sucrose) solution, PGE₂ (10⁻⁷ g/ml) neither depolarized the membrane nor reduced membrane resistance.

The effects of PGE₁ (10⁻⁷ g/ml) on the membrane resistances of the circular muscle of the pylorus and fundus were nearly the same as those observed by treatment with PGE₂.

Figure 7 shows the effects of PGE₁ (10⁻⁷ g/ml) on the current-voltage relationship recorded from sling muscle of the stomach. Beck and OsA (1971) conducted investigations on the guinea pig sling muscle and concluded that this muscle pos-
Fig. 6. Effects of prostaglandin E₂ (10⁻⁷ g/ml) on the current-voltage relationships recorded in circular muscle cells of the fundus and pylorus. a; circular muscle of the fundus, b; circular muscle of the pylorus. The microelectrode was inserted into the cell at a distance of 0.5 mm from the stimulating electrode throughout the experiments. Before and during the application of drug, the membrane potential was displaced to a hyperpolarized or to depolarized level by current injection. RMP; resting membrane potential level.

Fig. 7. Effects of PGE₁ (10⁻⁷ g/ml) on the current-voltage relationship recorded from sling muscle of the stomach. Symbols are indicated in the figure. The recording microelectrode was inserted at a distance of 0.5 mm from the stimulating electrode.
sesses the property of eliciting membrane activity by chemical stimulation, including the neurotransmitter, but not by electrical stimulation. PGE₁ depolarized the membrane and reduced membrane resistance at all membrane potential levels. This means that sling muscle shows different responses from the circular pylorus muscle to PGs.

These results suggest that the hyperpolarizing action of PGE₁ and PGE₂ on the membrane of the circular muscle of the pylorus is due to the increase in the ionic conductance of the membrane and their depolarizing action on the membrane of the circular muscle of the fundus is also due to an increase in the ionic conductance of the membrane.

**DISCUSSION**

The PGs constitute a group of naturally occurring C-20 unsaturated hydroxy fatty acids (prostanoic acid), of which the E and F series are known to be widely distributed in biological tissues. The action of PGs vary not only according to species but also tissues. Their occurrence, tissue distribution, biosynthesis, metabolism, physiological and pharmacological actions have been the subject of many comprehensive reviews (BERGSTROM et al., 1968; HORTON, 1969; PHARRISS and SHAW, 1974). Until now the effects of PGs on the alimentary canal have been investigated by many investigators not only on the smooth muscle activity but also in connection with the secretion of digestive juices (BERGSTROM et al., 1968).

In connection with the electrical and mechanical activities of the intestinal smooth muscles, BENNETT et al. (1968), WATANABE (1972), ISHIZAWA and MIYAZAKI (1973) reported that PGE accelerates the mechanical responses of the longitudinal muscle and suppresses the circular muscle, and that these actions are mediated by nervous elements. However, BENNETT et al. (1968) found that the site of PG action varied with each species, that is in the rat and in some strips of human tissue, PG appeared to have only direct action on or in the muscle cells. In other strips of human tissue and in guinea pig ileum, the PGs seemed to stimulate both the intrinsic cholinergic nerves and the muscle cells.

Recently BURNSTOCK et al. (1975) reported that rebound contraction generated by repetitive stimulation is suppressed by pretreatment with indomethacin, a PGE synthesis inhibitor. These results seem to indicate that the nonadrenergic-noncholinergic inhibitory nerves (purinergic nerve; BURNSTOCK, 1971) distributed between the muscle layers play an important role in PGs action. On the other hand, KADLEC et al. (1974) reported that indomethacin did not affect response of the ileum and taenia coli of the guinea pig to nonadrenergic-noncholinergic nerve stimulation. In the present experiments, the slow rebound depolarization generated by the inward current pulse in the circular muscle of pylorus was partly suppressed by PGE₁. However, either depolarization or hyperpolarization of the membrane produced by PGs was not markedly affected in the presence of tetrodotoxin. This
result might suggest that in the stomach muscle PGs mainly act directly on smooth muscles, and neural activations induced by PGs might play a minor role in the muscle activity. Recently, ISHIZAWA and MIYAZAKI (1973) reported that PGs relaxed the circular muscle motility in vitro but accelerated the peristaltic motility of the intestine in vivo. They, therefore, thought that amount of intrinsic nerves within the intestinal wall play an important role in PG action.

In the guinea pig ileum, SUZUKI and KURIYAMA (1975) reported that PGE$_1$ enhances the spontaneously generated and electrically evoked spike and contraction in the longitudinal muscle, but it suppresses the electrically evoked spike and contraction in the circular muscle. PGE$_1$ has no effect on the phasic response of K-induced contracture in either muscle layer. PGE$_1$ partially suppresses the tonic response of K-induced contracture, as observed by WATANABE (1972), in the circular muscle but not in longitudinal muscle preparations. When the effects of PGs are compared with those observed in the stomach, the circular muscle of the pylorus showed nearly the same electrical responses as those observed in the circular muscle of the ileum. However, circular muscle of the pylorus generated spikes with slow potential change but the ileum generated neither electrical nor mechanical activity.

The present experiments also indicate that the sphincter muscles of the upper and lower areas of the stomach, sling muscle and pylorus circular muscle, showed different responses to PGs and these responses might suggest different roles of sphincter action in both areas.

The effects of PGs on mechanical responses are similar to those with electrical responses. This means that different actions of PGs on the various regions of stomach would appear through the membrane events, and therefore different responses observed between the circular muscle of pylorus and other longitudinal and circular muscles by PGs might be due to the differences in the membrane properties, i.e. PGs might increase K-permeability of the circular muscle of the pylorus while mainly increasing the Na-permeability of other regions of stomach muscles.

The slow potential changes generated from the lower regions of the guinea pig stomach are complicated in nature (KURIYAMA, 1970; OHBA et al., 1975). After repeated stimulation to the tissue, the rebound contraction and slow potential appeared additively. As a consequence, a large amplitude of slow potential change appeared just after the electrical stimulation (ITO and KURIYAMA, 1975). In the circular muscle of the pylorus, not only repeated stimulation but also single stimulus produced the slow potential change which was suppressed by treatment with PGE$_1$. It is unlikely that the suppression is due to hyperpolarization of the membrane; it is likely due to a reduction of the membrane resistance by increased K-permeability of the membrane and also partly due to suppression of the nervous activity.

The PG actions on the electrical and mechanical activities of the various visceral smooth muscles are complicated. For example, in the rat and mouse myometria, all PGE$_1$, PGE$_2$, and PGF$_{2\alpha}$ increase the electrical activity in the longi-
PG ACTIONS ON STOMACH MUSCLE

Tudinal muscle more than that in the circular muscle, and the potency of drug action depends on the hormonal status (SUZUKI and KURIYAMA, 1975). On the other hand, PGE\textsubscript{1} and PGE\textsubscript{2} hyperpolarizes but PGF\textsubscript{2}a depolarizes the membrane of the longitudinal muscle of pulmonary artery (Suzuki, H., Kitamura, K., and Kuriyama, H.; unpublished observations). In the present observations and also from the previous reports described by SUZUKI and KURIYAMA (1975), longitudinal and circular muscles of the alimentary canal show different responses to PGs. We have not yet found a comprehensive explanation of PG action on electrical activity of the visceral muscles.

In the present experiments, topical differences of the membrane activity were elucidated. Further experiments are, however, required to understand whether such different responses of the membrane to PGs on the ionic permeability are due to tissue specificity of the property of the PG receptors with their allosteric conformation of the membrane protein, or to some other unknown mechanism.

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REFERENCES


