Prostaglandins and modulation of small bowel myoelectric activity

CONSTANTINE T. FRANTZIDES, ELIAS A. LIANOS, DITMAR WITTMANN, BEVERLY GREENWOOD, AND CHARLES E. EDMISTON
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Frantzides, Constantine T., Elias A. Lianos, Ditmar Wittmann, Beverly Greenwood, and Charles E. Edmiston. Prostaglandins and modulation of small bowel myoelectric activity. *Am. J. Physiol.* 262 (*Gastrointest. Liver Physiol.* 25): G488–G497, 1992.—We explored the effects of prostaglandins (PG) $F_{2\alpha}$ and E_2 on the motor and myoelectric activity of the small intestine using closed intra-arterial injections in conscious chronically instrumented dogs. $PGF_{2\alpha}$ (0.125–5 μg) and PGE_2 (1–10 μg) were injected via a T tube into a branch of the superior mesenteric artery perfusing a 15-cm segment of jejunum. Experiments were performed on four dogs in which the recording devices had been implanted above, below, and within the perfused segment. $PGF_{2\alpha}$ given during phase I of the migrating myoelectric complex cycle induced phasic contractions in the perfused segment of intestine in a dose-dependent manner. Atropine (50–100 μg), hexamethonium (15 mg), or TTX (10–15 μg) administered before the injection of $PGF_{2\alpha}$ failed to inhibit the effects of $PGF_{2\alpha}$. In contrast pretreatment of the perfused segment with verapamil (2.5 mg) or PGE_2 (1–5 μg) abolished the effects of $PGF_{2\alpha}$. Moreover, PGE_2 injected 5 min after the administration of $PGF_{2\alpha}$ inhibited the $PGF_{2\alpha}$-induced contractions. Administration of PGE_2 alone (3–10 μg) before the arrival of phase III activity in the perfused segment abolished phase III from this segment of intestine. Our studies indicate opposing effects of $PGF_{2\alpha}$ and PGE_2 on small intestinal myoelectric and contractile activities. $PGF_{2\alpha}$ has a direct excitatory effect on the intestinal smooth muscle, which is calcium channel dependent but independent of intrinsic nerves. PGE_2 has an inhibitory effect both on the spontaneous and $PGF_{2\alpha}$-induced small intestinal myoelectric and contractile activity.

migrating myoelectric complex; phase III; prostaglandin E_2; prostaglandin $F_{2\alpha}$; calcium channels; verapamil; slow waves

THE ENZYME FATTY ACID cyclooxygenase is distributed in the gastrointestinal tract and converts eicosatetraenoic acid (arachidonic acid) primarily to prostacyclin [prostaglandin (PG)I_2] and, to a lesser extent, to PGE_2, $PGF_{2\alpha}$, and thromboxane B_2 (16, 17, 19, 24). Because the main site of synthesis of these prostaglandins is in the lamina propria, where the sensory mucosal receptors of the submucosal plexus are also located, it has been postulated that prostaglandins may modulate the neurosensory stimulation of an intrinsic reflex arc of the enteric nervous system (20, 27). Depending on the prostaglandin series studied, different effects on intestinal motility have been reported. For example, prostaglandins of the E series contract the longitudinal smooth muscle layer of the small intestine and relax the circular layer (3, 29). In contrast, prostaglandins of the F series contract both smooth muscle layers (2, 3). Although their effects on intestinal smooth muscle are opposite, exogenous prostaglandins of E and F series induce diarrhea in humans and animals (15, 22, 24). Studies on the effect of prostaglandins on intestinal motility patterns in the conscious dog demonstrated that PGE_2 inhibits the migrating myoelectric complex (MMC) and reduces the intraluminal pressure (18). In contrast, $PGF_{2\alpha}$ induces electrical spike activity during phase I and increases spike activity during phase II of the MMC (6, 18, 26). $PGF_{2\alpha}$ also elevates the intraluminal pressure. Inhibition of endogenous prostaglandin synthesis by indomethacin appears to enhance intestinal motility by inducing a fedlike pattern (28). This suggests that endogenous prostaglandins may play a role in the control of intestinal motility.

We have developed a model of close intra-arterial perfusion of the small intestine in the dog, which enabled us to access intestinal neural reflexes (11) as well as the responses of intestinal smooth muscle and of intrinsic nerves to administration of defined pharmacologic agents (9). The present work utilizes this model in chronically instrumented dogs to assess the effects of $PGF_{2\alpha}$ and PGE_2 on small intestinal myoelectric and contractile activity and to explore their mechanisms of action.

METHODS

Experiments were conducted in four conditioned male dogs weighing 35–40 kg. The protocol for this study was approved by the Animal Welfare Committee of the Medical College of Wisconsin (MCW) Milwaukee. The animals were housed at the fully equipped animal facility at the MCW. After procurement, animals were quarantined for 45 days and a fixed routine was followed daily to maintain conditioning and to reduce the effects of environmental factors on the motility responses recorded. At laparotomy six bipolar electrodes and one extraluminal combination strain gauge transducer-bipolar electrode unit were sutured to the seromuscular layer of the small intestine as shown in Fig. 1. All operations were conducted after an overnight fast and by using aseptic surgical technique and under general anesthesia induced with pentobarbital sodium (25 mg/kg). For placement of the recording devices on the small intestine, a midline laparotomy incision was made and the desired bowel segments were identified. The electrode and strain gauge units were sewn to the bowel with 4.0 monofilament suture, pushing the electrode tips into the smooth muscle. The electrodes were aligned so that the exposed silver wires were oriented along the longitudinal axis of the gut. The location and the distance between the units were precisely recorded. The distance between the recording devices was 15 cm. The electrode-strain gauge unit was fabricated from a miniature strain gauge (EA-06-031DE-120, Measurements Group, Raleigh, NC) bonded to a copper-beryllium shim, together with two flexible stainless steel Teflon-coated wires all potted together in silicone rubber to form a unit 0.75 × 2 × 0.3 cm in size. The tips of the electrodes protruded 3 mm and were 5 mm apart. The combination electrode strain gauge unit recorded electrical and contractile events from the same bowel segment. In addition to the motility recording devices described above, a

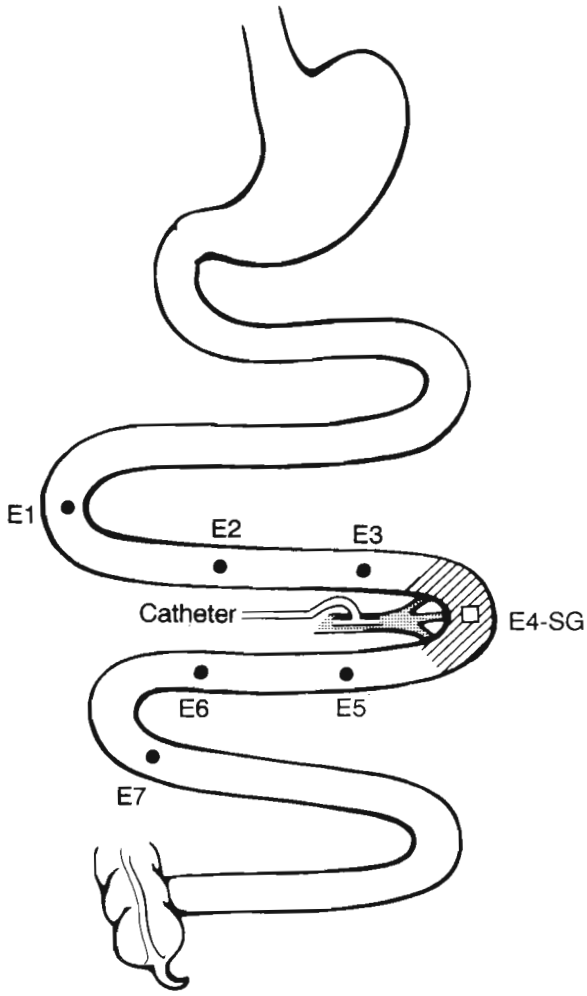

Fig. 1. Diagrammatic representation of arrangement of recording devices and intra-arterial T-shaped Silastic catheter.

T-shaped Silastic tube was implanted in a jejunal branch of the superior mesenteric artery, supplying a 15 ± 5-cm segment of jejunum (9–12). The long limb of the catheter was tunneled subcutaneously to the subscapula region and was protected by a jacket. The fascia was closed with a 2.0 monofilament suture, and the hide was closed with a subcuticular suture. Recovery from anesthesia and early postoperative care were provided in a designated area under close supervision of a specially trained animal handler. The animals were permitted to recover for 10 days, and fasting myoelectric and contractile activities were recorded from the small bowel thereafter, using a Grass recorder (model 7) with lower and upper cutoff frequencies set at 0.01 and 35 Hz for electrical recordings and direct current and 15 Hz for strain gauge recordings. At least one complete MMC cycle was recorded before the administration of the pharmacological agents. $PGF_{2\alpha}$ (0.125–5 μg) or PGE_2 (1–10 μg; Upjohn, Kalamazoo, MI) was administered through the T tube during phases I, II, and III of the MMC cycle. To exclude possible effect of exogenous $PGF_{2\alpha}$ via muscarinic receptors, atropine (50–100 μg) was administered through the T tube 3–5 min before the injection of $PGF_{2\alpha}$. Likewise the possible effect of $PGF_{2\alpha}$ via nicotinic ganglionic receptors or through the enteric nervous system was excluded by pretreatment of the perfused segment with hexamethonium (15 mg), and tetrodotoxin (10–15 μg), respectively. Inasmuch as prostaglandins have been proposed to modify calcium fluxes (23, 25), we explored such a possibility in our system by pretreatment of the perfused intestinal segment with the calcium channel blocker verapamil (2.5 mg). Furthermore, in separate experiments PGE_2 (1–5 μg) was administered through the T tube just before or after the administration of $PGF_{2\alpha}$.

As PGE_2 and $PGF_{2\alpha}$ are vasoactive compounds (vasodilatory and vasoconstrictive, respectively) (1, 26, 30), we reasoned that their effects on intestinal myoelectric activity could be mediated indirectly via the effects of these eicosanoids on the arterial vasculature perfusing the intestinal segment under study. To address such a possibility, we employed a known potent vasoconstrictive agent, *l*-norepinephrine (20 μg), which was given close intra-arterially during phase I of the MMC cycle to explore whether this vasoconstrictor would mimic the effect of $PGF_{2\alpha}$ on myoelectric activity pattern. The intra-arterial injections were given in a volume of 5 ml followed by 3 ml saline flush. The duration of injection of each pharmacological agent was 2 min (including the flushing of the catheter). Each pharmacological agent was administered at least three times in each dog. Several range doses of the pharmacological agents were used, and the doses chosen were the highest possible to be given locally without producing a systemic effect.

Myoelectric and contractile activities from the perfused intestine were compared with those of control tracings. Recordings were examined for alterations in the duration or frequency of contractions and spike bursts. The tracings were examined for the presence and duration of all phases of the MMC cycle and the extent of propagation of phase III along the small bowel. Values are expressed as means ± SE. The study was designed to utilize each dog as its own control. Data were analyzed by two-way analysis of variance and by using the paired *t* test. A two-tail probability of 0.05 or smaller was accepted as indicating a significant change.

RESULTS

Prostaglandin $F_{2\alpha}$ (0.125–5 μg) when given through the T tube during phase I of the MMC cycle (at ~30% of the MMC cycle) induced phasic contractions in the perfused segment of intestine in a dose-dependent manner. Figure 2 demonstrates a typical experiment in which $PGF_{2\alpha}$ (0.5 μg) was injected in the perfused intestinal segment. Note the intense myoelectric (E4) and contractile (SG) activities induced in the perfused segment on completion of $PGF_{2\alpha}$ administration. The $PGF_{2\alpha}$-induced contractions had a frequency of 10.6 ± 1.8 cycles/min, and contractions were found to correlate with spike bursts on a 1:1 basis. This type of activity lasted from 28 ± 3 to 73 ± 8 min depending on the dose administered (Fig. 3). The slow-wave frequency after injection of $PGF_{2\alpha}$ was 17 cycles/min, and it was equal to the frequency (17 cycles/min) before injection. The MMC cycle before the $PGF_{2\alpha}$ administration was 110 ± 16 min. There was no significant difference of MMC cycle after the administration of $PGF_{2\alpha}$ (123 ± 18). When $PGF_{2\alpha}$ was administered during phase II of the MMC cycle, it intensified the myoelectric and contractile activity in the perfused segment of intestine. It did not, however, affect or alter in any way phase III migration. This effect is shown in Fig. 4. Note also that the myoelectric and contractile responses due to $PGF_{2\alpha}$ administration continued even beyond the following phase I of the MMC cycle.

The effect of $PGF_{2\alpha}$ administration was also addressed following blockade of muscarinic and nicotinic receptors as well as a nonspecific neural blockade as described in METHODS. Atropine (50–100 μg), hexamethonium (15

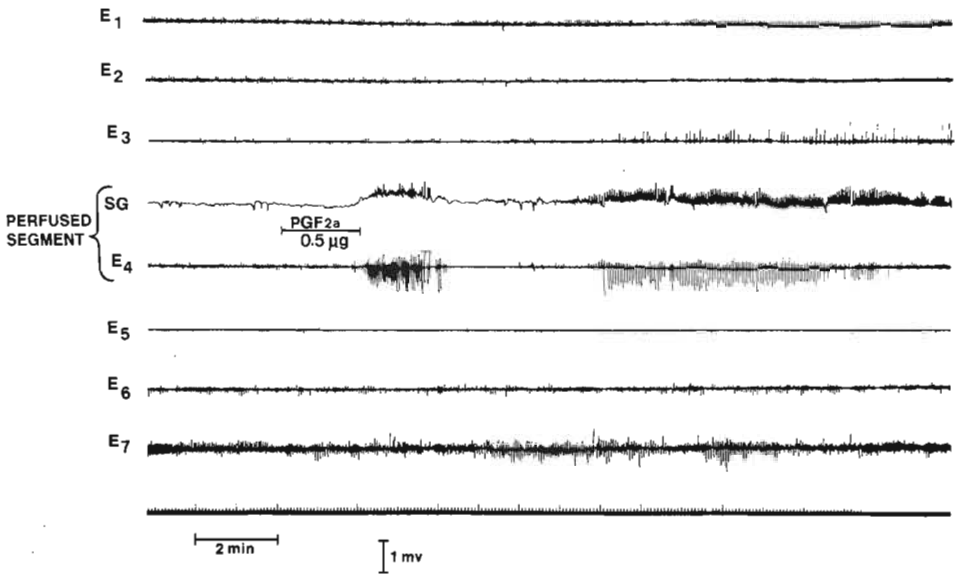

Fig. 2. Effect of prostaglandin (PG) $F_{2\alpha}$ on intestinal myoelectric activity. $PGF_{2\alpha}$ (0.5 μg) injected close intra-arterially initiated intense phasic myoelectric and contractile activities in perfused segment of intestine. Similar effects were seen in all 72 trials conducted with different doses of $PGF_{2\alpha}$ (0.125, 0.25, 1.0, 2.0, and 5.0 μg).

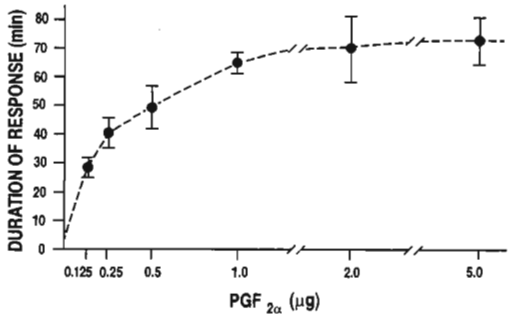

Fig. 3. Dose-response relationship between $PGF_{2\alpha}$ dose and duration of spike activity.

mg), or tetrodotoxin (10–15 μg) administered 3–5 min before the injection of $PGF_{2\alpha}$ failed to inhibit or alter the myoelectric and contractile activities induced by $PGF_{2\alpha}$ (Fig. 5, Table 1). Figure 6 demonstrates the effect of $PGF_{2\alpha}$ on myoelectric activity of the perfused segment following pretreatment with hexamethonium (15 mg). Note that hexamethonium did not alter the effect of $PGF_{2\alpha}$. Administration of tetrodotoxin through the T tube 3 min before the injection of $PGF_{2\alpha}$ was associated with retching. Tetrodotoxin, however, failed to alter the $PGF_{2\alpha}$-induced activity (Fig. 7).

The effect of $PGF_{2\alpha}$ was also addressed following calcium channel blockade using verapamil. Figure 8*A* demonstrates the effect of verapamil pretreatment on $PGF_{2\alpha}$-induced activity. Pretreatment of the perfused segment of intestine with verapamil (2.5 mg) dropped the slow-wave frequency from 17 to 8 ± 0.8 cycles/min (Fig. 8*B*) and abolished the effects of $PGF_{2\alpha}$ (Fig. 8*A*).

Figure 9, *A* and *B*, demonstrates the antagonistic effects of PGE_2 and $PGF_{2\alpha}$ on the myoelectric activity of the perfused segment. As shown in Fig. 9*A*, pretreatment of the perfused segment with PGE_2 prevented the effects

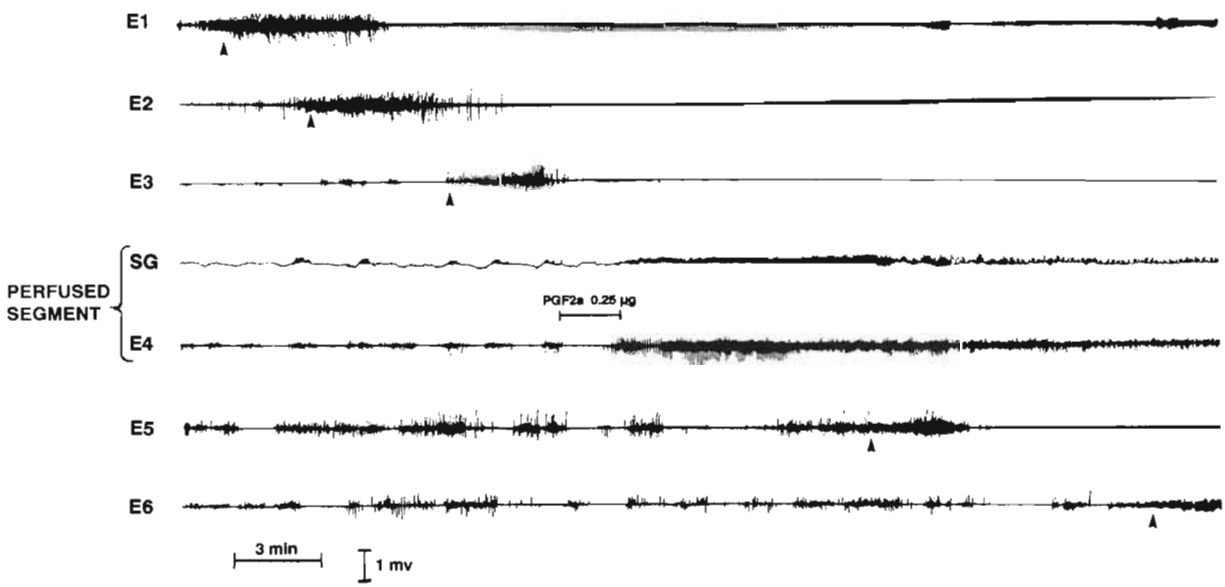

Fig. 4. $PGF_{2\alpha}$ injected through T tube during phase II, initiated spike bursts and contractions in perfused segment but had no effect on phase III migration. This effect was seen in all 16 trials conducted.

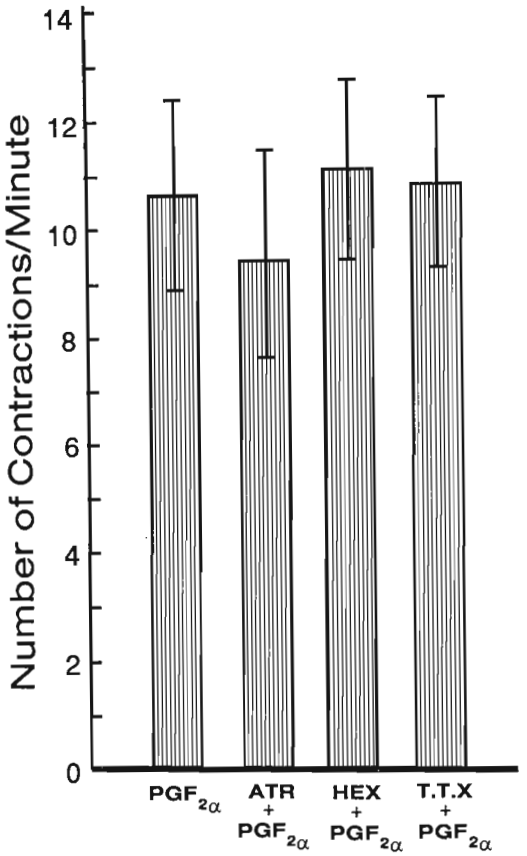

Fig. 5. Number of contractions per minute in perfused segment in response to $PGF_{2\alpha}$ (control), and after blockade with atropine (Atr), hexamethonium (Hex), and tetrodotoxin (TTX). There is no significant effect of blocking agents on $PGF_{2\alpha}$-induced activity.

Table 1. *Duration of spike activity in response to $PGF_{2\alpha}$ and after blockade by atropine, TTX, and hexamethonium*

$PGF_{2\alpha}$ Dose, μg	Duration of Spike Activity, min			
	$PGF_{2\alpha}$	Atr (100 μg)	TTX (15 μg)	Hex (15 mg)
0.125	28±3			
0.25	40±5	34±7	37±4	42±6
0.50	49±7	59±6	46±10	50±4
1.0	64±3	68±11	65±8	59±8
2.0	70±11		75±7	
5.0	73±8			

Values are means ± SE. $PGF_{2\alpha}$, prostaglandin $F_{2\alpha}$; Atr, atropine; TTX, tetrodotoxin; Hex, hexamethonium.

of $PGF_{2\alpha}$. When PGE_2 was given 5 min after the onset of the myoelectric activity induced by the prior administration of $PGF_{2\alpha}$, it completely abolished this activity (Fig. 9*C*).

To explore whether the effect of $PGF_{2\alpha}$ was mediated by the known vasoconstrictive action of this eicosanoid, we assessed the effect of the potent vasoconstrictor levarterenol. When *l*-norepinephrine (20 μg) was administered close intra-arterially during phase I of the MMC cycle, no effect on the myoelectric and contractile activities of the perfused segment was noted.

In Fig. 10, *A* and *B*, the effects of exogenous PGE_2 on phase III activity of the MMC are shown. Administration of PGE_2 in low doses (3 μg) before the arrival of phase III activity in the perfused segment of intestine abolished phase III activity from this segment but did not affect phase III progression beyond the perfused segment (Fig. 10*A*; cf. control, Fig. 10*C*). PGE_2 administered in higher doses (10 μg), in addition to abolishing phase III from the perfused segment, completely inhibited phase III migration (Fig. 10*B*; cf. Fig. 10*C*).

All the pharmacological agents used in this study had no effect on the myoelectric and contractile activity of the small intestine when given intravenously at these doses.

DISCUSSION

The present study evaluates the effects of two eicosanoids PGE_2 and $PGF_{2\alpha}$ on intestinal smooth muscle contractile and myoelectric activity. The close intra-arterial system utilized in the present studies allowed delivery of the pharmacological agents primarily to the perfused segment, thus generating a local myoelectric response. This is evident from the tracings obtained, which demonstrate myoelectric response in the perfused segment only (Fig. 2). Moreover, systemic intravenous administration of the pharmacological agents at the doses employed had no effect on bowel motility. The advantages of studying a segment of intestine in the intact animal, compared with the systemic intravenous injection, or the administration of pharmacological agents through the main stem of the superior mesenteric artery (18, 28) are threefold. *1*) Effective doses of the agent administered can be achieved locally, thus avoiding effects on other systems, i.e., circulatory and respiratory, which may secondarily affect intestinal motility. *2*) The local intra-arterial administration of agonists and antagonists allows evaluation of the myoelectric and contractile responses generated by the segment perfused without altering the myoelectric activity of the entire intestine, which may mask migratory patterns of phase III. Thus it becomes possible to evaluate the effect of pharmacological agents on phase III generation and migration. This objective may be difficult or impossible to accomplish if agonists or antagonists are given systemically or into the main stem of the superior mesenteric artery as previously employed (28). Administration of the pharmacological agent through the superior mesenteric artery can affect the entire gastrointestinal tract including the colon (5). *3*) In the case of eicosanoids, local administration via close intra-arterial system avoids the systemic enzymatic degredation by tissues such as the lungs (7, 14). Compared with the $PGF_{2\alpha}$ and PGE_2 doses used intra-arterially in previous studies (28), the doses of these eicosanoids administered to the perfused intestinal segment in the present study were 10-fold lower.

The effect of $PGF_{2\alpha}$ on the myoelectric and contractile activity is apparently independent of intrinsic nerves, because hexamethonium, atropine, and tetrodotoxin failed to block the pattern of activity induced by this eicosanoid. These observations indicate that $PGF_{2\alpha}$ exerts a primary effect on the intestinal smooth muscle. A receptor-mediated effect is most likely, since the presence of $PGF_{2\alpha}$ receptors has been described in smooth

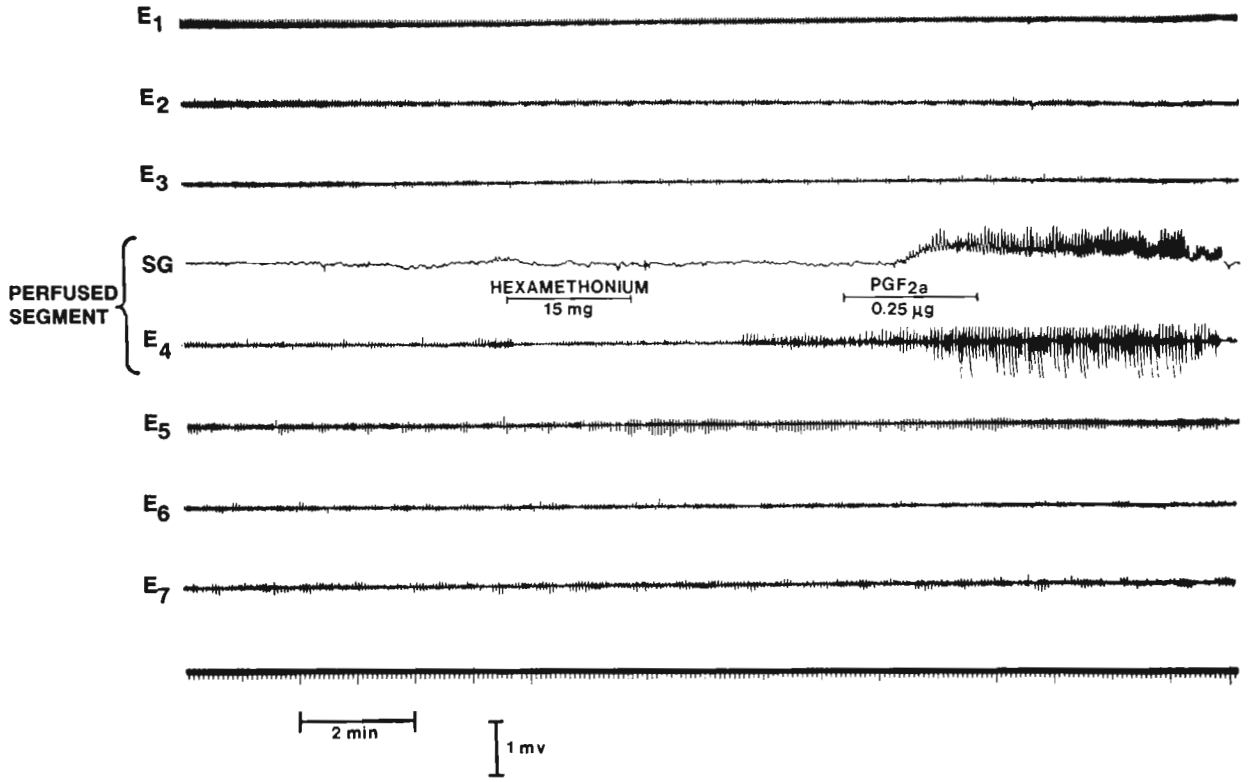

Fig. 6. Effect of hexamethonium pretreatment on $PGF_{2\alpha}$-induced myoelectric activity. Hexamethonium had no effect. Similar responses were seen in all 36 trials conducted.

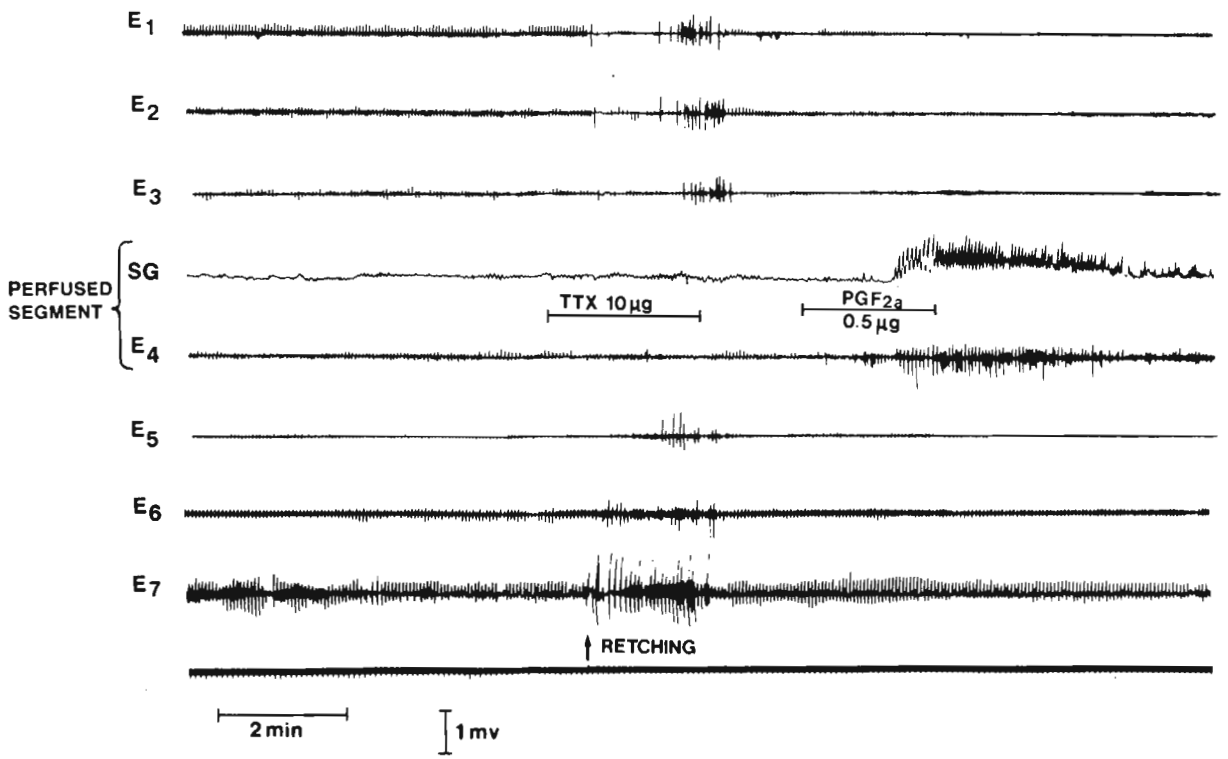

Fig. 7. Effect of TTX pretreatment on $PGF_{2\alpha}$-induced myoelectric activity. TTX administration was associated with retching and did not alter effect of $PGF_{2\alpha}$. Similar responses were seen in all 58 trials conducted.

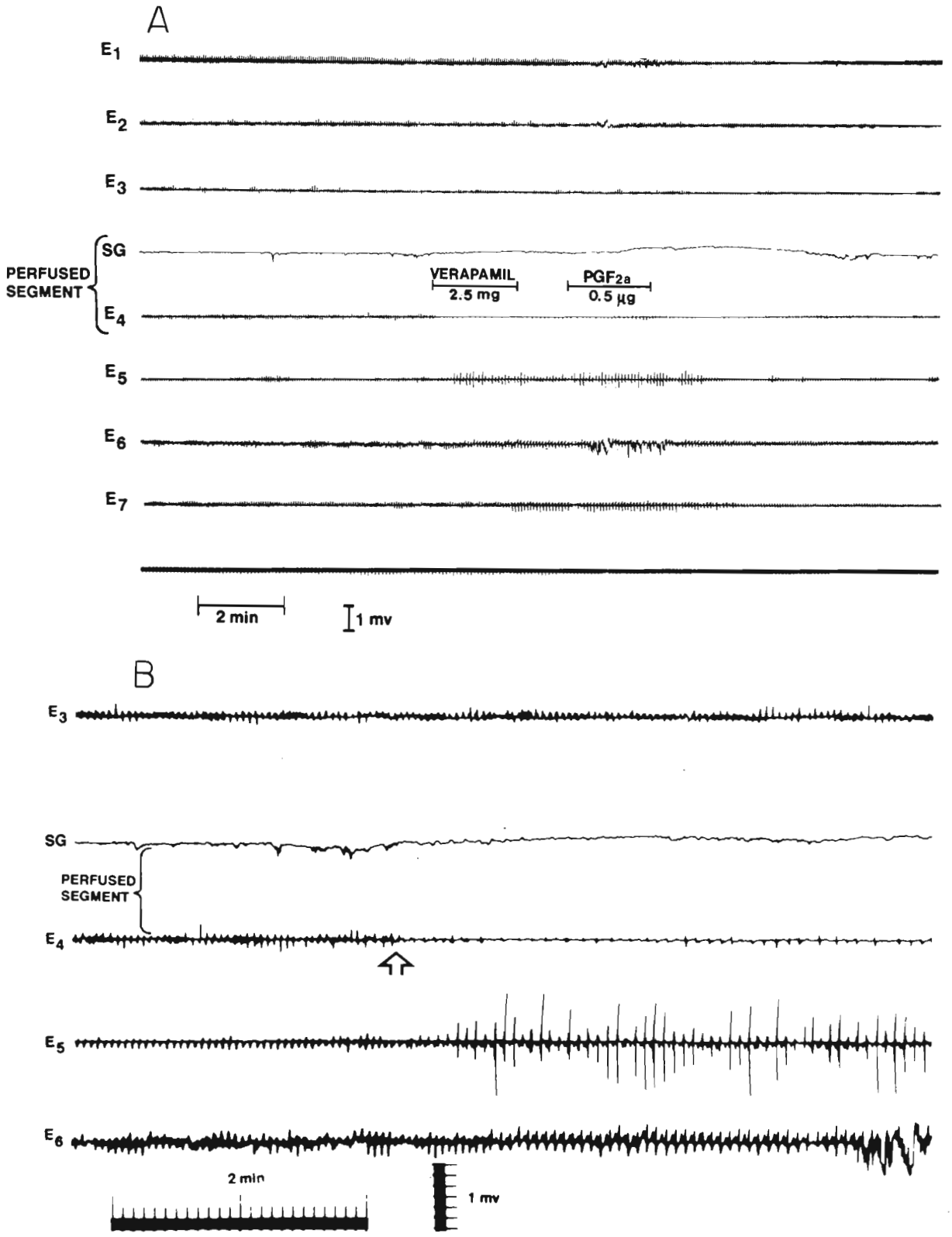

Fig. 8. *A*: effects of verapamil pretreatment on $PGF_{2\alpha}$-induced myoelectric activity. Pretreatment with verapamil abolished effect of $PGF_{2\alpha}$. *B*: magnification of *A* to show effects of verapamil on slow waves. Verapamil reduced amplitude and frequency of slow waves in perfused segment (arrow). These effects of verapamil, both on action of $PGF_{2\alpha}$ and slow waves, were observed in all 48 trials conducted.

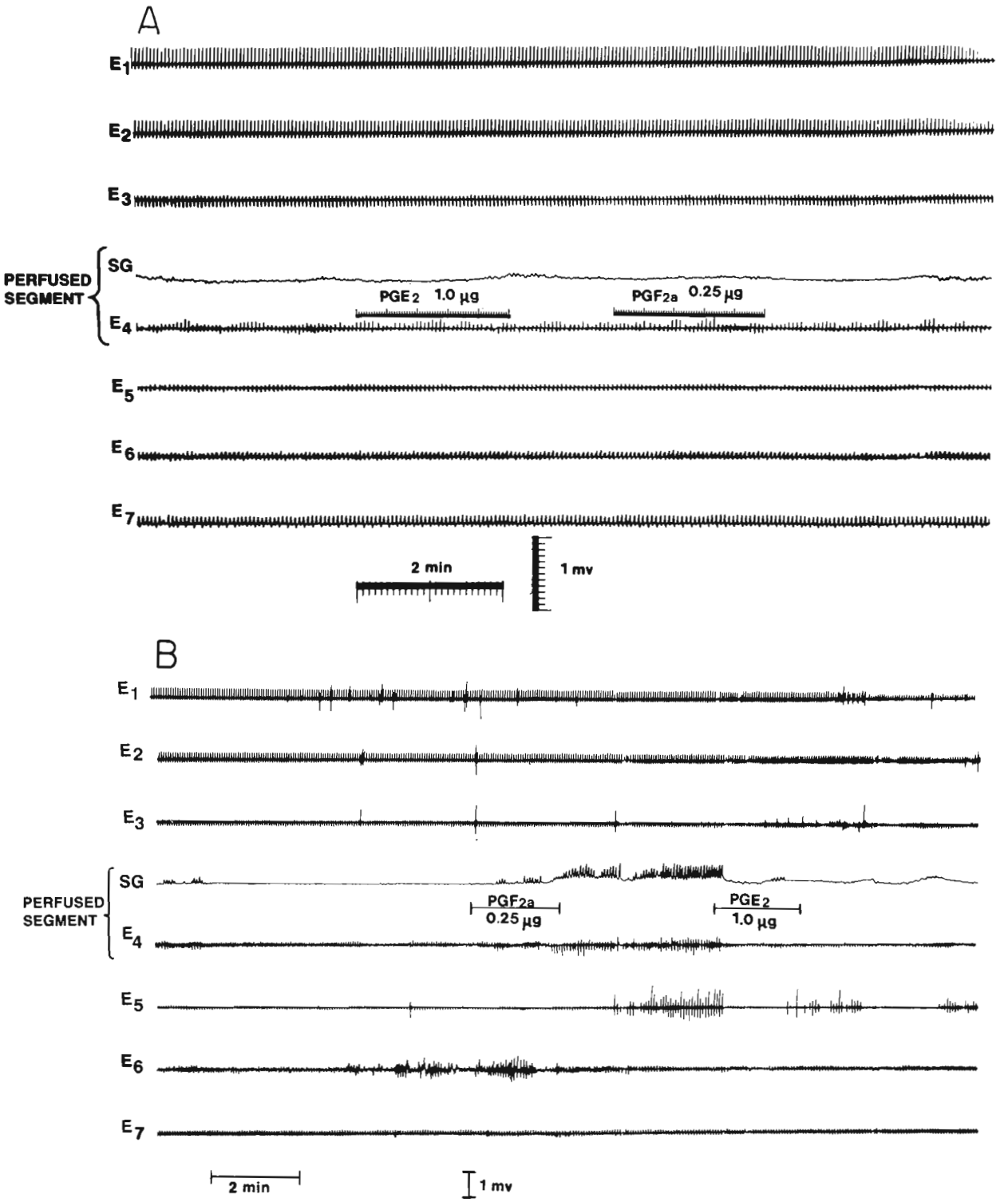

Fig. 9. *A*: effects of PGE_2 pretreatment on $PGF_{2\alpha}$-induced myoelectric activity. Pretreatment with PGE_2 prevented the action of $PGF_{2\alpha}$. *B*: PGE_2 blocked $PGF_{2\alpha}$-induced activity. These effects of PGE_2 were seen in all 48 trials conducted.

muscle and contractile cells of other tissues, such as arterioles and the glomerular mesangium (13, 21). Evidence suggests that $PGF_{2\alpha}$ acts directly on the smooth muscle membrane and affects calcium fluxes (25). Our observation that verapamil inhibited the $PGF_{2\alpha}$-induced myoelectric activity supports a calcium channel-mediated mechanism of action for this eicosanoid. As is apparent in Fig. 7*B*, verapamil reduced the amplitude and frequency of the slow waves in the perfused segments and this effect was noted before administration of $PGF_{2\alpha}$. This observation indicates that calcium channels are involved in the genesis of the slow waves (8) and may

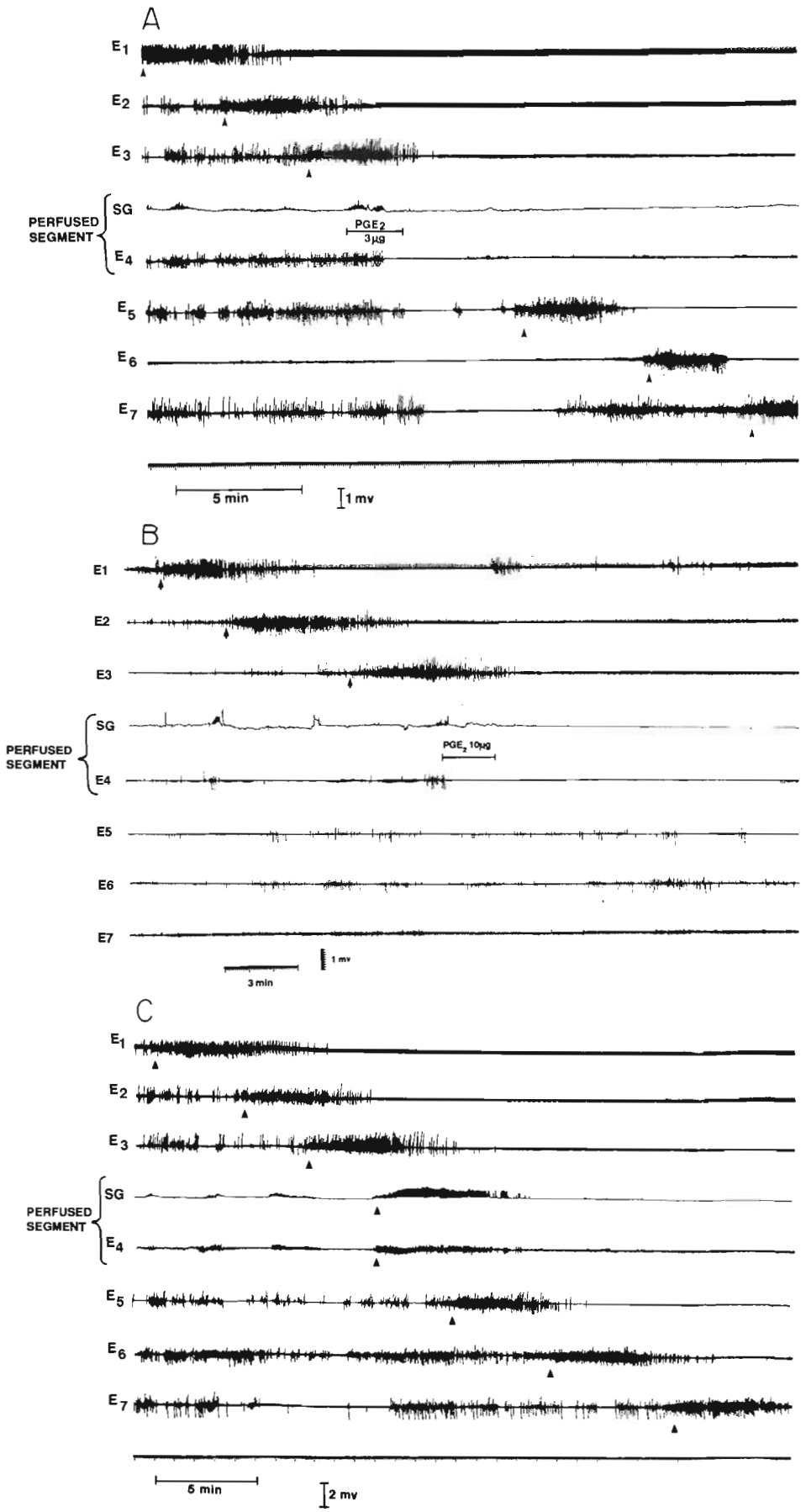

Fig. 10. *A*: effects of PGE_2 (3 μg) on phase III activity. Phase III activity was abolished in perfused segment, but there was no effect on phase III migration. Similar effects were seen in all 12 trials conducted. *B*: PGE_2 (10 μg) inhibited both phase III activity and migration. Similar effects were seen in 9 of 12 trials conducted. *C*: normal phase III migration in small intestine. Note synchronous myoelectric and contractile activity in perfused segment recorded by electrode-strain gauge unit.

explain the blunting effect of verapamil on the $PGF_{2\alpha}$-induced response (Fig. 8*A*).

In a number of systems, such as the vascular smooth muscle, PGE_2 antagonizes the vasoconstrictor effect of other eicosanoids, such as $PGF_{2\alpha}$ and thromboxane A_2 (18, 26, 31). An antagonistic effect of PGE_2 was also observed on the myoelectric activity pattern induced by $PGF_{2\alpha}$ (Fig. 9, *A* and *B*). From a reviewing of the data depicted in Fig. 9, *A* and *B*, it can be concluded that PGE_2 administration prevents the genesis of myoelectric activity in response to $PGF_{2\alpha}$ given subsequently (Fig. 9*A*). Moreover, PGE_2 abolishes the $PGF_{2\alpha}$-induced response (Fig. 9*B*). These observations indicate that these two eicosanoids act on different receptors on the intestinal smooth muscle and that these receptors mediate opposing events.

In contrast to verapamil, PGE_2 had no effect on the amplitude or frequency of slow waves, thus indicating a different inhibitory mechanism for PGE_2. The inhibitory effect of PGE_2 may involve changes in intracellular adenosine 3′,5′-cyclic monophosphate levels (23, 32). However, this speculation may be unlikely, since the effect of PGE_2 on intestinal motility may differ depending on the segment of intestine studied (4).

As shown in Fig. 4, administration of $PGF_{2\alpha}$ (0.25 μg) just before the arrival of phase III activity in the perfused segment of intestine had no effect on phase III migration despite the fact that it induced myoelectric and contractile activity in the perfused segment. This observation differs from those of Thor and co-workers (28), who reported that $PGF_{2\alpha}$ blocked the MMC and increased spike activity. However, this difference could be explained by the different technique of prostaglandin administration. In those studies $PGF_{2\alpha}$ was infused into the stem of the superior mesenteric artery, and it is possible that the $PGF_{2\alpha}$-induced intense spike activity in the entire small intestine by this model of administration might have masked phase III migration.

The dose-related effect of PGE_2 on phase III migration (Fig. 10, *A* and *B*) is puzzling. It is unclear why PGE_2 at 3 μg did not prevent migration of phase III, whereas at 10 μg it inhibited migration. This effect should be viewed as a "local" effect, since all drugs used in this study were also given by the systemic intravenous route to exclude the possibility of an overt systemic effect. In addition we defined the highest dose that could be given close intra-arterially without producing systemic response. The possibility exists, however, that after the administration of the high dose of PGE_2 a systemic effect may have occurred.

In conclusion, our studies assessed the effects of two eicosanoids with opposing biological actions on intestinal myoelectric and contractile activity. The effect of $PGF_{2\alpha}$ is excitatory, calcium channel dependent, and independent of intrinsic innervation. The effect of PGE_2 both on the spontaneous and $PGF_{2\alpha}$-induced small intestinal myoelectric and contractile activity is inhibitory and apparently independent of calcium channels.

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