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S J Shiff, R D Soloway, W J Snape Jr

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Research Article

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Mechanism of Deoxycholic Acid Stimulation of the Rabbit Colon

S. J. SHIFF, R. D. SOLOWAY, and W. J. SNAPE, JR., *Gastrointestinal Section, Department of Medicine, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania 19104*

ABSTRACT Previous studies showed that deoxycholic acid (DCA) stimulated migrating action potential complexes (MAPC) in the colon. The aim of this study was to clarify the mechanism of DCA-stimulated colonic motility.

Myoelectrical and contractile activity were measured in New Zealand White rabbits from a loop constructed in the proximal colon. During the control period, slow waves were present at a frequency of 10.8±0.5 cycle/min and there were 1.5±0.5 MAPC/h. After adding DCA (16 mM) to the loop the slow wave activity was unchanged. However, MAPC increased to 15.1±2.4 MAPC/h ($P < 0.001$). MAPC activity was not stimulated in the colonic smooth muscle outside the loop. The intraluminal addition of procaine or tetrodotoxin to the colonic loop inhibited the DCA-stimulated increase in MAPC activity (0.2±0.2 MAPC/h) ($P < 0.005$). Intravenous administration of atropine or phentolamine also inhibited MAPC activity that had been stimulated by DCA ($P < 0.005$). Pretreatment with 6-hydroxydopamine also inhibited an increase in MAPC activity. Propranolol, trimethaphan camsylate, or hexamethonium had no effect on DCA stimulation of MAPC activity. Although the concentration of bile salt increased in the mesenteric venous outflow from the colonic loop, the intravenous administration of bile salt did not stimulate colonic MAPC activity.

These studies suggest: (*a*) the action of DCA on smooth muscle activity is a local phenomenon, (*b*) the increase in MAPC activity is dependent on intact cholinergic and alpha adrenergic neurons, and (*c*) an increase in the concentration of bile salts in the serum is not associated with an increase in colonic MAPC activity.

INTRODUCTION

Recent studies showed that bacterial toxins within the intestinal lumen increase intestinal secretion and alter the motility pattern (1–4). The bacterial toxins stimulate migrating contractions that propulse the increased secretions through the intestinal tract (3, 4). Thus, in patients with infectious diarrhea, the increase in luminal fluid accumulation and the alteration in bowel motility may act together to cause severe diarrhea.

Deoxycholic acid (DCA)[1] stimulates increased colonic contractility in patients with the irritable bowel syndrome and reproduces their symptoms (5). DCA increases the colonic mucosal secretion and stimulates a propulsive migrating motor complex in the colon (5–9). The increase in mucosal secretion caused by DCA is related to an increase in intracellular cyclic 3′5′ AMP that can be inhibited by the administration of propranolol (10, 11). Similar to infectious diarrhea, the simultaneous presence of both secretory and motor abnormalities might lead to a greater degree of diarrhea.

The mechanism of the migrating action potential complex (MAPC) stimulated by DCA is presently unclear. The purpose of this study was to determine the mechanism of DCA-stimulated MAPC activity. Clarification of the mechanism of the motility disorder associated with a bile salt abnormality may help therapeutically in patients with bile acid associated gastrointestinal motility dysfunction.

METHODS

Studies were performed on 43 male New Zealand White rabbits weighing 2.5–3.8 kg. The rabbits were initially tranquilized with Innovar (0.2 ml/kg intramuscular) (Pitman-Moore, Inc., Washington Crossing, NJ) and anesthetized with sodium pentobarbital (25 mg/kg) administered intravenously through the ear vein. A tracheostomy was performed in each animal and respiratory activity was controlled by a small animal respirator (Harvard Apparatus Respirator, Harvard Apparatus Co., Inc., S. Natick, MA).

The proximal colon was located through a midline ab-

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[1] *Abbreviations used in this paper:* DCA, deoxycholic acid; MAPC, migrating action potential complexes.

dominal incision. The temperature of the abdomen was maintained at 37°C throughout the experiment by the use of a heat lamp. Beginning 2 cm from the ileocecal valve, a 15-cm loop was constructed. Four bipolar silver-silver chloride electrodes were sewn on the antimesenteric border of the serosa of the loop in contract with circular muscle. In some experiments a fifth electrode was placed 6 cm distal to the loop (8).

A strain gauge (R. B. Products, Madison, WI) was sewn to the serosal surface between the second and the third electrodes. The strain gauge was shaped to accomodate the curvature of the colon. The strain gauge was oriented in the circular direction on the antimesenteric wall of the colon with sutures attached only to circular muscle. In some experiments a second strain gauge was sewn onto the loop. It also was oriented in the circular direction.

A polyethylene tube (i.d. 0.030 in.) was inserted in the proximal end of the colonic loop through a small serosal puncture and it was secured with a purse-string suture. Test substances were administered through the proximal tube. A second polyethylene tube (i.d. 0.250 in.) was inserted into the distal end of the loop and it also was secured by a purse-string suture. The distal catheter permitted decompression of the loop.

In studies where blood was to be collected from the animals, a mesenteric vein draining the colonic loop was cannulated using a Teflon angiocatheter (20 gauge), which was secured by a suture. In two studies a mesenteric vein draining the distal colon, which was not part of the colonic loop and was not exposed to DCA, was cannulated by the same technique. Arterial blood was obtained by cannulating the right femoral artery with a polyethylene tube (i.d. 0.030 in.), which was secured by a purse-string suture. After the surgical procedure, the abdomen was covered with a clear plastic sheet allowing observation of the colonic loop during the study.

Each electrode was connected to a rectilinear recorder (Beckman Instruments, Inc., Fullerton, CA, R611 Dynograph) through AC couplers (9806A). Studies were performed with a time constant of 1.0 s and low pass filter of 22 Hz. A grounding wire was placed in the subcutaneous tissue of the left hind limb.

Each strain gauge was connected to the rectilinear recorder through a strain gauge coupler (9803). Respirations were recorded by a pneumograph placed around the chest and connected to a pressure transducer (Statham P321A, Statham Instruments, Inc., Oxnard, CA).

All animals were allowed to stabilize for at least 1 h after the surgical preparation. After this period 3.0 cm^2 of normal saline was added to the loop. Myoelectrical and strain gauge recordings were performed for a 1-h period. After the saline control period, 3.0 cm^3 of 16 mM deoxycholic acid (Sigma Chemical Co., St. Louis, MO) was added to the loop. Myoelectrical and strain gauge recordings were performed for 1–4 h after the addition of the DCA. After stimulating MAPC activity by DCA, neural antagonists were administered. 3.0 cm^3 of Procaine-HCl (1%) (Invenex, Inc., Hialeah, FL), or tetrodotoxin (40 mg/kg) (Calbiochem-Behring Corp., American Hoechst Corp., San Diego, CA) were added intraluminally through the proximal catheter. Atropine-sulfate (0.1 mg/kg) (Vitarine, New York), phentolamine mesylate (1 mg/kg) (Ciba-Geigy Corp., Summit, NJ), or propranolol-hydrochloride (1 mg/kg) (Ayerst Laboratories, New York), were added intravenously through an ear vein in a 5-min infusion. Trimethaphan camsylate was intravenously infused continuously (4 mg/min). Hexamethonium (40 mg/kg) (Sigma Chemical Co.) was injected into two animals. Three animals were pretreated 48 h before the study with 6-hydroxydopamine (50 mg/kg) (Sigma Chemical Co.) If more than one drug was used in a day, the second drug was added 1 h after MAPC activity returned to preantagonist levels.

During the saline control period and during the addition of DCA to the colonic loop, blood was obtained from the mesenteric vein leading from the colonic loop and from the femoral artery and analyzed for plasma bile acids. In two experiments blood was also taken from a mesenteric vein that was draining the colon 8–10 cm distal to the colonic loop. Plasma and intraluminal bile acid concentrations were determined by a modified method of Osuya et al. (12). The technique in this study used a double beam spectrophotometric analysis (13). Plasma was treated with isopropanol to extract bile acids.

In three animals DCA was continuously perfused intravenously through an ear vein at a rate of 21 μM/min for 1 h. The amount of DCA infused was calculated to raise the systemic plasma bile acid concentration to levels comparable to those observed in the mesenteric venous outflow when DCA was given intraluminally. The DCA used for the intravenous infusion was suspended in a 1% albumin-normal saline solution to prevent hemolysis of the erythrocytes. During this period myoelectrical and strain gauge activity were recorded and blood was collected from the femoral artery and mesenteric veins draining the loop. Blood samples were analyzed for plasma bile acid concentration. In addition, intraluminal contents were collected from the distal catheter of the loop and also analyzed for bile acid content.

Myoelectrical recordings were evaluated for slow wave frequency in cycles per minute. Spike activity was measured as the percentage of slow waves with superimposed spike potentials. Migrating action potential complexes were defined as a continuous band of spike potential discharge lasting for 2.5 s or longer and occurring on at least two consecutive electrode sites (8). The propagation velocity and the duration of the MAPC were measured.

Statistical analysis was performed using the unpaired Student's t test.

RESULTS

Fig. 1 shows a myoelectrical recording from colonic loops of rabbits after adding normal saline (1A) or deoxycholic acid (DCA) (1B) to the colonic loop. Fig. 1A shows a record after the intraluminal infusion of normal saline. Slow wave activity is present at a frequency of 9.3 cycles/min. Many of the slow waves have superimposed spike potentials. The strain gauges, monitoring circular muscle contractile activity, show no contractile response. Fig. 1B shows a recording from a colonic loop after adding DCA (16 mM) within the lumen of the colonic loop. Electrode E5 is placed on the distal colon outside the DCA-treated loop. MAPC are present, migrating aborad with a velocity of 17.6 mm/s. The MAPC occurs only in the DCA-treated length of colon and the MAPC does not propagate outside the loop. Stain gauges show that a circular muscle contraction occurred simultaneously with the MAPC activity. The MAPC never occurred outside the colonic loop that had been treated with DCA.

Table I shows the indices of myoelectrical activity obtained from the colonic loops of the rabbits studied. The mean slow wave frequency was 10.8±0.5 cycles/

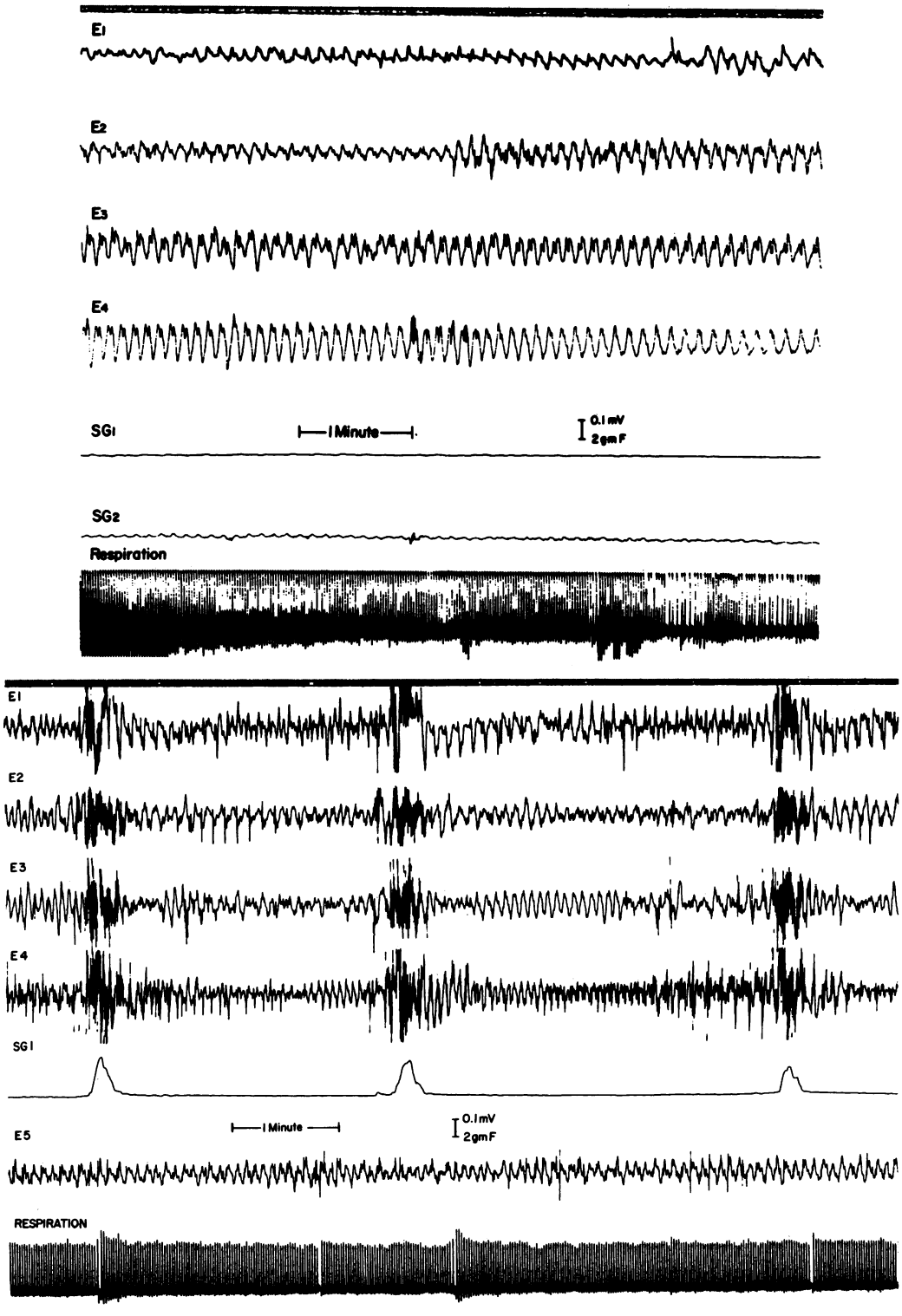

FIGURE 1 Myoelectrical recording from colonic loops from rabbits. Electrode, E_1 is orad and E_4 is caudad in the loop. (A) Myoelectrical recording after adding 3.0 cm^3 of normal saline to the loop. No MAPC are present. Strain gauge (SG_1 and SG_2) are sewn at the level of E_2 and E_3. (B) Myoelectrical recording after adding 3.0 cm^3 of 16 mM DCA to the loop. Electrode E_5 is 6 cm distal to the loop. 3 MAPC are present. The strain gauge (SG_1) is sewn between E_2 and E_3.

TABLE I
Myoelectrical Characteristics of Rabbit Colon

	Slow wave frequency	Slow waves with superimposed spike potentials
	cpm	%
Saline	10.8±0.5	75.1±4.3
Deoxycholic acid	10.2±0.3	82.1±3.4

min after the addition of saline to the loop. Spike potentials were superimposed on the majority of the slow waves after saline administration to the colonic loop (75.1±4.3%). The administration of 16-mM DCA did not significantly alter the slow wave frequency, or the percentage of slow waves with spike potentials.

During the control period, after adding saline to the loops, 1.8±0.5 MAPC/h occurred within the loop. These MAPC had a propagation velocity of 9.7±1.3 mm/s and a duration of 18.6±3.0 s. DCA increased the frequency of MAPC activity to 15.1±2.4/h ($P < 0.001$). After adding DCA, the velocity of the MAPC increased to 16.6±1.4 mm/s ($P < 0.005$) and the duration of the MAPC decreased to 12.1±1.0 s ($P < 0.025$).

Fig. 2 shows a myoelectrical recording from a colonic loop that had been stimulated by DCA. Procaine was added intraluminally at the arrow. After adding DCA, MAPC are stimulated with concurrent migrating contractions. The addition of procaine totally abolished the MAPC activity that had been stimulated by DCA within 1 min. No MAPC activity occurred after adding procaine intraluminally.

Fig. 3 shows the number of MAPC after adding DCA alone or after the simultaneous administration of the antagonists, procaine, intraluminally—or atropine, phentolamine, or propranolol, intravenously. DCA increased the MAPC activity to 15.1±2.4 MAPC/h ($P < 0.001$). The intraluminal administration of procaine reduced DCA-stimulated MAPC activity (0.2±0.2 MAPC/h) ($P < 0.005$). In two animals intraluminal tetrodotoxin also abolished DCA-stimulated MAPC activity. Atropine infusion reduced the MAPC frequency to 0.3±0.3 MAPC/h ($P < 0.025$). Phentolamine (1.0 mg/kg) an alpha adrenergic antagonist, similarly reduced the MAPC frequency to 0.3±0.3 MAPC/h ($P < 0.005$). A lower concentration of phentolamine (0.25 mg/kg) also completely inhibited the MAPC activity. Sympathetic denervation wth 6-hydroxydopamine prevented an increase in MAPC activity after DCA. However, after the administration of the beta adrenergic antagonist, propranolol, DCA continued to stimulate colonic MAPC activity (9.8±1.4 MAPC/h) ($P < 0.001$).

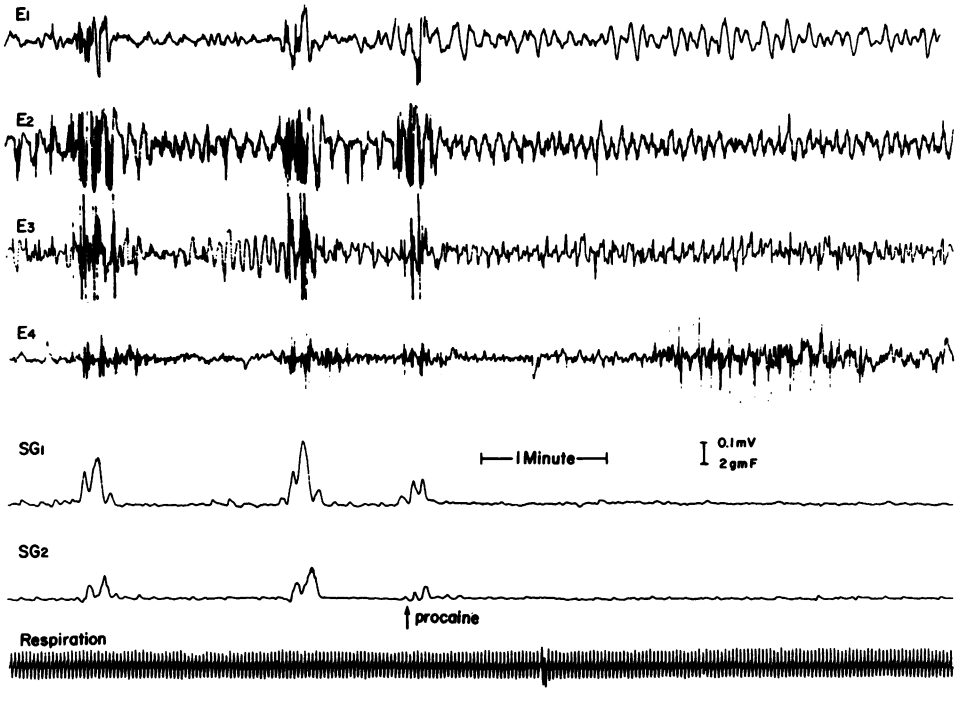

FIGURE 2 Myoelectrical recording from a colonic loop in which MAPC activity had been induced with 16 mM DCA. Procaine added to the loop (↑) abolished MAPC activity.

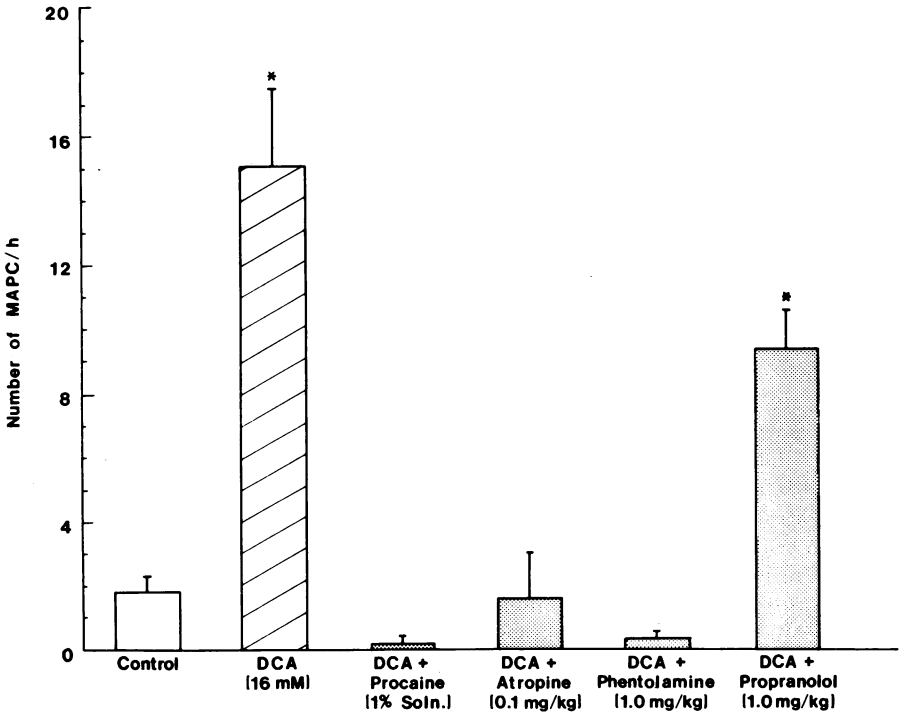

FIGURE 3 The number of MAPC per 1 h stimulated by 16 mM DCA when administered alone and simultaneously with antagonists. All values compared for significance with the saline control. The data is shown as a mean±SEM. Minimum of six animals was administered each compound.* $P < 0.001$.

Fig. 4 shows a myoelectrical recording after MAPC activity has been stimulated by the intraluminal administration of 16 mM DCA. Trimethaphan camsylate was infused intravenously at a rate of 4 mg/min. This dose of trimethaphan decreased the blood pressure, but had no effect on the MAPC activity.

Fig. 5 shows the effect on MAPC activity of DCA alone and the simultaneous administration of DCA and trimethaphan camsylate. DCA increases the MAPC activity from 1.2±0.7 MAPC/10 min to 3.5±0.6 MAPC/10 min ($P < 0.01$). Ganglionic blockade with trimethaphan camsylate did not block the DCA stimulation of MAPC activity 2.5±1.3 MAPC/10 min ($P > 0.05$). Similar results were obtained after the administration of hexamethonium in two studies (2.4±0.1 MAPC/10 min). Hexamethonium also decreased the systemic blood pressure, but had no effect on DCA-stimulated MAPC activity.

Fig. 6 shows the plasma bile acid concentration obtained from the mesenteric vein draining the colonic loop and from the femoral artery. After saline administration to the colonic loop, the plasma bile acid concentration was 13.3±1.7 μM from the mesenteric venous outflow and 4.9±0.4 μM from the femoral artery. After adding 16 mM DCA into the colonic loop, the plasma bile acid concentration in the mesenteric venous blood flowing from the loops increased to 150±26.3 μM ($P < 0.001$). The plasma bile acid concentration in the femoral arterial blood did not change from basal levels after the administration of 16 mM DCA (5.2±1.2 μM) ($P > 0.05$). Blood taken from a mesenteric vein draining the distal colon, not exposed to the intraluminal administration of DCA, showed a plasma bile acid concentration of 4.1±0.1 μM. Thus, the level of plasma bile acids was not changed in the venous outflow from the colon not included in the DCA-treated loop.

DCA was infused intravenously to assess the effect of high intravascular concentrations of DCA. Fig. 7 shows the effect of the intravenous infusion of DCA on plasma bile acid levels and the corresponding level of MAPC activity. The intravenous infusion of a 21-μM/min solution of DCA increased the plasma bile acid level to 214±85 μM in the mesenteric venous blood. Thus plasma concentration of the bile acid in the mesenteric vein draining the colonic loop is similar to the concentration after instillation of DCA into the colonic loop. The level of plasma bile acids in the femoral artery is similar to the mesenteric venous level. The increase in serum DCA concentration by the in-

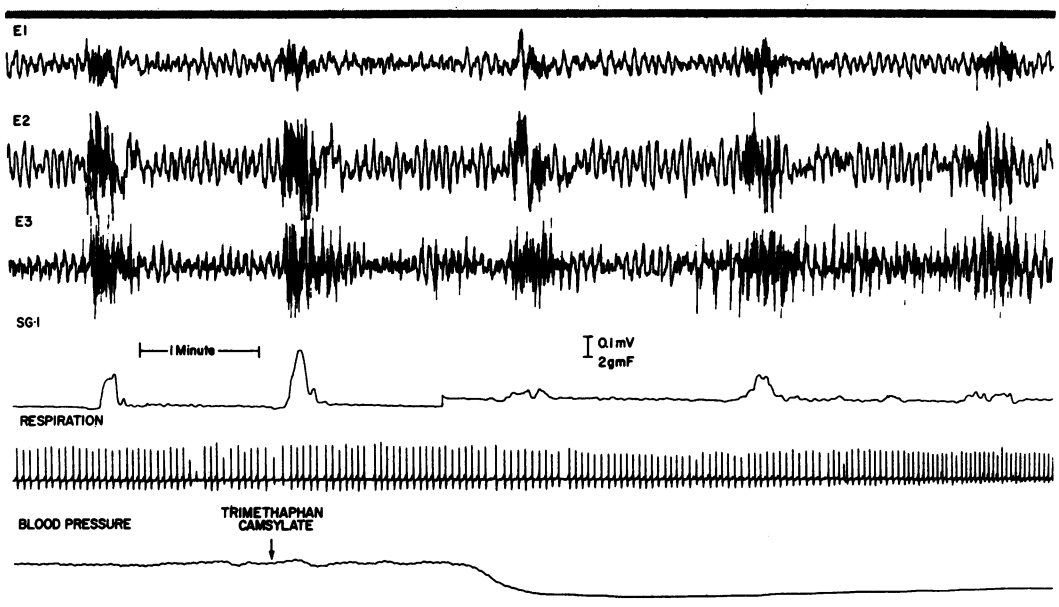

FIGURE 4. Myoelectrical recording from a colonic loop of a rabbit. DCA-stimulated MAPC activity is present. Trimethaphan camsylate (4.0 ml/min) decreased the blood pressure but did not affect the MAPC activity.

travenous administration of DCA did not increase the intraluminal concentration of bile salts (12.7±1.7 μM) over control levels (8.1±2.8 μM) ($P > 0.05$). Despite elevated plasma bile acid concentrations, there was no increase in colonic MAPC activity. Thus, stimulation of colonic MAPC activity appears more dependent on the intraluminal concentration of bile acids than the plasma levels of the bile acids.

DISCUSSION

High intraluminal concentrations of bile salts stimulate colonic motor activity (5, 8, 9). In the rabbit, DCA stimulated MAPC activity in the proximal colon, which propulsed intraluminal contents through the colonic loop (8). The increase in MAPC activity is re-

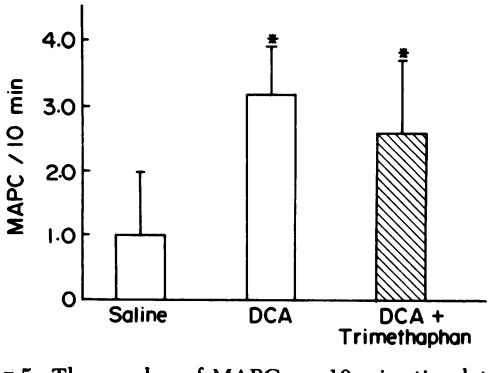

FIGURE 5 The number of MAPC per 10 min stimulated by 16 mM DCA. When administered alone and simultaneously with trimethaphan camsylate. The data is shown as a mean±SEM. The values are compared to the saline control for significance.* $P < 0.05$.

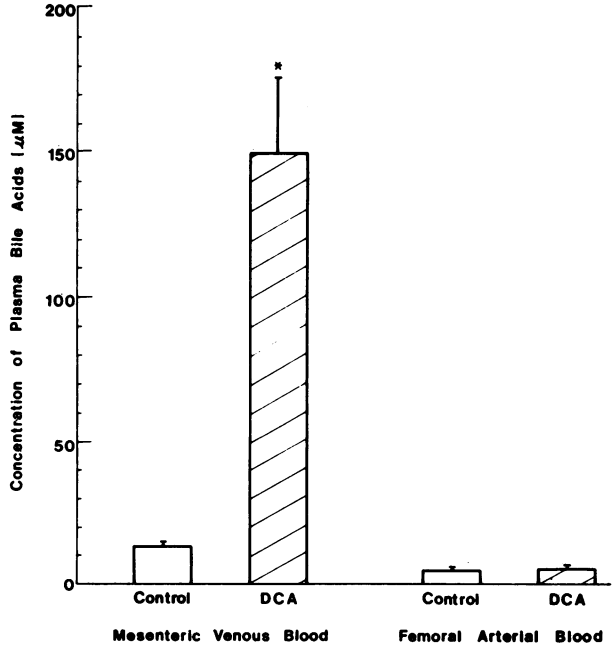

FIGURE 6 Plasma bile acid concentration in the mesenteric venous blood from the colonic loop and femoral arterial blood after the intraluminal administration of DCA (16 mM) to the colonic loop.* $P < 0.001$.

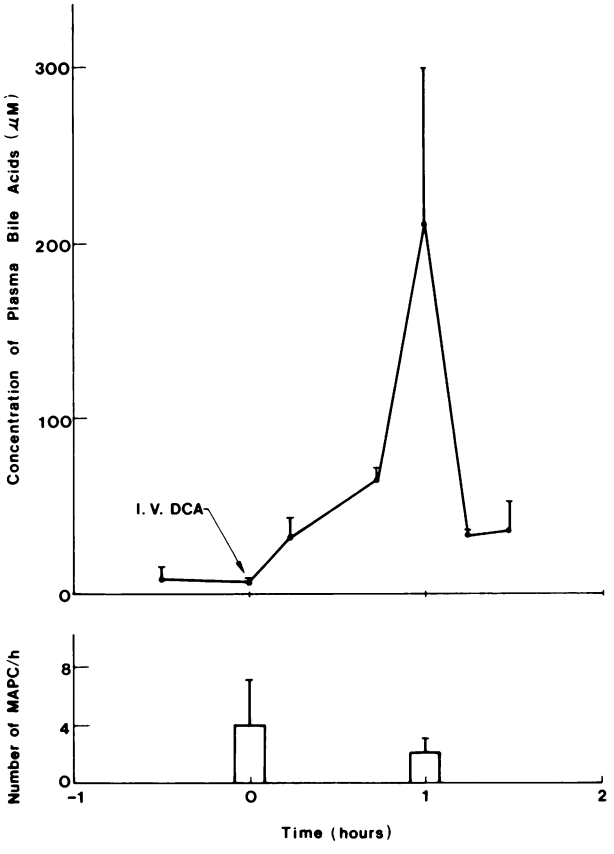

FIGURE 7 Plasma bile acid concentration from the mesenteric vein (above) and number of MAPC per hour (below) during the intravenous infusion of DCA. The infusion began at time 0 (shown by the arrow) and was discontinued at 1 h. The plasma bile acid level precipitously decreased when the infusion was stopped.

lated to the concentration and the total duration of the mucosal exposure to DCA (8). The purpose of these studies was to determine the mechanism through which DCA stimulated the colonic smooth muscle MAPC activity.

Mucosal contact by the DCA appears to be essential for the stimulation of colonic MAPC activity. The increase in MAPC activity occurred only within the smooth muscle included in the colonic loop and did not occur in the colon excluded from the loop containing DCA. In addition, intravenous infusion of DCA failed to stimulate colonic MAPC activity despite similar concentrations within the serum in the mesenteric vein. Thus, the effect of DCA on colonic smooth muscle appears to be a local phenomenon and the receptors that are sensitive to DCA seem to be present in the wall of the colonic loop.

DCA appears to stimulate MAPC activity within the colonic loop through a neural mechanism. Procaine is a local anaesthetic that acts as an antagonist of local neural reflexes (14, 15). Procaine blocks excitation of the neural membrane. The small diameter sensory afferent nerves are affected quickly (15). The intraluminal administration of procaine inhibited DCA-stimulated MAPC activity, despite the continued presence of DCA within the loop. Procaine possibly inhibits the DCA stimulation of MAPC activity by blocking the afferent neural receptors present within the mucosa or submucosa of the colonic loop or by blocking the transmission of impulses through the myenteric plexus. Because procaine inhibited the generation of DCA-stimulated MAPC activity, continuous stimulation of the neural receptors appears necessary for sustained MAPC activity. Inhibition of the DCA-stimulated MAPC activity by the local administration of tetrodotoxin confirms the importance of local neural reflexes in the generation of the MAPC activity.

Stimulation of colonic MAPC activity by DCA appears to require intact cholinergic and alpha adrenergic neural pathways. Both atropine, a muscarinic antagonist, and phentolamine, an alpha adrenergic antagonist, inhibit DCA stimulation of MAPC activity. Beta adrenergic blockade with propranolol does not alter DCA-stimulated MAPC activity. Ganglionic blockade by trimethaphan or hexamethonium also had no effect on DCA stimulation of MAPC activity. Trimethaphan and hexamethonium have their major antagonist effect on nicotinic-cholinergic synaptic junctions (16). The neural receptor antagonist drugs were used at doses that blocked the action of the agonist. Thus, these data suggest that DCA stimulated a neural reflex that requires intact muscarinic-cholinergic neurons and alpha adrenergic neurons, but does not require a synapse through a nicotinic-cholinergic junction.

These data suggest a complicated neural pathway. A muscarinic-cholinergic neuron may synapse with an adrenergic interneuron whose neurotransmission to a postganglionic neuron can be blocked with alpha adrenergic antagonists (17). This mechanism is consistent with the importance of muscarinic and alpha adrenergic receptors in DCA stimulation of the colonic loop and with the lack of an effect by the blockade of nicotinic ganglionic synapses.

DCA stimulation of colonic MAPC activity differs from DCA stimulation of colonic mucosal secretion. DCA stimulates mucosal secretion through an increase in adenylate cyclase, which is mediated through the beta adrenergic system (6, 10). Propranolol inhibits the increase in colonic mucosal secretion, but it has no effect on DCA stimulation of motor activity.

After demonstrating the importance of the neural pathways for DCA stimulation of the colon, it was necessary to evaluate the direct effect of high serum levels of DCA on the colonic smooth muscle. When the serum levels of DCA were increased to the level

observed in the mesenteric venous blood, there was no increase in the number of MAPC. Despite the local increase in serum and tissue levels of DCA, the binding of DCA to local intraluminal neural receptors appears to be most important.

These studies suggest that in addition to the known secretory response that occurs due to exposure to excessive luminal concentrations of dihydroxy bile salts in the colon, there is a locally initiated, neurally mediated abnormal colonic motor pattern. This response differs from the secretory response because the motor response can be inhibited by muscarinic or alpha adrenergic blockade rather than beta adrenergic blockade.

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