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Rectal response of cardiac origin in the cat: involvement of nitric oxide and acetylcholine

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Abstract

Local application of nicotine over the surface of the left ventricle and also occlusion of the left anterior descending coronary artery in the lightly anaesthetised, open-chested, artificially ventilated cat resulted a biphasic rectal movement – initial relaxation followed by sustained contraction. However, distension of the atrial appendage did not evoke any change in rectal motility, indicating the non-involvement of atrial volume receptors in initiating this rectal response of cardiac origin. The relaxation phase of this response was not abolished by pretreatment with atropine or with phentolamine or propranolol but was abolished by the nitric oxide inhibitor, N^G-nitro-L-arginine (LNNA), and this blockade of the relaxation phase by LNNA was reversed by L-arginine. The contraction phase, however, was abolished by atropine. From these observations it is clear that the relaxation phase of the rectal response to coronary occlusion or epicardial nicotine is mediated through neither cholinergic nor adrenergic pathways but through the release of nitric oxide whereas the contraction phase of such a cardio-rectal response is mediated through the release of the neurotransmitter, acetylcholine.

Keywords: Myocardial ischemia; Nicotine; N^G-Nitro-L-arginine (LNNA); L-Arginine (L-Arg)

1. Introduction

Local application of nicotine over the infero-posterior wall of the left ventricle produces myocardial ischemia and consequently cardiac pain which often excites sympathetic afferents (Casati et al., 1979; Pal et al., 1989). It has been demonstrated earlier that experimental occlusion of the coronary artery of the cat results in an increase of unit activity in the cardiac sympathetic nerves (Brown, 1967; Casati et al., 1979; Pal et al., 1989). It has also been demonstrated that application of algesic agents like nicotine, bradykinin and prostaglandins results in increased activity of the cardiac sympathetic afferents. Distension of the venoatrial junction also results in an increase of unit activity in the cardiac sympathetic (Schwartz et al., 1973) and vagus nerves (Paintal, 1973). Cardiac ischemia, produced by nicotine application or by experimental coronary artery occlusion, is associated with nausea, vomiting, urination and also evacuation of the bowels (Abrahamsson and Thoren, 1972; Johannsen et al., 1981; Koley et al., 1992, 1995a,b). Koley et al. (1992) have also reported gastric relaxation following occlusion of the coronary artery as well as application of nicotine. They have shown clearly that the afferent pathways for such a cardiogastric reflex lie in the cardiac sympathetic nerves while the efferent pathways lie in the gastric vagus. Recently Koley et al. (1995a) reported biphasic rectal movement following local application of nicotine, lactic acid or coronary artery occlusion. Afferent pathways have been described in the cardiac sympathetic nerves, but the neurotransmitters involved in such a cardiorectal reflex are still not clear. Attempts have been made to investigate the neurotransmitters involved in eliciting these rectal responses of cardiac origin.

2. Materials and methods

Experiments were carried out on 48 cats of either sex, body weight 2–3 kg, after an overnight fast with water ad libitum. The animals were anaesthetised with α-chloralose at a dose of 60 mg/kg body weight after an initial

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induction with anaesthetic ether. Anaesthesia was kept up throughout the experiment with a maintenance dose of chloralose (10 mg/kg, i.v.) if and when required. The femoral artery, the femoral vein and the trachea were routinely cannulated. A glucose solution (5%) in physiological saline (0.9%) was administered by drip feed into the femoral vein (1 ml/min) throughout the experiment to maintain body fluids and pH. Blood pressure was recorded from the femoral artery on a Beckman RM Dynograph using a pressure transducer (Type 4-327-0129). For monitoring body temperature a thermometer was placed into the anal canal and body temperature was maintained at 37°C with a heating pad. Studies were performed on animals given pancuronium (1 mg/kg, i.v.), a skeletal muscle relaxant, to eliminate the participation of external anal sphincter and other adjoining skeletal muscles in the resting intrarectal pressure (Rattan et al., 1992).

2.1. Opening of the chest

Before the chest was opened the animals were artificially respired with a Starling Ideal Respiratory Pump (INCO, India). A left thoracotomy was performed by removing thoracic ribs 2–6. The pericardium was cut longitudinally and a cradle was made around the heart with the cut ends of the pericardium. The heart was kept moistened with a cotton film soaked with warm physiological saline from time to time. An operating table lamp was also used to maintain the epicardial temperature near 37°C. To stimulate the cardiac sensory receptors by local application, nicotine (200 μg/ml) was applied over the epicardial surface of the left ventricle, using a cotton applicator, for 60 s taking care to prevent mechanical disturbance of this region. After 60 s, the cotton applicator was removed and the ventricular surface was washed with physiological warm saline at least three times to remove all traces of nicotine. The left stellate ganglion and the left inferior cardiac nerve were exposed carefully and cleaned from the surrounding connective tissues under a dissecting microscope (Vickers Instrument, UK). The central cut end of the left inferior cardiac nerve was stimulated electrically by a Grass SD9 stimulator with square-wave pulses (40–60 Hz, 6 V, 0.6 ms for 30–60 s).

2.2. Occlusion of coronary artery

In the experiments where effects of myocardial ischemia were to be investigated, the main left anterior descending coronary artery was separated along its length (2–3 mm) from the surrounding tissues under a dissecting microscope. The coronary artery was occluded with the help of a snare. The snare was made with a fine nylon thread placed loosely around the left anterior descending coronary artery and the ends of the thread were passed through a narrow, short polyethylene tube. Fully reversible occlusion was induced by pulling the nylon thread forward and pushing the polyethylene tube over the coronary artery (Koley et al., 1985).

2.3. Recording of rectal motility

A balloon (1.0–1.5 cm of a condom distended with 8–12 ml of warm saline) connected to a pressure transducer via a hard polyethylene tube was introduced into the rectum aborally by a small incision in the descending colon. The position of the balloon was fixed by tying the polyethylene tube at the incision on the descending colon. Rectal motility in the form of intrarectal pressure was recorded on an INCO polygraph (Koley et al., 1995a).

2.4. Stimulation of atrial receptors

A small balloon connected with the polyethylene tube was introduced into the left atrial appendage by a small incision over the appendage wall and the incision was closed along the tube with a fine nylon thread. The balloon was distended with 0.5–2 ml of warm physiological saline via the polyethylene tube to stimulate the atrial receptors.

In all the animals, the experiments were repeated after recording of at least 3 reproducible cardiorectal reflexes. After the administration of various neurotransmitter blockers, standard time intervals were allowed for completion of their blocking actions and the blockade was checked with appropriate drug. In such animals the application of nicotine or coronary artery occlusion was repeated to obtain reproducible results.

2.5. Statistical analysis

The results were expressed as means ± S.E.M. Significance was tested using Student's *t*-test. In the case of control rectal responses of cardiac origin, significance was tested using the average initial intrarectal pressure (in mmHg) and the intrarectal pressure during the relaxation and contraction phase. The percentage changes in intrarectal pressure during relaxation and contraction were compared between the control group and each neurotransmitter-pretreated group.

2.6. Drugs used

α-Chloralose (Koch-Light Lab, UK); nicotine hydrogen tartrate (BDH, UK); atropine sulphate (Bengal Immunity, India); phentolamine mesylate (Regitine, Ciba-Geigy, UK); *d,l*-propranolol hydrochloride (ICI, India); hexamethonium bromide (Koch-Light Lab, UK); pancuronium (Pavulon, Infar (India), India); N^G-nitro-L-arginine (Sigma, USA) and L-arginine (Sigma, USA). All the drugs used, including the neurotransmitter blockers, were dissolved in physiological saline at a concentration such that no more than 0.5 ml was needed for drug application.

3. Results

3.1. Rectal responses of cardiac origin

3.1.1. Effect of coronary artery occlusion

Occlusion of the left anterior descending coronary artery for a period of 90–120 s (depending on the condition of the heart) caused myocardial ischemia as evidenced by blackening of the ventricular surfaces, fall of blood pressure and heart rate. At the same time it caused a biphasic rectal response – initial inhibition or decrease of the spontaneous movement with or without relaxation followed by a large sustained contraction (Fig. 1A). In five out of 42 observations no relaxation was observed but inhibition of the spontaneous motility of rectum followed by contraction persisted. Table 1 shows clearly that during the relaxation phase the intrarectal pressure was reduced to 25.18 ± 0.90 mmHg ($P < 0.001$) and in the contractile phase the intrarectal pressure was increased to 47.24 ± 1.54 mmHg ($P < 0.001$) from a normal intrarectal pressure of 30.75 ± 0.82 mmHg.

3.1.2. Effect of nicotine

Local application of nicotine (200 μg/ml) for 60 s over the left coronary blood vessels induced a similar biphasic rectal response (Fig. 1B). In six out of 48 observations there was no relaxation but the inhibition of the spontaneous motility followed by contraction persisted. During the relaxation phase the mean intrarectal pressure was reduced to 26.16 ± 0.92 mmHg ($P < 0.001$) and during the contractile phase the mean intrarectal pressure was increased to 43.82 ± 0.90 mmHg ($P < 0.001$) from the normal intrarectal pressure (Table 1).

3.1.3. Effect of atrial receptors on rectal motility

Stimulation of atrial receptors ($n = 8$) by distension of the left atrial appendage with 0.5–2 ml warm physiological saline through a balloon did not evoke any change in rectal movement (Fig. 1C). There was no significant change of mean intrarectal pressure (29.28 ± 1.62 mmHg) from the normal intrarectal pressure (30.75 ± 0.82 mmHg). This indicates that atrial receptors have no role in the initiation of such a rectal response of cardiac origin and only ventricular receptors are involved in the manifestation of this response.

3.2. Effect of hexamethonium on rectal responses of cardiac origin

Intravenous administration of hexamethonium (1 mg/kg), the ganglionic blocking agent, reduced the spontaneous motility of the rectum, which did not return to its initial level throughout the experiment. The mean intrarectal pressure was reduced from 33.73 ± 1.56 mmHg to $29.73 + 1.38$ mmHg after hexamethonium administration. Table 1 shows that, after 15–20 min of hexamethonium pretreatment, occlusion of the left anterior descending coronary artery or epicardial nicotine application failed to induce the reflex biphasic rectal change. There was a significant reduction in percentage change in intrarectal pressure during both the relaxation ($P < 0.001$) and the contraction phase ($P < 0.001$) from that of control experiments (Fig. 2).

3.3. Effect of phentolamine and propranolol on rectal responses of cardiac origin

Administration of phentolamine (2.5 mg/kg, i.v.) reduced the intrarectal pressure from 30.25 ± 1.00 mmHg to 24.32 ± 2.10 mmHg but the intrarectal pressure regained its original level within 5–10 min. Occlusion of the left anterior descending coronary artery or epicardial nicotine application was performed after 15–20 min of phentolamine administration. In animals thus treated, occlusion of the left anterior descending coronary artery or epicardial nicotine induced a rectal response of the same magnitude (Table 1). Fig. 2 shows that during occlusion of the left anterior descending coronary artery the intrarectal pressure was reduced by $16.12 \pm 3.06\%$ during the relaxation phase and was increased by $50.2 \pm 2.53\%$ during the contractile phase, as was that of control animals.

Propranolol administration (1 mg/kg, i.v.) caused a significant rise of normal intrarectal pressure which returned to its initial value after 3–5 min. In propranolol-pretreated animals (after 20–30 min) the cardiorectal reflexes also remained unaltered (Table 1).

3.4. Effect of atropine on rectal responses of cardiac origin

Administration of atropine (1 mg/kg, i.v.) caused a marked decrease in spontaneous movement, for both frequency and amplitude. Intrarectal pressure was reduced from 34.7 ± 2.37 mmHg to 29.16 ± 0.48 mmHg and did not return to its original level throughout the experiment. Epicardial nicotine ($n = 10$) or left coronary artery occlusion ($n = 8$) after 30 min of atropinisation failed to induce the contractile phase of the rectal response of cardiac origin, leaving the relaxation phase unaltered. Table 1 shows that, during the contractile phase of the rectal response, intrarectal pressure was reduced significantly ($P < 0.001$) compared to that of control animals. Fig. 3B shows one actual response pattern to left coronary artery occlusion in atropinised cats.

Electrical stimulation of the central cut ends of the left inferior cardiac sympathetic nerve ($n = 7$) induced similar biphasic rectal movements in control animals. During relaxation the mean intrarectal pressure was reduced from 29.6 ± 2.12 mmHg to 24.8 ± 1.28 mmHg, and during contraction the mean intrarectal pressure was increased to 45.6 ± 2.80 mmHg. In atropinised animals, similar stimulation of left inferior cardiac sympathetic nerve ($n = 7$)

Table 1
Intrarectal pressure (IRP) during control and rectal biphasic response induced by left anterior descending (LAD) coronary artery occlusion or epicardial nicotine application under different experimental conditions

Experimental condition	Initial mean IRP ± S.E.M. (*n*)	LAD occlusion				Nicotine application			
		Relaxation		Contraction		Relaxation		Contraction	
		Mean IRP ± S.E.M. (*n*)	% Fall ± S.E.M.	Mean IRP ± S.E.M. (*n*)	% Rise ± S.E.M.	Mean IRP ± S.E.M. (*n*)	% Fall ± S.E.M.	Mean IRP ± S.E.M. (*n*)	% Rise ± S.E.M.
Control	30.75 ± 0.82 (48)	25.18 ± 0.90 (42) [b]	17.22 ± 0.65	47.24 ± 1.54 (42) [b]	54.98 ± 4.50	26.16 ± 0.92 (48) [b]	16.03 ± 0.75	43.82 ± 0.90 (48) [b]	43.32 ± 3.70
Hexamethonium	29.73 ± 1.38 (6)	29.96 ± 1.36 (6)	2.60 ± 0.77	30.70 ± 1.12 (6)	3.40 ± 1.69	28.53 ± 1.11 (6)	2.73 ± 1.05	29.93 ± 1.18 (6)	3.55 ± 1.65
Phentolamine	30.25 ± 1.00 (6)	24.56 ± 1.40 (6) [a]	16.12 ± 3.06	44.13 ± 2.29 (6) [b]	50.2 ± 2.53	23.75 ± 1.16 (6) [a]	15.95 ± 2.37	41.0 ± 1.42 (6) [b]	35.65 ± 2.91
Propranolol	25.37 ± 1.30 (8)	19.65 ± 0.96 (8) [a]	20.6 ± 1.77	37.6 ± 1.06 (8) [b]	52.27 ± 4.19	20.85 ± 1.11 (8) [a]	15.63 ± 1.65	35.37 ± 1.53 (8) [b]	43.75 ± 3.32
Atropine	29.16 ± 0.48 (10)	23.31 ± 1.57 (8) [a]	18.08 ± 1.59	29.75 ± 1.59 (8)	4.25 ± 1.01	24.48 ± 1.67 (10) [a]	16.1 ± 1.88	30.33 ± 1.79 (10)	4.45 ± 1.08
LNNA	30.0 ± 2.21 (8)	29.00 ± 2.19 (6)	3.31 ± 1.21	48.66 ± 5.48 (6) [b]	59.98 ± 6.80	28.60 ± 2.34 (8)	4.65 ± 1.42	48.33 ± 5.30 (8) [b]	60.03 ± 6.35
LNNA + L-Arg	31.0 ± 1.21 (6)	25.4 ± 1.10 (6) [a]	19.6 ± 2.6	49.0 ± 5.69 (6) [b]	58.5 ± 7.6	25.0 ± 1.0 (6) [a]	17.8 ± 2.1	46.33 ± 4.24 (6) [b]	49.0 ± 5.9

[a] $P < 0.01$; [b] $P < 0.001$; numbers in parentheses indicate the number of observations. In all cases the value of mean IRP is in mmHg.

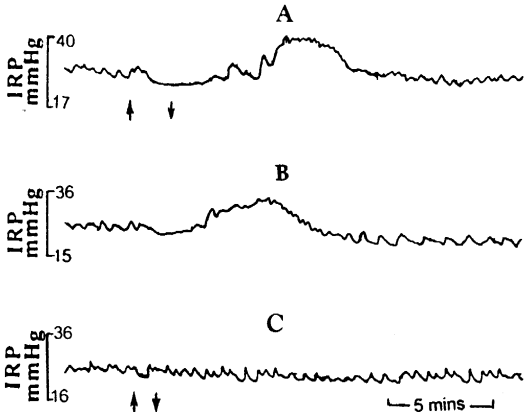

Fig. 1. Typical recording of the rectal movement (intrarectal pressure, IRP) before and after left anterior descending coronary artery occlusion (A), local application of nicotine (B) and distension (0.5 ml) of left atrial appendage (C). Arrows (↑ ↓) indicate the duration of coronary artery occlusion, nicotine application or atrial appendage distension.

failed to elicit the rectal contractile phase though the rectal relaxation persisted. In atropinised animals the mean intrarectal pressure during the relaxation phase was reduced from 29.16 ± 0.48 mmHg to 22.12 ± 2.32 mmHg but during the contractile phase there was no significant rise in mean intrarectal pressure above the normal mean intrarectal pressure.

3.5. Effect of N^G-nitro-L-arginine (LNNA) and L-arginine on rectal responses of cardiac origin

Intraarterial administration of the nitric oxide synthase inhibitor, LNNA, or the nitric oxide precursor, L-arginine, did not induce any significant alterations in spontaneous rectal movement. After administration of either of these drugs (8–10 min) their effect on the occlusion of the left anterior descending coronary artery or of epicardial nico-

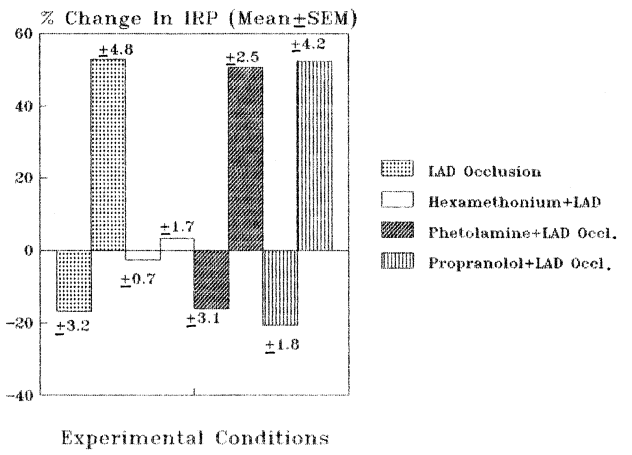

Fig. 2. Average percentage change in intrarectal pressure (IRP) ± S.E.M. in response to left anterior descending (LAD) coronary artery occlusion in control ($n = 14$), hexamethonium- ($n = 6$), phentolamine- ($n = 6$) or propranolol- ($n = 8$) pretreated animals.

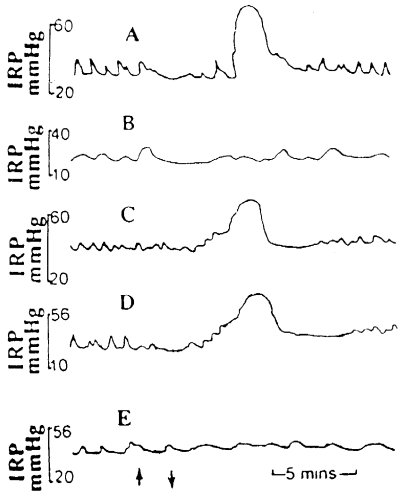

Fig. 3. Typical rectal movement (intrarectal pressure, IRP) in response to left anterior descending coronary artery occlusion in control animals (A), atropine- (B), N^G-nitro-L-arginine- (C), N^G-nitro-L-arginine + L-arginine- (D), or N^G-nitro-L-arginine + atropine- (E) pretreated animals. Arrows (↑ ↓) indicate the duration of coronary artery occlusion.

tine-induced rectal response was studied. It was observed that, in such nitric oxide synthase blocker (LNNA)-pretreated (4 mg/kg) animals, nicotine ($n = 8$) or coronary artery occlusion ($n = 6$) could not induce the initial rectal relaxation though the contractile phase remained unaffected (Table 1). Fig. 3C shows the pattern of one rectal response to coronary artery occlusion in a nitric oxide synthase blocker-pretreated animal. This blockade of the relaxation phase of the rectum by the nitric oxide synthase blocker (LNNA) was reversed (Table 1) after intraarterial administration of L-arginine (50 mg/kg). In other words, coronary artery occlusion (Fig. 3D) or epicardial nicotine application caused a significant relaxation in N^G-nitro-L-arginine (LNNA) + L-arginine-pretreated cats similar to that observed in the control. Both the relaxation phase and the contraction phase of the rectal response were completely abolished by simultaneous administration of both LNNA and atropine. Fig. 3E shows that the left coronary artery occlusion-induced cardiorectal response is totally absent in atropine + LNNA-pretreated animals.

3.6. Rectal responses of cardiac origin: relation with blood pressure changes

Occlusion of the left anterior descending coronary artery for 2 min caused only hypotension (Fig. 4A) along with rectal biphasic movement whereas epicardial nicotine resulted in biphasic blood pressure changes – an initial transient fall followed by hypertension (Fig. 4C). Sectioning of the left inferior cardiac nerve or left stellatectomy did not alter such blood pressure changes in response to left coronary artery occlusion (Fig. 4B) or epicardial nicotine application (Fig. 4D). Electrical stimulation of the central cut end of left inferior cardiac nerve with a Grass

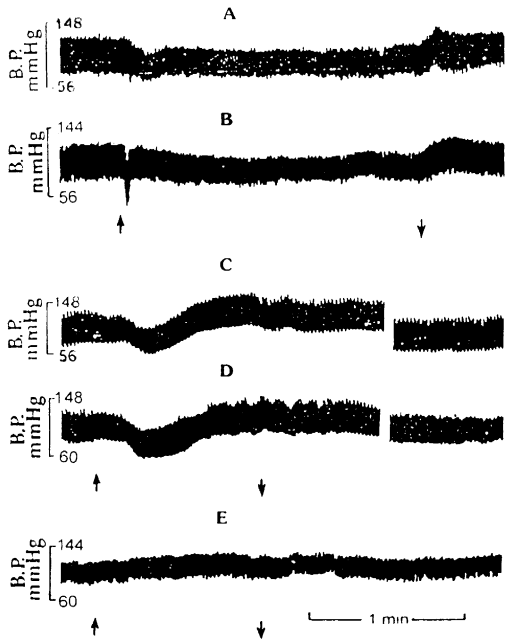

Fig. 4. Typical blood pressure (B.P.) response pattern to left coronary artery occlusion (upper set) and epicardial nicotine application (middle set) in intact (A and C) and after left inferior cardiac sympathetic nerve sectioning (B and D). Tracing E shows the effect of left inferior cardiac nerve stimulation on blood pressure. Arrows (↑ ↓) indicate the duration of left coronary artery occlusion, nicotine application or left inferior cardiac nerve stimulation.

SD 9 stimulator also did not induce any change in blood pressure (Fig. 4E).

4. Discussion

Occlusion of the coronary artery causes myocardial ischemia which is often associated with cardiac pain (Brown, 1967). This cardiac pain in turn initiates some pseudoaffective reactions as described by Sherrington, 1906. It has also been reported that nicotine possesses nociceptive properties presumably due to the release of prostaglandins (Wennmalm et al., 1974) in the cardiac muscle which excites Aδ and C afferents (Malliani et al., 1969; Koley et al., 1980, 1985). This cardiac nociception also initiates biphasic cardio-rectal reflexes (Koley et al., 1995a). The present observations also indicate that the cardiac nociceptors are excited during the haemodynamic alterations of the cardiac musculature due to the local accumulation of various metabolites and the impulse is transmitted through the cardiac sympathetic afferents as reported earlier (Guzman et al., 1962; Uchida and Murao, 1974, 1975; Koley et al., 1985; Pal et al., 1989).

Distension of left atrial appendage produced no change in rectal motility. This indicates that atrial volume receptors (Paintal, 1953) probably are not involved in the induction of such a response.

It has been reported that occlusion of the coronary artery or stimulation of ventricular receptors by different algesic agents causes a significant fall in blood pressure and heart rate (Thoren, 1973; Malliani et al., 1973). Our study also revealed that occlusion of the coronary artery causes a fall in blood pressure as long as occlusion is continued. Epicardial nicotine causes biphasic changes in blood pressure – initial hypotension followed by hypertension. These blood pressure changes in response to epicardial nicotine or left coronary artery occlusion are, however, unrelated to the rectal response as sectioning of the cardiac sympathetic nerve abolishes the cardio-rectal reflex (Koley et al., 1995a), keeping the blood pressure changes unaltered. Moreover, electrical stimulation of the sympathetic afferents does not elicit any change in blood pressure but their stimulation induces the rectal biphasic response as observed after left coronary artery occlusion or epicardial application of nicotine (Koley et al., 1995a). Thus it may be presumed that though the blood pressure changes are associated with the cardiorectal reflex, the rectal response of cardiac origin is not due to blood pressure changes and vice versa.

Motor activity of the colon and rectum depends on intrinsic properties of smooth muscle cells and neural control from the enteric nervous system (Garry and Gillespie, 1955; Hulten, 1969). However, extrinsic reflexes involving the sacral parasympathetic neurone play a major role in the regulation of colon and rectal motility, especially during defaecation (Garry and Gillespie, 1955; Hulten, 1969). It has also been reported that the parasympathetic outflow to the large intestine is composed of two sets of axons. One set, connected with intramural cholinergic neurones, is excitatory for smooth muscle whereas the other set of axons, connected with intramural non-adrenergic non-cholinergic (NANC) neurones, is inhibitory for smooth muscle cells (Furness, 1969; Jule and Gonella, 1976). In the present study, in atropinised animals, application of nicotine or coronary artery occlusion resulted in relaxation of the rectum only, whereas the contractile phase of the rectal response was absent. It was reported that sectioning of the left inferior cardiac nerve abolishes such a cardio-rectal reflex completely and the same reflex can be reproduced fully on stimulation of the central cut end of left inferior cardiac nerve (Koley et al., 1995a). In the present study stimulation of the central cut ends of the left inferior cardiac nerve after atropinisation failed to induce the contractile phase of the biphasic rectal response, keeping the relaxation phase unaltered, which indicated the involvement of a cholinergic mechanism in the contractile phase of the rectal response. Therefore, the neurotransmitter involved in the contractile phase of this response appears to be acetylcholine acting at the muscarinic receptors, but the neurotransmitters involved in the relaxation phase are neither cholinergic nor adrenergic since pretreatment with an α-adrenoceptor antagonist, phentolamine, and also with the β-adrenoceptor antagonist, propranolol,

failed to evoke any change in the rectal response induced by local application of nicotine or coronary artery occlusion. However, in animals pretreated with a nitric oxide inhibitor, N^G-nitro-L-arginine (LNNA), the relaxation phase of the rectal response is absent. Recently, Toda et al. (1992) and Rattan et al. (1992) have demonstrated the absence of the rectal relaxation induced by rectal balloon distension after treatment of the animals with LNNA. They have also demonstrated the reversal of the effect of a nitric oxide inhibitor after treating the animals with L-arginine, from which nitric oxide is synthesised (Palmer et al., 1988). In our series of experiments we also observed the reversal of the relaxation phase induced by coronary artery occlusion or nicotine application in animals pretreated with LNNA + L-arginine. Thus, it seems that the relaxation phase of the rectal response of cardiac origin is induced by the release of nitric oxide from the NANC neurones. From the present set of experimental results it may be concluded that the contraction phase of the rectal response induced by left anterior descending coronary artery occlusion or epicardial nicotine is mediated through acetylcholine whereas the relaxation phase is due to the release of nitric oxide.

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