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Cardiac Nociceptors and Ischemia: Role of Sympathetic Afferents in Cat

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Abstract In total, 86 units were recorded from T_2 and T_3 left thoracic rami of cat. These receptors were located on the circumflex coronary artery, anterior descending coronary artery, and its adjacent myocardial ragions. The conduction velocity of these fibres was in the range of "C" (0.5 to 1.8 m/s) and "A δ" (5.96 to 17 m/s) fibres. Out of these 86 units, only 28 units were activated by coronary occlusion. The average resting frequency of the spontaneous unit was 0.8 ± 0.06 impulses/s which increased to 35 ± 4.8 impulses/s on mechanical probing. In order to examine whether the units sensitive to coronary occlusion were also responsive to algesic agents, some of these units were studied applying lactic acid, bradykinin, prostaglandins, and nicotine. It was observed that these ischemia-sensitive units are also sensitive to lactic acid (10 units), bradykinin (16 units), prostaglandins (12 units), and nicotine (15 units). These ischemia-sensitive units are presumably nociceptors and activated by algestic agents that cause cardiac ischemic pain.

Key words: cardiac nociceptors, sympathetic afferents, ischemia, coronary occlusion, algesic substances.

Myocardial ischemia in man causes pain (LINDGREN and OLIVECRONA, 1947). The afferent pathways involved in such pain sensation presumably course in the dorsal root ganglia of the first five thoracic segments of the spinal cord. Studies in animals have shown that the sensory receptors within the myocardium, as well as in coronary vessels, may increase afferent sympathetic nerve activity during experimental coronary artery occlusion or intracoronary infusion of a number of algesic agents (BROWN, 1965; UCHIDA and UEDA, 1969; BROWN and MALLIANI, 1971; UCHIDA and MURAO, 1974a, b, c, d, 1975; UCHIDA *et al.*, 1974; UCHIDA, 1975; BOSNJAK *et al.*, 1979, 1981). When coronary artery occlusion results in the development of systolic bulge of the ventricular wall in the ischemic area, increased

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activity of cardiac sympathetic afferents originating from the receptors located within the ischemic myocardium or within the coronary vessels can occur (BROWN and MALLIANI, 1971; UCHIDA *et al.*, 1971; UCHIDA and MURAO, 1974b, c; BOSNJAK *et al.*, 1979). Myocardial ischemia has been known to cause acidosis and an increase in H^+ concentration (CONN *et al.*, 1959; SCOTT *et al.*, 1970; HADDY and SCOTT, 1971; OPIE *et al.*, 1973) as well as liberation of bradykinin and prostaglandin (STASZEWSKA-BARCZAK *et al.*, 1976). It has been reported that some classes of prostaglandins participate in nociception and are also released from the heart within a minute of onset of hypoxia or ischemia (FURUKAWA *et al.*, 1969; ALEXANDER *et al.*, 1973; WENNMALM *et al.*, 1974; BLOCK *et al.*, 1975).

In the present investigation an attempt has been made to elucidate the behaviour and reactivities of cardiac receptors to different algesic substances which are likely to be associated with ischemic pain in acute experimental animals.

METHODS AND MATERIALS

Investigations were carried out on 45 adult cats (2.5 to 3.5 kg body weight) of either sex. These were anaesthetised with sodium pentobarbital (Nembutal, Abbott Laboratories, India), using an initial intraperitoneal dose of 35 to 40 mg/kg and with a maintenance intravenous dose of 10 mg/kg. The trachea, femoral vein, femoral artery, and carotid artery were routinely cannulated. Blood pressure was recorded from the femoral artery cannula connected to a pressure transducer (Type 4-327-0129, Bell and Howell, CBC Division, Pasadena, U.S.A.), coupled to a Beckman RM-Dynograph (Beckman, U.S.A.). 5% glucose in saline was administered by drip into the femoral vein to maintain the normal body fluid balance. The body temperature was also monitored by a rectal thermometer and maintained within 37–38°C by a heating blanket.

The chest was opened by removing the upper T_1 to T_7 ribs on the left side of the chest and the animal was kept under artificial respiration with a Starling Ideal Respiratory Pump (INCO, Ambala, India). The pleural membrane of the thoracic cavity was separated out carefully and extended medially without any rupture, to isolate the stellate ganglion and 1st to 5th sympathetic rami, so that a liquid paraffin pool for nerve dissection could be prepared. The left stellate ganglion and its branches were exposed carefully and a suitable length of the thoracic sympathetic rami were cleaned from the surrounding connective tissues under a stereoscopic dissecting microscope (Vickers Instruments, England). Afferent activity was recorded sequentially from the 4th to the 1st thoracic rami. Peripheral cut end of each rami (T_4–T_1) was placed on a black ebonite dissecting plate immersed in a warm paraffin pool. A small length of the nerve was desheathed and split into fine filaments under a stereoscopic dissecting microscope. A fine filament was placed on a pair of silver-silver chloride recording electrodes. Activity was displayed on a dual-beam oscilloscope (Model 5112, Tektronix Inc., Beaverton, U.S.A.) after initial amplification through a differential preamplifier (AM 502, Tektronix Inc.). The

output of the amplifier was led to an audio-amplifier for sound monitoring and a parallel connection was made with a 4 FM tape recorder (Racal-Thermionic Ltd., Southampton, England); later the recorded activity was played back to a storage oscilloscope (Model 5113, Tektronix Inc., Beaverton, U.S.A.) for further analysis and photography.

The situation of the receptor sites were located by probing the epicardium of the heart. Receptor locations were subsequently confirmed after sacrificing the animals. The conduction velocities of these fibres were measured by the peripheral stimulation technique (IGGO, 1958). The receptor site was stimulated by a square wave monophasic pulse (7 to 10 V, 1 ms, 0.2–1 Hz) delivered from a stimulator (Grass S48, Grass Instrument Co., Quincy, U.S.A.) via an isolation unit (SIU 5 Grass Instrument Co. U.S.A.). To study cardiac receptors during ischemia, coronary occlusion was performed. The pericardium was removed and the coronary arteries were exposed along its length (2 to 3 mm) from the surrounding tissues. Occlusion of the coronary vessels was done mainly in circumflex, proximal part of the anterior descending branches of the coronary arteries by means of a fine snare around the vessels. While placing the snare around the arteries initially there might be some mechanical irritation but we had to wait until such afferent activities due to irritation subsided. Drugs were infused intravenously or intraarterially. For the intraarterial injections, a polythene catheter with a 1 mm bore was introduced through the left common carotid artery down to the origin of the ascending aorta, keeping its tip near the coronary orifice. The tip position was always verified by injecting a dye (methylene blue) immediately after sacrificing the animals. Furthermore, with this technique blood flow to the coronary vessels remained undisturbed. Local application of the drugs was performed by placing a small piece of blotting paper soaked with different concentrations of the drugs.

Drugs used. Lactic acid and bradykinin triacetate (Sigma Chemical Co., Milwaukee, U.S.A.), PGE_2 and $PGF_{2\alpha}$ (Upjohn Co., Kalamazoo, U.S.A.), nicotine and acetylcholine (BDH, England).

RESULTS

Action potentials were recorded from the T_2 and T_3 left thoracic rami. Eighty-six units were identified in the region of the left coronary artery and its adjacent myocardium. These units had both spontaneous (58 units) and nonspontaneous (28 units) activities and were localised by gentle mechanical probing with a fine blunt glass probe (diameter, 0.4–0.6 mm). Units were located at different regions of the left coronary arteries: on the circumflex coronary artery and its adjacent myocardial regions (36 units); in the anterior descending coronary artery and its adjacent myocardial region (50 units). The average resting frequency of the spontaneous units was 0.8 ± 0.06 impulses/s and increased to 35 ± 4.8 impulses/s on mechanical probing (Fig. 1). Out of the 86 units, 52 were slowly adapting in nature (Fig. 2). Twelve out of the 86 units had 1 to 4 punctate receptive sites, which were generally

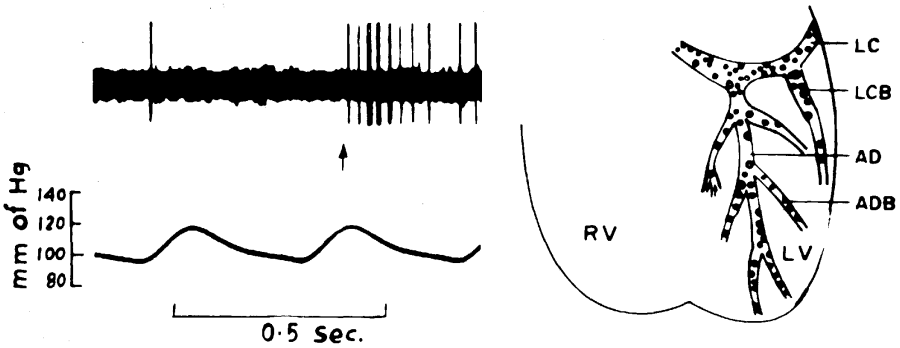

Fig. 1. Diagrammatic representation of distribution of spontaneous (filled circle) and nonspontaneous (open circle) receptors of cat's heart (right panel). The left panel shows the evoked action potential of one spontaneous unit (upper) and arterial blood-pressure (lower) to mechanical probing. The arrow indicates the point of stimulation applied. RV, right ventricle; LV, left ventricle; LCB, left circumflex branch; AD, anterior descending; ADB, anterior descending branch; LC, left circumflex.

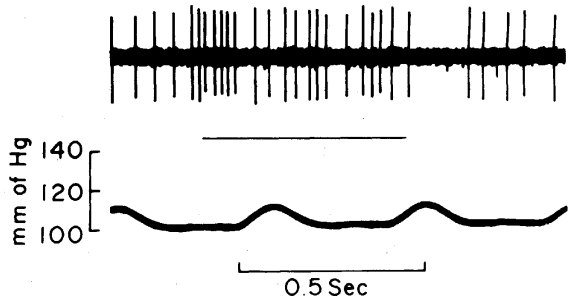

Fig. 2. The activity recorded from afferent sympathetic fibre with the receptive field located in the anterior descending branch of the coronary artery of cat. The upper tracing shows the slowly adapting nature of the spontaneous unit as the ehanced activity persisted as long as the mechanical probing (indicated by the bar) was maintained; the lower tracing is the systemic blood pressure.

situated at the branching points of the fine blood vessels of the circumflex and anterior descending branches of coronary arteries. The conduction velocities of the fibres were in the range of 5.96 to 17 m/s and 0.5 to 1.8 m/s (Fig. 8). After locating, all the 86 units were tried with coronary occlusion. Only 28 units were excited during coronary occlusion. These units were also studied with lactic acid, bradykinin, prostaglandins, and nicotine in order to examine whether receptors sensitive to coronary occlusion (ischemia) are also responsive to such algesic agents.

Response of receptors to coronary artery occlusion

Twenty-eight units responded to occlusion of the anterior descending coronary

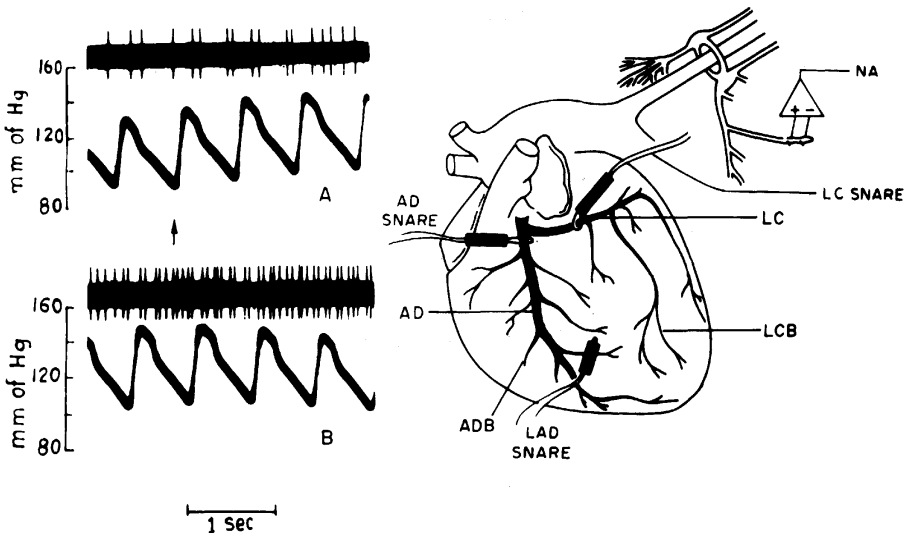

Fig. 3. Response pattern (left panel) of one spontaneous unit to occlusion of descending coronary artery. In left upper panel (A), arrow indicates initiation of coronary occlusion which is continued in the lower panel (B). Within the panels (A and B) the upper tracing shows the discharge pattern and lower tracing shows the arterial pressure. The right panel shows the location of conronary artery occlusion with snare in the heart. NA, neural activity; LC, left circumflex; AD, anterior descending; LAD, left anterior descending branch; LCB, left circumflex branch.

artery (20 units) and circumflex coronary artery (8 units). On occluding the coronary artery, an increased rate of firing was observed. The endings were not pressure dependent as no excitation of the fibres was observed after raising the coronary vascular pressure manually by occluding the descending aorta. The average discharge rate of these spontaneous units was 1.3 ± 0.4 impulses/s. For a period of 10 to 15 s of coronary occlusion, the spike rate increased to 8 ± 1.8 impulses/s ($p < 0.001$) and such enhanced discharge rate persisted for 30 s and occasionally 2 min even after releasing the occulsion (Fig. 3). However, no proper correlation was observed between the duration of the occlusion and the duration of this increased activity. The conduction velocity of these fibres ranged from 5.96 to 17.0 m/s and 0.5 to 1.8 m/s (Table 1). To determine whether these units are nociceptors in nature, algesic agents such as lactic acid, bradykinin, prostaglandins, and nicotine were applied.

Response of receptors to lactic acid

Ten out of 12 fibres which were responsive to coronary occulsion were activated when lactic acid was applied locally or intraarterially (Fig. 4). The frequency of their discharge was dependent on the concentration of the lactic acid applied. The "C" fibre afferents were stimulated with lactic acid applied both

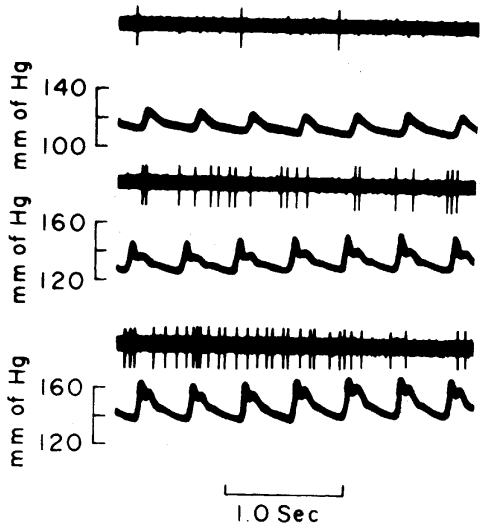

Fig. 4. The response pattern of one spontaneous coronary occlusion-sensitive receptor to intraarterial application of 20 μg/kg lactic acid. Upper panel: the resting discharge. Middle and lower panels: increased discharge rate after 20 s and 2 min of drug administration, respectively. Within the panels, upper tracing shows the discharge pattern and lower tracing shows the arterial blood pressure.

locally (10–70 μg/ml) and intraarterially (10–20 μg/kg) whereas the "Aδ" fibres were excited with much higher concentration of lactic acid applied both locally (500 μg/ml) and intraarterially (40 to 100 μg/kg). The average resting discharge rate of the 10 spontaneous units was 1.5 ± 0.3 impulses/s which was increased (maximum) to 7.8 ± 1.2 impulses ($p < 0.001$) with lactic acid. Out of 10 units, 4 were "Aδ" fibres (6.5 to 15 m/s) and 6 were "C" fibres (0.92 to 1.7 m/s) (Table 1).

Response of receptors to bradykinin

Sixteen out of 19 units which responded to coronary occlusion were activated by application of bradykinin. The dose range depends on the route of drug administration. The receptors were activated with bradykinin both locally (100 ng/ml) and intraarterially (400 ng/kg). A higher dose (0.5 to 10 μg/kg) was required when given intravenously. Upon intravenous administration of bradykinin (a bolus of 5 to 10 μg), the spontaneous discharge rate (7 ± 1.4 impulses/s) increased to 28 ± 3.1 impulses/s ($p < 0.001$), even though systemic pressure dropped (Fig. 5). The conduction velocity of these fibres ranged from 5.96 to 15.30 m/s (10 units) and 0.5 to 1.6 m/s (6 units) (Table 1).

Response of receptors to prostaglandin

Twelve out of 16 units which responded to coronary occlusion were activated by prostaglandins E_2 and $F_{2\alpha}$: 7 units responded to $PGF_{2\alpha}$, either applied locally

Table 1. Substances applied and number of coronary receptors that responded

Substances	Dose levels	No. of units studied	No. of units that responded	Spontaneous units	Nonspontaneous units	Conduction velocity range (m/s)
Lactic acid	10–70 (μg/ml, local) 10–20 (μg/kg, i.a.) 500 (μg/ml, local) 40–100 (μg/kg, i.a.)	12	10	10	—	0.92–1.7 6.5 –15
Bradykinin	100–400(ng/ml, local) 400 (ng/kg, i.a.) 0.5–10 (μg/kg, i.v.)	19	16	12	4	0.5 –1.6 5.96–15.30
$PGF_{2\alpha}$	5 (ng/ml, local) 5–10 (μg/kg, i.v.)	8	7	5	2	0.7 –1.8 7.6 –13.3
PGE_2	5 (ng/ml, local) 5–10 (μg/kg, i.v.)	8	5	3	2	7.3 –11.5
Nicotine	10–20 (μg/kg, i.a. and i.v.)	19	15	12	3	0.7 –1.3 8.9 –17.0
Acetylcholine	250–500 (μg/kg, i.v.)	7	5	4	1	0.9 –12.2

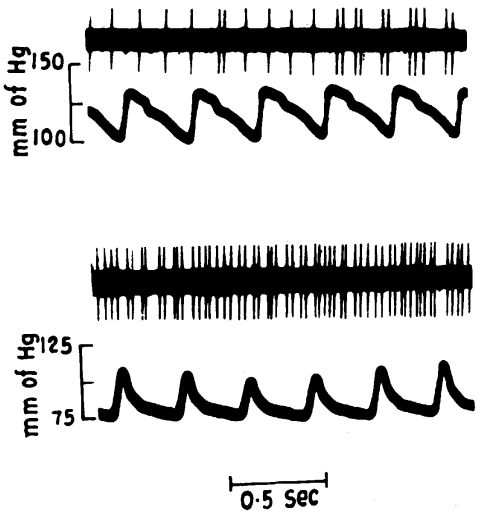

Fig. 5. The response pattern of one spontaneous coronary occlusion-responsive receptor (upper tracing) and blood pressure (lower tracing) before (upper panel) and after (lower panel) intravenous administration of bradykinin (5 μg/kg).

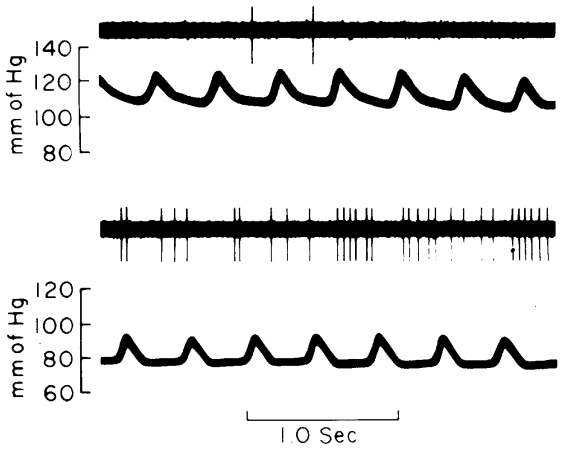

Fig. 6. Response pattern of one coronary occlusion-sensitive unit to PGE_2 (5 μg/kg, i.v.). The upper panel shows the resting discharge pattern of the unit and lower panel shows the increased rate after 40 s of PGE_2 application (i.v.). Within the panels, upper tracing shows the unit activity and lower tracing, the systemic blood pressure.

(5 ng/ml) or intravenously (5 to 10 μg/kg); 5 out of these 7 fibres had conduction velocity ranging from 7.6 to 13.3 m/s and the other 2 had conduction velocities 0.7 and 1.8 m/s.

Prostaglandin E_2, with the same local or intravenous dose levels as that of $PGF_{2\alpha}$, stimulated the remaining 5 units. The response evoked after drug application persisted for a considerable period of time. The response pattern of one spontaneous receptor to PGE_2 is shown in Fig. 6. The resting discharge rate (0.7 ± 0.06 impulses/s) was increased to 8 ± 2.0 impulses/s ($p < 0.01$). The conduction velocity of the fibres was within 7.3 to 11.5 m/s (Table 1).

Response of receptors to nicotine

Fifteen out of 19 units which responded to coronary occlusion, responded with nicotine (10 to 20 μg/kg) intravenously. Nicotine excited both spontaneous and nonspontaneous receptors. When the drug was administered intravenously, the discharge rate (1.8 ± 0.7 impulses/s) increased (11.5 ± 2.1 impulses/s, $p < 0.001$) with the rise of systemic blood pressure. A typical response pattern is shown in Fig. 7. The nonspontaneous units were less adaptive than the spontaneous ones. Occasionally, nonspontaneous units became spontaneous following nicotine administration and such activity was maintained for a fairly long period of time. The conduction velocities of ten fibres were in the range of 8.9 to 17 m/s and the other five fibres were 0.7 to 1.3 m/s (Table 1).

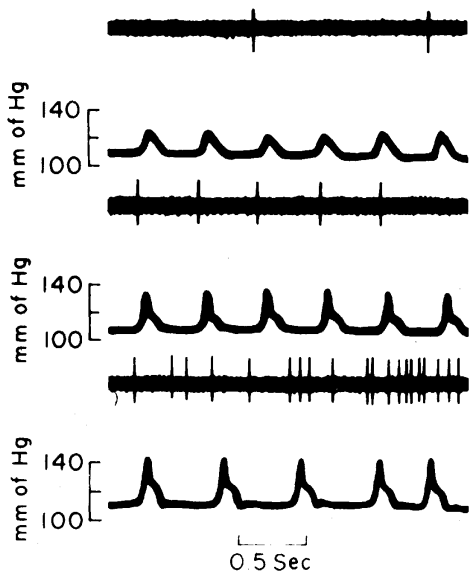

Fig. 7. The discharge pattern of one spontaneous coronary occlusion-sensitive unit before and after the application of nicotine (10 μg/kg, i.a.). The top panel shows the normal spontaneous activity of the unit while the middle and lower panels are 15 and 30 s after nicotine application, respectively. Within the panels, upper tracing shows the unit activity and lower tracing, the systemc blood pressure.

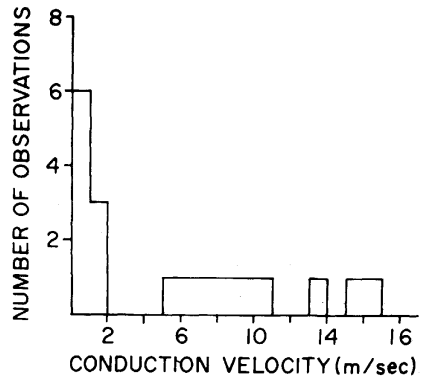

Fig. 8. Frequency histogram of conduction velocity from 18 coronary occlusion sensitive single units recorded from T_2 and T_3 sympathetic rami of cat.

Response of receptors to acetylcholine

Five receptors located near the wall of the coronary vessel were excited by acetylcholine (250 to 500 μg/kg, i.v.). Along with the increase of afferent activity there was fall of systemic blood pressure and heart rate. After administration of

acetylcholine, the discharge rate (3 ± 1.1 impulses/s) increased to 9.1 ± 1 impulses/s ($p < 0.01$). The conduction velocity of these fibres ranged from 0.9 to 12.2 m/s (Table 1).

DISCUSSION

Cardiac sympathetic afferent axons in the left T_2 and T_3 rami arise from receptors distributed over the circumflex and anterior descending coronary arteries. These receptors can respond to both mechanical and chemical stimuli (MALLIANI *et al.*, 1969; BROWN and MALLIANI, 1971; UCHIDA and MURAO, 1974a, b, c, d, 1975; KOLEY *et al.*, 1979, 1980). The afferents which can be excited by various chemicals have "Aδ" and "C" axons (Fig. 4 to Fig. 7). The present study has confirmed that receptors which respond to chemical can also respond to mechanical changes indicating their polymodal behaviour.

Myocardial ischemia and hypoxia are associated with pain (SUTTON and LUETH, 1930; BURCH and DEPASQUALE, 1962; GUZMAN *et al.*, 1962) and are accompanied by accumulation of lactic acid (UCHIDA and MURAO, 1975), bradykinin and prostaglandins (KIMURA *et al.*, 1973; UCHIDA and MURAO, 1974d; STASZEWSKA-BARCZAK *et al.*, 1976; NISHI *et al.*, 1977; BAKER *et al.*, 1980; LOMBARDI *et al.*, 1981; KOLEY *et al.*, 1985). Earlier it had been suggested by LINDGREN and OLIVECRONA (1947) as well as WHITE and BLARD (1948) that sympathetic afferents participate in transmitting impulses leading to cardiac pain in man.

In experimental animals too it has been shown that afferent axons in cardiac sympathetic nerves are activated by acute myocardial ischemia produced by coronary occlusion. It has been postulated that such afferent activity might initiate the pseudo-affective reaction associated with angina (SUTTON and LUETH, 1930; WHITE and BLARD, 1948; WHITE, 1957; BROWN, 1967; BROWN and MALLIANI, 1971; UCHIDA and MURAO, 1974b; BOSNJAK *et al.*, 1979, 1981). The present investigation supports the idea that the cat's cardiac sympathetic afferents of both the "Aδ" and "C" types responded to coronary occlusion and also to algesic drugs. This suggests that the cause of excitation of these receptors could be oxygen deficiency (hypoxia) and/or changes of the chemical environment of the cardiac muscle. GUZMAN *et al.* (1962) and UCHIDA and MURAO (1975) have demonstrated that intracoronary injection of lactic acid can elicit a pseudo-affective response in lightly anaesthetised dogs. Similar pseudo-affective response in lightly anaesthetised cat was reported by KOLEY *et al.* (1987, 1988). The present study corroborates that lactic acid can excite cardiac afferent receptors in anaesthetised cats, and that lactic acid activates receptors with both "Aδ" and "C" afferents. However, excitation of "Aδ" fibres required a higher concentration of lactic acid than did that of "C" fibres. The threshold concentration of lactic acid required for "Aδ" fibres was 500 μg/ml applied locally and 40 to 100 μg/kg intraarterially. During myocardial ischemia, myocardial lactic acid concentration increases from a control value of 500 μg/g to 1.6 mg/g of tissue (CONN *et al.*, 1959). Thus the amount of lactate administered

locally or intraarterially may add to that produced endogenously and thus achieve the threshold level for excitation of sensory nerve endings.

In this study bradykinin has been found to markedly increase the activity of all spontaneously active receptors with unmyelinated ("C") and myelinated ("Aδ") afferents. This is in agreement with the findings of other workers (BROWN, 1967; BROWN and MALLIANI, 1971; MALLIANI *et al.*, 1973; UCHIDA and MURAO, 1974c; CASATI *et al.*, 1979). GUZMAN *et al.* (1964) reported that aspirin antagonised the pain induced by bradykinin and attributed this to the competitive occupation of the pain receptors by aspirin at chemosensitive sites. However, the role of aspirin as an inhibitor of prostaglandin biosynthesis (FERREIRA *et al.*, 1971; SMITH and WILLIS, 1971; VANE, 1971) together with the reported ability of prostaglandins to sensitize the pain receptors (FERREIRA *et al.*, 1973) suggest that prostaglandins may be the causative factors evoked by bradykinin. Indeed, the present study shows that PGE_2 and $PGF_{2\alpha}$ alone are capable of exciting both "Aδ" and "C" fibres. This is consistent with the findings of STASZEWSKA-BARCZAK *et al.* (1976), that bradykinin and prostaglandins might be the natural chemical stimuli in exciting the sensory receptors for signalling pain during ischemia. Nicotine has been found to stimulate cardiac sympathetic afferents in cats. Earlier, SLEIGHT and WIDDICOMBE (1965) had demonstrated the effect of nicotine on vagal unmyellinated afferents in the epicardium of cats. WENNMALM and JUNSTAD (1976) have shown that nicotine initiates the release of prostaglangins in the cardiac muscle of rabbit. Therefore, it is possible that the nicotine activates the cardiac nociceptor through prostaglandins. However, the effect of aspirin on such response has not been checked in the present investigation. Besides bradykinin, prostaglandins, nicotine, and lactic acid, acetylcholine has also been found to activate receptors with "Aδ" and "C" fibres. NISHI *et al.* (1977) reported that the afferent fibres in the cardiac sympathetic nerve of cat could be excited after an intravenous infusion of acetylcholine. HADHAZY *et al.* (1973) and JUNSTAD and WENNMALM (1974) have reported that acetylcholine leads to the release of PGE_2 in the cardiac tissues.

The present studies have thus shown clearly that cardiac nociceptors are polymodal in nature and that they are activated by ischemia and algesic agents. The cause of anginal pain is the excitation of the cardiac sympathetic nociceptors during ischemia that alters the chemical environment of its surroundings through liberation of lactic acid, bradykinin, and prostaglandins.

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