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Acid-induced excitation of afferent cardiac sympathetic nerve fibers

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UCHIDA, YASUMI, AND SATORU MURAO. *Acid-induced excitation of afferent cardiac sympathetic nerve fibers.* Am. J. Physiol. 228(1): 27–33. 1975.—The effect of acids on activity of afferent sympathetic nerve fibers from the left ventricle has been examined. Action potentials were derived from the upper thoracic communicating rami of the left side of anesthetized dogs. Application of a solution of lactic acid to the left ventricular surface caused excitation in both myelinated and unmyelinated fibers. The minimum concentration required for excitation was 7.5–75 μg/ml for the unmyelinated fibers and 375–750 μg/ml for the myelinated fibers. Excitation of the unmyelinated fibers induced by coronary occlusion was suppressed by pretreatment with sodium bicarbonate, 500 mg/kg. However, excitation of the myelinated fibers was influenced little by the agent. Pretreatment with a large dose of Trasylol failed to suppress excitation induced by coronary occlusion. The result suggests that acidosis plays a role in excitation of the unmyelinated fibers induced by myocardial ischemia, but not in excitation of the myelinated fibers.

myelinated fibers; unmyelinated fibers; lactic acid; hydrochloric acid; coronary occlusion; sodium bicarbonate; acetylsalicylic acid; Trasylol; atropine

MYOCARDIAL ISCHEMIA leads to development of acidosis and an increase of H^+ ion concentration (3, 9, 22, 24). Intracoronary injections of lactic acid can elicit a pseudaffective response in lightly anesthetized dogs (7, 8). This evidence suggests participation of acids or H^+ ion in the pathogenesis of anginal pain produced by myocardial ischemia.

Several workers have demonstrated that the afferent sympathetic nerve fibers from the left heart have an action as nociceptor (1, 7, 27, 29). Anginal pain can be eliminated by transection of the stellate ganglia through which the afferent sympathetic nerve fibers pass (17, 35).

Although myocardial ischemia leads to excitation of the afferent sympathetic nerve fibers from the left ventricle (1, 2, 29, 31, 34), the mechanisms for excitation during myocardial ischemia are still unclear. Our study was undertaken to examine the effect of lactic acid and hydrochloric acid on activity of afferent sympathetic nerve fibers from the left ventricle and also the effect of sodium bicarbonate, a buffer of acids, on excitation of the afferent fibers induced by myocardial ischemia.

METHODS

Surgical preparations. Experiments were carried out on adult mongrel dogs under intravenous pentobarbital sodium anesthesia (35–40 mg/kg). The trachea was intubated for artificial positive-pressure respiration with air. The upper eight ribs on the left side were removed. The left thoracic sympathetic trunk below the fourth communicating ramus, the upper four rami, the rostral limb of the left ansa subclavia, and the left cervical vagosympathetic trunk were transected. The anterior aspect of the left heart was exposed by pericardiotomy. A strain-gauge arch was sewn to the anterior wall of the left ventricle to monitor the active force achieved by the region of the myocardium.

Recording electrically and mechanically evoked action potentials. One of the nerve filaments dissected from either the second or third communicating ramus of the left side was placed on bipolar platinum-iridium electrodes connected to an AC-coupled preamplifier. Another pair of electrodes was placed on the ventral limb of the left ansa subclavia. The nerve filament and the electrodes were covered with liquid paraffin warmed to 36–37°C. Stimuli were led from an isolation unit connected to a square-wave stimulator. Pulses were monophasic and 1 ms in duration. The electrical shocks were applied to the ansa via the stimulating electrodes before and after each experiment. The stimulation voltage was raised stepwise for separate recording of each action potential. In general, the nerve filament contained one to eight live fibers. The action potentials, stimulation artifact, and time base were displayed on the screen of a cathode-ray oscilloscope from which photographic records were made. Conduction velocity was calculated from the time of the stimulation artifact to the beginning of each action potential. Classification of the afferent fibers was made by conduction velocity (6). The fibers whose conduction velocities were below 36 and over 4.5 m/s were classified as myelinated Aδ fibers. The fibers whose conduction velocities were below 2 m/s were classified as unmyelinated C fibers (4, 6, 11, 23). The fibers whose conduction velocities were below 4.5 and over 2 m/s were not included in this study since opinions on classification of these fibers are still contradictory (4, 11, 23).

In order to examine mechanosensitivity of the fibers that responded to electrical stimulation, the cardiac surface, the great vessels, and the pleurae were tapped by a finger tip. If a fiber responded to tapping the anterior wall of the left ventricle, the region was tapped by the blunt tip of a bamboo bar 1 mm in diameter for accurate determination of the receptive field. Constriction of the descending thoracic aorta was also carried out in each

preparation to examine the effect of a rise in intraventricular pressure on activity of the fiber (28).

Recording chemically evoked action potentials. Twenty dogs were used for this series of experiments. Lactic acid (75 wt/vol %) was dissolved in physiological saline since this solvent was ineffective in exciting the afferent sympathetic nerve fibers in our previous study (30). The pH of the solutions was measured by a pH meter (Nihon Kohden). Concentrations of the solutions were 7.5 (pH 4.58), 75 (pH 3.55), 375 (pH 3.11), 750 (pH 2.86), 3,750 (pH 2.55) and 7,500 (pH 2.18) μg/ml. A solution of 0.1 ml was dripped to the receptive field determined by tapping and another 0.1 ml to the ventricular surface between the limbs of the strain-gauge arch. After each application, the ventricular surface was washed with physiological saline; about 5 min later the next application of a solution of a higher concentration was made. Application of the solutions was also done in 20 filaments in which response to tapping and aortic occlusion was not observed.

In a similar way, hydrochloric acid dissolved in physiological saline was dripped to the anterior wall of the left ventricle in 10 fiber preparations. Concentrations of the solutions were 0.365 (pH 5.60), 1.82 (pH 4.93), 3.65 (pH 4.53), 18.2 (pH 3.85), and 36.5 (pH 3.20) μg/ml. Action potentials evoked by these chemical agents were recorded on continuous film strips. Classification of the fibers that were excited by these agents was made by comparing the spike height, spike duration, and configuration of the action potentials evoked chemically with those evoked electrically. The action potentials were employed to trigger a square-wave generator and the output was integrated by a pulse integrator. The height of the integrated record indicated the number of the action potentials per second and was expressed as impulses per second. The integrated action potentials, femoral arterial pressure, and the active force of the myocardium expressed as left ventricular tension (LVT) were recorded on an ink recorder.

Recording action potentials evoked by coronary occlusion. Forty-four dogs were used for this series of experiments. The proximal segment of the anterior descending branch of the left coronary artery was dissected free of surrounding tissues and a screw clamp was placed on it for occlusion. A catheter 1 mm in external diameter was inserted into a small vessel arising from the anterior descending branch in order to monitor the peripheral pressure of the occluded branch. A strain-gauge arch was sewn to the anterior wall of the left ventricle for measurement of the active force of the region of the myocardium. A catheter was also inserted into the right femoral artery for measurement of systemic blood pressure.

In 14 fiber preparations, the effect of coronary occlusion on activity of the afferent fibers was compared before and after the intravenous injections of sodium bicarbonate (500 mg/kg) since this agent is a buffer of acids and therefore might block excitation of the afferent fibers induced by coronary occlusion.

Furukawa et al. (5) noted that bradykinin is formed during myocardial ischemia and a dose of Trasylol 50,000 kallikrein inhibition units (KIU)/kg can block bradykinin formation in the dog. Therefore, the effect of coronary occlusion was compared before and after intravenous injections of 50,000 KIU/kg in this study.

Acetylsalicylic acid acts as a competitive antagonist and occupies the receptor site (15). This agent was found to block excitation of the afferent splenic nerves caused by bradykinin (13), bradykinin-induced excitation of the afferent cardiac sympathetic nerves (32), and pseudaffective response to intracoronary injections of bradykinin, potassium ion, and lactic acid (8, 32). Therefore, the effect of coronary occlusion was compared before and after intravenous injections of 50, 100, and 150 mg/kg acetylsalicylic acid in 11 fiber preparations.

Atropine is effective in alleviating anginal pain in a certain group of patients with coronary insufficiency (21). Therefore, the effect of coronary occlusion on activity of the afferent fibers was compared before and after intravenous injections of 500 μg/kg atropine, which in our preliminary study was enough for blocking the effect of vagal stimulation on the heart.

RESULTS

Action potentials of 980 fibers were evoked by electrical stimulation of 221 nerve filaments of 64 dogs. Of these fibers, 54 were also excited by tapping the anterior wall of the left ventricle. Thirty-two belonged to the Aδ and the other 22 to the C group. Response to tapping the other regions in the thoracic cavity was observed in 91 fibers. The other 735 did not respond to tapping nor to aortic occlusion.

Lactic acid dissolved in physiological saline was dripped to the receptive fields determined by tapping in 6 of 32 Aδ and in 4 of 22 C fiber preparations. The remaining mechanosensitive fibers were used for the other series of experiments.

Application of the solutions to the anterior wall of the left ventricle was also carried out in 20 filaments in which no response to tapping and aortic occlusion was observed. Application of the solutions in a concentration of 750 μg/ml or more caused an increase in active force of the myocardium and a rise in systemic blood pressure. On the other hand, no obvious change in the active force and systemic blood pressure was produced with a concentration of 75 μg/ml or less. Application of the lactic acid solutions caused excitation in all mechanosensitive fibers tested. Excitation was also set up in five C fibers that did not respond to tapping and aortic occlusion. Both Aδ and C fibers, irrespective of their mechanosensitivity, fired irregularly in response to the solutions. The latency required for excitation was 2–7 s. There was a tendency for the latency to become shorter with increasing concentration. The duration of excitation ranged from 30 s to 7 min (Figs. 1, 2, and 3). In two preparations, both Aδ and C fibers were excited by the solutions. The C fiber was excited by a concentration of 75 μg/ml, whereas the Aδ fibers were excited by a concentration of 750 μg/ml. Thus, the minimum concentration required for excitation of the C fibers was lower than that for the Aδ fibers (Fig. 4).

In a similar way, the solutions of hydrochloric acid were applied to the left ventricular surface in 10 mechanosensitive fiber preparations. All these fibers were excited by the solutions. The minimum concentration required for excitation of the C fibers was lower than that for the Aδ fibers as in the case of lactic acid (Fig. 4). The latency for excitation dropped to the range for lactic acid.

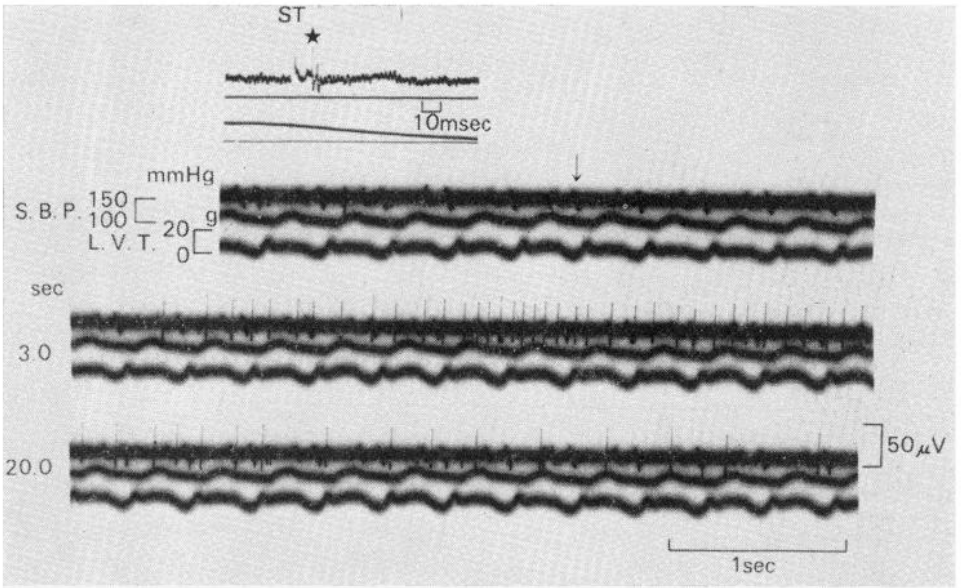

FIG. 1. *Top photograph:* electrically evoked action potential of an Aδ fiber (labeled with star). Conduction velocity = 8.6 m/s. ST = stimulation artifact. *Middle and bottom traces:* action potentials evoked in same nerve filament by application of 750 μg/ml lactic acid to anterior wall of left ventricle. Spike height, spike duration, and configuration of action potentials correspond to those of potential in top photograph. SBP = systemic blood pressure; LVT = left ventricular tension measured from a strain-gauge arch. Downward arrow indicates QRS of electrocardiogram.

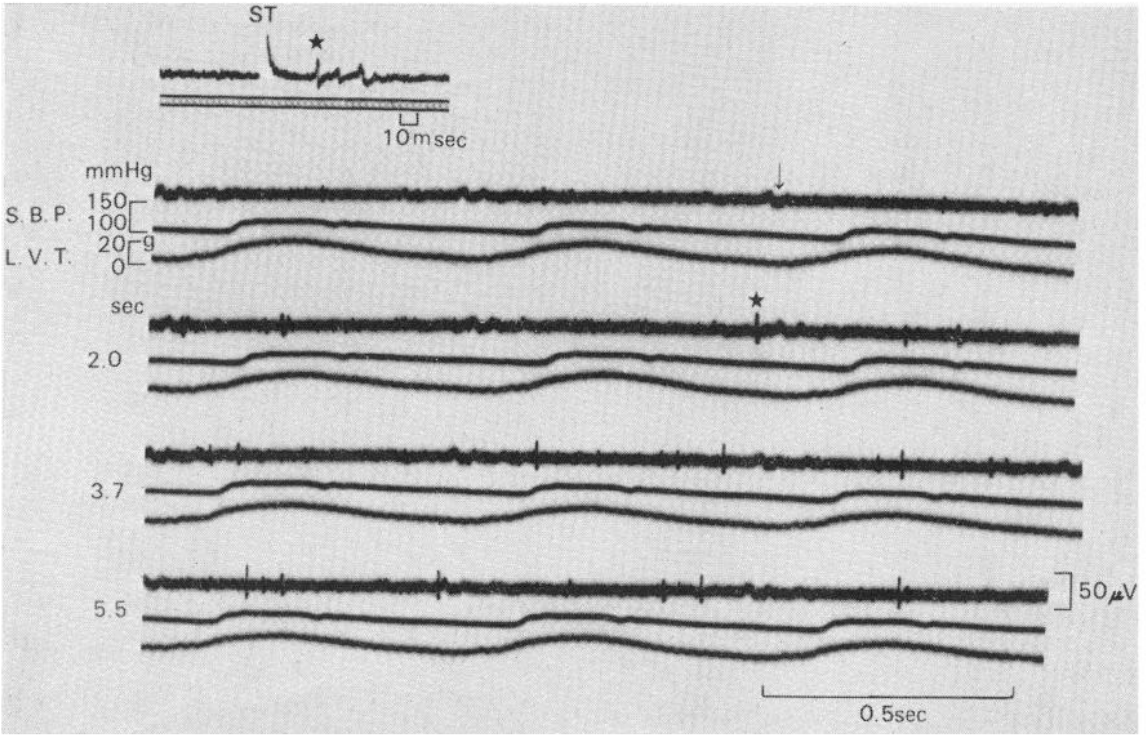

FIG. 2. *Top photograph:* electrically evoked action potential of 3 C fibers. Conduction velocities of these fibers are 1.7, 1.2, and 1.0 m/s, respectively. *From 2nd to 5th photographs:* control, 2s, 3s, 6s, and 5.3s after application of 7.5 μg/ml lactic acid to anterior wall of left ventricle. Action potential labeled with star corresponds to fastest C potential in top photograph. SBP = systemic blood pressure; LVT = left ventricular tension. Time at beginning of each photograph indicates time after application of lactic acid.

In 10 fiber preparations used for determination of the threshold concentration of lactic acid, a solution of 750 μg/ml lactic acid was dripped to the anterior wall of the left ventricle before and after the intravenous administration of 250 and 500 mg/kg sodium bicarbonate. Immediately after the administration of sodium bicarbonate, a transient rise followed by a fall in systemic blood pressure was observed. In addition, the pulse pressure became wider and the active force of the myocardium was reduced. Lactic acid failed to cause obvious excitation of the fibers when it was applied 3–5 min after the administration of 500 mg/kg sodium bicarbonate. However, application of lactic acid 8–10 min after caused excitation of the fibers again.

Occlusion of the anterior descending branch of the left coronary artery was carried out for 2–5 min in 44 fiber preparations. Thirty-nine of these fibers were mechanosensitive. The other five fibers responded to coronary oc-

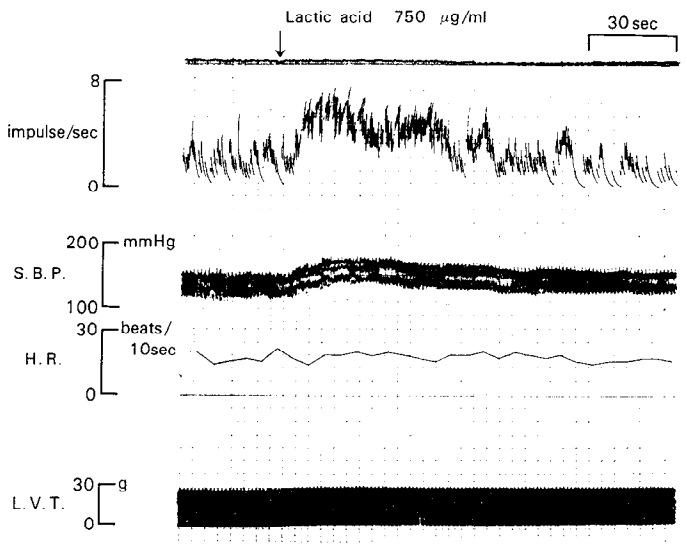

FIG. 3. Effect on activity of an Aδ fiber of application of 750 μg/ml lactic acid to left ventricular surface. *From top down:* integrated action potentials, systemic blood pressure, heart rate, and left ventricular tension. Downward arrow indicates application of agent.

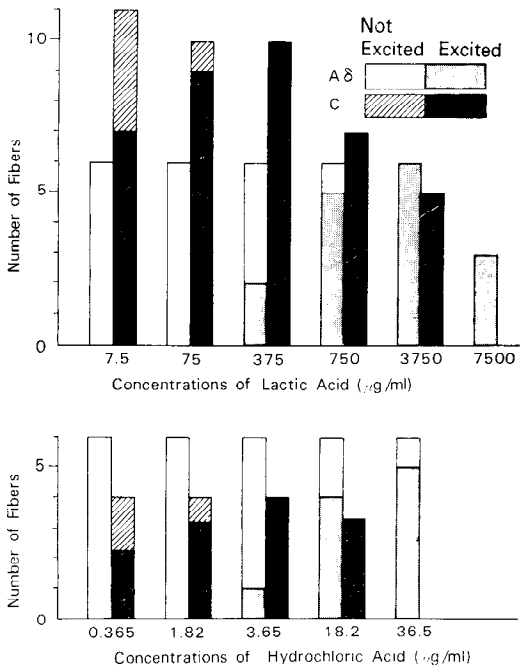

FIG. 4. Relationship between concentration of acid solutions and excitation of afferent sympathetic nerve fibers.

clusion but not to mechanical stimuli. After coronary occlusion, the active force of the myocardium was reduced during the early phase of systole, indicating passive extension of the myocardium, the systolic bulge. The force returned to the control levels during the late phase of systole, indicating passive shortening. All the Aδ fibers fired regularly synchronous with passive extension and/or shortening of the ischemic myocardium. However, the C fibers fired irregularly and independently. Both groups of fibers continued to fire even after release of coronary occlusion. The discharge after release of occlusion, the afterdischarge, was irregular and independent from the cardiac cycle in both groups of fibers. Details on modality of excitation during and after release of occlusion have been reported elsewhere (29, 31).

The effect of intravenous injection of 500 mg/kg sodium bicarbonate on excitation induced by coronary occlusion was examined in seven Aδ and seven C fiber preparations. Coronary occlusion was performed before and 3–5 and 10–15 min after the injection of the agent. Immediately after the injection, a transient excitation of the afferent fibers was occasionally observed. Coronary occlusion was performed 3–5 min after the injection. Excitation of all the C fibers induced by occlusion was suppressed; the number of the action potentials per 30 s calculated from the records on continuous film strips became 0–40% of the control occlusion experiments and the latency for excitation became longer ($P < 0.005$) and the duration of afterdischarge became shorter ($P < 0.005$) than those of the control occlusion experiments. Occlusion was again performed 10–15 min after the injection. However, no significant suppression of excitation was observed. In contrast to the C fibers, suppression of excitation during occlusion was not observed in three Aδ fibers and suppression of the remaining Aδ fibers was up to 25% of the control occlusion experiments. On the other hand, the duration of afterdischarge became shorter ($P < 0.001$) than that of the control occlusion experiments (Figs. 5 and 6).

The effect of intravenous Trasylol injections of 50,000 KIU/kg was examined in 14 fiber preparations. Coronary occlusion was performed before and 5, 10, 15, and 30 min after the injection. The number of the action potentials per 30 s was compared before and after the injection. A slight suppression of excitation up to 20% of the control occlusion experiments was observed in both Aδ and C fibers when occlusion was performed 5 min after the injection, but not in the later periods (Fig. 7).

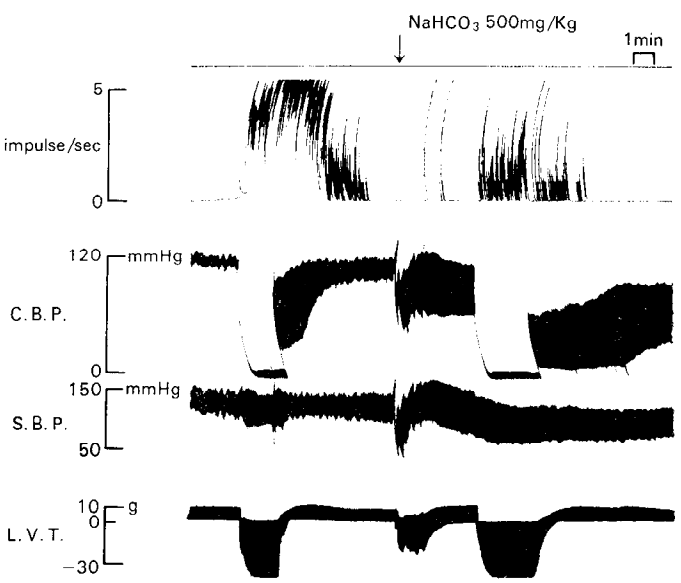

FIG. 5. Effect of intravenous administration of 500 mg/kg sodium bicarbonate on excitation of a C fiber induced by coronary artery occlusion. *From top down:* integrated action potentials, peripheral blood pressure of anterior descending branch of left coronary artery, systemic blood pressure, and left ventricular tension. An abrupt fall in CBP indicates occlusion. Sodium bicarbonate was administered at arrow.

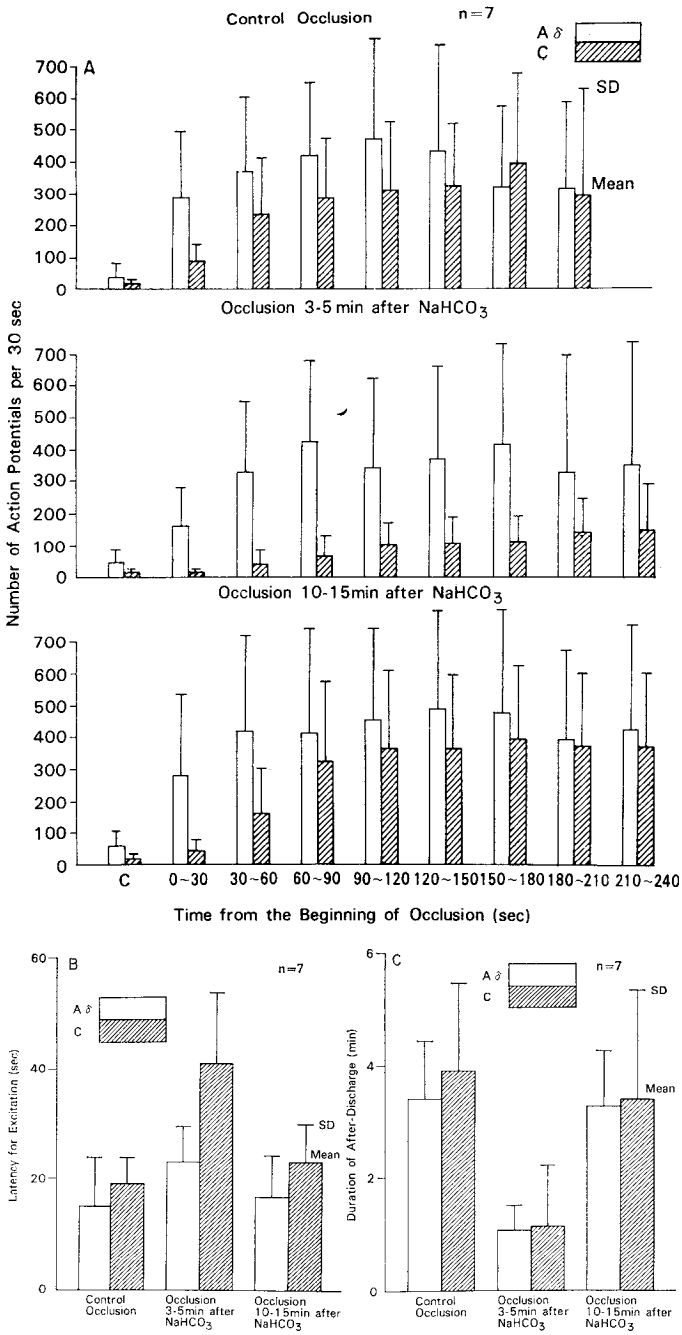

FIG. 6. *A:* effect of 500 mg/kg sodium bicarbonate on excitation of afferent fibers during occlusion. C = number of action potentials before coronary occlusion; SD = standard deviation. *B:* effect of 500 mg/kg sodium bicarbonate on latency for excitation of afferent fibers. *n* = number of fibers. *C:* effect of 500 mg/kg sodium bicarbonate on afterdischarge.

The effect of intravenous administration of acetylsalicylic acid was examined in 11 fiber preparations. Coronary occlusion was performed before and 5, 10, 15, and 30 min after the administration. Ten to 15 min after the administration of 100 mg/kg or more, excitation during occlusion and the afterdischarge were suppressed by the agent. Suppression of the C fibers was up to 72%, whereas that of the Aδ fibers was up to 38% of the control occlusion experiments (Fig. 8). On the other hand, development of systolic bulge was influenced little by pretreatment with the agent.

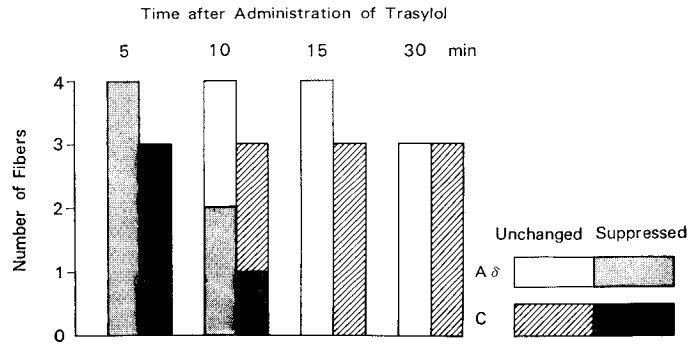

FIG. 7. Effect of Trasylol on excitation of afferent fibers induced by coronary occlusion.

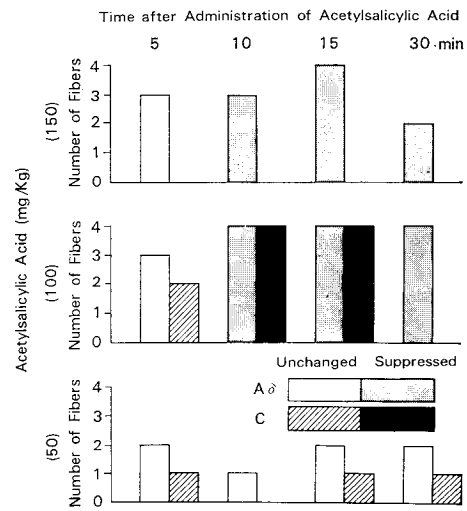

FIG. 8. Effect of acetylsalicylic acid on excitation of afferent fibers induced by coronary occlusion.

The effect of intravenous injection of 500 μg/kg atropine was examined in four Aδ and one C fiber preparations. Coronary occlusion was performed before and 5–10 min after the injection. A slight increase in heart rate was produced by the injection. Excitation of the afferent fibers induced by coronary occlusion was augmented up to 24% of the control occlusion experiments.

DISCUSSION

The left ventricular wall is innervated by afferent sympathetic nerve fibers (1, 2, 18, 27, 34). These fibers are composed of slowly conducting myelinated fibers and unmyelinated fibers (28). Their afferent functions as nociceptor and vasopressor have been demonstrated by many workers (2, 18, 27, 29, 32).

The injection of potassium ions into a skeletal muscle bed has been found to elicit cardiovascular responses caused by C fibers (19). Uchida et al. observed excitation of the afferent sympathetic nerve fibers from the left ventricle after application of potassium ions (30) and bradykinin (32) in a concentration that can be achieved during myocardial ischemia (5, 9, 24). In addition, they observed a definite difference in modality of excitation induced by myocardial ischemia between the myelinated and unmyelinated fibers. Namely, the myelinated fibers fired synchronously with passive extension and/or shortening of

the ischemic myocardium in which the nerve endings were imbedded, whereas the unmyelinated fibers fired irregularly and independently. They therefore suggested that mechanical factors were responsible for excitation of the myelinated fibers and chemical factors for the unmyelinated fibers (31).

In this study, the effect of lactic acid and hydrochloric acid was examined since myocardial ischemia leads to accumulation of acids and an increase of H^+ ion concentration (3, 22, 24). It was revealed that the unmyelinated fibers, irrespective of their mechanosensitivity, were more sensitive to lactic acid and hydrochloric acid. The minimum concentration required for excitation of the unmyelinated fibers (C fibers) was 7.5–75 μg/ml of lactic acid and 0.365–3.65 μg/ml of hydrochloric acid. These threshold concentrations correspond to pH values of 4.58–3.55 and 5.60–4.53, respectively. On the other hand, the threshold concentrations required for activation of the myelinated fibers were 375–750 μg/ml (pH 3.11–2.86) for lactic acid and 18.2–36.5 μg/ml (pH 3.85–3.20) for hydrochloric acid. Conn et al. (3) noted that lactate in the myocardium increased from the control value of 500 μg/g to 1.6 mg/g during myocardial ischemia. Opie et al. (22) found that the pH of the local coronary vein blood was lowered from the control value of 7.4 to 7.25 during myocardial ischemia. The value of change in lactate concentration in the myocardium is above the threshold concentration of lactic acid required for activation of the afferent fibers. However, the value of change in pH is far less than that required for activation of the fibers.

Singleton (25) and Moore and Moore (20) observed that the intra-arterial injection of acids (below pH 5.3) solutions evoked pain in man and pseudaffective response in the dog. Lindahl (16) noted that pain was felt in the skin when pH of the skin fell to 6.2. Carotid sinus baroreceptors are affected when the pH of the environment is lowered below 6.0, whereas carotid chemoreceptors can respond to a much smaller change in pH (10). In this study, lactic acid and hydrochloric acid were dissolved in physiological saline whose pH was 6.0. Physiological saline did not excite the afferent fibers. Therefore, the receptors of the afferent fibers in this study had a pH sensitivity similar to that of carotid baroreceptors and cutaneous and vascular "pain" receptors, but far less sensitive than carotid chemoreceptors.

Pretreatment with a large dose of sodium bicarbonate effectively suppressed excitation of the unmyelinated fibers induced by coronary occlusion. Although Trasylol blocks formation of bradykinin (5), its effect on ischemia-induced excitation of the afferent fibers was very slight. Ischemia-induced excitation was also suppressed by acetylsalicylic acid. However, this does not mean that bradykinin participated in excitation since this agent is a nonspecific antagonist (8). Atropine, which is effective in alleviating anginal pain in a certain group of patients with coronary insufficiency, could not suppress ischemia-induced excitation of the afferent fibers. On the contrary, this agent augmented excitation, probably through elimination of the action of the efferent vagal nerves to the heart.

Although the lowering in pH that can be achieved during myocardial ischemia is far less than that required for excitation of the afferent fibers, the fact that sodium bicarbonate suppressed excitation of the unmyelinated fibers suggests that accumulated acids or H^+ ions played a role in ischemia-induced excitation at least of the unmyelinated fibers. The result therefore supports the concept of Lewis (12) on the mechanism of excitation of pain receptors.

The myelinated fibers were less sensitive to a lowering of pH. In addition, their excitation during coronary occlusion was less suppressed by sodium bicarbonate. Furthermore, it was demonstrated in our previous study that systolic bulge is responsible for excitation of the myelinated fibers (31). Therefore, it is unlikely that acids or pH played a major role in ischemia-induced excitation of the myelinated fibers.

Unlike the excitation during occlusion, the afterdischarge of the myelinated fibers was suppressed by sodium bicarbonate and acetylsalicylic acid. Excitation of the myelinated fibers after release of coronary occlusion, the afterdischarge, is irregular and independent of cardiac motion and continues even after normal modality of myocardial contraction is restored as in the case of unmyelinated fibers (31). These findings suggest that the afterdischarge of the myelinated fibers was due to chemical mechanisms as in the case of the unmyelinated fibers.

Both myelinated and unmyelinated fibers can be stimulated by potassium ions in a concentration that can be achieved during myocardial ischemia (24, 30, 33). However, whether potassium ions participated in ischemia-induced excitation was not examined.

The majority of the afferent fibers were not suppressed completely by pretreatment with sodium bicarbonate and acetylsalicylic acid. The dose used may have been insufficient or other chemical agents such as potassium ions may have also participated in ischemia-induced excitation. Nevertheless, the results in this and in the previous studies (29, 31) suggest that myocardial ischemia excites the myelinated fibers through mechanical mechanisms and the unmyelinated fibers through chemical mechanisms, leading to pain in man and the pseudaffective response in animals.

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