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REFLEX CARDIOVASCULAR AND RESPIRATORY RESPONSES ORIGINATING IN EXERCISING MUSCLE

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SUMMARY

1. In anaesthetized and decerebrate cats isometric exercise of the hind limb muscles was elicited by stimulating the spinal ventral roots L7–S1. This caused a rise in arterial blood pressure, with small increases in heart rate and pulmonary ventilation. These changes were abolished by cutting the dorsal roots receiving afferents from the exercising muscle.

2. When the triceps surae muscle was made to exercise by ventral root stimulation, occlusion of the femoral artery and vein through and beyond the period of exercise caused the blood pressure to remain raised until the occlusion was removed. The ventilatory and heart rate responses were not markedly altered or prolonged by such circulatory occlusion.

3. Injection of small volumes of 5 % NaCl or isotonic KCl into the arterial blood supplying hind limb muscles gave cardiovascular and respiratory responses similar to those evoked by exercise. Like the responses to exercise, these responses were abolished by dorsal root section.

4. Direct current anodal block of the dorsal roots receiving afferents from the exercising muscle was used to block preferentially large myelinated fibres: this form of block did not abolish the evoked cardiovascular and respiratory responses. Local anaesthetic block of the dorsal roots was used to block preferentially unmyelinated and small myelinated fibres: this form of block abolished the cardiovascular and respiratory responses. It is concluded that the reflex responses are mediated by fibres within groups III and IV (small myelinated fibres and unmyelinated fibres).

INTRODUCTION

That reflexes originating in exercising muscle can give cardiovascular and respiratory responses has been suggested from work done on man (Alam & Smirk, 1937, 1938; Asmussen, Nielsen & Wieth-Pedersen, 1943;

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Lind, McNicol & Donald, 1966; Dejours, 1967) and has been proved by experiments on animals (Kao & Ray, 1954; Coote, Hilton & Perez-Gonzalez, 1971).

Voluntary isometric exercise in man is accompanied by marked increases in blood pressure, cardiac output, heart rate (Lind *et al.* 1966), and pulmonary ventilation (Wiley & Lind, 1971; Myhre & Andersen, 1971). Isometric exercise in the hind limb of the anaesthetized or decerebrate cat induced by stimulation of the appropriate spinal ventral roots causes an increase in the arterial blood pressure accompanied by small increases in heart rate and ventilation (Coote *et al.* 1971).

It has been suggested that the responses described during exercise in animals were reflexly induced by small myelinated and unmyelinated afferents from muscle, since electrical stimulation of such nerve fibres produces similar responses (Gordon, 1943; Johansson, 1962; Senapati, 1966; Mitchell, Mierzwiak, Wildenthal, Willis & Smith, 1968; Coote & Perez-Gonzalez, 1970). The present study demonstrates by the use of nerve-blocking techniques that these afferent fibres are responsible for the cardiovascular and respiratory responses that come from muscle during exercise. A preliminary report of these observations has been published (McCloskey & Mitchell, 1972).

METHODS

Experiments were done on twenty-eight cats which weighed between 1·6 and 3·2 kg. They were anaesthetized by one of two methods: (1) I.P. injection of pentobarbitone sodium, 35 mg/kg (Nembutal: Abbott), (2) I.V. injection of chloralose, 80 mg/kg (α-chloralose: B.D.H. Chemicals Ltd) after induction with ether; or were decerebrated at the intercollicular level after preliminary anaesthesia with ether. In the anaesthetized animals small additional doses of the original anaesthetic were given I.V. as required.

Experimental procedures

The trachea was cannulated low in the neck. Blood pressure was recorded from either the left common carotid artery or the left axillary artery, via a saline-filled nylon cannula connected to a pressure transducer (SE Laboratories: SE 4-82). Respiratory flow was recorded by a pneumotachometer attached to the tracheal cannula, integrated electronically, and calibrated to record ventilatory volumes. The outputs of the blood pressure and ventilatory records, plus the electrocardiogram, were amplified and displayed on a 4-channel U.V. recorder (SE Laboratories: SE 3006).

A laminectomy was performed to expose the spinal cord segments L4–S1. The skin high at the back of the limb to be exercised was opened to expose the sciatic nerve. In several experiments all muscles on the experimental side were denervated except the triceps surae: in these animals the completeness of this denervation was confirmed when only the triceps contracted upon stimulation of the ventral roots, L6, L7, S1. Also in these animals a cannula was inserted retrogradely into the artery supplying the gracilis muscle with its tip just in the femoral artery. Drugs injected through this cannula rapidly reached the triceps muscle (this was confirmed by

injection of dilute Evans blue dye) and could be held in the muscle by occluding the femoral artery and vein with a thread drawn into a thin polyethylene tube. In some experiments the skin of the hind limb to be exercised was removed from thigh to ankle in order to denervate the skin, and then stitched back.

Animals were fixed in a prone position on a table by pins driven into the iliac crests and through the bones of the knee and ankle joints on the experimental side. Pools were made with paraffin warmed to 37 °C and bubbled with 95% O_2+5% CO_2 over the laminectomy and in the upper thigh where the sciatic nerve was exposed. The spinal cord was exposed by a lengthwise incision through the dura.

A diagram of the experimental preparation used for stimulation and recording of spinal and peripheral nerves is shown in Fig. 1. Spinal roots L5, L6 and S2 downwards were always cut, and L4 was also cut in most experiments. The dorsal roots

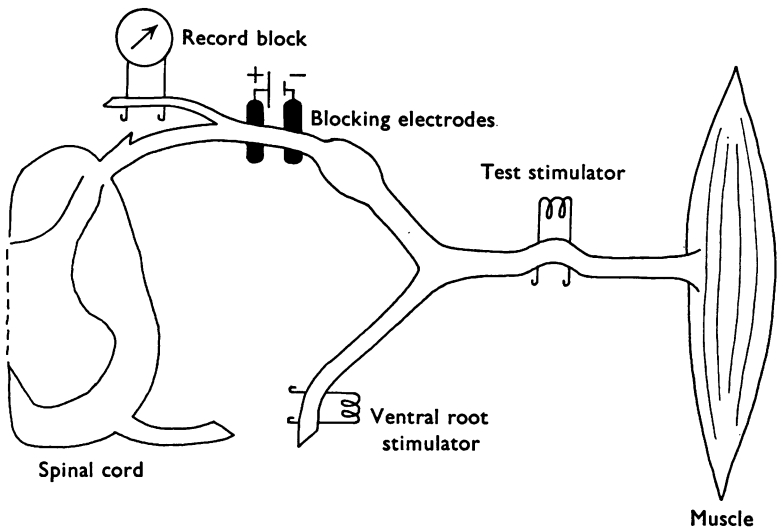

Fig. 1. Diagram of experimental set-up. Muscles in a hind limb were caused to contract isometrically by applying trains of stimuli to the peripheral cut ends of the ventral roots of spinal segments L7 and S1. Afferent nerves from the contracting muscle entered the spinal cord in the dorsal roots of these segments: other dorsal roots supplying the hind limb were cut. Direct current could be passed between two electrodes placed under the intact dorsal roots in order to produce an anodal block. Alternatively, lignocaine (0·125%) could be applied to the dorsal roots where they passed over these electrodes in order to produce a local anaesthetic block. The degree of block achieved by either method could be gauged by stimulating the sciatic nerve high in the back of the thigh with a test stimulator, and monitoring the changes produced by the block in a compound action potential recorded monophasically in a slip of the dorsal root after it had passed the blocking region.

of L7 and S1 were carefully placed across a pair of Ag–AgCl electrodes individually bound in saline-soaked cotton wool, and these electrodes were used to apply direct-current for anodal block. A small slip of the dorsal root of L7 was cut close to the cord after passing over the blocking electrodes, and was placed over a pair of Ag–AgCl electrodes, with its cut end crushed, to monitor the dorsal root action potentials

during blocks. The ventral roots of L 7 and S 1 were cut close to their exit from the spinal cord and placed over a pair of Ag–AgCl electrodes. Stimulation of the ventral roots at 20–50 Hz, with square-wave pulses of 0·1–0·2 msec duration, delivered by an isolated stimulator, was used to elicit contraction of the hind-limb muscles. An additional pair of stimulating Ag–AgCl electrodes was placed under the sciatic nerve in the upper thigh. Test stimuli delivered here by a further isolated stimulator at 1/sec (0·1 msec duration) elicited the compound action potentials which were picked up from the sampling slip of dorsal root beyond the blocking electrodes in the spinal cord. Action potentials picked up in this way were amplified in a Tektronix type 122 pre-amplifier and then displayed on an oscilloscope and could be photographed with a Cossor camera.

Periods of exercise of 10–45 sec were usually given. The exposed spinal cord and nerve roots were washed, every 20–30 min, with warmed Ringer solution made up as described by Brown, Lawrence & Matthews (1969), and bubbled with 95 % O_2 and 5 % CO_2. Rectal temperatures were maintained at 36–38° C throughout.

Nerve blocking techniques

In the experiments performed, two types of nerve block were used. In these experiments it was not always possible to distinguish reliably the Aδ- and C-waves of the sampled compound action potential, and so the nerve block achieved was inferred from the presence or absence of the A-wave only – this represents the large myelinated nerve fibres. The A-waves of the compound action potentials recorded in these experiments covered the range of conduction velocities 20–120 m/sec: that is, they were A$\alpha\beta\gamma$-waves. Direct current anodal block was achieved by passing a direct current between the two electrodes under the dorsal roots, the anode cephalad: for this a 9 V battery was used with a variable resistance placed in series with the nerve. Block of the A wave of the sampled potential was achieved with a current of 50–250 μA. A period of at least 1 min was always allowed to elapse from application of the block to testing of cardiorespiratory responses, as it is known that the blocking procedure can stimulate the nerve to be blocked during the first minute of its application (Casey & Blick, 1969; Trenchard & Widdicombe, 1972). The completeness of the block was checked immediately before and after such tests.

The local anaesthetic, lignocaine (0·125 %), was used for the second type of reversible differential block. Here, cardiorespiratory responses were tested every 60–90 sec after application of a few drops of the local anaesthetic to the dorsal roots as they passed over the DC electrodes. With this form of block it is the unmyelinated and small myelinated fibres which should be blocked first, and so the A-wave beyond the block was watched for a reduction in its amplitude.

RESULTS

Response to induced isometric exercise

Tetanic contractions of the hind-limb muscles elicited by stimulation of the ventral roots L 7 and S 1 for 10–45 sec usually caused a rise in arterial blood pressure of 20–50 mm Hg (Fig. 2). This response was most consistently seen in those preparations in which all the muscles innervated by these ventral roots were exercised (nineteen cats): in preparations in which only the triceps surae was exercised (nine cats) the pressor response was often small (10–20 mm Hg), and occasionally there was no pressor response.

The magnitude of the pressor response appeared from these observations to be dependent upon the mass of muscle exercising, although it is possible that the denervation procedure may have damaged the responsiveness of the triceps-only preparations. At the conclusion of an exercise period the blood pressure frequently dropped below the resting level for some 10–20 sec before returning to normal.

The pressor response was seen in all preparations in which the skin of the

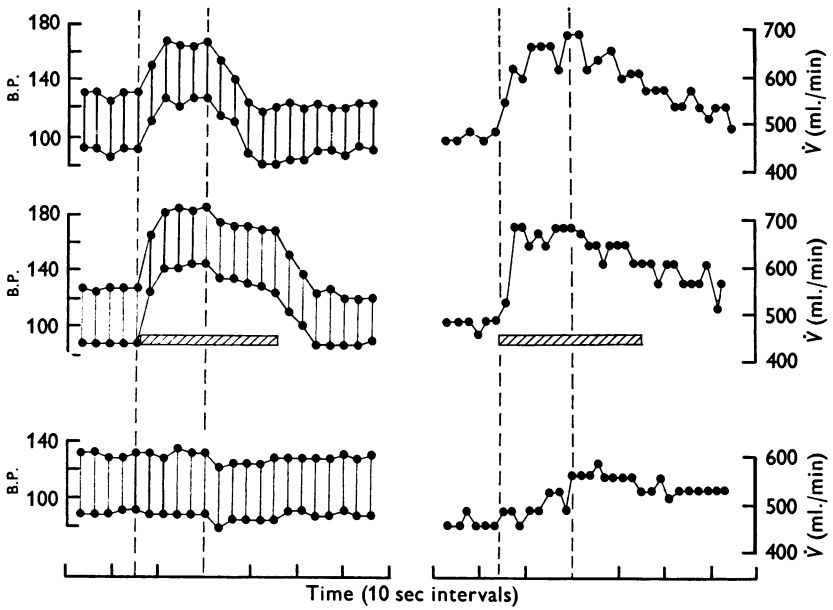

Fig. 2. Cat, chloralose. Records of arterial blood pressure and ventilation (calculated breath by breath from tidal volume and frequency). The records are in pairs, pressure on the left and ventilation on the right, taken in the same periods of exercise. From above downwards three periods of isometric exercise in the triceps surae are shown. The upper pair of records show the pressor and ventilatory responses to a control period of exercise. The middle pair show the responses when the femoral artery and vein were occluded from the commencement of exercise until 15 sec after the conclusion of exercise: the duration of the occulsion is indicated by the bar underlying each record. The lower pair of records shows a further period of exercise after the dorsal roots receiving afferents from the exercising muscle were cut.

exercising limb was denervated (six cats). It was prolonged, usually at a level slightly less than the exercise level, if arterial and venous occlusion was applied during the exercise, lasting for as long as the occlusion was maintained (Fig. 2). Occlusions lasting up to 30 sec after the conclusion of exercise were used.

In the exercise confined to the triceps surae, the cardiovascular and

respiratory responses were similar whether the ventral roots were stimulated at 1·5 times the threshold voltage for motor contraction, or, as was more usual, at 10 times that voltage.

All the pressor responses described were abolished by cutting the dorsal roots which remained in connexion with the exercising muscle (Fig. 2).

In preparations giving a pressor response there was usually a tachycardia in response to exercise. The increase in heart rate was small ($< 5\%$). In cats in which the heart rate was over 250 beats/min before exercise began, no heart rate changes were seen. In no experiments did a slowing of the heart accompany exercise, although the carotid sinus baroreceptors responded to clipping of the common carotid arteries by causing a reflex hypertension and tachycardia both at rest and during exercise. The increases in heart rate were also abolished by cutting the remaining dorsal roots.

An increase in both the rate and depth of breathing was seen in preparations giving pressor responses (Fig. 2). Breathing was always increased within two breaths of the commencement of exercise, and usually continued to increase to a maximum at 15–20 sec after the exercise began. Ventilation usually increased by approximately 50 % of its resting level during exercise. At the conclusion of exercise, ventilation did not decrease abruptly, but slowly declined over the succeeding 30–45 sec to reach its resting level. After cutting the dorsal roots from the exercising muscle, no fast ventilatory response was seen, although ventilation did show increases of up to 25 % over the resting level late in the period of exercise, or commonly in the 15 sec after exercise. These remaining ventilatory changes were interpreted as being due to metabolic effects on chemoreceptors remote from the muscle.

Response to arterial injections

Cardiovascular and respiratory responses similar to and often larger than those seen during exercise were seen when 1 ml. 5 % NaCl (850 m-equiv/l.) was injected beyond an occlusion in the femoral artery into the blood supplying the triceps-surae in eight animals in which only this muscle group remained innervated. These responses were maintained for as long as the occlusions trapping the NaCl in the muscle were maintained.

Similar but less striking responses followed injections of 1 ml. isotonic KCl (150 m-equiv/l.). No response was seen to injection of isotonic NaCl.

Response to exercise during dorsal root blocking experiments

Two types of differential nerve block were used on the dorsal roots. Anodal block with direct current blocks nerve fibres of large diameter before smaller ones and local anaesthetic agents block small fibres before larger ones.

Anodal block was applied to the dorsal roots receiving afferents from the exercising muscle in eighteen cats. The current passed was gradually increased until the A wave of the compound action potential sampled beyond the block was just abolished. Exercise of the limb during this block produced the same reflex pressor, heart rate, and ventilation changes

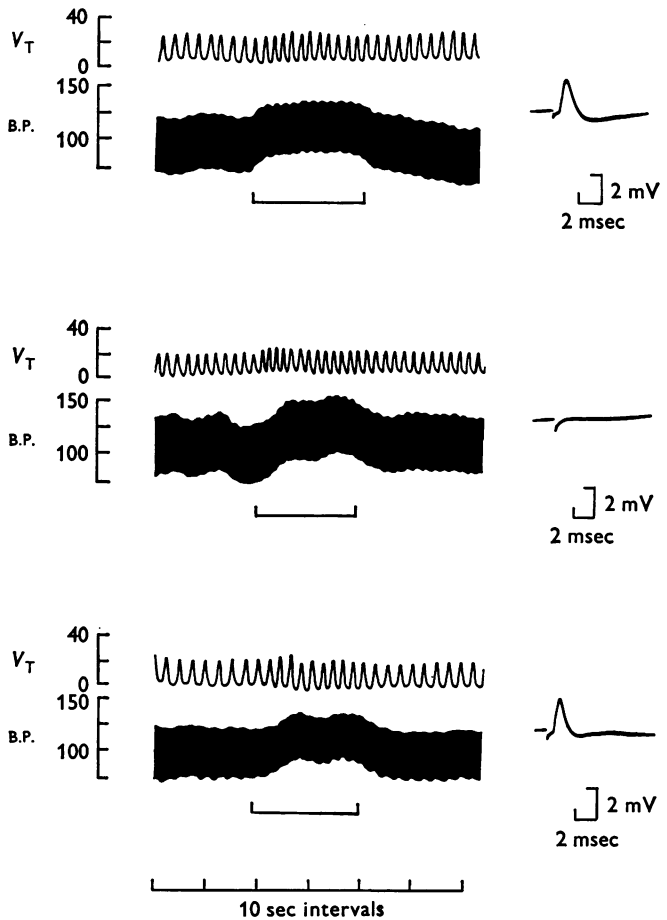

Fig. 3. Cat, pentobarbitone. Records of tidal volume and arterial blood pressure are shown from three periods of isometric hind-limb exercise. Together with each pair of records is shown the compound action potential sampled from a slip of dorsal root beyond the experimental blocking region: the action potential was evoked by a supramaximal test stimulus applied to the sciatic nerve about 5 cm from the sampling electrode. From above downwards are shown: a control period of exercise before anodal block was applied; a period of exercise 1 min after application of anodal block just sufficient to block the A-wave of the compound action potential; and a further control period after removal of the anodal block. Ventilation and pressure are retouched U.V. records.

as had been produced before the block was applied (Fig. 3). In three experiments in which 5% NaCl or isotonic KCl solutions were injected into the blood supplying triceps-only preparations, anodal block of the A wave did not block the responses to these agents.

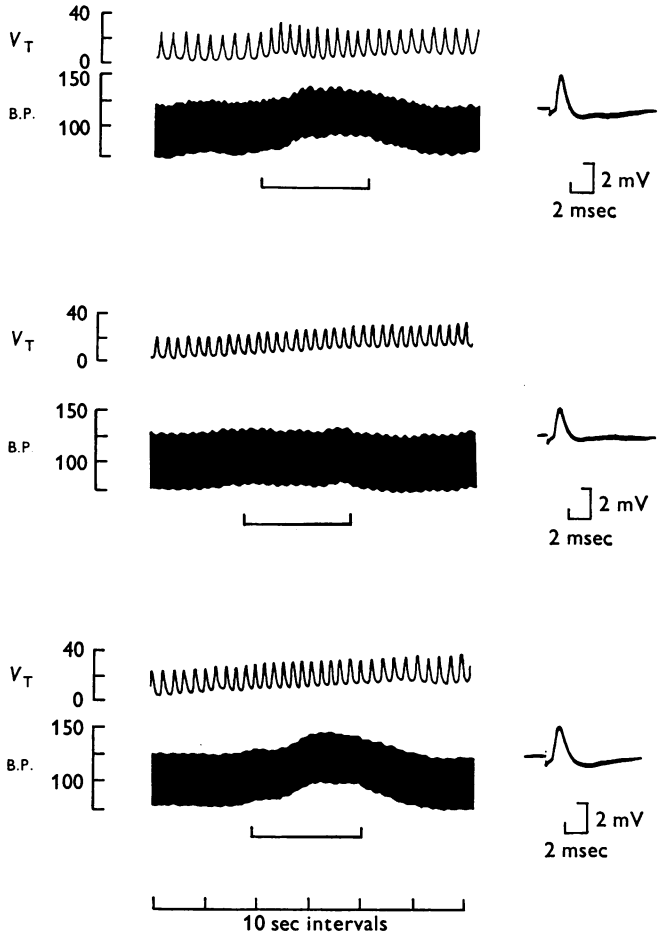

Fig. 4. Cat, chloralose: same cat as Fig. 3. Records of tidal volume, arterial blood pressure, and dorsal root compound action potential from three periods of isometric hind-limb exercise. From above downwards are shown a control period of exercise; a period of exercise which commenced 3½ min after application of a few drops of 0·125% lignocaine solution to the dorsal roots. Note that this period of exercise produced no pressor or ventilatory response, although the A-wave of the compound action potential was little, if at all, reduced; and in the bottom set of records, a further control period of exercise begun some minutes after the lignocaine had been washed away with warm saline. Ventilation and pressure are retouched U.V. records.

Local anaesthetic block was achieved with lignocaine (0·125 %) applied to the dorsal roots. In a sequence of periods of exercise given about one minute apart after applying this drug, it was possible to find one or two periods of exercise when the A wave of the compound action potential was unaltered but the cardiovascular and respiratory responses were abolished. This usually occurred between 2 and 5 min after applying the lignocaine. In many experiments the compound A wave was partly reduced before the exercise responses were completely gone, but in three experiments the A wave was unaffected when the exercise responses were entirely abolished (Fig. 4).

Both forms of block are reversible, and in some experiments several observations with each could be made. The margin between the desired degree of anodal block and a level which caused irreversible damage to the nerve roots was narrow, and frequently its misjudgment prematurely ended experiments. The block with lignocaine always proceeded to complete block of the sampled compound A-wave. Full recovery from the lignocaine block, both of the sampled action potential and of the cardiovascular and respiratory responses, was usual after the treated nerve roots had been washed 2 or 3 times with warm Ringer solution.

DISCUSSION

The reflex cardiovascular and respiratory responses seen during isometric exercise in this study and in that of Coote *et al.* (1971) are initiated within the muscle: neither denervation of the skin of the exercising limb, as described here, nor section of the articular nerves as done by Coote *et al.*, alters the responses.

Although Coote *et al.* (1971) showed some effect of arterial occlusion on the pressor response, they did not look at the effects of arterial and venous occlusion. In the present study at the conclusion of exercise performed during circulatory occlusion there was a slight fall of blood pressure, but this did not fall completely to normal until the occlusion was removed (Fig. 2). This suggests that a chemical factor activating the endings of afferent nerves causes the pressor response, although the initial fall despite occlusion may implicate mechanoreceptors as well. In human subjects in which circulatory occlusion is maintained in the exercising limb beyond the exercise, it has been reported that the blood pressure rises over the succeeding minute (Alam & Smirk, 1937), that it remains at the level reached in exercise (Lind *et al.* 1966), that it falls half-way back towards the resting level (D. J. C. Cunningham, T. G. Pickering & P. Sleight, personal communication), and that it falls and then rises again to the exercise level (Wiley & Lind, 1971). These conflicting descriptions have in common the

possibility that at least part of the pressor response seen is attributable to a chemical factor exciting nerve endings in the muscle.

Although circulatory occlusion extending beyond the end of exercise gave valuable information regarding the initiation of the pressor reflex described, it was of less value in investigating the heart rate and ventilatory responses. The heart-rate changes were small, and it cannot be said with certainty whether or not they remained during the post-exercise occlusion; in human subjects doing isometric work, where the tachycardia is greater, they are not (Lind *et al.* 1966). The ventilatory responses were complicated late in exercise, and after, by effects attributable to chemoreceptors elsewhere in the body: for circulatory occlusion to have yielded important information on this point considerable efforts would have had to be made to correct for changes in these remote effects and this was not done here. In human subjects circulatory occlusion of the working limb does not prolong hyperventilation (Wiley & Lind, 1971).

The increments in heart rate seen during isometric exercise in the cat were small. Much larger increments of heart rate are seen in human subjects doing isometric exercise (Alam & Smirk, 1938; Lind *et al.* 1966). It might be that the rise in blood pressure caused by the stimulated exercise acts through the arterial baroreceptors to obscure a larger reflex tachycardia in the cat. In man, where the exercise is done voluntarily, the sensitivity of the baroreceptor reflex is reduced during exercise (Bristow, Brown, Cunningham, Howson, Petersen, Pickering & Sleight, 1971), and would permit larger changes in heart rate initiated by muscle reflexes. Alternatively it might be that the greater part of the tachycardia in man has its stimulus elsewhere than in the exercising muscle.

The ventilatory responses to exercise were small in comparison with the four- to fivefold increases seen in isometric exercise in humans (Wiley & Lind, 1971; Myhre & Andersen, 1971), and followed a different time course. The responses commenced promptly enough to correspond to the fast increases in ventilation described by Dejours (1967) for rhythmic exercise in man (that is, within the first two breaths), but such prompt responses are not seen during isometric exercise in man (Wiley & Lind, 1971; Myhre & Andersen, 1971). Dejours has suggested from several lines of work that the muscle spindle primary afferents may be responsible for the fast responses he describes (Dejours, 1967; Leitner & Dejours, 1971). The present study suggests that these afferents do not cause the prompt responses seen here because the anodal block of large myelinated fibres does not abolish them. Nor, for the same reason, are the large myelinated afferents from Golgi tendon organs likely to be involved in the responses. Moreover, low threshold motor stimulation, which, by activating principally the alpha motor efferents, unloads the muscle spindles and should

maximally activate Golgi tendon organs (Harvey & Matthews, 1961), leads to the same exercise responses as higher threshold motor stimulation which activates alpha and gamma efferents. This, and the observation that the cardiovascular and respiratory responses to both high- and low-threshold motor stimulation were unaffected by anodal block, point against either the muscle-spindle afferents or the Golgi tendon organs being involved in the responses described.

It is possible that some of the ventilatory response mediated by the muscle afferents was due to an increase in peripheral chemoreceptor drive. It is known that sympathetic nervous activity can increase the discharge rate of peripheral arterial chemoreceptors (Lee, Mayou & Torrance, 1964; Biscoe & Purves, 1967). However, Parida, Senapati & Kalia (1969) showed that the ventilatory response to exercise was unaffected by denervation of the carotid body chemoreceptors. No attempt was made in the present study to investigate this possibility.

Anodal block as used in this study was established by Mendell & Wall (1964) as a technique in which conduction could be blocked in larger before smaller diameter fibres according to the magnitude of current passed. Casey & Blick (1969) in experiments testing the reliability of this technique showed that the Aδ-wave in a compound action potential was the first to disappear as current was increased, then the A-wave, leaving an almost normal C-wave. Simultaneous single fibre studies showed that the Aδ-wave had disappeared because some of its component fibres had been blocked while others had only been slowed, and consequently spread out. Although single A-fibres were also slowed, none were found to conduct after the 'A' compound action potential had disappeared. Similar results have recently been found by Trenchard & Widdicombe (1972) on the vagus nerve. Nevertheless, it is conceded that a possible weakness of this method is that some apparently blocked fibres may only have had their conduction slowed. It would be necessary, however, for these fibres to retain the full cardiovascular and respiratory reflex potency of the whole population of such afferents if the responses described here were to be considered as carried in them.

Since Gasser & Erlanger (1929) used cocaine to block smaller before larger myelinated fibres, various local anaesthetic agents have been used to achieve differential nerve blocks. In the present study this technique proved difficult to manage and gave less clear-cut separation of A-fibre conduction from reflex responsiveness than did anodal block. The technique requires repeated testing of reflexes after application of the anaesthetic agent, and at its best provided only one or two periods of separation of reflex response from A-fibre conduction. Usually the reflexes were not fully abolished until the A-wave had begun to be diminished. It was always

found, however, that some of the A-wave remained when the responses had been stopped, so that one is again forced to argue about the reflex potency of the unblocked myelinated fibres if their involvement is supported, only this time the view must be taken that the reflex potency is reduced greatly by a slight reduction in the number of conducting fibres. Moreover, three experiments did produce full separation of block of the response from block of the A-fibres.

Because the Aδ- and C-waves were not reliably distinguished in the sampled compound action potentials in this study, it is not possible to say more than that the A-fibres (groups I and II) were not involved in the reflexes observed. Fibres in either or both of group III (small myelinated fibres) or group IV (unmyelinated C-fibres) were responsible. These fibre groups are heterogeneous, containing mechanoreceptor fibres and pressure–pain fibres amongst others. It has been argued that fibres contributing to the responses are activated by metabolites from the exercising muscles (Lind *et al.* 1966; Wildenthal, Mierzwiak, Skinner & Mitchell, 1968; Hník, Hudlická, Kučera & Payne, 1969; Coote *et al.* 1971), and the present study supports this while not ruling out as well a contribution from mechanoreceptors. Coote *et al.* have outlined the reasons for believing that the reflex responses are not responses to pain. Responses to stimuli other than exercise, such as muscle squeezing (Kalia, Senapati, Parida & Panda, 1972) or the injection of KCl or 5% NaCl as reported here, although similar to the exercise responses, are probably at least in part responses to pain.

The experiments reported here give no information about the relative contributions of this peripheral reflex mechanism during exercise. Krogh & Lindhard (1913) proposed that an important stimulus for the cardiovascular and respiratory responses in exercise might be the 'irradiation' of the command to exercise upon the mass transport control centres. This idea has had recent support in the work of Freyschuss (1970) and Goodwin, McCloskey & Mitchell (1971). The muscle reflex effects described here must be considered together with this direct 'irradiation' as peripheral and central components of the neural drives present in exercise, though these neural drives are but part of the whole stimulus pattern of exercise.

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