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FACTORS AFFECTING THE CAT CAROTID CHEMORECEPTOR AND CERVICAL SYMPATHETIC ACTIVITY WITH SPECIAL REFERENCE TO PASSIVE HIND-LIMB MOVEMENTS

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SUMMARY

1. Recordings have been made of the activity in carotid body chemoreceptor afferent fibres and in the cervical sympathetic of the cat during passive movement of the hind limbs.

2. The chemoreceptor activity increases immediately the limbs are moved and is maintained at a raised level with preservation of the chemoreceptor rhythm fluctuations throughout. In some cases, the increase persists for a time after the movements are stopped.

3. This early change does not occur if the cervical sympathetic on the same side as the carotid body from which recordings are made is cut, nor does it occur if the femoral and sciatic nerves are cut.

4. The carotid artery oxygen tension (P_{a,O_2}) increases early; in the majority of experiments, there was no significant change in end-tidal P_{CO_2} although the minute volume of ventilation ($\dot{V}$) increased by about 20 % of control with passive movement of the hind limbs.

5. Passive movement of the hind limbs also causes an immediate rise in cervical sympathetic activity which is sustained, and which is abolished if the femoral and sciatic nerves are cut.

6. Electrical stimulation of the cervical sympathetic causes an increase in chemoreceptor afferent discharge.

7. Bilateral cervical sympathectomy causes the respiratory lag to increase from approximately 1 sec to some 20 sec and, when passive movements cease, the fall in $\dot{V}$ is more sluggish than control.

8. These results are discussed in the light of the controversy regarding humoral and neurogenic causes for the increase in respiration in exercise.

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INTRODUCTION

In the preceding papers (Biscoe & Purves, 1967*a*,*b*), it was shown that, in the cat, carotid body chemoreceptors may discharge nerve impulses in groups and that these groups have the same period as respiration. While studying this fluctuating signal, it was decided to investigate the effects of passive hind-limb movements upon it. It was argued that, if such a manoeuvre caused an increase in metabolic rate, there should be a corresponding increase in the amplitude of the alveolar oxygen and CO_2 tension ($P_{A,\,O_2}$ and $P_{A,\,CO_2}$) fluctuations within each respiratory cycle and hence the amplitude of these gas tensions in arterial blood (P_{a,O_2} and P_{a,CO_2}).

Such a change in $P_{A,\,CO_2}$ with exercise has been predicted by Dubois, Britt & Fenn (1952), Dubois, Fowler, Soffer & Fenn (1952), Chilton, Barth & Stacy (1954), Yamamoto & Edwards (1960) and Grodins & James (1963). Fluctuations of arterial pH which are related to respiration have been recorded by Marshall & Nims (1938), Nims & Marshall (1938), Bjurstedt (1946) and Åstrom (1952) and an increase in the fluctuation of $P_{a,\,CO_2}$ in exercise has been reported in the brachial artery blood in man (Buhlman, 1960).

If such arterial fluctuations are increased in magnitude in exercise, then the arterial chemoreceptors should sense this change and the amplitude of the fluctuations of their signal should alter accordingly. The results obtained were unexpected and are described in this paper. A short account of this work has been presented to the Physiology Society (Biscoe & Purves, 1965).

METHODS

Cats were anaesthetized with sodium pentobarbitone 30 mg/kg, injected intraperitoneally. Further injections were given as necessary through a radial vein cannula. Recordings were made from groups of chemoreceptor afferents dissected from the sinus nerve or from the whole nerve after stripping the adventitia of the carotid sinus and hence destroying the baroreceptors (Biscoe & Purves, 1967*a*, *b*). The animal's hind limbs were passively moved by strapping the hind paws to the pedals of a 'bicycle', pedal radius 5 cm, and rotating the driving pulley by hand at various rates so that the pedals rotated at rates between 50 and 100 rev./min. In later experiments, the bicycle was driven by an electric motor so that the speed could be accurately varied and controlled. A potentiometer was connected to the bicycle to give an oscillating voltage whose frequency was proportional to the pedalling frequency. One voltage cycle equalled three of those of the pedals. The output of the potentiometer was fed into a d.c. amplifier of the multi-channel recorder (Electronics for Medicine) together with the respiratory, blood pressure and nerve recording signals. The pelvic crests were clamped to minimize movement artifacts.

The anaesthesia was not deep enough to abolish the limb reflexes and, in the experiments, the movements imposed on the hind limbs met with some resistance.

RESULTS

In thirteen out of fifteen cats, the onset of passive movement of the hind limbs was always associated with an immediate rise in the chemoreceptor discharge rate. If the movements were continued at constant rate, then the chemoreceptor rate settled at the new level and remained

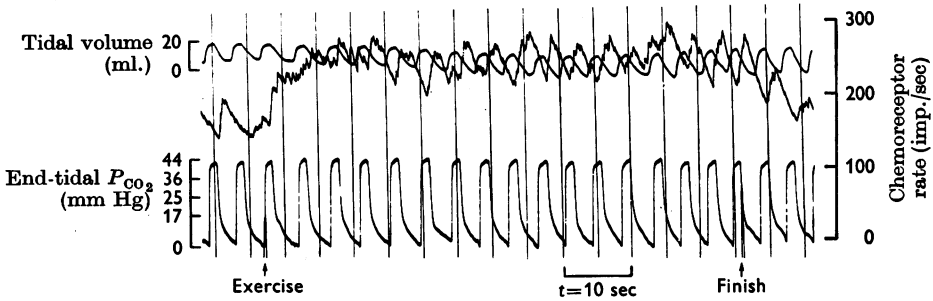


Fig. 1. Cat, pentobarbitone sodium: effect of passive movement of the hind limbs on chemoreceptor discharge. From above down: tidal volume, ml., rate-meter output showing carotid body chemoreceptor activity, in impulses/sec (rate-meter time constant, 0·33 sec), end-tidal P_{CO_2}, mm Hg. Passive hind-limb movements between the arrows. The control period was representative of the preceding 30 sec. Timing lines at 5 sec intervals.

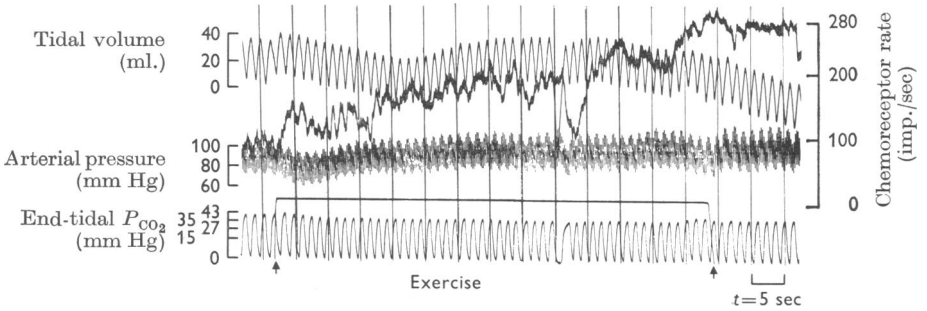


Fig. 2. Cat, pentobarbitone sodium: effect of passive movement of the hind limbs on chemoreceptor activity. From above down: tidal volume, ml., rate-meter output of chemoreceptor activity in impulses/sec (rate-meter time constant, 0·33 sec), carotid artery blood pressure and end-tidal P_{CO_2}, mm Hg. Hind-limb movements between the arrows.

there for the 1–1½ min movement period while the fluctuations in rate associated with respiration were usually preserved about this level. A record illustrating this is shown in Fig. 1 in which the chemoreceptor discharge started to increase within 1 sec. In this example, the chemoreceptor rate started to fall as soon as the pedalling was discontinued. The small 'saw-tooth' effects consisted of small fluctuations at irregular inter-

vals and are therefore unlikely to have been caused by the heart beat either through the baroreceptors (which had been denervated) or through movements of the carotid artery. It is most likely that these effects were related to the low time constant of the rate-meter (0·33 sec). The rapid fall in chemoreceptor activity after pedalling had ceased was not always seen. Figure 2 shows an example in which the chemoreceptor fluctuations with

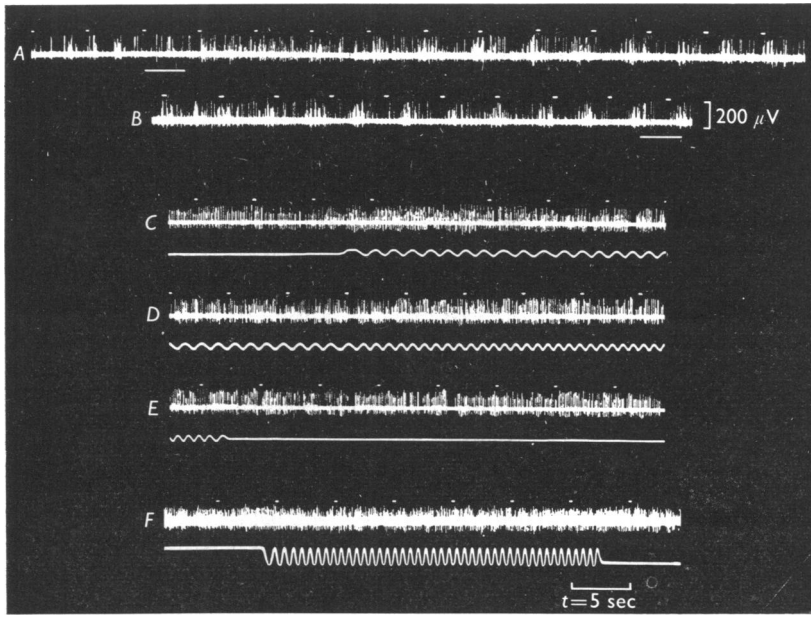


Fig. 3. Cats, pentobarbitone sodium: filmed records of continuous oscilloscope traces showing carotid body chemoreceptor discharge before and during passive movement of the hind limbs. *A* and *B*, continuous record shows the grouping of the discharge which was in phase with respiration. Hind-limb movements between the marks. *C*, *D* and *E*, a second cat, before and during passive movements of the hind limbs, the rate of which was marked in the lower trace from a potentiometer (gear ratio 1:3) on the 'bicycle'. *F*, a third cat, chemoreceptor activity during exercise showing a fall in activity. t = 5 sec, calibration 200 μV.

respiration were not so marked and in which the increased level of chemoreceptor discharge persisted after exercise ceased. In this case, the increase in minute ventilation was sufficient to lower end-tidal P_{CO_2} by approximately 5 % of control: such a reduction was not seen in Fig. 1. In addition, a spontaneous gasp occurred during passive movements and 2–3 sec later the chemoreceptor discharge fell almost to control levels. In most experiments, filmed records were taken of chemoreceptor action potentials recorded from the sinus nerve and some examples from the series are shown in Fig. 3. The first pair of records, Fig. 3*A* and *B*, again illustrate the in-

crease in chemoreceptor discharge which occurred in the majority of cats with obvious preservation of the very well marked rhythmic grouping. Figure 3*C–E* shows the effect of a progressive increase in the rate of pedalling. The increase in activity is not obvious in this type of record, but a comparison of the rate of firing towards the end of trace *D* with the

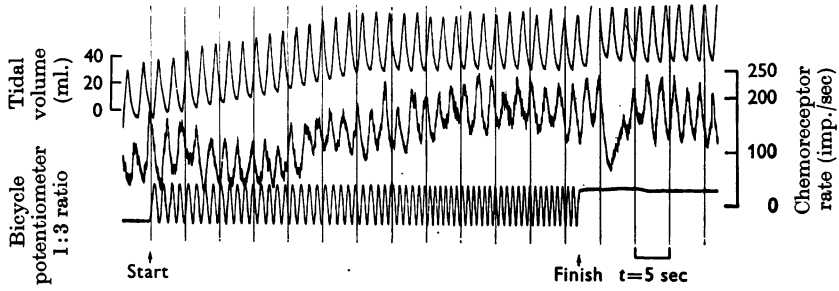


Fig. 4. Cat, pentobarbitone sodium: the effect of passive movements of the hind limbs on chemoreceptor activity after section of the ipsilateral post-ganglionic sympathetic fibres. Same cat as in Fig. 2. The trace shows from above down: tidal volume, ml., rate-meter output of chemoreceptor activity, in impulses/sec (rate-meter time constant, 0·33 sec) and 'bicycle' potentiometer output. t = 5 sec.

control period shows that a change has occurred. Lastly, Fig. 3*F* is one of the two examples out of fifteen cats where the chemoreceptor activity decreased when the hind limbs were moved. In both these cats, other runs had shown an increase in mean chemoreceptor rate. Both animals had low blood pressures and recurrent, unrelievable respiratory obstruction.

The effect of cutting the sympathetic nerve to the carotid body. The increase in chemoreceptor rate occurred so soon after the onset of movement of the hind limbs that it could not be due to some 'humoral' factor transmitted by the blood stream. Accordingly, the increase must have been mediated through a reflex arc. The only nerve supplying the carotid body other than the sinus nerve is the post-ganglionic branch from the superior cervical ganglion (Gerard & Billingsley, 1923) and this could provide the efferent part of the reflex pathway.

In five cats, the response to hind-limb movements was observed and then either the preganglionic cervical sympathetic nerve or the post-ganglionic branch of the superior cervical ganglion to the carotid body was cut and movement of the hind limbs repeated. In all cases, cutting either of these nerves on the recording side abolished the immediate increase in chemoreceptor activity. After 20 sec, there was a slow rise in the mean rate with preservations of the fluctuations in rate as is shown in Fig. 4, a trace taken from the same cat as in Fig. 2. During the 2–3 min control period before this trace, the mean chemoreceptor rate was approximately 75 im-

pulses/sec and there was an irregular fluctuation, ± 25 impulses/sec. This was the order of instability which we have observed on a number of occasions when the sympathetic supply to the carotid body is divided

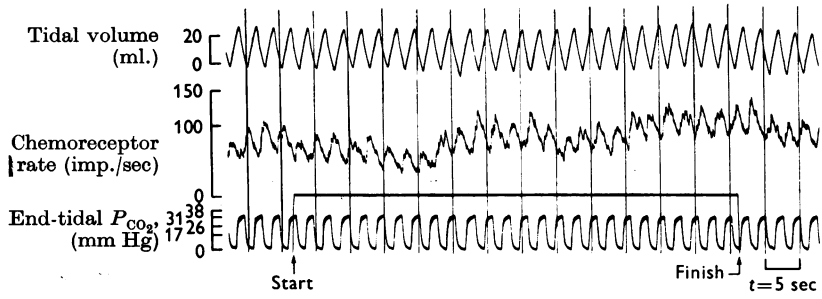


Fig. 5. Cat, pentobarbitone sodium: effect of passive movement of the hind limbs on chemoreceptor activity after section of the femoral and sciatic nerves. From above down: tidal volume, ml., rate-meter output showing chemoreceptor activity, in impulses/sec (rate-meter time constant, 0·33 sec), and end-tidal P_{CO_2}, mm Hg. Hind-limb movements for the period marked by the horizontal line between the arrows. t = 5 sec.

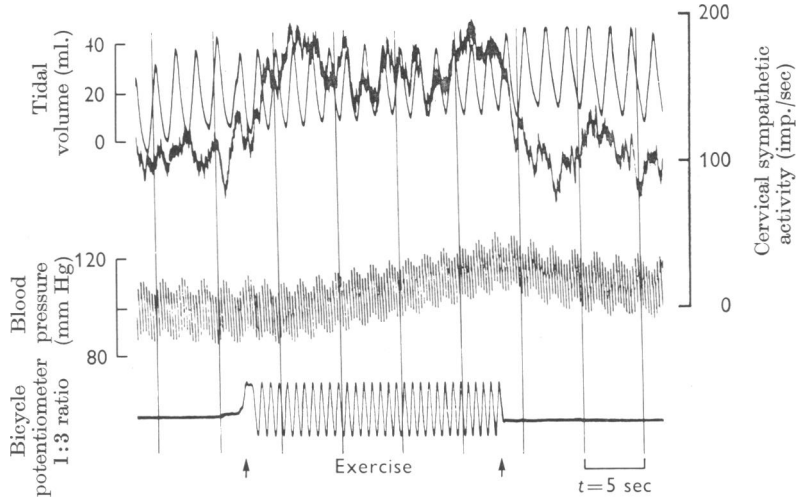


Fig. 6. Cat, pentobarbitone sodium: effect of passive hind-limb movements on preganglionic cervical sympathetic discharge. From above down: tidal volume, ml., rate-meter output of cervical sympathetic activity, in impulses/sec (rate-meter time constant, 0·33 sec), carotid artery blood pressure, mm Hg, and output from 'bicycle' potentiometer. t = 5 sec.

(see Biscoe & Purves, 1967*a*). Thus the rise in chemoreceptor activity immediately on starting movements was not significant: the subsequent rise in activity to a mean level of about 175 impulses/sec was considered to be

significant. Furthermore, this rise in rate persisted after the movements were stopped, slowly returning to control levels over the next minute. The gasp which occurred after the end of movements in Fig. 4 shows the rapid chemoreceptor response.

The effect of cutting the femoral and sciatic nerves. The increase in chemoreceptor rate which appeared to be mediated via a reflex arc through the cervical sympathetic should have as its afferent pathway the sensory nerves from the hind limbs being moved. In three out of four cats, cutting the femoral and sciatic nerves with the cervical sympathetic intact abolished the immediate increase in chemoreceptor activity previously seen (Fig. 5). This figure shows a small fall in chemoreceptor activity immediately after the hind-limb movements were started which was within the variation seen during the previous 2–3 min control period. Thereafter, there was usually a delayed slow increase in mean chemoreceptor rate coming on after 20–25 sec and often persisting after the movements on the hind limbs had ceased. There was no obvious change in end-tidal P_{CO_2} to account for this late rise in activity.

Recording from the cervical sympathetic. In two cats, recordings were made from the preganglionic cervical sympathetic and in two cats from the post-ganglionic branch to the carotid body. The results from the two nerves were qualitatively the same.

The onset of hind-limb movements was associated with an increase in sympathetic activity which rose over 5 sec to a peak and which lasted as long as the limbs were moved and then fell rapidly to control levels when the movements stopped (Fig. 6). In addition, $\dot{V}$ increased. Figure 6 also illustrates the rise in arterial blood pressure which was commonly seen to occur with passive hind-limb movements and the delays of approximately 5 sec for the onset of the increase and 15–20 sec for the attainment of the maximum increase were typical. Cutting the femoral and sciatic nerves abolished this increase in sympathetic activity. Figure 7 shows that when the movements were started, there was then a small fall in sympathetic activity which was within the variation seen during the control period. There was, as before, a small and delayed rise in $\dot{V}$ while the changes seen in arterial blood pressure were variable. Usually, filmed records of the action potentials were taken and examples of some of these records are shown in Fig. 8. In each case, both pre- and post-ganglionic nerves exhibited an immediate and sustained increase in mean discharge on hind-limb movement. These records, we should add, were unusually good and were not typical of the numerous others which we obtained.

Changes in arterial oxygen tension. In two experiments, arterial oxygen tension was continuously measured in addition to chemoreceptor activity. On both occasions, carotid P_{a,O_2} started to rise shortly after hind-limb

movement was started. The maximum increase observed was 12 mm Hg above control levels in the 1–1½ min movement periods. Possibly owing to anaesthesia and surgery, carotid arterial oxygen tension during the control period was low, i.e. 72 and 74 mm Hg. It is probable therefore that the

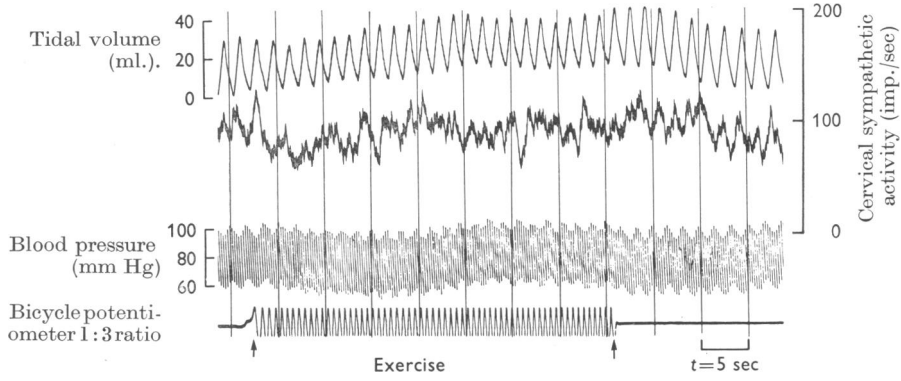


Fig. 7. Cat, pentobarbitone sodium: effect of passive hind-limb movement on preganglionic cervical sympathetic discharge after the femoral and sciatic nerves had been cut: same cat as in Fig. 6. From above down; tidal volume, ml., rate-meter output of sympathetic activity, in impulses/sec (rate-meter time constant, 0·33 sec), carotid artery blood pressure, mm Hg, and output from 'bicycle' potentiometer.

alveolar–arterial oxygen difference was not less than 25 mm Hg since end-tidal P_{CO_2} varied between 32 and 35 mm Hg. It is possible that part of this increase in P_{a,O_2} was due to an increase in alveolar ventilation as $\dot{V}$ increased and so small areas of uneven ventilation were reduced. A further possibility is that cardiac output did not increase in proportion to $\dot{V}$ and this would cause a further increase in P_{a,O_2}. In both experiments, we observed that chemoreceptor activity *rose* in the face of a rising P_{a,O_2} and, as $\dot{V}$ increased, in the face of either no change in end-tidal P_{CO_2} or a reduction by 7 % of control.

The effect of stimulating the cervical sympathetic on chemoreceptor activity. Floyd & Neil (1952) found that stimulation of the sympathetic fibres to the carotid body caused an increase in the discharge from the chemoreceptors. Eyzaguirre & Lewin (1961) have found the same response on stimulating either the pre- or post-ganglionic cervical sympathetic. The latter authors showed that this response may be confounded by an increase in the discharge of non-chemoreceptor fibres, presumably post-ganglionic sympathetic fibres in the sinus nerve. Under our experimental conditions, stimulation of either of the sympathetic nerves with square pulses of 100 μsec duration and at 50/sec caused an increase in chemoreceptor activity. As the stimulus intensity was increased, the artifact and compound action potential from fibres passing through the cervical ganglion-carotid body loop

also increased although the latter potential was usually very small in dissected strands of the sinus nerve. Above a stimulus intensity of 4–6 V, the amplitude of the artifact and sometimes the compound action potential exceeded that of the chemoreceptor action potentials and, at this level of intensity, the artifact could not be eliminated from the count rate by the

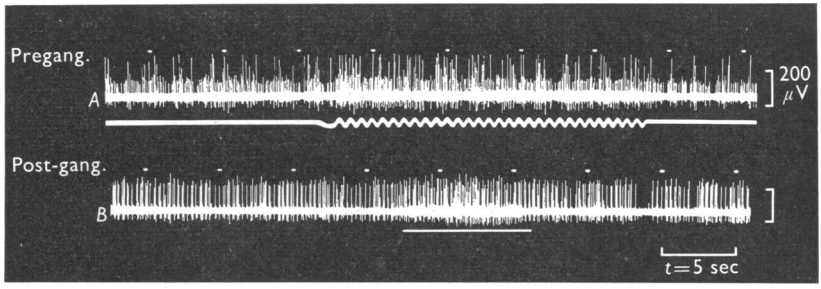


Fig. 8. Cat, pentobarbitone sodium: a filmed record of oscilloscope traces showing the effect of passive hind-limb exercise on preganglionic, *A*, and post-ganglionic, *B*, cervical sympathetic activity. The duration of exercise in the upper trace is shown by the output of the 'bicycle' potentiometer and by the mark in the lower trace. t = 5 sec. Calibration, 200 μV.

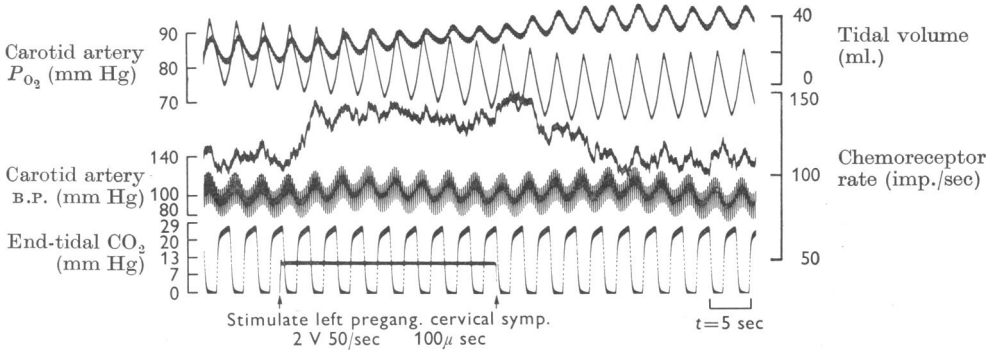


Fig. 9. Cat, pentobarbitone sodium: effect of stimulating left preganglionic cervical sympathetic nerve on carotid body chemoreceptor discharge. From above down: carotid artery P_{O_2}, mm Hg, tidal volume, ml., rate-meter output of chemoreceptor activity, in impulses/sec (rate-meter time constant, 0·33 sec), carotid artery blood pressure and end-tidal P_{CO_2}, mm Hg. Between the arrows, the left preganglionic cervical sympathetic was stimulated at 50/sec; with square pulses of 2 V amplitude and 100 μsec duration. t = 5 sec.

discriminator. At lower voltages, artifacts and the compound action potential barely emerged from the noise level and chemoreceptor action potentials only could be counted. The response to stimulation with 2 V is shown in Fig. 9. The maximum increase was less than the stimulation frequency and no slow compound action potential at constant latency was

observed. Stimulation with 4 V caused only a slightly greater increase in chemoreceptor activity. Figure 9 also shows that chemoreceptor frequency of discharge increased at the same time as carotid P_{a,O_2} was rising. The reason for this increase in P_{a,O_2} is not clear. We observed it on all occasions

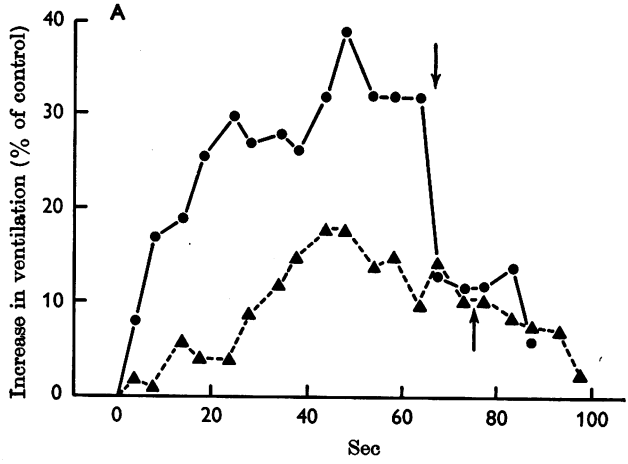
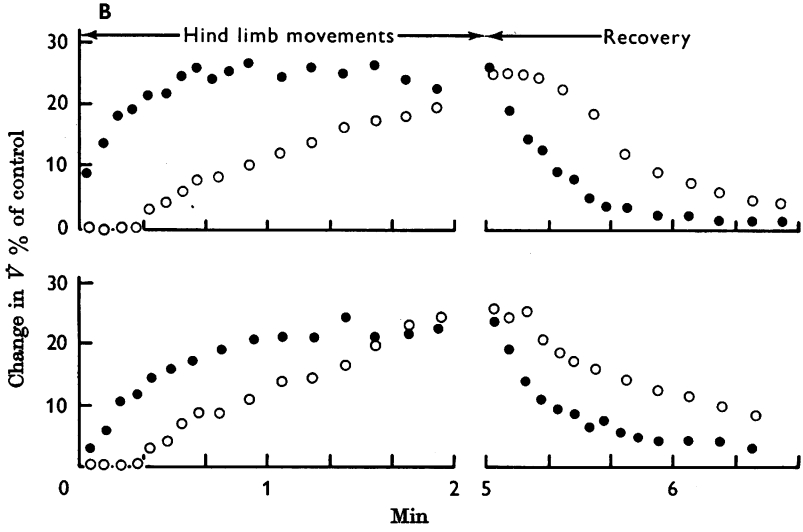


Fig. 10. (A) Time course of changes in $\dot{V}$ (% of control): Effect of passive hind-limb movements, all nerves except L. sinus nerve intact (filled circles) and after section of the femoral and sciatic nerves (filled triangles). The stimulus was applied at $t = 0$ and discontinued at the arrows. Cat, pentobarbitone sodium.



(B) The changes in $\dot{V}$ expressed as % of control during the first 2 min of passive hind-limb movements and the first 2 min of recovery after the stimulus had been discontinued. Two cats, pentobarbitone sodium. In each example, changes in before (filled circles) and after (open circles) bilateral section of the post-ganglionic sympathetic nerves.

on which the sympathetic was stimulated. Possibly some of the factors outlined in the previous section may have operated although we did not observe an increase in $\dot{V}$.

Changes in $\dot{V}$. An increase in $\dot{V}$ was observed within three breaths taken after movements of the hind limbs were begun in twelve out of fifteen cats. In the other three, this increase was delayed for 20–30 sec. The increase in $\dot{V}$ was mainly due to an increase in respiratory frequency: in four cats, tidal volume actually fell during the first 20–30 sec but, in all cats, tidal volume subsequently increased. In the majority of experiments, hind-limb movement was of short duration, 1–1½ min, and in this time, $\dot{V}$ had increased by 14–37 % of control, average 22 %, S.D. ± 8·4 %. The time course is shown in Fig. 10*A*, ●, in which all the nerves except the left sinus nerve were intact. When passive movements were stopped, $\dot{V}$ fell abruptly over the first 1–3 sec and, thereafter, fell more slowly to control levels over the next 1–1½ min.

When the femoral and sciatic nerves were cut in six cats, steady passive movements of the hind limbs caused only a small, < 5 % increase in $\dot{V}$ above control levels over the first 20–25 sec before a more marked increase in $\dot{V}$ occurred (Fig. 10*B*, ▲). This delay is similar to that seen in the chemoreceptor discharge under similar conditions. Further, in each cat, the increase in $\dot{V}$ which occurred after the femoral and sciatic nerves had been cut was always smaller than with intact nerves and there was no abrupt fall in $\dot{V}$ when the limb movements ceased.

On four occasions, we measured the respiratory response to a standard stimulus (pedalling at a constant rate, 120 rev/min for 5 min) before and after the post-ganglionic sympathetic nerves had been cut on both sides. Two examples, showing the on and off transients, are given in Fig. 10*B*. On each occasion, $\dot{V}$ increased to approximately the same level before and after sympathectomy. The most obvious difference was that the interval after pedalling started at which an increase in ventilation was first noted increased from approximately 1 sec before sympathectomy to an average of 19 sec afterwards. This lag was similar to that observed before chemoreceptor activity started to rise when the sympathetic supply on the recording side had been divided (see Fig. 4). Further, whereas the increase in $\dot{V}$ was asymptotic to a maximum before sympathectomy, the mean time to 95 % completed response being 45 sec, $\dot{V}$ increased more nearly linearly after sympathectomy and reached a maximum in 2–4 min. Similarly, when pedalling stopped, before sympathectomy, $\dot{V}$ fell rapidly within the first 30 sec; after sympathectomy, $\dot{V}$ remained unchanged for 10–15 sec and, on each occasion, the fall towards control was more gradual.

DISCUSSION

The questions which immediately arise are: first, is an increase in the noise counted in the experiments and not an increase in the nerve impulse traffic and, secondly, if nerve impulses are counted, is an increase in post-ganglionic sympathetic activity rather than chemoreceptor activity observed? The second point is valid for Eyzaguirre & Lewin (1961) have shown that nerve impulses are conducted from the post-ganglionic branch of the superior cervical ganglion to the sinus nerve, presumably in the sinus nerve non-medullated fibres (Ask-Upmark & Hillarp, 1961; Eyzaguirre & Lewin, 1961; Eyzaguirre & Uchizono, 1961). Both points will be discussed together.

In some hind-limb experiment trials, an increase in noise and especially in large movement artifacts was observed and counted. Such trials were always rejected either at the time of the experiment or subsequently when the film records of the action potentials and the pulse height selector output revealed that a noise increase had been counted. The pulse height selector was always adjusted to count spikes well clear of the noise during the control period. (The use of the pulse height selector has been described and discussed in an earlier paper, Biscoe & Purves, 1967*a*.) The filmed records, especially those taken of records from dissected nerves, gave unequivocal results. For example, Fig. 3*A–E* in this paper and Fig. 1 in Biscoe & Purves (1967*b*) show clear evidence of an increase in the frequency of the same action potentials. If an increase in post-ganglionic sympathetic activity was counted, instead of an increase in chemoreceptor activity, then there should certainly have been recruitment of other very small spikes for, during the control period, all the counted activity in the strands studied was reduced to zero transiently by raising the carotid P_{a,O_2}. This does not reduce sympathetic activity (Biscoe & Purves, 1967*b*). Moreover, it is unlikely that post-ganglionic sympathetic action potentials were counted as these potentials must be very small under our conditions since stimulation of the post-ganglionic nerve at lower voltages (*ca.* 2 V) has not revealed compound action potentials above the noise level in the undissected sinus nerve. Further evidence that the activity is truly chemoreceptor in origin may be seen in the frequent persistence of the increase after the hind limb movements have ceased (Figs. 2, 4). The decline in rate is smooth and there is no sudden fall in the rate such as occurs with the sympathetic recording (Fig. 6), and would occur if an increase in noise or movement artifacts were being counted and had been the cause of the initial rise. Additionally, in Figs. 2 and 4, a spontaneous deep breath during or immediately after exercise was followed by a fall in the counted rate towards control levels, a change which only occurs with chemoreceptors.

It has been shown (Purves, 1966) that a deep breath is followed by a transient 5–10 mm Hg rise in carotid P_{a,O_2} and the effect of this upon chemoreceptor activity has been measured (Biscoe & Purves, 1967*a*; Fig. 6). Biscoe & Purves (1967*b*) have also shown that a comparable rise in carotid P_{a,O_2} has no effect upon cervical sympathetic activity.

Further evidence against the view that the recorded increase in rate is in fact an increase in noise is found in the experiments where the immediate increase on starting passive hind-limb movements was abolished by nerve section (Figs. 4, 5, 7). It would be expected that the movements would have identical effects under these conditions if the rise in rate was an artifact. We have not repeated these experiments at different levels of inspired oxygen tension; such further experiments would be of considerable value in confirming that a rise in chemoreceptor activity takes place or is modified with 100 % oxygen.

Passive hind-limb movements and exercise. In earlier papers, e.g. Comroe & Schmidt (1943), the term 'passive exercise' was placed in inverted commas to indicate literary convenience rather than a precise physiological stimulus and this convention is followed by referring only to passive hind-limb movements. The question arises, what, if anything, have hind-limb movements in the anaesthetized cat to do with active voluntary exercise. There are a number of factors which may make our results relevant to the problem of exercise.

First, it has been shown that passive movements of the hind limb cause an increase in ventilation which is of the same magnitude as that which has been reported in other experiments on the anaesthetized cat (Bilge, 1961; Bilge, Velidedeoglu & Terzioglu, 1963) and in man, cats, dogs or rabbits, whether awake or lightly anaesthetized (Harrison, Harrison, Calhoun & Marsh, 1932; Comroe & Schmidt, 1943; Grandpierre, Franck, Violette & Arnould, 1952; Honda & Minoguchi, 1957; Dejours, Labrousse & Teillac, 1959). We have also confirmed the observations of the authors cited above that passive movements of the limbs cause a very rapid rise in minute ventilation.

Secondly, we have confirmed that this increase in minute ventilation is dependent on intact, functioning afferent nerves from the moved limbs (Comroe & Schmidt, 1943; Honda & Minoguchi, 1957; Bilge *et al.* 1963).

Thirdly, in a proportion of our experiments, we observed that whereas $\dot{V}$ increased by an average of 20 % of control, there was either a small or no significant reduction of end-tidal P_{CO_2}. This suggests that there was a proportional increase in the minute volume of expired CO_2 and therefore, probably, in oxygen consumption. A number of workers (Bahnson, Horvath & Comroe, 1949; Dejours, Teillac, Labrousse & Raynaud, 1956; Dixon,

Stewart, Mills, Varvis & Bates, 1961) have also shown that oxygen consumption rises with passive limb movements and their results suggest that the relation between $\dot{V}$ and oxygen consumption in passive limb movements is qualitatively similar to that in active exercise: the difference is quantitative, though in two of these papers (Bahnson *et al.* 1949; Dejours *et al.* 1956) the values for $\dot{V}$ and oxygen consumption during passive limb movements and active exercise with minimal load overlap considerably.

The stimulus to ventilaton in exercise. Despite the points made in the previous section, we are reluctant to draw too close a parallel between the results of the present experiments in the anaesthetized cat and the numerous experiments on the physiology of exercise, recently reviewed by Dejours (1959, 1964). There are, however, three points of interest which arise from a study of the changes in chemoreceptor activity.

1. The increase in chemoreceptor activity occurred either with no significant change in end-tidal P_{CO_2} or, in the face of a reduced end-tidal P_{CO_2} and a rising $P_{a,\,O_2}$, changes which either separately or together in other circumstances would depress ventilation and chemoreceptor activity. This suggests that the initial increase in $\dot{V}$ cannot have been due to chemical changes in arterial blood and also, that whatever changes occurred within the carotid body they altered the sensitivity of the chemoreceptors to chemical stimuli.

2. The fact that the fluctuations of chemoreceptor activity were preserved at the control amplitude, but at an increased mean rate of chemoreceptor discharge, is of interest for two reasons. This response is in marked contrast to that which is seen when the inspired CO_2 is increased; in such a situation (Biscoe & Purves, 1967*a*), the mean rate of chemoreceptor discharge is increased but the fluctuations in rate progressively diminish—This provides further evidence that the effective stimulus to respiration in these passive hind-limb movement experiments is not an increase in $P_{a,\,CO_2}$. In additicn, it should be remembered that the amplitude of the chemoreceptor fluctuations was preserved although the frequency of respiration had considerably increased, a factor which itself leads to a reduction in the amplitude of chemoreceptor fluctuation (Biscoe & Purves, 1967*a*; Fig. 13).

3. A further point which emerges is that although the speed at which the chemoreceptor discharge starts to increase when passive movements are commenced clearly suggests reflex involvement, it is clear that some other factor (which is not a change in mean $P_{a,\,O_2}$ or $P_{a,\,CO_2}$) is implicated. Thus a small but definite and delayed rise in chemoreceptor activity, $\dot{V}$ and $P_{a,\,O_2}$ with a fall in end-tidal P_{CO_2} was observed with passive limb movements when the sympathetic supply to the carotid body had been

cut. The nature of this other or 'humoral' factor has been reviewed in detail by Dejours (1959, 1964).

The reflex arc. The reflex arc which, we suggest, would explain our results consists of afferents which arise in the limbs and of efferents which are composed of the sympathetic supply to the carotid body. We then propose that, in particular, the rapid rise and fall in chemoreceptor activity and of $\dot{V}$ which occurs at the start and finish of limb movements is associated with the rise and fall in sympathetic activity. We have provided support for this contention in Fig. 10*B*. Further, if Fig. 10*A* and *B* are compared with that given by Dejours (Fig. 9; 1964), the similarity of the time course of changes in $\dot{V}$ suggests that the reflex which we are proposing may contribute to the 'fast' or neurogenic component of the ventilatory response in exercise.

Comroe & Schmidt (1943) first showed that the respiratory response in passive exercise was blocked in man, dogs and cats after spinal anaesthesia or chordotomy. They suggested that the neural stimulus to respiration in exercise could explain some but not all of the response. With this we would agree and we have confirmed that the respiratory response in passive hind-limb movements is sluggish and reduced after the majority of the hind-limb afferents are cut.

Complementary studies have shown that stimulation of nerves from the hind limb leads to hyperpnoea (e.g. Henderson, 1910; Bessou, Dejours & Laporte, 1959; Kao, 1963). It should not be overlooked that in some of these and other studies, pathways conducting pain fibres may have been stimulated since Meyer (1914) showed that painful stimulation also led to hyperpnoea.

There is also evidence that the sympathetic is involved very early in exercise. Asmussen & Neilsen (1951) showed that an increase in heart rate, systolic and diastolic blood pressure and a reduction in pulse pressure could be observed within 1–2 sec of starting exercise. This is analogous to the observation by Krogh & Linhard (1913) and confirmed by us in the majority of experiments that an increase in ventilation is observed with the first breath. This certainly suggests reflex activity in our experiments and either similar reflex activity or a pathway involving the cortex and hypothalamus in the active exercise experiments: in either case whichever pathway is involved, the sympathetic seems to be clearly involved at the start and finish of exercise.

The simplest explanation for the increase in chemoreceptor activity which accompanied that in the sympathetic is that blood flow within the carotid body was reduced. Daly, Lambertsen & Schweitzer (1954) have shown that sympathetic excitation has this effect. It is possible that such a mechanism would be too slow to account for the very rapid rise

both in chemoreceptor activity and in respiration which occur at the start of exercise. Although the time course of changes in carotid body blood flow require further study, other ways in which the sympathetic may act upon the chemoreceptors are possible and these have been reviewed by Biscoe & Silver (1966).

Although the sequence of events which we have described is consistent with previous studies of the respiratory and circulatory adjustments which take place in exercise, we have no means of knowing how important the proposed reflex arc is in the respiratory response to muscular exercise in intact unanaesthetized subjects. We think that it is quite possible in active exercise, for example, that sympathetic activation is augmented by a flood of other humoral and neural stimuli. On the other hand, the efferent pathway of the reflex arc which we propose could have some importance in the numerous situations, e.g. fear, in which there is good evidence of a widespread sympathetic discharge. How far this reflex activity interacts with other activity awaits further analysis.

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