

THE RESPONSES OF CHEMORECEPTORS AT REDUCED TEMPERATURES

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(Received 9 September 1970)

SUMMARY

1. The responses of aortic chemoreceptors and pulmonary stretch receptors of cats were studied by recording impulses in individual fibres at normal body temperatures and thereafter at various temperatures down to 24–26° C while cooling the cat with ice.

2. Reduction of metabolism by lowering the temperature did not *obviously* slow the P_{O_2} sensing mechanism of chemoreceptors but it greatly slowed the development of excitation after circulatory arrest. It also greatly reduced the excitatory effect of hypoxia.

3. The Q_{10} for the frequency of discharge of chemoreceptors (during maximal activity) was estimated by comparing the activity of the endings at normal body temperature after circulatory arrest (i.e. at a local P_{O_2} of 0 mm Hg) with similar activity at reduced body temperatures. This averaged 2.5 in nine endings. The Q_{10} for the peak frequency of discharge also averaged 2.5 in seven endings. These values are similar to those of some mechano-receptors.

4. Apart from the reduction in the frequency of discharge ($Q_{10} = 2.6$) lowering the temperature did not alter the stimulus–response relationship of pulmonary stretch receptors.

5. The poor responses to ACh at lower temperatures indicate that ACh is not likely to be a transmitter at chemoreceptors.

INTRODUCTION

The question as to whether chemoreceptors are stimulated by the liberation of a metabolite (Heymans & Neil, 1958; Joels & Neil, 1963) or transmitter (Eyzaguirre & Zapata, 1968) or whether they are stimulated by some mechanical deformation of the generator region (Paintal, 1967, 1968)

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still remains to be answered. In this connexion one of the complicating factors is that the metabolism of the chemoreceptor cells is considerable (Daly, Lambertson & Schweitzer, 1954) and it is therefore necessary to dissociate the metabolic mechanism of chemoreceptors from their sensing mechanism in order to study the latter. This has been partially achieved in the present investigation by lowering body temperature. The responses of a mechanoreceptor (pulmonary stretch receptor) have also been studied under identical experimental conditions for comparing the responses of mechanoreceptors with those of aortic chemoreceptors.

METHODS

Experiments were carried out on adult cats weighing 2.0–4.8 kg. They were anaesthetized with chloralose (75 mg/kg i.v.) after induction with ether or trichloroethylene.

Impulses from individual fibres of aortic chemoreceptors were recorded from the cut peripheral end of the aortic nerve using certain techniques and identification criteria described earlier (Paintal, 1967).

Right atrial temperature was used as an index of the temperature of the aortic bodies. It was measured with a thermocouple passed down the right external jugular vein so that its tip lay in the right atrium. The temperature could be read correctly to 0.1° C on a spot galvanometer (Cambridge). The reference junction was kept in crushed ice in a vacuum flask and the calibration of the whole set-up was checked at the end of each experiment.

For cooling the cat its thorax, abdomen and hind limbs were surrounded with ice. The nerve filament was kept on the recording electrodes throughout cooling so that one could keep track of the identity of the fibre by observing the impulses evoked by stimulating the nerve (see Paintal, 1953, 1967).

The aortic blood pressure and intratracheal pressure were recorded using pressure transducers (Statham type P 23 G and P 23 Db).

In fourteen cats the arterial P_{O_2} (P_{a,O_2}) was measured using Clarke-type oxygen electrodes (Radiometer type E 5046). The arterial P_{CO_2} and pH were also measured in some experiments using the electrodes supplied with the Radiometer units. In most experiments the temperature of the bath surrounding the oxygen electrodes was kept at 38° C and the values of P_{O_2} so obtained were corrected for temperature variations using nomograms prepared by Severinghaus (fig. 2 in Severinghaus, 1965). The arterial P_{CO_2} was also measured in the same way in some experiments. In two experiments the temperature of the bath was kept at 30° C and 28° C since the main measurements related to the arterial P_{O_2} at about 28° C. The results from these two experiments constitute a minority of the total results and therefore unless specifically mentioned it should be assumed that the temperature of the P_{O_2} electrodes was 38° C. Measurements at the lowest ranges of P_{O_2} were checked repeatedly by measuring the P_{O_2} of solutions equilibrated with 1–2 % O_2 . Temperature corrections for pH were made using the factor of 0.0147 pH units per degree fall of temperature under anaerobic conditions (Rosenthal, 1948).

Gas mixtures of different compositions were prepared in Douglas bags and analysed with a Scholander 0.5 ml. gas analysis apparatus except in the initial experiments when a paramagnetic O_2 analyser (Servomex) was used for determining the percentage of O_2 in the gas mixtures. Each time the gas mixtures were administered for 3½ min by a Starling Ideal (Palmer) respiratory pump with a stroke

volume of 65–70 ml. at a rate of 13/min. The dead space between the pump and the tracheal cannula was 55 ml. The cats were adequately anaesthetized with additional sodium pentobarbitone before putting them on the respiratory pump so as to abolish spontaneous respiratory movements.

As done before (Paintal, 1967) circulatory arrest was produced by injecting 30 ml. air rapidly into the right atrium. This produced a precipitous fall in blood pressure that set in within 0.8–2.0 sec (mean latency, 1.1 sec at normal temperature and 1.4 sec at reduced temperature of about 27° C). The blood pressure fell to 40 mm Hg at a mean interval of 7 sec after injection of air at normal temperatures; at reduced temperatures the mean interval was 10 sec. In every experiment post mortem examination showed no air bubbles in the left atrium or aorta.

Atropine 1 mg/kg was injected i.v. in those cats in which the responses of the chemoreceptors to intra-aortic injections of acetylcholine (ACh) were studied. ACh (Roche Products) was injected through a catheter (in the aorta) whose tip lay at the semilunar valves. It was diluted in 0.9 % NaCl solution, the concentration of the solution being about 63 $\mu\text{g/ml}$. The stock solution of ACh was prepared and assayed as reported earlier (Paintal, 1967). In one experiment commercial ACh solution (100 $\mu\text{g/ml}$.) contained in an ampoule (Laboratoires Lematte & Boinot, Paris) was used.

For determining the peak frequency of discharge, the least interval between two impulses was measured with a binocular microscope ($\times 25$). The maximum error in these measurements was less than $\pm 5\%$ except in the case of two measurements where the peak frequencies were 172 and 196/sec; here the maximum error was $\pm 20\%$ (fibre no. 9, Table 2). The actual magnitude of the errors was estimated by comparing the values obtained using the binocular microscope with those obtained from records of relatively fast sweeps recorded simultaneously in the last eleven experiments in which the errors of measurement had been reduced to 1 % or less. A schematic diagram of the circuit that made this possible is shown in Fig. 1A and the wave forms generated by it in Fig. 1B.

The circuit of Fig. 1 was devised so as to ensure not only that the interval between impulses could be measured accurately but also to ensure that the shape and size of these impulses could be identified. This is necessary because it is particularly difficult to isolate single active chemoreceptor fibres and it is therefore not uncommon to find two fibres with similar spike heights active in the same filament; under such conditions it is possible to identify the fibres only by the shape of the impulses and to establish the identity of these with the electrically evoked impulses produced by stimulating the whole nerve (see Paintal, 1967). The impulses from a chemoreceptor fibre were recorded along with blood pressure, etc., on one oscilloscope in the usual manner; the photographic record obtained on moving paper is shown in the lower part of Fig. 2. The same impulses were recorded on a second oscilloscope using a vertical sweep that was added algebraically to the output of the pre-amplifier for nerve impulse. This was easy as the Tektronix 422 oscilloscope has a circuit for making this possible. The horizontal plates of this oscilloscope were connected to an amplifier in such a way that each nerve impulse triggered a saw-tooth that was of 1–2 msec duration and it produced a sweep 1.5 cm in length on the oscilloscope. Thus as shown in the upper part of Fig. 2 simple vertical sweeps of 50 msec duration were recorded in the absence of any impulses and whenever an impulse appeared the vertical sweep was interrupted by a horizontal sweep of 2 msec duration. The interval between two impulses was therefore conveniently determined by measuring the distance between these impulses. Thus in the case of the two impulses indicated by the first arrow, the frequency of discharge could be accurately determined (error $< 2\%$) using a simple measuring magnifier. If the duration of the vertical sweeps is

made about 10 msec, the error of measurement can be reduced to less than 2% at frequencies of 500/sec. But this would require that the photographic paper be moved at about 7 cm/sec.

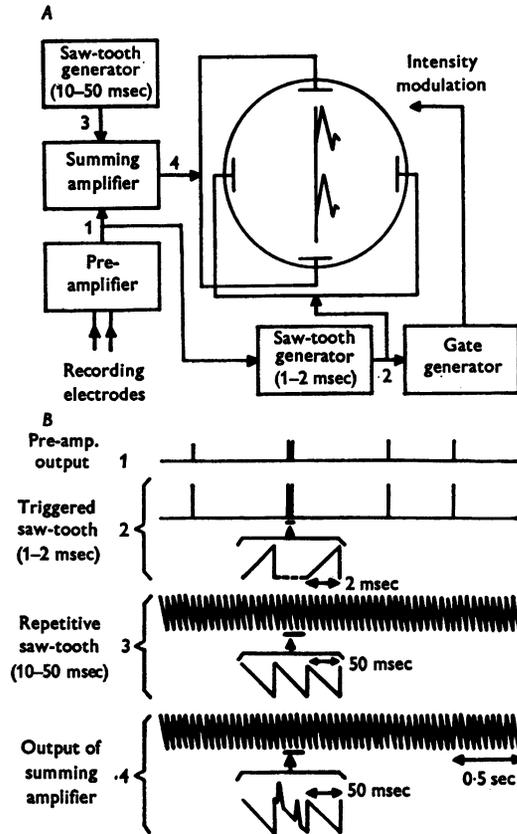


Fig. 1. Schematic block diagram of the circuit (A) used for measuring the interval between impulses accurately and displaying the size and shape of each impulse. The wave forms generated at points 1-4 of this circuit are shown in B. The essential feature of the set-up is the algebraic addition of the amplified impulses (1) to a repetitive saw-tooth (3) combined with an expanded display of the impulses on the cathode ray tube by a saw-tooth of 1-2 msec duration (2) which is triggered by the amplified impulses. A sample of the records obtained using this circuit is shown in Fig. 2.

RESULTS

Speed of response of chemoreceptors. It is known that the activity in chemoreceptors produced by ventilating the lungs with hypoxic mixtures (e.g. 4% O₂) is reduced within a few seconds on administration of air or oxygen (Leitner, Pagès, Puccinelli & Dejourns, 1965; Paintal, 1967). This 'off latency' is not increased by lowering the temperature of the chemo-

receptors by about 10°C . Thus whereas the mean latency in eight fibres (in seven cats) at a mean temperature of 37.7°C (range $35.0\text{--}39.6^{\circ}\text{C}$) and a mean blood pressure of 122 mm Hg (range 80–179 mm Hg) was 8.0 sec (range 6.0–10.5 sec; s.e. 0.54), the mean latency in the same eight fibres at a mean temperature of 28.1°C (range $26.1\text{--}31.0^{\circ}\text{C}$) was practically unchanged, i.e. 8.1 sec (range 4.0–12.0 sec; s.e. 0.97). The mean blood pressure at the lower temperature was 93 mm Hg (range 72–119 mm Hg),

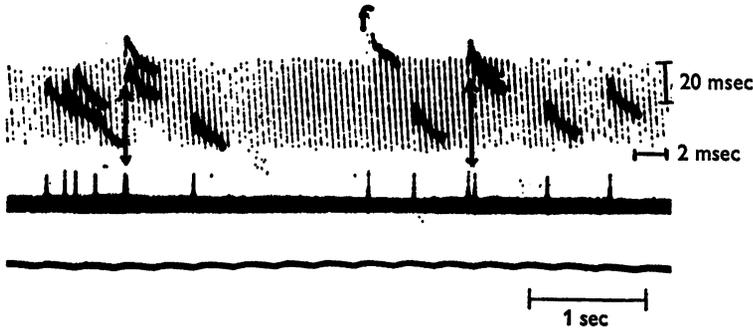


Fig. 2. Record of activity in a chemoreceptor fibre using the circuit of Fig. 1. The lower traces recorded on one oscilloscope in a conventional manner show respectively impulses in the fibre and aortic blood pressure (mean B.P. = 104 mm Hg). The upper part of the record shows on a second oscilloscope the sweeps generated by the 50 msec repetitive saw-tooth at 20/sec. This is interrupted for 2 msec each time an impulse triggers a 2 msec duration sweep thereby displaying the shape and size of each impulse. The frequency of discharge is determined from the vertical distance between the impulses. Thus in the case of the impulses shown at first arrow, the frequency of discharge is 79.6/sec. The interval between impulses falling on adjacent vertical sweeps is determined in the same way except that 50 msec is added algebraically since the interval between sweeps is 50 msec. Thus the frequency of discharge of two impulses with no vertical separation falling on adjacent sweeps would be 20/sec. In the case of the impulses at the second arrow it is 18.2/sec. Impulses falling during the fly back of the 50 msec saw-tooth (e.g. the impulse marked **f**) cannot be used for measurement of impulse intervals.

i.e. less than the mean pressure at normal temperatures. These results indicate that a fall in the metabolic rate of the cells does not *obviously* reduce the speed of response of the sensing system. They also indicate that the speed of the circulation in the glomus is not reduced by lowering the temperature. This is relevant to the effects of ACh at low temperature (see below).

Effect of circulatory arrest. Table 1 shows the responses of aortic chemoreceptors at normal and reduced body temperatures. Characteristically, at normal temperatures the increase in activity set in within 4.5–8.6 sec after circulatory arrest in eight fibres; peak activity was obtained within

40–55 sec in seven of these eight fibres at a mean interval of 52 sec. As described before (Paintal, 1967) this activity was not sustained but it started to decline within 50–106 sec (Table 1). On the other hand at reduced temperatures Table 1 shows that the start of stimulation was greatly slowed and the time to reach peak activity was increased considerably (mean value 6.7 min). These observations were made on ten other

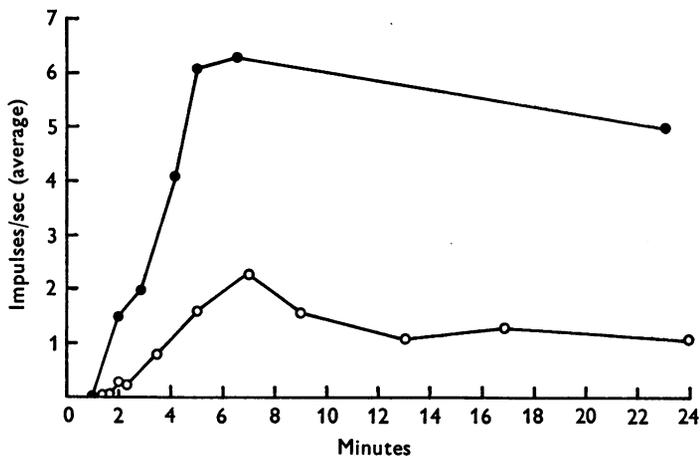


Fig. 3. Development of activity in two chemoreceptors after circulatory arrest at zero time. The temperatures of the two cats were 27.5° C (upper curve) and 27.8° C (lower curve) when circulatory arrest was produced. Ordinate represents the frequency of discharge averaged over 10–20 sec.

TABLE 1. Intervals between onset of circulatory arrest and (1) start of stimulation of chemoreceptors, (2) peak stimulation and (3) onset of decline at normal temperature (eight fibres) and at reduced temperatures (ten fibres)

	Normal temp. (mean 37.4° C)			Reduced temp. (mean 27.2° C)		
	Mean (sec)	Range (sec)	S.E. (sec)	Mean	Range	S.E.
Start of stimulation	6.7	4.5–8.6	0.5	59 sec	10–135 sec	12.6 sec
Peak stimulation	52	40–90	6.1	6.7 min	3.5–15.0 min	0.7 min
Decline	80	50–106	9.2	—	—	—

endings. Typical responses of these endings at reduced temperatures are shown in Fig. 3. Thus at about 27.6° C the discharge started to increase after 80 sec in two fibres following arrest, it reached its peak at about 7 min and it continued for several minutes thereafter (Fig. 3). One significant feature of the response at reduced temperature was that the discharge continued for several minutes near its maximum level in several fibres (e.g. Fig. 3).

For this reason it was not easy to determine precisely when the decline in discharge set in; the figures for the decline in discharge at reduced temperatures have therefore been omitted in Table 1.

It may be presumed that peak activity occurs when the local P_{O_2} near the sensing mechanism has fallen to approximately 0 mm Hg and as shown in Fig. 3 and Table 1 it takes about 7 min for this to occur at about 27.5° C. This provides an indication of the marked reduction in the metabolic activity of the glomus cells that must occur by reducing the temperature by about 10° C since peak activity is attained in less than a minute at normal body temperature in most fibres. The influence of possible efferent activity (see Neil & O'Reagen, 1969) on the above responses was absent since the aortic nerve was cut. The possible influence of sympathetic activity was also reduced by deeply anaesthetizing the cat before producing circulatory arrest.

Prediction of discharge at P_{O_2} of 0 mm Hg. In connexion with certain measurements (cf. below) it is of value to be able to predict the likely maximum intensity of discharge of a chemoreceptor after circulatory arrest (i.e. at 0 mm Hg P_{O_2}) at normal body temperatures without having to kill the cat i.e., during circulatory arrest. The following procedure was adopted: first the maximum intensity of discharge (at normal body temperature) between 2 min 45 sec and 3 min 25 sec after start of ventilation with 4% O_2 was measured. Thereafter circulatory arrest was produced while ventilating the cat with air and the maximum activity recorded. The ratio of the discharge (averaged over 20 sec in both cases) at 0 mm Hg P_{O_2} to that during ventilation with 4% O_2 was then determined. The mean ratio in nine cats was 1.47 (range 1.2–2.0; s.e. 0.08). The mean temperature of these nine cats was 37.4° C (range 35.8–38.5° C) and the mean blood pressure during ventilation with 4% O_2 was 117 mm Hg (range 71–164 mm Hg). The P_{a,O_2} which was also measured in five of these cats during ventilation with 4% O_2 averaged 18.9 mm Hg (range 15.6–20.2 mm Hg). In subsequent experiments this ratio of 1.47 was used for predicting the frequency of discharge of a chemoreceptor at 0 mm Hg P_{O_2} , i.e. by recording the maximum frequency of discharge during ventilation of the cat with 4% O_2 and multiplying this value by 1.47. The measurement of the maximum activity during ventilation with 4% O_2 was fixed between 2 min 45 sec and 3 min 25 sec so that the time for adaptation of the ending was the same in all cases, i.e. in those used for determining the ratio and in those used for predicting the discharge at 0 mm Hg P_{O_2} using this ratio.

The peak frequency of discharge (i.e. reciprocal of the smallest impulse interval) was also measured during ventilation with 4% O_2 and after circulatory arrest. The ratio in this case averaged 1.1 (range 1.0–1.3; s.e. 0.03) in eight fibres.

Q_{10} for maximal chemoreceptor activity. Table 2 shows how the Q_{10} for maximal chemoreceptor activity was estimated in nine fibres. First the intensity of discharge during ventilation of the cat with 4% O_2 (at normal body temperature) was recorded and from this, using the ratio of 1.47 determined above, the likely intensity of discharge at 0 mm Hg P_{O_2} was computed (column 4 of Table 2). The cat was then cooled to about 28° C and the maximum average discharge after circulatory arrest (i.e. at 0 mm Hg P_{O_2}) was recorded (column 6, Table 2). Finally, the Q_{10} was determined

TABLE 2. Data used for determining the Q_{10} (column 7) of aortic chemoreceptors at 0 mm Hg P_{O_2} by comparing the computed activity at normal body temperature (column 4) with that at reduced temperatures (column 6)

Serial no. of of fibre	Responses at normal body temp.			Responses at low temp.			
	Temp.	Discharge during 4% O_2 * (impulses/ sec)	Computed discharge at 0 mm Hg (impulses/ sec)	Temp. (° C)	Dis- charge at 0 mm Hg (impulses/ sec)	Q_{10} at 0 mm Hg	Q_{10} (peak fre- quency)
6	37.4	3.8	5.6	27.5	3.3	1.7	3.7
7	38.6	3.6	5.3	27.8	2.3	2.2	2.0
8	39.5	8.3	12.2	29.0	6.0	2.0	1.6
10	38.3	1.9	2.8	31.0	1.6	2.2	2.6
16	38.0	11.3	16.6	27.6	6.3	2.5	—
18	36.3	3.3	4.9	26.1	2.3	2.1	1.8
28	38.2	8.9	12.9	26.2	4.1	2.6	2.2
40	37.0	7.8	11.5	26.1	5.1	2.1	—
41	37.0	4.4	6.4	26.7	1.3	4.9	3.3
					Mean	2.5	2.5

* Averaged over 20 sec.

from these two values and is set down in the second last column of Table 2 which shows that the Q_{10} lay between 1.7 and 4.9 (mean 2.5; s.e. 0.32). The average mean blood pressure during ventilation with 4% O_2 (at 37.8° C mean temperature) in the case of the fibres of Table 2 was 116 mm Hg, i.e. of the same order as that used for determining the ratio of 1.47 for the prediction of the discharge at 0 mm Hg (see above). Moreover, the arterial P_{O_2} during ventilation with 4% O_2 which averaged 18.1 mm Hg (range 16.3–19.6 mm Hg) in five of these nine cats was also the same as that recorded in the five cats used for computing the ratio of 1.47.

The same procedure was followed for determining the Q_{10} for the peak frequency of discharge in the same fibres. The values obtained are shown in the last column of Table 2. In seven fibres the mean Q_{10} was 2.5 (range 1.6–3.7; s.e. 0.3).

Effect of temperature on response to hypoxia. In Fig. 4 are shown the responses of three chemoreceptors during ventilation with 4% O₂ for 3½ min at different temperatures. This activity was measured as described above (i.e. between 2 min 45 sec and 3 min 25 sec after start of ventilation with 4% O₂). These results are typical of the ten endings studied in ten cats. In five of these cats the arterial P_{O₂} was 17.7–19.2 mm Hg at normal temperatures. In two of them, on lowering the temperature to 27–29° C the P_{O₂} rose slightly (by 0.6 mm Hg) above the value obtained at normal temperature in the cat. In the remaining three cats it was reduced by 2.1–3.7 mm Hg. These values indicate that the marked reduction in the

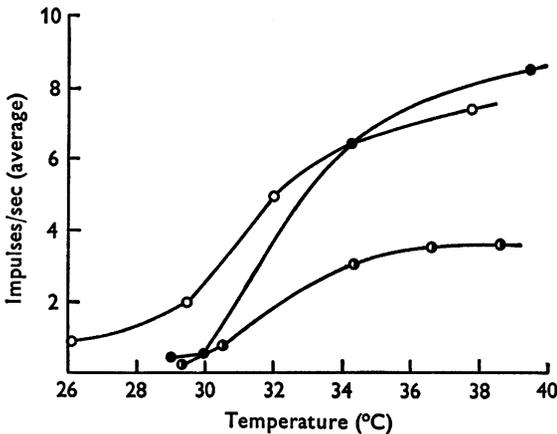


Fig. 4. Effect of lowering the temperature on the responses of three chemoreceptors in three cats to hypoxia (4% O₂). The ordinate represents the frequency of discharge averaged over 20 sec. The mean blood pressure was 54 mm Hg at 39.5° C and 51 mm Hg at 29° C in the case of the experiment relating to the filled circles. The corresponding values at normal and reduced temperatures for ending with open circles were 83 and 63 mm Hg; for the one with half-filled circles the corresponding values were 135 and 95 mm Hg. Note: the fall in blood pressure (at lower temperature) would tend to increase the activity of the ending.

response to 4% O₂ at lower temperatures was not due to a rise in the arterial P_{O₂}. The P_{CO₂} and pH could not be measured in these cats but in four other cats the P_{CO₂} fell to 16–21 mm Hg (at lower temperatures) from an initial level of 28–23 mm Hg at normal temperature. The pH increased by 0.15 units on lowering the temperature by 10° C.

Fig. 5A shows the relation of the activity in a chemoreceptor to P_{a,o₂} at 36.5° C and 26.5° C. A noteworthy point is that if one were to calculate the 'Q₁₀' from Fig. 5A, one would find that it varies with the level of P_{a,o₂}, being about 2.1 at 0 mm Hg, 8 at 10 mm Hg and about 34 at about 19 mm Hg. These variations can be attributed to the reduction of meta-

bolism and the shift in the oxygen dissociation curve to the left at lower temperatures (see Discussion).

Fig. 5*B* depicts the results of Fig. 5*A* with impulse activity plotted as a percentage of the activity at 0 mm Hg P_{O_2} (i.e. maximum activity) so as to eliminate the effects attributable to the actual Q_{10} of the ending (see

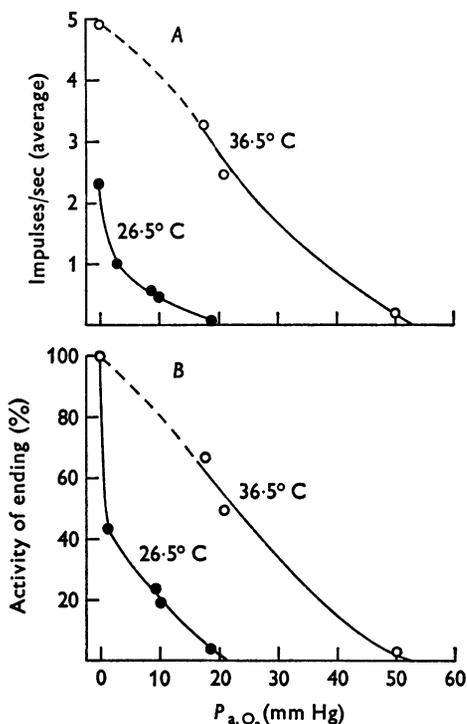


Fig. 5. The relation of activity in a chemoreceptor (fibre no. 18, Table 2) at two different temperatures to P_{a,O_2} . In *A*, the ordinate represents the frequency of discharge averaged over 20 sec. The interrupted portion of the curve at 36.5° C represents the extrapolation of this curve to 0 mm Hg (in arterial capillary blood) by using the ratio of 1.47 (see text). *B* shows the same data. Here the ordinate represents the activity of the ending expressed as a percentage of its activity at 0 mm Hg P_{O_2} i.e. after circulatory arrest. The pH was about 7.4 at 36.5° C; this rose to 7.55 at 26.5° C.

Fig. 8 and related text). The responses of three other endings at lower temperatures were examined in the same way; in all three the responses were similar to those shown in Fig. 5.

From the graph of Fig. 5*B* it is possible to state that 10% activity would be expected to occur at a P_{a,O_2} of 15 mm Hg at 26.5° C. Assessed in this way in the case of six endings (in six cats and at a mean temperature of 27.2° C) the arterial P_{O_2} at 10% activity averaged 16 mm Hg (range

13–22 mm Hg; s.e. 1.3 mm Hg). On the other hand at normal temperatures 10% of maximal activity was estimated at an arterial P_{O_2} of 49, 46 (Fig. 5*B*) and 44 mm Hg respectively in three cats. The difference between the values obtained at normal and at lowered temperatures can be attributed to differences in the local P_{O_2} obtaining at the two levels of temperature (see Discussion).

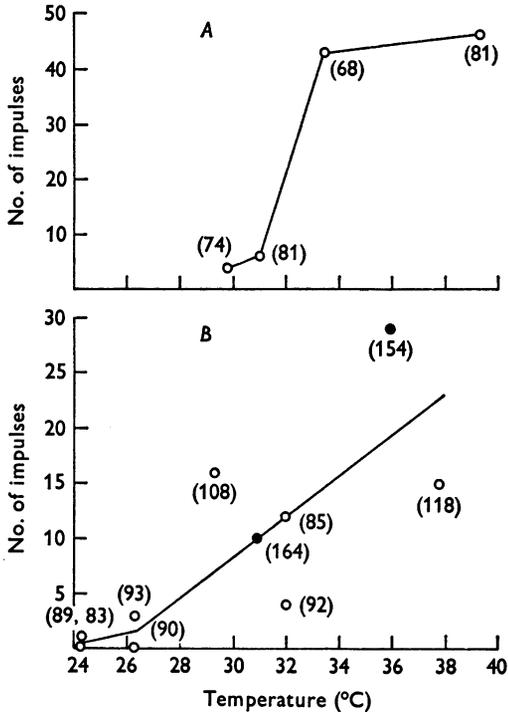


Fig. 6. Responses of two chemoreceptors in two cats following injections of a fixed dose of ACh into the aorta at different temperatures while cooling the cat. The dose of ACh used in *A* was 63 μ g, in *B* it was 100 μ g. The ordinates represent the total number of impulses produced after each injection. The fibres of both endings were non-medullated. The numbers in brackets, which indicate the mean blood pressure before each injection, show that the variation in the responses of the endings to ACh was not due to variations in blood pressure. Filled circles in *B*, which represent responses to ACh after rewarming the cat, indicate that the weak responses at lower temperatures were not due to tachyphylaxis. Records obtained from this fibre are shown in Fig. 7.

Effect of temperature on excitation by ACh. The influence of temperature on the excitation of aortic chemoreceptors by ACh was examined on eight endings which were specially selected for their sensitivity to ACh; the many others that were not stimulated by ACh (see Paintal, 1967) were discarded. The total number of impulses produced by a particular dose of

ACh was first recorded at normal body temperature. The temperature of the cat was then lowered and the response of the ending to the same dose of ACh (injected in the same way intra-aortically) was recorded. In one ending lowering the temperature by 8.5° C did not reduce the number of impulses produced by a fixed dose of ACh. In another there was 60% reduction in activity. However, in the remaining six endings the excitation was markedly reduced (by 75–100%) by lowering the temperature by 10° C. In three of these the excitatory effect was abolished by reducing the temperature to 32, 26 and 29° C respectively. At these temperatures the first two endings yielded a significant discharge (3–5 impulses/sec averaged over 10–20 sec) during ventilation with 3–4% O₂; the third was weakly stimulated during hypoxia.

The actual relation between temperature and the number of impulses produced by a fixed dose of ACh was variable. Whereas the relation between the two appeared to be linear in two fibres, in others it took the form shown in Fig. 6*A*. Here (i.e. Fig. 6*A*), reducing the temperature by 5° C had practically no effect on the number of impulses produced but lowering it further by 2.5° C produced a drastic reduction. The graphs of Fig. 6 bear some resemblance to those of Fig. 4. This is misleading because while the chemical stimulus in the case of Fig. 6 is fixed, it becomes less and less on lowering the temperature in the case of hypoxia (Fig. 4) (see Discussion).

Fig. 7*F* shows the peak frequency of discharge at different temperatures during ventilation of the cat with 3% O₂ and after intra-aortic injections of ACh. The interesting point here is the disparity in the peak frequency of discharge attained during application of the two stimuli at lower temperatures. Thus at 26.3° C, 100 µg ACh produced only 3 impulses in one trial (peak frequency = 9 impulses/sec) and no impulses in another. This poor response cannot be attributed to a fall in blood pressure as there is no correlation between blood pressure and the responses to ACh (Fig. 6). Nor can it be attributed to a sluggish circulation in the glomus itself because the speed of response of the ending (cf. above) was not obviously reduced at this temperature since the 'off latency' on administration of air was 9 sec at 32.3° C (Fig. 7*B*), 11 sec at 26.3° C and 12 sec at 30° C after re-warming the cat. However, at 26.3° C the peak frequency of discharge during ventilation with 3% O₂ was about 62/sec. It was still about 50/sec at about 24.4° C (Fig. 7*D* and *F*) but ACh yielded only one impulse (if this impulse is not part of natural background activity) after one injection and none after another. After re-warming this cat, the same ending yielded 29 impulses at 36° C (Fig. 6*B*). This is to be expected as there is little, if any, tachyphylaxis in the case of ACh (Paintal, 1967).

Observations similar to those of Fig. 7 were made on five other endings.

These are set out in Table 3. Thus as shown in column 4 of Table 3, at normal body temperature, the peak frequency of discharge (reciprocal of least interval between two impulses) after injection of ACh was approximately the same as that attained during hypoxia in three of the six fibres, the average peak frequency of all fibres being 76 % of that attained during hypoxia. On the other hand at lower temperatures the peak frequency

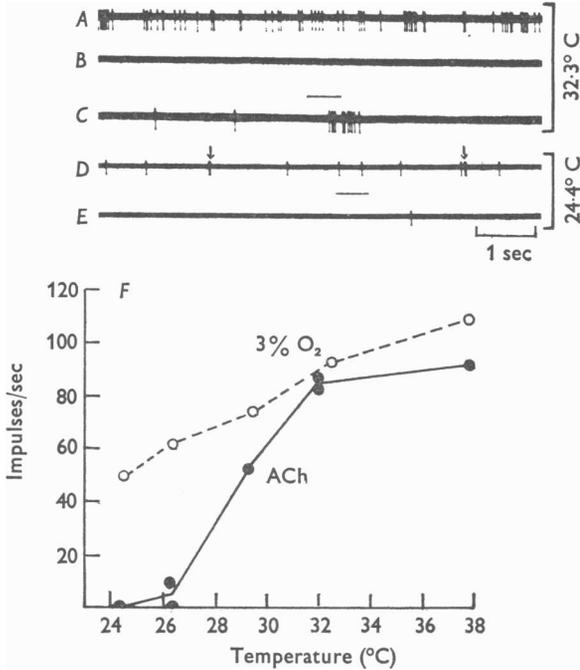


Fig. 7. Effect of temperature on the responses of a chemoreceptor to hypoxia (3 % O₂) and ACh. *F* shows the peak frequency of discharge during hypoxia (open circles and after injection of 100 μ g ACh into the aorta (filled circles) at different temperatures. *A* to *E* are samples of records from which the graphs in *F* were plotted. They show the effect of cooling by about 8° C on the response to hypoxia in *A* and *D* and to ACh injected at signals in *C* and *E*. *B* is a record showing no activity 9 sec after switching from 3 % O₂ (in *A*) to air indicating that neither the circulation or the P_{O₂} sensor is obviously slowed at 32° C. Mean blood pressure in *C* and *E* was 85 and 89 mm Hg respectively. Arrows in *D* mark grouped impulses.

after ACh was relatively much less, being on the average 11 % of that during hypoxia. It should be noted that the actual local P_{O₂} will be higher at lower temperatures even though the lungs are ventilated with the same gas mixtures (see Discussion). In two endings increasing the arterial P_{CO₂} by 21 mm Hg did not increase the excitatory effect of ACh.

Effect of temperature on pulmonary stretch receptors. Altogether the responses of nine pulmonary stretch receptors in three cats were studied.

In these experiments the cats were ventilated with a Starling Ideal respiratory pump (Palmer) at constant stroke volume and the responses of the endings to this stimulus were recorded first at normal body temperature and thereafter as the temperature was lowered. In all experiments the thoracic cavity communicated with the outside through two wide openings on either side. Since the actual stimulus for the endings is apparently the increase in transpulmonary pressure (Davis, Fowler & Lambert, 1956), the responses of the endings (at different temperatures) were compared at the same transpulmonary pressure, i.e. intratracheal pressure, which increased a little (Fig. 8) on lowering the temperature.

TABLE 3. Peak frequencies of discharge in chemoreceptors during hypoxia (3–4 % O₂) and after intra-aortic injection of 63–100 µg ACh at normal and low temperatures

Serial no. of fibre	Responses at 38–40° C			Responses at 24–29° C		
	Peak frequency during hypoxia (impulses/ sec)	Peak frequency after ACh		Peak frequency during hypoxia (impulses/ sec)	Peak frequency after ACh	
		(impulses/ sec)	%*		(impulses/ sec)	%*
4	114	92	81	50	0	0
7	54	23	43	5.3	1.3	25
8	87	74	85	39	10	30
9	172	196	114	48	8	16
16	79	85	108	29	0	0
44	85	20	23	15	0	0
			76%			11%
			(average)			(average)

* This represents the peak frequency after ACh as a percentage of the peak frequency during hypoxia.

As expected, reducing the temperature reduced the frequency of discharge at the height of inflation as well as the frequency at all other levels of inflation (Fig. 8). Using the frequency at the peak of inflation as an index, it was found that the Q_{10} of nine endings averaged 2.6 (range 1.9–3.4; s.e. 0.18). Apart from this change, lowering the temperature by about 10° C had no other obvious effect. For example, there was no obvious change in the threshold of five endings as indicated by the level of intratracheal pressure at which the first impulse was initiated, or any change in the pattern of response that would indicate that the adaptation of the endings had changed (Fig. 8). In four endings the increase in threshold was less than 1 cm H₂O. From these results it may be concluded that lowering the temperature *in vivo* produces little or no change in the relation of the

stimulus to the response of the ending apart from the reduction in the frequency of discharge. This is borne out when the frequency of discharge is expressed as a percentage of the peak frequency. As shown in Fig. 8B the two curves at the two temperatures are, apart from minor variations, similar. Such similar responses were seen in most of the pulmonary stretch receptors.

Attempts to study the effect of temperature on the adaptation rate of

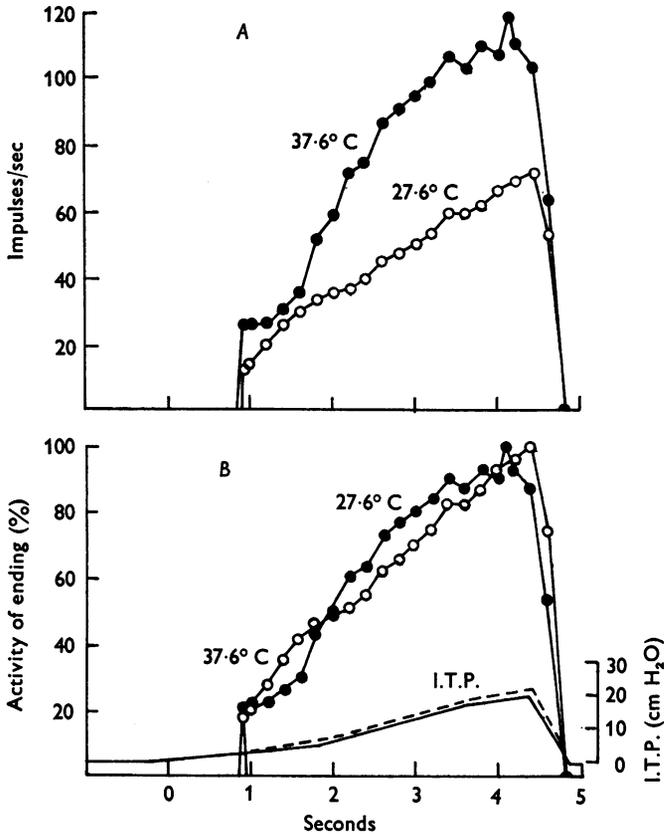


Fig. 8. Typical response of a pulmonary stretch receptor to inflation of the lungs at normal body temperature and after lowering it by 10°C . The ordinate in *A* represents the frequency of discharge (reciprocal of impulse interval). The same information is presented in *B* but with the ordinate showing the activity of the ending expressed as a percentage of the frequency of discharge at the peak of inflation so as to take into account the Q_{10} for the ending. Note the curves show that apart from the reduction in the frequency of discharge, lowering the temperature by 10°C does not alter the stimulus-response relationship. The lowest curves in *B* show the intra-tracheal pressures (I.T.P.) ordinate on the right at the two temperatures; this increased a little at the lower temperature as indicated by the interrupted curve.

the receptors using graded volumes of rapid maintained inflation were unsuccessful. This was because some endings normally without a cardiac rhythm during cyclical ventilation, acquired such rhythm when the pump was stopped before applying the stimulus.

DISCUSSION

One of the significant observations of the present investigation is that the Q_{10} for the frequency of discharge of chemoreceptors at maximal activity is the same as that of pulmonary stretch receptors, i.e. about 2.5. In this important respect, therefore, aortic chemoreceptors are similar to mechanoreceptors in general since the Q_{10} for the frog's muscle spindle (Matthews, 1931; Ottoson, 1965) and carotid baroreceptors (Diamond, 1955) is about 2.0.

At present it has been possible to determine the temperature coefficient of chemoreceptor activity only at a local P_{O_2} of about 0 mm Hg (i.e. maximal activity after circulatory arrest) because it is only at this level of P_{O_2} that one can be *relatively* certain about the local P_{O_2} in the aortic body. In the absence of circulatory arrest and at various levels of arterial P_{O_2} , the local P_{O_2} will depend on O_2 availability and the metabolism of the glomus cells (Paintal, 1967). Therefore at present it is not possible to state what the local P_{O_2} will be for any given arterial P_{O_2} . On the other hand after circulatory arrest it would be expected that the local P_{O_2} will remain at 0 level P_{O_2} at least for as long as the tissue is metabolically active.

The effect of cooling on the response to hypoxia is quite marked (Fig. 4). Clearly the order of reduction ($Q_{10} > 10$) is far in excess of what would be expected if the effect was due entirely to the modification of the response of the sensing mechanism with a Q_{10} of 2.5. Since the blood pressure did not rise on reducing the temperature (Fig. 4) the reduction in activity can be attributed to the reduction in the metabolism of the glomus and the fact that the O_2 dissociation curve shifts to the left leading to a rise in the O_2 content of the blood at low levels of P_{O_2} . Both these factors particularly the first would tend to raise the local P_{O_2} and thus reduce the activity to a greater extent than would have happened if the local P_{O_2} had remained constant at different temperatures. The fall in P_{CO_2} from about 28–34 mm Hg at normal temperatures to 16–21 mm Hg at lower temperatures may possibly play some part in reducing the activity of the chemoreceptors at lower temperatures although the activity of aortic chemoreceptors is not obviously altered by variations of P_{CO_2} of this order and at this level of P_{CO_2} (Paintal & Riley, 1966) and the same is true in the case of some carotid chemoreceptors (see points below 45 mm Hg P_{CO_2} at normal pH in Fig. 4 in Biscoe, Purves & Sampson, 1970). Similarly, the

increase in pH by about 0.15 units on lowering the temperature by about 10° C could play only a minor role, if any, in reducing the discharge particularly since the level of pH at normal temperature was 7.4 (see Fig. 2 in Hornbein & Roos (1963) and Fig. 10 in Biscoe, Bradley & Purves, 1970). It also needs to be remembered that although the cats were deeply anaesthetized so as to reduce possible reflex alterations in aortic body blood flow and distribution of blood between capillaries, some reflex alterations in blood flow may have occurred during hypoxia.

Reduction in metabolism is largely responsible for the shift in the stimulus-response relation to the left as shown in Fig. 5*B*. Had metabolic activity of the glomus been zero at about 26.5° C then the curve at about this temperature in Fig. 5*B* would have represented the actual relation between the local P_{O_2} and the activity of the ending. However, since metabolic activity cannot be zero at 26.5° C, it follows that the true stimulus-response relation must be to the left of the curve at 26.5° C in Fig. 5*B*. This needs to be determined.

ACh as a transmitter. The present results show that the excitatory effect of a selected dose of ACh is abolished in some endings on cooling although the excitatory effect of hypoxia is present. This supports the earlier conclusion that ACh is not likely to be a transmitter at chemoreceptors and that ACh acts on the regenerative region of the ending in some non-specific manner (Paintal, 1967). It appears that cooling reduces the sensitivity of the regenerative region to chemical excitants.

If ACh is the transmitter it is difficult to explain the type of response shown in Fig. 7*F*, i.e. why the difference between the peak frequency of discharge produced by ACh and by hypoxia at low temperatures is so large when there is hardly any difference between the two responses at higher temperatures. Thus if the peak frequency is determined by the maximum rate of release of quanta of transmitter released and if this maximum rate is assumed to remain unchanged with fall in temperature one could account for the peak frequency of discharge during hypoxia being about 40–50/sec in some endings (Fig. 7*F* and Table 2). However, it is not easy to explain why at lower temperatures the peak frequency of discharge during hypoxia is much greater than the peak frequency following injections of ACh even though the dose of ACh injected at lower temperatures is the same as that used at normal body temperatures. This suggests that the groups of two or three impulses (during hypoxia at low temperature) at relatively high frequency (e.g. Fig. 7*D*) are not due to the release of ACh.

This work was aided by an equipment from the Wellcome Trust London and a grant from the Atomic Energy Commission, India. I am grateful to Professor M. de Burgh Daly for his hospitality and for provision of laboratory facilities and to the Commonwealth Commission for support. I am thankful to Dr S. K. Jain for

kindly making the measurements of blood gas tensions. Finally I am much indebted to Professor Sir Bernard Katz, F.R.S., and Professor Richard L. Riley for their invaluable comments on the manuscript.

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