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THE SIGNIFICANCE OF THE TIMING OF CHEMORECEPTOR IMPULSES FOR THEIR EFFECT UPON RESPIRATION

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Abstract. Alveolar partial pressure of carbon dioxide ($PACO_2$) and alveolar partial pressure of oxygen (PAO_2) oscillate at the frequency of respiration and the oscillations persist into the arterial blood as oscillations of arterial partial pressure of carbon dioxide ($PaCO_2$) and arterial partial pressure of oxygen (PaO_2). Arterial chemoreceptors respond quickly enough to changes in $PaCO_2$ and PaO_2 for the arterial oscillations to give rise to oscillations in their afferent discharge at the frequency of respiration. The respiratory centre responds with short latency to afferent impulses reaching it. If a burst of impulses reaches it during an inspiration, the depth of that inspiration, is increased but if the burst arrives during expiration, the succeeding inspiration is little affected. Thus if the peaks of chemoreceptor afferent discharge coincide with inspiration, they have a greater effect on respiration than if they coincide with expiration. The phase relation between the activity of the respiratory centre and the oscillations it produces is determined, inter alia, by the frequency of respiration and the heart output. Thus it may well change in exercise.

We have published in outline (Black and Torrance 1967*ab*) and in detail (Black and Torrance 1971) the observations which led us to these conclusions. Here I shall discuss recent observations made by N. Goodman and B. Nail which clarify some of the uncertainties left in the earlier paper.

Oscillations in afferent discharge

1. Effect of frequency of ventilation and of metabolism upon amplitude

If the frequency of respiration increases but the oxygen consumption remains unchanged, the amplitude of oscillations in gas tensions in the

alveolar air and also in the arterial blood is reduced. It is not surprising therefore that the amplitude of the oscillations in the output of chemoreceptors also decreases (Biscoe and Purves 1967, Leitner and Dejours 1968). In the anaesthetized cat oscillations in discharge can often be seen up to a respiratory frequency of 25/min; though they may be substantially attenuated at this frequency (Fig. 1). Biscoe and Purves (1967) show

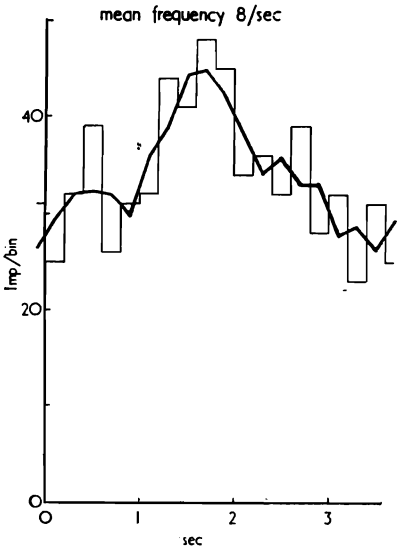

Fig. 1. Discharge from single chemoreceptor fibre of carotid nerve of spontaneously breathing cat. Impulses for a long train were collected into 200 msec bins and the probability density histogram shows the relation between the number in any bin and the timing of that bin from the beginning of inspiration. The thick line shows a running average of the number of impulses in groups of three bins (*see* Band et al. 1971).

them at a frequency of 42/min. They are more marked at lower frequencies (Fig. 3).

If oxygen uptake rises in exercise, oscillations in alveolar gas tensions increase and so one might expect that the oscillations in the discharge of chemoreceptors would increase, provided the respiratory frequency does not rise too much. We have used dinitrophenol, DNP, to mimic the picture of gas transport seen in exercise: by uncoupling oxidative phosphorylation, it can increase the oxygen consumption of a cat by up to tenfold and through lactic acid formation, may give an RQ above unity. Figure 4 shows that it may increase the amplitude of the oscillations in discharge strikingly when the frequency of respiration changes little after DNP, and Fig. 5 shows that it may increase the amplitude of oscillations in discharge even though the frequency of respiration is substantially increased. It should be born in mind, however, that DNP does itself affect chemoreceptors directly.

The experiments that Cunningham has just described are interesting in this context for in them the chemoreceptors of man seem to follow

a respiratory oscillation in their stimulus even though the respiratory frequency has been raised to 25/min and is nearly double its resting value but the metabolism is still that of rest.

2. Phase relation between ventilation and discharge

The discharge starts to fall at about 2–3 sec from the start of an inspiration and observations on an animal breathing irregularly show that the fall is to be attributed to the inspiration occurring 2–3 sec before the fall rather than to an earlier one. The fall can be delayed by clipping the external carotid in order to slow blood flow along the common carotid artery and it is also delayed by clipping the common carotid artery so that the carotid body is supplied by anastomotic channels. The fall in

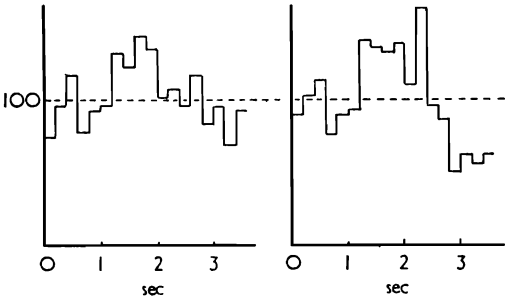

Fig. 2. Two simultaneously recorded chemoreceptor fibre discharges of the carotid sinus nerve of a cat. Probability density histogram as in Fig. 1 except that on the abscissa 100 represents the mean rate of discharge with zero on the ordinate. Note the similarity of the shapes of the histograms, which justifies regarding the activity of a single fibre summed over many breaths as indicating the activity of many fibres summed over a single breath.

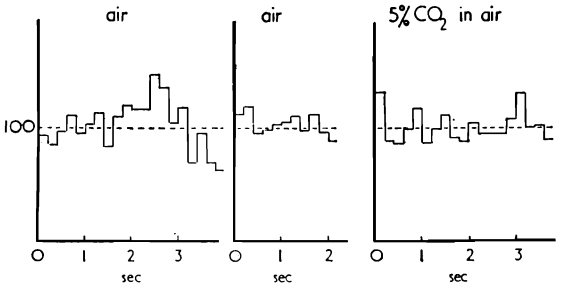

Fig. 3. Discharge of single chemoreceptor fibre of carotid sinus nerve of artificially ventilated paralysed decerebrate cat. Probability density histograms. These show a clear variation in the discharge when the respiratory period is 4 sec but only a slight variation when the period is reduced to 2.2 sec. The respiratory variation is abolished by ventilation with 5% CO_2 in air.

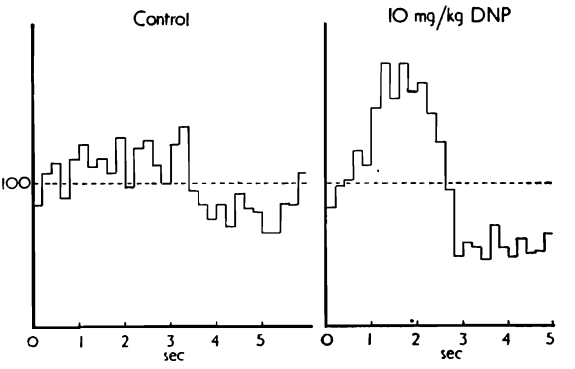

Fig. 4. Discharge of single chemoreceptor fibre of carotid sinus nerve of spontaneously breathing vagotomised cat under pentobarbitone anaesthesia. Dinitrophenol (DNP) accelerates respiration but increases strikingly the amplitude of the oscillation in discharge.

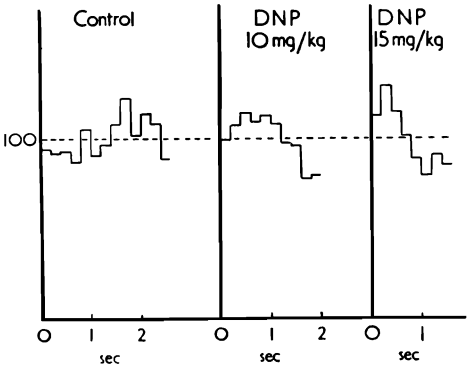

Fig. 5. Discharge of carotid chemoreceptor fibre of spontaneously breathing cat under pentobarbitone anaesthesia. Vagi intact. Dinitrophenol (DNP) accelerates respiration and increases amplitude of oscillation in discharge.

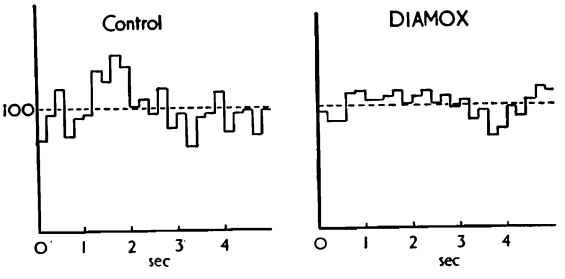

Fig. 6. Discharge of carotid chemoreceptor fibre of spontaneously breathing vagotomised cat under pentobarbitone anaesthesia. Poisoning carbonic anhydrase with Diamox (acetazolamide) reduced amplitude of oscillation in discharge in this experiment but it did not always do this in other experiments.

discharge may occur earlier after DNP, presumably as a result of the increase in heart output caused by DNP (J. Banister and R. W. Torrance, unpublished data). This is shown clearly in Fig. 4 but the phase relations are uncertain in Fig. 5.

These timings mean that, in a cat breathing at 20–30/min, inspiration could be taking place at the minimum or at the maximum of discharge. Also commonly (Fig. 2, 3 and 4), but not always (Fig. 6), the discharge drops suddenly so that a small shift in the phase relation in one direction could give a sudden change in the discharge arriving at the centre during inspiration whilst a shift in the opposite direction would give a more gradual change in discharge.

3. The stimulus responsible for the oscillations

Chemoreceptors are sensitive to hypoxia and to hypercapnia. Both the PO_2 and PCO_2 of the arterial blood oscillate. Which of these oscillations gives rise to the oscillation in the discharge?

If an animal breathes CO_2, the oscillations in the arterial pH are reduced (Band et al. 1969) and the $PaCO_2$ is above the range over which the sigmoid CO_2 response curve of chemoreceptors is very steep: the oscillations in discharge are also reduced (Fig. 3). Acetazolamide reduces the speed of response of chemoreceptors to CO_2 (McCloskey 1968, Black et al. 1971): it also may reduce the amplitude of oscillations in discharge (Fig. 6). The discharge that persists at a high PO_2 varies with respiration but at a high PO_2 chemoreceptors are insensitive to small changes in PO_2. Chemoreceptors respond to CO_2 promptly and with adaptation but respond to hypoxia more slowly and with little adaptation (McCloskey 1968, Black et al. 1971) and they will follow hypercapnic oscillations better than hypoxic ones (Fitzgerald et al. 1969).

These observations all suggest that CO_2 is important in producing naturally occurring oscillations in discharge and this is a view that Cunningham has just propounded. It does however raise an awkward problem. A fair approximation to the steady state response curve of chemoreceptors to PCO_2 between 25 and 45 torr is a straight line cutting the PCO_2 axis at about 20 torr (Euler et al. 1939, Hornbein 1968, Biscoe et al. 1970) and having a steeper slope the lower the PO_2 (Fitzgerald and Parks 1971). The respiratory oscillation in arterial pH is less than 0.015 units and indicates that the amplitude of the oscillation of PCO_2 is 1 torr or less (Band et al. 1969). Thus if $PaCO_2$ is above 30 torr, the discharge should oscillate by less than 10% of its mean value. And if one uses Fitzgerald and Parks (1971) results to take the PaO_2 into consideration also, the oscillation would only be about doubled. One has to invoke

adaptation of the response to CO_2 (McCloskey 1968, Black et al. 1971) if one is to account for amplitudes of oscillation in the discharge equal to 30–150% of the mean level of discharge and that order of amplitude of oscillations has been observed by Biscoe and Purves (1967) and Band, Saunders and Wolff (1971). Indeed Band et al. (1971) take "30% of mean" as their criterion of whether there is an oscillation in the discharge and they usually find one. Black, McCloskey and Torrance (1971) found that the response to a big step change in PCO_2 adapted down to about 20% of its initial peak with half time of 5–10 sec. It would need an adaptation of this order to small changes of PCO_2 also, to reconcile the idea that respiratory oscillations in discharge are principally due to CO_2, with what is known about the steady state response curves of chemoreceptors to CO_2.

At low respiratory frequency, hypoxia could, of course, be involved.

Responses of the respiratory centre to chemoreceptors

A volley of impulses reaching the medulla along carotid chemoreceptor nerve fibres during inspiration increases the depth of that inspiration. If it starts early in inspiration it has a smaller effect than if it starts later in inspiration (Black and Torrance 1967*a*). This is true both when the volley is set up by a saline solution of high PCO_2 injected retrogradely down the external carotid artery (Black and Torrance 1967*a*) and when it is set up by electrical stimulation of the carotid sinus nerve. However, CO_2 saline produces a volley of impulses that lasts longer than the whole process of inspiration so that it would appear that the striking effect of volleys starting late in inspiration is the result of there being an *increase* in afferent discharge late in inspiration rather than the result of there being a high *intensity* of afferent discharge at that time. This conclusion is supported by the finding that if electrical stimulation of the carotid sinus nerve is started late in inspiration, it has a greater effect on inspiratory activity than it does if it is started early in inspiration and is sustained throughout inspiration.

Effects on functional residual capacity

So far I have concentrated upon the effects of bursts of impulses reaching the respiratory centre in inspiration. If a burst arrives early in expiration, it has little effect on the volume of air in the chest but it may delay the onset of the next inspiration. Arriving late in expiration, it may bring on the next inspiration early. In view of this it is perhaps surprising that in steady hypoxia, though not in steady hypercapnia, there is an increase in functional residual capacity (*see* Bouverot and Fitzgerald 1969, for reference) and the effect is more pronounced if the

vagi have been cut (P. S. Rao and R. W. Torrance, unpublished data). This shows that a *sustained* discharge from chemoreceptors does give rise to tone in inspiratory muscles in expiration in contrast to a brief burst of discharge.

Rao and Torrance also found that after vagotomy, there was not a unique relation between tidal volume and frequency in the cat under pentobarbitone. After vagotomy, hypoxia and hypercapnia still usually increased frequency and, when the functional residual capacity increased in hypoxia, tidal volume was less at any value of frequency than it was in hypercapnia.

The significance of the phase relation between the oscillations in chemoreceptor discharge and the respiratory cycle

We have described elsewhere (Black and Torrance 1967*b*, 1971) an experiment in which we set up oscillations in chemoreceptor discharge which had a varying phase relation to the activity of the respiratory centre. We did this by artificially ventilating vagotomised cats with widely opened chests at a frequency a little less that of inspiratory bursts of discharge in the phrenic nerve. We found that the size of the phrenic bursts varied with the phase of the respiratory cycle at which they started and that the effect was abolished by cutting the carotid sinus nerve.

These experiments showed that when the respiratory centre is discharging slowly after vagotomy it can be made to play certain tricks. But are they just tricks? or are they perhaps something more than that?.

The discharge of chemoreceptors varies with respiration at or below resting respiratory frequencies. If the respiratory frequency increases and the metabolism also increases the amplitude of the oscillations in discharge can increase. The inspiratory centre responds to brief bursts of impulses with a latency of 100 msec or less. It too responds quickly enough.

At rest, the minimum of the cycle of discharge of chemoreceptors might coincide with inspiration so that conditions would be worst for any mean level of discharge to produce ventilation; but with increasing exercise, the amplitude of the oscillations in chemoreceptor discharge would increase and their maximum might gradually move towards coinciding with inspiration, so that conditions would tend towards the optimal for producting ventilation. Heart output increases in exercise in a greater proportion than does respiratory frequency so this phase shift could well occur.

Teleologically at least, such a system could be satisfying, for it might hold the mean level of a variable quite constant by changing the phase

of an oscillation of that variable which is effective in generating feedback. For the moment, however, we can only say that it is not inconceivable that something like this happens and that the possibility that it does happen is something one needs to bear in mind.

Effect of body size

We, like Semple, have made our observations in cats but Cunningham has worked on man. Can observations on cats be used to analyse what happens in man and can observations on man be used to tell us how an array of separate phenomena discovered in dissected cats are integrated in the intact animal.

We are discussing the amplitude of oscillations of gas tensions at the frequency of respiration and their phase relation to respiration. It can be shown that the amplitude of oscillations in alveolar gas tensions and their attenuation by the time they reach the carotid bifurcation are independent of body size because oxygen uptake and cardiac output are proportional to $W^{0.73}$, where W is body weight, respiratory period is proportional to $W^{0.27}$ and lung and blood volumes are proportional to $W^{1.0}$ (Black and Torrance 1971).

The time lag from a change in alveolar gas tension to a change in arterial gas tension will be in proportion to the volume of blood between the pulmonary capillaries and the systemic arteries, divided by the flow through this volume, so it will be proportional to $W^{1.00} \div W^{0.73} = W.^{0.27}$. But the period of the oscillation is equal to the duration of a breath and that is proportional to $W.^{0.27}$. Thus if the lag is expressed in units of the period of the oscillation, it is independent of W. It is then of course being expressed as a phase lag rather than a time lag. These predictions that the amplitudes and phase relations of respiratory oscillations are independent of body size suggest that observations on one animal can be used to interpret observations on another of substantially different size. In support of this treatment is Semple's finding that arterial oscillations of pH are similar in amplitude in man and in the cat. We find that the lag from the start of inspiration to a drop in the discharge of chemoreceptors is 2–3 sec in 2–3 kg cats and is 3–5 sec in 25 kg dogs. The ratio of the weights is about 10 and so the ratio of the time lags should be $1:10^{0.27}$, i.e. 1:1.87.

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