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RESPIRATORY CHEMOSENSITIVITY IN THE MEDULLA OBLONGATA

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Abstract. Respiratory regulation is considered as a feedback mechanism serving the homeostasis of the hydrogen ion concentration in brain extracellular fluid during rest as well as during exercise. Only in hypoxia the working range of the regulator is shifted in such a way that a sufficient O_2 partial pressure is maintained at the cost of hydrogen ion concentration. The main sensing element of the regulator is the 'central' chemosensitivity. The location of the chemosensitive mechanism in two plaques of a superficial layer of the ventral medulla oblongata is amply discussed. This region is separated from the respiratory centres and provides the centres with a tonic pH sensitive impulse flow. It is not necessary to assume additional chemosensitivity of the centres. In muscular exercise additional impulses reach the centres which are able to compensate the otherwise expected deviation of extracellular pH in brain caused by the increased CO_2 production in the body. If the brain is considered as a computer the described homeostatic mechanism may be viewed as assuring the reproducibility of the nerve cells as units of the computer.

After the discovery of the peripheral chemoreceptors by Heymans and Heymans (1927) there was general agreement that the ventilation of the lungs is driven mainly by the impulse traffic originating at the peripheral chemoreceptor and by the drive originating in the centres which were considered to be chemosensitive. Experiments with crosscirculation by Heymans may be interpreted as indicating that in rest usually no further major specific drive operates on ventilation. Since the afferent impulse flow driving ventilation is dependant upon the chemical composition of the fluid surrounding the receptors and since increase of ventilation diminishes the chemical stimuli this system acts as a controlled system or 'chemostat' maintaining the level of the chemical stimuli close to normal

at the site where they are 'measured' or in other words transduced into an impulse traffic by the chemosensitive mechanisms. It has been shown, however, by several authors (*see* Hugelin and Cohen 1963) that unspecific drives acting on the reticular formation reach the respiratory centres and modify ventilation. Other modifications are caused by reflexes connected with speech, vomiting, swallowing and so on. In muscular exercise neural impulses from muscles or joints provide an additional flux of impulses to the respiratory centres which acts as if resetting the control system to a lower setting point. There is no doubt that the action of the respiratory centres may also be influenced from higher centres, for example those which serve temperature regulation or those which are implied in the mechanism of sleep. The pathways of cortical influences on ventilation are not very well understood, they may be partially acting on motoneurons directly and partially on the respiratory centres.

The control of the chemical composition serves the whole body. However, since — as long as there is no deficiency of oxygen — the main chemical drive is central and since the central chemosensitive mechanism can only measure the chemical composition of the extracellular fluid surrounding the cells, the 'chemostat' may be considered as mainly serving the homeostasis of brain extracellular fluid. This shows the decisive role the central chemosensitivity plays for the homeostasis of the surrounding of the brain cells and therefore for the reproducibility of their function.

This paper will be concerned with recent advances on central chemosensitivity. It will first discuss location of the chemosensitive mechanism and then deal with its functional aspect.

Location of the chemosensitive mechanism

After Leusen's (1950) observation that breathing could be controlled by alteration of the acid-base characteristics of the cerebrospinal fluid, Loeschcke and Koepchen (1958*a*) observed that perfusion of the cerebrospinal fluid spaces with a solution containing procaine in a peripherally chemodenervated cat caused respiratory arrest (Fig. 1). If, however, procaine was applied to the roof of the fourth ventricle no such effect could be observed. During the respiratory arrest caused by procaine perfusion electrical stimulation of the respiratory centres was as affective as before. The arrest, in the authors' hypothesis, was therefore not caused by an action of procaine on the centres but on structures providing impulses for the centres, probably the central chemosensitive structures. Such a hypothesis was in good agreement with the concept of Åström (1952) who was led to assume a 'chemocentre' separated from the inte-

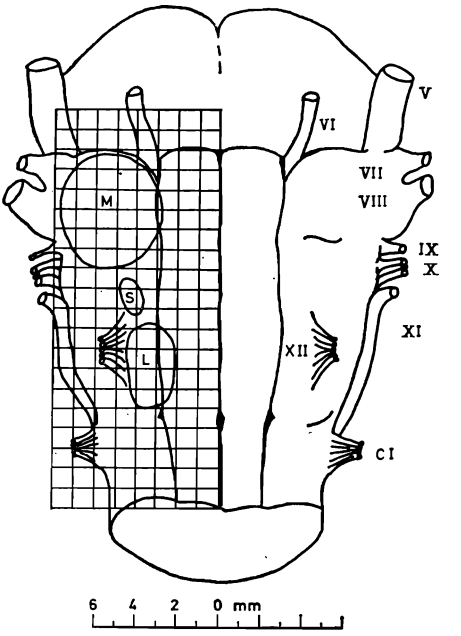

Fig. 1. Ventral aspect of the cat's medulla. The area described by Mitchell et al. (1963*b*) is indicated by M, the area described by Schlaefke and Loeschcke (1967) by S and the area described by Loeschcke et al. (1970) by L.

grating respiratory centres by the observation that central chemosensitivity was very easily eliminated by deep anaesthesia at a time when respiratory reflexes for example from peripheral chemoreceptors which imply the function of the integrating centres were fully active. It was also in agreement with the observation of von Euler and Söderberg (1952) who picked up impulses from units in the medulla oblongata discharging in a continuous sequence which depended on the CO_2 concentration inhaled. They therefore may have been considered as impulses on a pathway originating in chemoreceptors. Mitchell et al. (1963*b*) by local application of pledgets soaked with buffers or solutions containing drugs succeeded in demonstrating the existence of an area (Fig. 1) on the rostral ventrolateral surface of the medulla oblongata, the application to which of acid buffers, acetylcholine or nicotine caused inrease of ventilation. Conversely procaine and cooling inhibited ventilation. The method does not allow a very precise localisation because the applied solution tends to spread on the medullary surface.

In order to study local effects with better spatial resolution Schlaefke, See and Loeschcke (1970) developed a 'chemode', that is a device for spotwise superfusion with a desired buffer or drug solution with which the surrounding of the superfused spot is washed with artificial cerebrospinal fluid of constant composition thereby counteracting the spreading effect. With this method they found two areas responding to acid

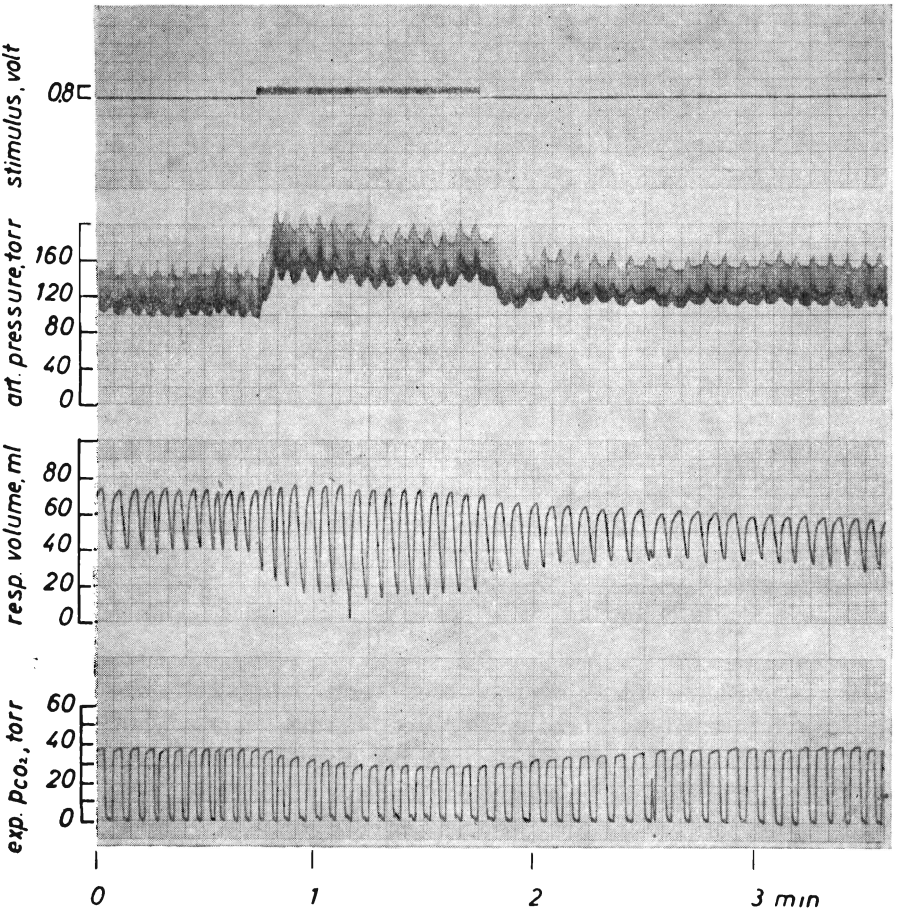

Fig. 2. Stimulus (0.8 v, 40/sec, 1 msec rectangular), arterial pressure, respiratory volume changes and expiratory PCO_2 in an anaesthetized cat (chloralose-urethane). During stimulation on area L, increase of tidal volume and of arterial pressure. (From Loeschcke et al. 1970.)

buffers by causing ventilation to increase. The one was identical with Mitchell's area and the other one was located more caudally medial to the hypoglossial root, as can be seen in Fig. 1. Because the responses to the spotwise chemical stimulation were small, again the borders of the chemosensitive areas could not be determined with precision. Between the two areas Schlaefke, See and Loeschcke (1970) obtained a diminution of ventilation if acid buffers were applied and an increase with alkaline buffer. Electrical stimulation on the medullary surface of both chemosensitive areas is followed by an increase of ventilation (Fig. 2 and 3) (Loeschcke et al. 1970). Stimulation in the area between the two chemo-

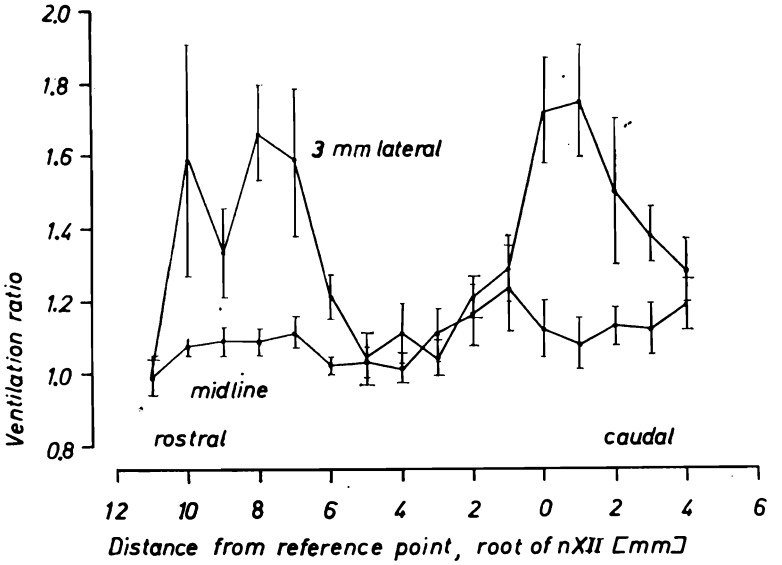

Fig. 3. The ventral surface of the medulla oblongata was stimulated (data *see* Fig. 2) with a concentric electrode on the midline and on a line 3 mm lateral of it in a series of points 1 mm distant from each other in rostral and in caudal directions starting from the middle of the hypoglossal root. Not much effect was observed by stimulation at the midline. In 3 mm lateral distance, however, two areas may be distinguished where stimulation causes an increase of ventilation (mainly tidal volume) and of arterial pressure. (From Loeschcke et al. 1970.)

sensitive zones in the average had no effect on ventilation, however in the single experiment in very close neighbourhood an increase or decrease of ventilation could be observed. It may be suspected that in this region structures of different functions are located very close to each other. The effects of electrical stimulation in the described areas in general are much more impressive than those of chemical stimulation. One reason for this may be that the chemosensitive structures are not located directly on the surface but probably at a short distance underneath and that the chemical stimulus is already diminished by exchange with the local blood perfusion before it reaches the chemosensitive structure. It turns out that by electrical stimulation two areas can be defined with satisfying precision which in general are concordant with the areas responding to chemical stimuli.

By applying the laws of diffusion Mitchell et al. (1963*a*) calculated the gradient of PCO_2 from the surface into the depth of the medulla under the conditions of the experiments. It was not yet possible to assign a definite distance from the surface to the receptor. But it was reasoned

that the receptor must be located in a rather superficial layer of the medullary surface to be influenced by experimental variations of CSF PCO_2.

Other arguments for a more superficial location are that relatively large molecules like procaine, nicotine or veratridine reach the receptors easily and in a short time to inhibit or to stimulate them respectively (Loeschcke and Koepchen 1958*b*, Mitchell et al. 1963*a*).

It is not completely certain that the structures which are activated by electrical stimulation of the medullary surface are identical with the chemosensitive structure. Everywhere, however, where chemosensitivity was demonstrated electrical stimulation leads to an increase of ventilation. If in the region medial to the hypoglossal root an electrode is introduced into the medulla oblongata (Trouth 1969) the maximum increase of ventilation is seen with stimulation between the surface and a depth of 0.2 mm while at greater depths the response is diminished and at about 0.8–1.0 mm may be completely absent. If the electrode tip is introduced further, again increased ventilation is observed and at about 1.5 mm usually a marked increase of ventilation and in some cases inspiratory arrest is seen. At greater depths usually inspiratory arrest at high lung volume is obtained and even deeper this will turn into expiratory arrest, the two latter responses being typical for location in the inspiratory and in the expiratory half-centres. This experiment suggests that there is a structure between the ventral surface and a depth of about 0.5 mm which if activated by electrical stimuli is able to drive ventilation and which may be the neural mechanism connected to the chemosensitive mechanism.

Another qualitative argument about the location of the chemoreceptor is provided by experiments of Berndt, Berger and Trouth (1970*b*). The authors introduced a stimulating electrode into the inspiratory half-centre of one side in an anaesthetized cat. The tip of the electrode was located 1.5 mm underneath the ventral surface. If 2% procaine was applied to the ventral surface spontaneous ventilation stopped, but the response to electrical stimulation of the inspiratory half-centre remained unchanged. If instead of procaine a solution containing 100 meq/litre of K^+ was applied, again respiratory arrest was observed and the centres responded to stimulation, but in contrast to the procaine application the central response was abolished after a time period which always exceeded the period necessary to stop spontaneous ventilation. This indicates that the chemoreceptive structure is more superficial than the inspiratory half-centre and more superficial than 1.5 mm. If the electrode was put to a depth of 200 μm electrical stimulation caused an increase of ventilation. After superfusion with 100 meq/litre of KCl the

response to electrical stimulation vanished at the same time as spontaneous ventilation. The chemosensitive structure may therefore be looked for at a distance of about 200 μm underneath the ventral surface.

Recently Berndt and Berger (1971) tried an approximate calculation of the pH gradient from the surface of the medulla into the depth, in experiments in which the pH on the ventral medullary surface was changed by superfusion of bicarbonate buffers, and during superfusions with different buffers while arterial PCO_2 was varied by inhalation of CO_2. A number of unproved assumptions are necessary for such a calculation but it is possible to estimate how much the result may depend upon these assumptions. In their discussion the authors state that there is only one distance from the surface at which all responses to CO_2 inhalation and to variation of CSF pH may be related to the extracellular pH in the medulla by one unique function. Though location of this point may be dependent upon errors in the premises it is most probable that this point is at a depth of about 250 to 300 μm. This point may be considered as the point of gravity of the chemoreceptive field.

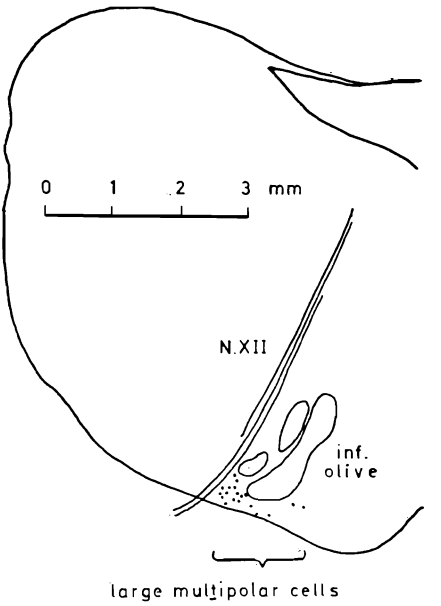

Fig. 4. Cross section of the medulla oblongata at the level of the hypoglossal root and the inferior olive of a cat. The multipolar cells described by Trouth and Loeschcke (1969) observed in a series of consecutive sections are projected on this section.

Trouth and Loeschcke (1969) searched for the locus of maximal response to electrical stimulation at the medullary surface medial to the XIIth nerve root. They then introduced an electrode and marked by electrolysis the spot where the response was greatest. In histological examination they found regularly a group of multipolar nerve cells

ventral to the inferior olive which so far seems not to have been described (Fig. 4). These cells, they suggested, may be part of the chemosensitive mechanism. They can be found from directly under the terminal glia on the surface until about 0.6 mm deep, which is almost the border of the olive. It is not yet possible to follow up the connexions of these cells which are the only large cells in this region. Underneath Mitchell's area the situation is more complicated. There are cells and they continue into the reticular formation but no special grouping of cells has been observed.

Shimada, Trouth and Loeschcke (1969) introduced microelectrodes of tungsten or steel into the superficial layer of the caudal area and action potentials were picked up. Several types of units were observed, mainly one type which was activated from the skin receptors of the foreleg and the shoulder and another type which did not show such a relation. The first type fired independently of the pH of fluid superfused on the ventral surface of the medulla, while the second type displayed high activity at a pH of about 7.0 and became almost or completely silent if surface pH was brought to 7.6. To reach the steady state firing rate about 10 min of superfusion with constant pH were necessary which is similar to the time course of ventilatory changes in such an experiment, and easily explained by the fact that diffusion through the extracellular spaces is necessary to reach the cells. The firing pattern approximated a Poisson-distribution of the intervals. Of course, it will be necessary to establish the relation between pH and firing rate more quantitatively, but it seems that Shimada, Trouth and Loeschcke (1969) picked up the afferent signals to the respiratory centres from the central chemoreceptor.

Functional aspects

Among the functional aspects the nature of the adequate stimulus to and the role of central chemosensitivity in body homeostasis will be discussed.

Leusen (1950) stated that in his experiments the magnitude of respiratory drive triggered by changing acid-base characteristics in the fluid perfusing CSF-spaces was proportional to the ratio of PCO_2 to HCO_3^-. He did not consider this as contradictory to the hypothesis that CO_2 exerted a specific effect. However, the above ratio is proportional to the hydrogen ion concentration and Winterstein (1955) as well as Loeschcke, Koepchen and Gertz (1958) quoted Leusen's data as supporting a hydrogen ion specificity.

Loeschcke et al. (1958) subjected this question to a direct test, perfusing CSF spaces either with solution in which pH was varied and PCO_2 kept constant or PCO_2 was varied at constant pH. Between pH 7.0 and

7.8 ventilation increased about linearly with the diminution of pH. Increase of PCO_2 at constant pH, however, was followed by slight diminution of ventilation. In general, therefore this investigation supported the hypothesis of a specific effect of hydrogen ions. In the light of the more recent investigations of Berndt and Berger (1971) it is possible to explain the unexpected negative CO_2 effect by the special boundary conditions for diffusion from the surface into the matter of the medulla oblongata.

The hydrogen ion hypothesis was very well established by the experiments of Pappenheimer, Fencl, Heisey and Held (1965) and by Fencl, Vale and Broch (1969). In the experiments of this group in goats, dogs and human subjects it was demonstrated that in respiratory as well as in metabolic acidosis ventilation followed the pH of cerebrospinal fluid as a unique function. This agreed very well with a hypothesis proposed by Loeschcke (1965) that by a limited exchange of bicarbonate between blood and CSF the reaction of central chemosensitivity to local pH might be able to explain the ventilatory drive of the PCO_2 and the H^+ factor in Gray's (1950) multiple factor theory. The same result was obtained by Berndt and Berger (1971) in the already mentioned experiments. In conclusion there seems now to be a general agreement that the main factor acting on the central chemosensitive mechanism is the hydrogen ion concentration in the extracellular fluid surrounding the chemosensitive cells and that under normal conditions in the steady state the hydrogen ion concentration of this fluid varies in strict correlation with the hydrogen ion concentration of cerebrospinal fluid. Czerr (1965) has already demonstrated that diffusion from CSF into the extracellular spaces of the brain is unrestricted and for this reason the ionic composition of cisternal CSF may be used as an indicator of the composition of the extracellular fluid inside the medulla.

When a bicarbonate gradient from CSF to extracellular fluid was experimentally induced Pappenheimer et al. (1965) found that the response of ventilation followed the pH on a point $^3/_4$ of the gradient from CSF to blood. In the calculation of Berndt and Berger (1971) in a similar deduction such a point could be defined as being located approximately at 250 to 300 μm underneath the ventral surface of the medulla. In Fig. 5 the response of ventilation to extracellular pH at this location is plotted.

Effects of other ions on the chemosensitive system have already been observed by Verstraeten (1950) and more recently by Berndt et al. (1969, 1970*a*). The authors described the effects of K^+, Ca^{++} and Mg^{++} and their interaction with pH. A comprehensive theory of the ion effects is still missing.

The question arises whether or not the chemosensitive mechanism just described which can be influenced by experimental variation of the

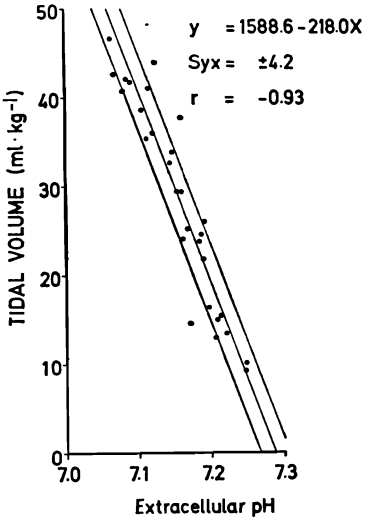

Fig. 5. Dependence of tidal volume of an anaesthetized cat (chloralose-urethane) on the calculated extracellular pH in the medulla at a depth of 250 μ from the surface. In this experiment $PACO_2$ was varied between 29 and 81 torr, $P_{CSF}CO_2$ between 35 and 49 torr, $[HCO^-]_{CSF}$ between 5 and 63 mM/litre, and pH_{CSF} between 6.532 and 7.516. In spite of these large variations of the acid-base characteristics which were exerted separately in blood and in CSF the tidal volume follows a unique function of the extracellular pH. At every other depth this would not be the case. The regression line ± standard deviation is drawn. (This plotting is part of a slide presented by J. Berndt to the XXV Int. Congr. U. Physiol. Sci. Munich 1971.)

CSF composition may be identified with 'central chemosensitivity', that is the question whether this mechanism is identical with a part of or the total chemosensitivity which remains after elimination of the peripheral chemoreceptors, and whether it is the same mechanism which is responsible for the effects of inhaled CO_2 and of metabolic acidosis. The latter is already answered by the described experiments showing that a unique function of ventilation in dependence upon the extracellular pH in all cases of respiratory or of metabolic acidosis has been established. This is only possible if there is no additional type of receptor reacting with a different stimulus-response characteristic. Another argument is provided by the experiments in which in a peripherally chemodenervated cat procaine in the CSF causes complete respiratory arrest though central excitability remains unaffected. It may be added that this is also the case if CO_2 is inhaled. This means that the anaesthesia of the superficial layer of the ventral medullary surface by procaine knocks out all chemosensitivity remaining after peripheral denervation.

Similar conclusions must be drawn from the experiments of Schlaefke and Loeschcke (1967) in which in peripherally chemodenervated cats the local cooling of a very small area (S in Fig. 1) between the two chemosensitive areas is followed by respiratory arrest even during inhalation of CO_2. One explanation is that at this spot it is possible to interrupt the complete central chemosensitive impulse traffic to the centres. Recently Schlaefke et al. (1971) have succeeded in coagulating this area bilaterally and letting the animals survive. These animals displayed irregular and insufficient spontaneous breathing with a resulting high increase of end-tidal PCO_2. They showed a much diminished and in some cases no reaction at all to inhaled CO_2 in the unanaesthetized awake state. This suggests that superficial coagulation of a small area in between the two chemosensitive areas abolishes all or almost all response to inhaled CO_2. One possible hypothesis is that at this spot the afferent fibres from the central chemoreceptors are running together into a small bundle which may there be blocked by cooling or eliminated by coagulation.

In conclusion it may be stated that all or the major part of chemosensitivity is located in the described areas and that it seems not to be necessary to look for other chemosensitive structures in the medulla. The consequence is that the respiratory centres — if this means inspiratory and expiratory half-centres — are not chemosensitive as has been assumed for about 80 years. This of course does not exclude that CO_2 or hydrogen ion concentration may have some additional effect on central synaptic transmission. It does mean, however, that respiration cannot be driven by an automatism of the centres themselves or in other words that the centres for their action must rely on afferent inputs.

In control theory the central and the peripheral chemosensitive mechanisms together must be considered as the sensing elements of a negative feedback regulator. The negative feedback is exerted by the ventilation which determines PCO_2 and pH of the arterial blood. The two sensing elements (peripheral and central) under physiological and most experimental conditions act together. They, however, have different characteristics of adaptation to a steady stimulus and different delays of response if a rectangular change of the composition of the arterial blood is induced (Bouverot et al. 1965, Black et al. 1966).

The time course of the central response to a suddenly induced metabolic acidosis in this theory depends upon the speed of bicarbonate exchange between blood and extracellular fluid. This exchange probably takes place in minutes but this evidence is indirect and no direct data are available. In the recent experiments of Pannier, Weyne and Leusen (1971) it was shown that the HCO_3^- concentration of CSF was not or not only dependent upon the blood HCO_3 concentration but rather upon the

PCO_2. An active regulation is postulated and it seems that the brain as a source of base plays a bigger role than was thought earlier.

The value controlled by the regulator must be identical with the value measured by the sensing element. Under normal conditions under which

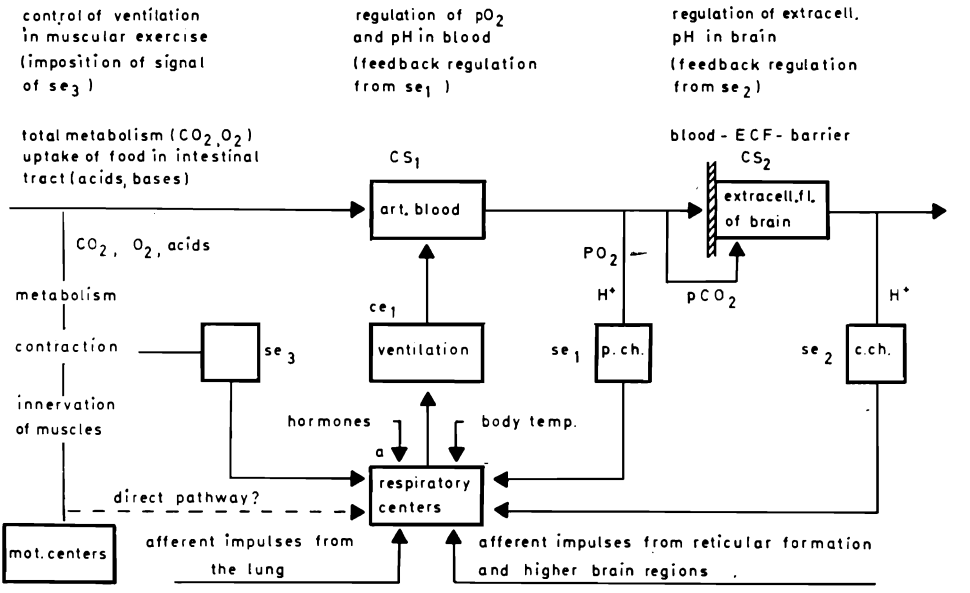

Fig. 6. The controlled system. Peripheral chemoreceptors, central chemoreceptors and receptors reacting during muscular contraction serve as sensing elements and contribute to the afferent drive of the centres (actuator). The ventilation serves as controlling element. The peripheral chemoreceptor senses PO_2 and H+ in the arterial blood and maintains arterial PO_2 in the case of oxygen deficiency. The central chemoreceptor senses hydrogen ion concentration in the extracellular fluid of the brain and controls blood H+ and PCO_2 by the ventilation in such a way that brain extracellular pH is kept close to normal. The muscular receptors cause an additional input of signals to the centres in muscular exercise thus apparently changing the setting point of the system in such a way that in muscular excercise ventilation is adapted to the metabolic needs. Furthermore the composition of the blood depends upon haemoglobin and protein breakdown and regeneration, upon the magnitude and quality of total metabolism (for example acid production, secretion and reabsorption of gastric and intestinal fluids, food uptake and waste products in faeces). The kidney (not in the schema) regulates the total blood buffer base mainly by bicarbonate, phosphate and ammonia secretion in urine or bicarbonate retention. Other influences on the respiratory centres like temerature, effects of hormones and of afferent impulses from the lung and from higher brain structures are indicated in the schema.

PO_2 is high the influence of hypoxia which is sensed by the peripheral chemoreceptor may be neglected. Then the central chemoreceptor is the main sensing element. It responds to variation of the hydrogen ion concentration in the extracellular fluid of the brain. The peripheral chemoreceptor responds among other influences to the hydrogen ion concentration of the blood but in more normal conditions this plays a minor role only. Usually then the regulator serves the homeostasis of the pH of the extracellular fluid of the brain that is the surrounding, or in Claude Bernard's language the 'milieu interieur', of the brain cells. A schematic representation of the controlled system is given in Fig. 6.

This gives a new aspect to respiratory regulation. During rest ventilation is much more directed to maintain the extracellular pH of the brain than to secure the oxygen supply. Of course this latter function is coupled to this main task of the regulator. Local pH depends mostly upon local PCO_2. Local PCO_2 is determined mainly by blood flow, by local CO_2 production and by arterial PCO_2. Arterial PCO_2 is dependent upon ventilation and tissue CO_2 production. If all the other variables would stay constant the regulator would adapt ventilation to tissue CO_2 production which is approximately equal to tissue oxygen consumption. Under normal conditions oxygen supply is not endangered and such a rough adaptation may suffice. In metabolic acidosis — as is well known — PCO_2 is kept below normal and PO_2 above normal. The opposite is the case in metabolic alkalosis. Therefore the regulator is set to care for extracellular brain pH in preference to oxygen supply, and many authors have shown that in these two cases the CSF pH stays extremely constant at the expense of blood pH and of oxygen availability (*see* Loeschcke and Sugioka 1969).

If, however, the body is threatened by oxygen deficiency the role played by the peripheral chemoreceptor which is sensing arterial PO_2 is of increasing relevance. In this case brain extracellular fluid homeostasis is sacrificed to the need of oxygen supply which now becomes vital. Other mechanisms like lactic acid production in the brain cells may have a homeostatic effect on extracellular brain fluid pH in such a case and help to avoid an alkaline shift which otherwise may be expected (Sørensen 1971).

SUMMARY

A review of more recent results of several authors on the localization and on the functional aspects of the central chemosensitivity of respiration is given.

1. Localisation of chemosensitive structures was tried by the methods

of local application of buffers with varying pH and of drugs like nicotine or acetylcholine, by local cooling, by differential elimination by procaine or potassium, by electrical stimulation and by searching for the best correlation between stimulus and response on the bicarbonate or pH gradient. Two fields of chemosensitivity on the ventrolateral surface of the medulla oblongata have been described, one at the level of the roots of the vagus nerves and the other at the level of the hypoglossial nerve. In the area between these fields a small area has been described where cooling stops spontaneous ventilation in the peripherally chemodenervated animal and which may be a spot at which the chemosensitive afferent fibres converge. Underneath the more caudal field a typical group of multipolar nerve cells has been described which may be part of the chemosensitive mechanism. The chemosensitive structures are located in a superficial layer extending not further than 0.6 mm into the medulla. Action potentials depending upon the pH on the medullary surface have been observed.

2. The chemical stimulus acting on the chemosensitive mechanism is identified as the hydrogen ion concentration in the extracellular fluid by applying buffers of constant PCO_2 but varying $[H^+]$ and vice versa and by establishing unique responses to pH on a given point of an experimentally induced bicarbonate gradient in metabolic and respiratory acidosis, as well as during superfusion of the medulla with varying pH and at the same time varying PCO_2 by inhalation of CO_2 mixtures.

3. The described mechanism can be identified with what is called central chemosensitivity to CO_2 or hydrogen ions because its elimination by cooling, by procaine or by coagulation abolishes spontaneous ventilation in the peripherally denervated animal in the acute experiment, and coagulation diminishes ventilation rigorously in a chronic animal and abolishes the response to inhaled CO_2. It is not necessary to ascribe chemosensitivity to the integrating centres.

4. The central chemosensitive mechanism in resting ventilation serves the homeostasis of the pH of the extracellular fluid in the brain and may be considered as thereby serving the reproducibility of the responses of the brain cells. In hypoxia increasingly the control of respiration serves the availability of oxygen in preference to the control of the extracellular brain fluid. In muscular exercise the controller is reset in such a way that ventilation is adapted to the metabolic needs and at the same time brain extracellular fluid homeostasis is maintained.

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