THE INTERACTION OF CENTRAL AND PERIPHERAL CHEMICAL CONTROL OF BREATHING

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Before the chemoceptive function of the carotid and aortic bodies was known, the chemical control of breathing seemed a relatively simple problem. Lack of O₂ and excess of CO₂ were regarded as normal respiratory stimuli operating solely at the respiratory center, and the changes in pulmonary ventilation of such chemical origin appeared to harmonize with changes in acidity of the respiratory center (Gesell, 1925, 1929). But when reflexogenic chemical control (Heymans, Bouckaert and Dautrebande, 1930) as well as centrogenic control of breathing was established new problems developed. Not only was it desirable to know the relative parts played by centrogenic and reflexogenic control, and the response of the center and of the chemoreceptor to O₂ lack and CO₂ excess, but it was of equal interest to determine the interaction of the central and peripheral mechanisms. Our present experiments bear on these fundamental issues and we believe offer a simple reconciliation of facts with the acid mechanism of control.

METHOD. Our method was relatively simple. It consisted essentially of temporary bilateral blocking and deblocking of Hering's nerve during normal and modified breathing. The vagus nerves were sectioned to permanently eliminate those chemoreceptor signals arising in the aortic bodies and to abolish interfering pressure reflexes arising in the aortic arch. Hering nerve block, therefore, prevented all known remaining chemoreceptive signals from reaching the center and thus revealed breathing of purely centrogenic origin. Deblocking returned the reflexogenic component.

The cold blocks were made of copper, shaped to fit neatly into the region of the nerve after removal of the larynx. They were chilled and warmed with rapidly circulating alcohol. Temperature changes between 37°C and -3°C required 30 seconds. The moment of blocking and deblocking was signaled when the temperature reached 0°C and 30°C respectively.

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In preliminary experiments it was found that temporary Hering nerve block during eupnea might produce one of three effects,—increased breathing, decreased breathing, or no observable change. Such variability of results, noted by others as well (see Stella, 1935), is readily explained by the simultaneous elimination of two sets of signals ascending Hering's nerve: a, excitatory signals coming from actively discharging chemoreceptors of the carotid bodies, and b, inhibitory signals coming from stretched endings of the carotid sinuses. Should the inhibitory action of the carotid sinus be greater than the excitatory action of the carotid body an increased volume of breathing would be expected to occur during nerve block. On the other hand, should the excitatory action of the carotid body be greater than the inhibitory action of the carotid sinus decreased breathing would occur. Should both actions be equal there would be no change in breathing at all.

The correctness of these assumptions was confirmed by further orientation experiments in which blood pressure changes were automatically compensated at relatively low pressure levels or in which the carotid sinuses were collapsed. Under these circumstances block never produced an increase of breathing. There was either a diminution or no effect at all. Each sinus was, therefore, routinely collapsed.\(^3\)

Our observations were made exclusively on dogs (anesthetized with morphine (3.5 mgm/kilo) and chloralose (100 mgm/kilo)) under the following conditions:

1. During hypocapnia produced by excessive artificial ventilation with a room air mixture.
2. During acute hypercapnia produced by the administration of 10 and 15 per cent CO\(_2\) mixtures in 65 per cent O\(_2\).
3. During progressive hypercapnia produced by rebreathing a small volume of a high O\(_2\) mixture without reabsorbing the exhaled CO\(_2\).
4. During acute O\(_2\) lack of graded intensities produced by breathing varying O\(_2\) mixtures in N\(_2\) (40 to 6 per cent O\(_2\) in N\(_2\)).

Centrogenic and reflexogenic breathing in the eupneic range of chemical

\(^3\)The sinuses were relieved of their normal distention by tying one ligature around the common carotid artery approximately an inch below the sinus, a second around the internal carotid just distal to the sinus and a third around the external carotid above and as close to the sinus as possible (Gollwitzer-Meier, 1934) and then puncturing the common carotid peripheral to ligature 1. As Winder (1933) and Winder, Bernthal and Weeks (1938) point out, most effective anastomoses act to preserve a uniform flow of blood through the carotid body on occluding the common carotid artery. A concomitant rise in systemic pressure from elimination of the sino depressor reflex acting through the circle of Willis would tend to maintain a uniform head of pressure in the occipital artery supplying the carotid body. In that event our results would give a fairly reliable indication of the relation rôle of the chemoreceptors during eupnea.
stimulation. The capacity of the center and chemoreceptor to respond to the major respiratory stimuli (i.e., O₂ lack or CO₂ excess) is now accepted as fact. (For references see Heymans and Bouckaert, 1939; Gesell, 1939; and Schmidt and Comroe, 1940.) The similarity of the respiratory tracing during CO₂ administration, before and after chemoreceptive denervation, leaves no doubt of the capacity of the center to respond to chemical changes occurring within itself. The smallness or the absence of response to O₂ deficiency after chemoreceptive denervation shows the effectiveness of reflexogenic breathing. Despite the general agreement on this point considerable discussion still remains regarding the relative effectiveness of CO₂ excess and O₂ deficiency at the center and chemoreceptor respectively. Heymans and his associates (1939) insist on the predominating rôle of the carotid body, for CO₂ as well as O₂ regulation. This view was supported by the intense hyperpnea which they and others produced by a localized hypercapnia in the vascularly isolated carotid body. They pointed to the significant observation that this hyperpnea persisted despite an undoubted overventilation and an hypocapnic condition of the respiratory center. Comroe and Schmidt (1938), Schmidt and Comroe (1940) and Schmidt, Dumke and Dripps (1939), however, arrive at opposite results and conclude 1, that the vascularly isolated carotid body exhibits a low reactivity to changes of arterial carbon dioxide and oxygen; 2, that denervation of the carotid and aortic bodies produces no uniform effect upon alveolar carbon dioxide and, therefore, has no important effect upon eupneic breathing, and 3, that denervation neither retards nor diminishes the respiratory response to carbon dioxide. In their opinion “Carotid body reflexes constitute an accessory mechanism, brought into action by emergencies such as foreign chemicals, anoxemia, and unusually great increases in the CO₂ tension of the blood, rather than an essential part of the normal respiratory regulating system; the control of breathing under ordinary conditions is accomplished entirely by the direct effects of chemical stimuli (mainly CO₂) upon the cells of the center.” The denervation experiments of von Euler and Liljestrand (1936) differ in turn from those of Schmidt and Comroe. They found an increased alveolar CO₂ pressure after denervation during eupnea and interpreted this change as a sign of diminished breathing. Bernthal and Weeks (1939) found that breathing and vasomotor activity were reduced when the carotid bodies were cooled. Bogue and Stella (1935), Samaan and Stella (1935) and von Euler, Liljestrand and Zotterman (1939) found low CO₂ thresholds for activation of the carotid body and Bernthal (1938) found a reaction to small changes in carbon dioxide pressures. These results must be interpreted to mean that the center and the chemoreceptors participate jointly in the control of eupneic breathing and that a higher intensity of chemical stimulation
is required to drive the respiratory machine when the chemoceptors are out of function. Our own orientation experiments already cited indicate the same for at least a portion of the animals.

The central response to oxygen deficiency is either missing or decidedly diminished when tested under anesthesia (see reviews of Heymans and Bouckaert, 1939; Gesell, 1939; Schmidt and Comroe, 1940) and, therefore, must be of little practical value to the animal. Reflexogenic breathing is without doubt the important component under such conditions. Only in the absence of anesthesia is central hyperpnea said to approach hyperpnea in the intact animal, (Dautrebande, 1939) a finding denied by Bouckaert, Heymans and Samaan (1938). While Schmidt and Comroe (1938) find a relatively high threshold for anoxemia in the carotid body preparations, Bernthal (1938) and von Euler, Liljestrand and Zotterman (1939) find the threshold within the eupneic range of oxygen pressure.

Our methods under conditions 1, (hypocapnia from overventilation) yield further information on the relative effectiveness of centrogenic and reflexogenic breathing during eupnea with a slightly different procedure. Dogs were connected with rebreathing tanks containing room air. Respiratory stimulation was then diminished by artificial overventilation of the lungs, sufficient to reduce or stop natural breathing after artificial ventilation was ended. As soon as standard conditions yielding a dependably uniform series of apneas or subnormal respiration had been established, Hering’s nerves were blocked at the end of every second period of artificial ventilation. They were deblocked after natural breathing had returned. In the first of the two experiments used to illustrate our results, the respiratory tracing is seen to begin in eupnea and was presently followed by two minutes of artificial ventilation (see upper record). As indicated by the horizontal bar, nerve block began about one minute before the end of artificial ventilation and deblocking occurred shortly after the end of apnea. Whenever the chemoceptor signals were blocked in this experiment nearly one minute was required to rebuild a stimulus strong enough to interrupt the apnea produced by overventilation. But when the centrogenic and reflexogenic components were allowed to complement each other, breathing started immediately after cessation of ventilation. In the second experiment, in which overventilation was more effective (see records 2 and 3 of fig. 1) the duration of apnea was increased threefold whenever Hering’s nerves were blocked. This was interpreted to mean that the threshold stimulus required to reinitiate breathing after the production of apnea is lower for the intact respiratory mechanism than for the center alone, working without the aid of the chemoceptor signals.

It seems most significant that the rôle of the chemoceptors should be so strikingly revealed in the duration of apnea when their influence upon the depth of eupneic breathing is disproportionately less (see the effects of
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(blocking and de-blocking in the lower record). For that reason, the shortening of apnea might readily be interpreted as a different phenomenon from that of the tonic stimulation of the center. But if alveolar oxygen pressures fell more precipitously than carbon dioxide pressures rose during apnea, it is probable that breathing was re-initiated at a moment when both oxygen and carbon dioxide pressures were below eupneic levels, as happened in Haldane's experiments on man (1922). Oxygen lack, thereby, becomes the logical initiator of breathing in our experiments on the dog as well as in those on man. But in reaching this conclusion it is essential to remember that the effects of oxygen and carbon dioxide cannot possibly be separated if eH is the common stimulus to both. Lack of oxygen which leads to lactic acid formation must of necessity decrease the buffer base and increase the effectiveness of the prevailing carbon dioxide pressures. Theory, therefore, demands that the sub-eupneic carbon dioxide pressures at the moment of re-initiation of breathing contribute towards the stimulation of oxygen lack. Haldane's belief that lack of oxygen in some way increases the excitability of the center to carbon
dioxide agrees with this conception. This reasoning implies great responsibility of the chemoreceptors as tonic controllers of oxygen pressures within the normal range of physiological stimulation.

Hypercapnia. The effects of high concentrations of carbon dioxide before and after deafferentation of the carotid and aortic bodies have already been described. The fact that only one comparison is possible upon a single animal makes a quantitative analysis of the relative importance of centrogenic and reflexogenic breathing difficult. This disadvantage is overcome in our experiments. Dogs were connected, as usual, with rebreathing tanks containing high carbon dioxide mixtures (10 to 15 per cent CO₂ in 65 per cent O₂ in N₂) and after hyperpnea had been well established Hering’s nerves were alternately blocked and deblocked. The nerves remained unmolessted in blocking position during comparative observations which eliminated the possibility of mechanical disturbance. Though the continuity of recording permitted a detection of the smallest changes in pulmonary ventilation, at no time did we notice a change in either the depth or frequency of the hyperpnea on nerve block. Subsequent tests with low O₂ or cyanide showed that the nerves must have been in good condition. Whatever the interpretation of our results may be, we see for the moment that the findings are not in complete accord with a predominant rôle ascribed to the chemoreceptors in CO₂ control by Heymans. On the other hand if 10 or 15 per cent CO₂ in the inspired air can be regarded as an “emergency” they are in no better agreement with the position of Schmidt and Comroe whose schematic representation of centrogenic and reflexogenic breathing shows a powerful peripheral stimulation at high CO₂ pressures (1940).

This lack of reflexogenic breathing at high CO₂ pressures is in accord with the general evidence from many groups of experimentes mentioned above on hypercapnia, before and after denervation. It is puzzling in face of the common findings that local carotid body activity actually does increase with increasing CO₂ pressures as is so very clearly indicated by the increased breathing produced by localized hypercapnia and by the linear relation of frequency of chemoceptive impulses to CO₂ pressures, ranging up to 14 per cent in the inspired air (von Euler, Liljestrand and Zotterman, 1939). Could it be that a generalized hypercapnia abolished in some way the central action of the signals which CO₂ set up in the periphery? And if this were true, at what pressures does the reflexogenic component fall out? These questions were studied by administering a 65 per cent O₂ mixture in N₂ with the aid of a rebreathing tank and allowing a rapid accumulation of the expired CO₂ in a limited volume of gas. Hering’s nerves were blocked and deblocked and gaseous samples extracted from the tanks at appropriate intervals. Reference to figure 2 reveals the type of results obtained. It will be seen at once that breathing was
reduced by nerve block at the lower CO₂ pressures (expressed in per cent of CO₂ in the inspired O₂ mixtures) but not at the higher pressures and that the effect of blocking was no longer noticeable when the CO₂ in the inspired air had increased to approximately 5 to 6 per cent. We have, therefore, arrived at a rather paradoxical conclusion regarding the rôle of the carotid bodies. As physiological controllers of CO₂ pressures they are least effective when subjected to powerful stimulation and most effective when subjected to weak stimulation.

An explanation of the vanishing reflexogenic component was suggested by the earlier experiments of Gesell and Moyer (1935) in which hypercapnia was found to reduce or abolish respiratory reflexes, such as retardation and acceleration of breathing produced by central stimulation of the vagus and saphenous nerves respectively. Does carbon dioxide also abolish the central action of the very signals which it sets up in the carotid bodies? We believe it does.

![Image](image-url)

**Fig. 2.** Effects of blocking chemoreceptor signals on pulmonary ventilation during progressively increasing hypercapnia.

Though our findings are incompatible with a predominant rôle ascribed to the carotid bodies by Heymans when carbon dioxide pressures are high they agree better with his views when the pressures are low. They fail, however, to harmonize with the views of Schmidt and Comroe at either high or low carbon dioxide pressures. According to their statement and curves (1940) they “actually found” an increasing reflexogenic component which at high carbon dioxide pressures was greater than the centrogenic component. So far as we are aware no confirmation of such results exists in the literature and our results indicate a progressively decreasing reflexogenic component replaced by an increasing centrogenic component as carbon dioxide pressure increases. The curves of Schmidt and Comroe were probably compiled from data taken during localized carotid body hypercapnia without consideration of the functioning of the respiratory mechanism as a whole.

**Oxygen lack.** Typical effects of O₂ lack on centrogenic and reflexogenic breathing are shown in the nerve block tests of figure 3 in which a dog successively breathed five mixtures of oxygen in nitrogen (40.0 per cent, 19.7 per cent, 16.6 per cent, 12.5 per cent and 8.6 per cent). The tests
began with a high oxygen mixture and showed the diminished breathing which so often occurred during Hering nerve block when the arterial blood was supposedly saturated with oxygen. Granting an absence of ischemia in the carotid bodies, the centrogenic breathing which remained and the reflexogenic breathing which was removed by block were probably the result of the stimulating action of CO₂. The effects of oxygen

![Figure 3](http://ajplegacy.physiology.org/)

Fig. 3. Effects of withdrawing reflexogenic support during progressively increasing hypoxia.

lack were as readily demonstrated when the oxygen of the inspired air was lowered. It will be seen that when the dog was simply switched from the 40 per cent O₂ mixture to the 19.7 per cent O₂ mixture, breathing was augmented. This in itself is indicative of a sensitive response of the respiratory mechanism to a slight reduction of arterial oxygen pressure for hyperventilation of this kind is always associated with a marked drop in carbon dioxide pressures. That the respiratory stimulation actually
occurred in the chemoceptor is seen in the large reduction of breathing which occurred when the chemoceptor signals were blocked (compare the results of the first and second blocks). Since the centrogenic breathing in the second observation was less than in the first, reflexogenic breathing must have been increased by the oxygen deficiency. The hyperpnea, which prevailed before nerve block, occurred despite a diminished central support.

This diminished central support became more marked as rebreathing continued and oxygen want increased. In the experiment under consideration it reached its limits in the prolonged apnea when the oxygen in the inspired air stood at 8.6 per cent. Such diminishing central support is a most significant phenomenon in relation to the chemical mechanism of respiratory control. It is conceivably due to two causes. One is the ultimate paralyzing action of oxygen lack. The other is the alkalinizing effects related to increased elimination of CO$_2$ from increased ventilation of the lungs and blood, increased volume flow of blood, and increased CO$_2$ carrying capacity and pH of the blood. As the alkalinizing influence of oxygen deficiency increases, either from an increasing ventilation or from a long continuance of hyperpnea, centrogenic stimulation would decrease in proportion. Therefore, successive Hering nerve blocks would be expected to reveal a decreasing magnitude of centrogenic breathing. This view was expressed some years ago (Gesell, Krueger, Nicholson, Brassfield and Pelecovich, 1932) on the basis of direct measurement of the amount of CO$_2$ eliminated and of the increase of the respiratory quotient during anoxemia.

An acid interpretation of the diminishing centrogenic breathing during oxygen deficiency is of course tenable only on the assumption that the so-called central "paralysis" is not an important factor. The sudden increase of pulmonary ventilation occurring at the moment of deblocking of Hering's nerves indicated a fitness of the centers for they responded immediately to the burst of signals released from the carotid bodies. The sudden and pronounced acceleration of breathing produced by deblocking of the vagus nerves (not illustrated) showed a similar fitness of the centers to react to proprioceptive signals. We are, therefore, inclined to believe that the apneas noted at low oxygen pressures were not paralytic, that the hyperpneas were reflexogenic and occurred despite a condition of central hypocapnic apnea. In this connection it is well to recall that hyperpnea and central acapnia are not incompatible. As Gesell and Moyer (1935) showed, a center made apneic by the injection of Na$_2$CO$_3$ is more highly responsive to central stimulation of the saphenous nerve.

But the prolonged apnea (at 8.6 per cent O$_2$) was eventually broken in the absence of any known change of peripheral stimuli. Control experiments showed that the renewed breathing cannot be alternately explained
by an accidental incomplete block permitting conduction of chemoceptive
signals at the peak of a heightened carotid body discharge, because the
same type of renewed breathing occurred after bilateral distal section
of the sinus nerves during the apnea of cold block. Provided unknown
reflexogenic stimulation from sources other than the carotid and aortic
bodies can be disregarded, the renewed breathing must be considered
of centrogenic origin. For the present, the nature of the stimulus reini-
tiating breathing can only be conjectured by a process of elimination.
Had the apnea been caused entirely by a paralyzing action, that action
would have been expected to increase and to have terminated in death.
Had the stimulation of breathing been one of direct action of O₂ lack, there
should have been supernormal rather than subnormal centrogenic breath-
ing when cold block took effect. But if the apnea was due to acapnia,
time was essential for a reaccumulation of acid and a rebuilding of the
central stimulus. We suggest that this occurred partly as a result of the
high anaerobic acid metabolism in the brain and partly as an effect of the
reaccumulating acid in the blood.

For completeness it must be mentioned that apneas frequently did
terminate in death without outward signs of respiratory stimulation. It
is, therefore, reasonable to assume that depression capable of completely
counteracting stimulation can and does occur. Signs of such depression
are visible in the falling blood pressure during the last two nerve blocks of
figure 3.

DISCUSSION. The summation of centrogenic and reflexogenic breathing.
One point seems clear from the experimental findings of other laboratories,
and those which we have described. Eupneic breathing in anesthetized
animals is a sum of the two respiratory components—centrogenic breathing
plus reflexogenic breathing. But, so far as we are aware, there has been
no attempt to establish a mechanism by which they are combined.
Some common denominator must, therefore, be found to account for
the complementary action between centrogenic and reflexogenic breathing.
The inherent forces arising in the neuron proper and those forces arising
from the impingement of signals at the synapse must in some way be
combined.

The electrotonic theory of nerve cell discharge and synaptic drive (Gesell,
1939, 1940) lends itself to such speculation and offers a relatively simple
schema. (See figs. 4 and 5.) Due to a steep metabolic gradient between
the dendrites and the axon hillock, estimated as 10 to 1, (Holmes, 1932)
an electrotonic current is conceived to flow within the cell from the den-
drites to the axon hillock. Because of the high lineal resistance of the
neuraxon, the current is deflected at the axon hillock where it leaves the
cell body, to return in the immediate external environment, back to the
dendrites. On leaving the axon hillock, it is thought to fire this structure
at a frequency proportional to the intensity of the electronic current. Metabolic physico-chemical fluctuations, such as result from changes in $\text{O}_2$ and $\text{CO}_2$, are thought in turn to modify the intensity of this current. Changing intensity of and changing response to the electrotonic current would thus represent our so-called "centrogenic component" of respiratory control.

Each of these cells (probably the reticular cells of the medulla) is covered with a dense layer of hundreds or thousands of synapses, delivering signals from all quarters, including the chemoreceptors. Each signal, regardless of its origin, is thought to produce a local negativity at its point of impingement and thereby increase the potential drop of the receiving neuron.\textsuperscript{4} The intensity of the reflexogenic drive (or the reflexogenic component of breathing) is accordingly determined by the sum total of signals arriving per unit of time. Complementary action of the centrogenic and reflexogenic components thus becomes a simple matter of the addition or subtraction of one current to or from the other. The interaction of this dual mechanism of nerve cell activation allows not only a change in the sum total of centrogenic and reflexogenic components but gross differences in the relative proportions. At one extreme in which

\textsuperscript{4} This hypothetical negativity may conceivably arise from either a specific activation or from an increased dendritic metabolism, initiated by a local electrical discharge or a chemical deposition at the synapse. Both could increase the metabolic or potential gradient and thereby the nerve cell discharge. The fact that breathing diminished gradually during the course of a continued Hering nerve block (see the lower record of fig. 1 and all of the records of fig. 3) suggests that synaptic effects long outlast the moment of their initiation. This might be regarded as a new interpretation of the general phenomenon of "after discharge." More specifically the results suggest that chemoreceptor signals help to maintain the respiratory neurons at a higher degree of reactivity.
central apnea is produced by excessive pulmonary ventilation during oxygen deficiency, the central neurons would still retain their ability to respond to increasing reflexogenic electrotonic current even though the centrogenic electrotonic current is weakening. And this condition can shift to the other extreme of hypercapnia in which centrogenic breathing continues to increase long after reflexogenic breathing is abolished (see fig. 6).

The existence of two mechanisms of respiratory control, one central and the other peripheral, carries most interesting implications. Since both mechanisms seem to react to the common stimulus of $\text{pH}$, both may be expected to participate in the control of $\text{CO}_2$ and $\text{O}_2$ pressures in the body. Nevertheless hyperpnea, caused either by oxygen scarcity, or carbon dioxide excess, tends to become exclusively reflexogenic or centrogenic. In other words, one mechanism gains the upper hand of the other and maintains primary control. This paradoxical situation, we believe, is explainable with the aid of the reaction theory. During $\text{O}_2$ lack the chemoceptors by virtue of a disproportionately high reactivity to changes in their own acid metabolism (Winder, 1937; Bernthal, 1938; Bernthal and Weeks, 1939; Winder, Bernthal and Weeks, 1938; von Euler, Liljestrand and Zotterman, 1939) gain the advantage and give increasing predominance to reflexogenic breathing as scarcity of oxygen grows. As
a result of increasing ventilation and of the other alkalinizing influences, centrogenic breathing is diminished. We have attempted to indicate these trends of centrogenic and reflexogenic breathing under theoretically ideal conditions in figure 6 in which so called central paralysis is missing. Both types of breathing are plotted on the ordinates against oxygen percentage of the inspired air on the abscissas. The solid black area $ECD$ represents the centrogenic component, rapidly diminishing as a result of increasing hypocapnia, and the cross hatched area $ABFD'DC$, the more rapidly increasing reflexogenic component, possibly potentiated by synaptic alkalinization. The stippled area $DFD'$ indicates diminution of the subliminal centrogenic component.

According to this conception the chemoceptors are not fully protected against increasing acidity by the increased ventilation which they set up. They alone withstand increased acidity and thus guard the more delicate central nervous system. This will explain why it was unreasonable to expect an increased amount of lactic acid in the circulating blood of an individual exposed to low $O_2$ pressures. The amount of lactic acid contributed to the circulating blood by approximately one millionth of the body could not possibly be detected.

The diametrically opposite changes in centrogenic and reflexogenic breathing during progressive hypercapnia must have some deep rooted significance (see two lower schema of fig. 6). $GJ$ represents the volume of eupneic breathing of which $KJ$ is the centrogenic fraction produced by the stimulating action of $CO_2$ and $KG$ the reflexogenic fraction. In agreement with the linear relation of the discharge frequency of the carotid body to the prevailing $CO_2$ pressures (von Euler, Liljestrand and Zotterman) we may assume an hypothetical reflexogenic breathing increasing along the gradient $MN$ of the lower graph. The area $MNOP$ would accordingly represent the theoretical increase of reflexogenic breathing with increasing hypercapnia. The actual amount of reflexogenic breathing, however, is represented by area $MQP$ or $GHK$ above. It is, therefore, proposed that most of the reflexogenic component $PQNO$ is obliterated by a central action of $CO_2$, possibly by a blocking action at the synapse. As this obliteration progresses, direct central stimulation replaces that lost from the chemoceptors. Whether $KI$ (centrogenic increase) runs more steeply than $MN$ (reflexogenic increase) has not been determined. These graphs are of course schematic. However, one cannot avoid the question at this point, why teleologically the center takes complete control against $CO_2$ excesses when the chemoceptors take complete responsibility during oxygen deficiencies. The evolutionary forces which were responsible for this unique arrangement can only be conjectured. The brain is well known to require a uniformly abundant supply of oxygen while on the other hand it tolerates high pressures of $CO_2$ with relative impunity.
Outlying protection against the development of central oxygen deficiency is, therefore, useful. On the other hand the weakening of respiratory reflexes by a general hypercapnia may have been the issue forcing the evolution of a centrogenic mechanism of control against CO₂ excesses. A flood of carbon dioxide liberated in combat might otherwise have put an end to pulmonary ventilation when it was needed most.

**SUMMARY AND CONCLUSIONS**

Repeated withdrawal of known chemo-reflex support to the respiratory center (bilateral reversible cold blocking of Hering’s nerve after double vagotomy and permanent sinus collapse in chloralosed dogs) during various respiratory states yielded data and conclusions as follows.

During eupneic breathing of atmospheric air or O₂ rich air, chemoceptive nerve block usually reduced the volume of pulmonary ventilation. The reduction was smaller with an O₂ rich mixture than with a mixture containing but slightly less O₂ than room air. Reasons were presented for concluding that both CO₂ and O₂ pressures prevailing during eupnea are sources of reflexogenic respiratory support.

Apnea produced by overventilation with room air was markedly prolonged by chemoceptive nerve block. This effect was much greater than the reduction of breathing by chemoceptive block during eupnea. It was concluded that the chemoceptors exert an important tonic stimulation of breathing and that they are particularly responsive to oxygen lack occurring at the end of apnea.

Repeated withdrawal of reflexogenic support during progressive hypercapnia caused a diminishing absolute reduction in breathing which disappeared at 5 to 6 per cent CO₂ in the inspired air. It was concluded that hyperpnea of high grade hypercapnia is purely centrogenic.

The peculiar absence of reflexogenic stimulation could not be explained by central paralysis, for pulmonary ventilation continued to increase with increasing CO₂ well above the 6 per cent level.

In view of the linear relation of chemoceptor discharge to CO₂ pressure, and of the progressively increasing centrogenic activity in these experiments, it is concluded that increasing CO₂ exerts an increasing central blocking action on the signals which it sets up in the chemoceptors.

Conversely, diminishing pressures are thought to diminish the central blocking action of CO₂ and, thereby, potentiate the signals arising in the chemoceptors. This relationship will explain the stimulating action of low CO₂ pressures obtaining during eupnea, and at the end of experimental apneas.

Repeated chemoceptive nerve blocks during progressively increasing hypoxic hyperpnea produced progressively increasing reduction of breathing, vigorous breathing being finally converted to apnea. It is
concluded that hyperpnea of high grade O₂ deficiency is purely reflexogenic.

In view of the abrupt resumption of hyperpnea on chemoceptive deblock and of the suddenly increased frequency of breathing on vagal deblock, it is concluded that central depression or paralysis was but a minor factor in the reduction of the centrogenic component and that progressive hypocapnea and alkalinization from several causes was a major factor in the diminishing centrogenic component. It is further proposed that the progressively increasing hypocapnia leads to a progressively increasing potentiation of the reflexogenic signals thereby assuring an increasing dominance of the reflexogenic component.

Prolonged apneas resulting from maintained withdrawal of chemoceptive support during hypoxic hyperpnea, frequently gave way to renewed breathing. This was attributed to reaccumulation within the center of acid derived from its own acid metabolism and to increasing acidemia.

Granting that a localized acidity of the chemoceptors is the stimulating influence producing a general alkalinization of the body during hypoxia, the basic physiological chemical control of breathing (acid excess and O₂ deficiency) is again broadly interpretable in terms of the reaction theory. Not only is the activity of the center and of the chemoceptors explained but the changing relations of centrogenic and reflexogenic breathing during varying intensities of hypercapnia and oxygen deficiency are accounted for as well.

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