THE INFLUENCE OF HYPERPNEA AND OF VARIATIONS OF O_2- AND CO_2-TENSION IN THE INSPIRED AIR UPON HEARING

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It is generally known that in no other branch of physiological research is it more difficult to apply the results obtained on animals to human physiology than it is in observations concerning the brain. For this reason attempts have been made in recent times to perform experiments on anthropoids. However, even in these animals the study of sensory functions and their dependence on certain parts of the brain is extremely difficult as soon as a finer analysis is desired, because sensory disturbances become evident to the experimenter only in an indirect way through alterations in the motor behavior. For these reasons it seems desirable to study the functions of the central nervous system in the human, as far as circumstances permit.

The natural way of approach is, of course, that of a study of the functions of the sense organs under conditions which influence the excitability of the central nervous system. By making use of a spinal irradiation induced by peripheral stimuli some deeper insight into spinal physiological processes has been gained in previous experiments dealing with cutaneous sensations (Gellhorn, 1931–33). The present series of investigations concerns an alteration of the excitability of the cortex in humans and the effects brought about on various sensations, which were studied quantitatively. The factors to be investigated in this paper are variations in the O_2- CO_2-tension in the respiratory air, and thus indirectly in the blood and tissues. They were chosen not only because of the generally recognized importance of O_2 and CO_2 for the excitability of any living substance in general and of the nervous system in particular but also because of the rapidity of the gas exchange which restores normal conditions in the blood almost immediately. One of these factors (O_2-lack) has been frequently investigated for theoretical and practical reasons (aviation). However, even here a quantitative study in regard to sensations is only in the beginning. The relevant papers will be discussed later.

METHOD. The hearing experiments were conducted in a nearly sound-

proof room with a 2A Western Electric audiometer with which the threshold for hearing can be determined for eight different frequencies. The intensity is expressed in sensation units in percentages of the average hearing threshold for normal individuals. Ninety-six experiments were performed on six subjects who, after having been trained for several weeks, gave an almost absolute constancy of the hearing threshold. The procedure was as follows: The subject was connected with an audiometer and just prior to the release of the sound, a signal was given to start. Then followed sounds lasting from one to two seconds each in irregular intervals, starting with a sound twenty per cent stronger than that corresponding to the threshold and then gradually decreasing its intensity until the threshold was reached. The latter is defined by the correct response of the subject in three successive trials. The determinations were made in intervals of from 1 and 5 minutes since it had been found that readings taken in 1-minute intervals may cause fatigue particularly in experiments which extend over more than 40 to 60 minutes. The gas mixtures were prepared in several Douglas bags. The gas analysis was made with a Newcomer-Haldane apparatus.

RESULTS. *Oxygen-lack.* The first group of experiments is concerned with the influence of O_2-lack on hearing. Thirty-three experiments were made with O_2 concentrations varying from 7.5 to 15.8 per cent. The duration of the O_2-lack period varied between 8 and 30 minutes.

Oxygen-air mixtures of from 9 to 12 per cent O_2 showed a very marked effect. There was a gradual decrease in hearing, which began more or less rapidly, depending on the individual sensitivity of the experimental subject, the O_2-concentration used, and the duration of the O_2-lack period. In some cases the effects were immediately reversible after readmission of air; in others the hearing acuity remained diminished for various lengths of time.

Two experiments performed on the same experimental subject on different days are reproduced in figure 1. In both experiments the same concentration of oxygen was inhaled (10.4 per cent), but the duration of the O_2-lack period varied considerably. With the increasing duration the effect on hearing was intensified and the recovery delayed. In contrast to these findings it must be stated that the respiration returned to normal almost immediately after the readministration of air.

A series of experiments was then conducted to determine whether the slow recovery observed after a long period of O_2-lack could be hastened by the administration of 50 to 60 per cent O_2. The experiment reproduced in table 1 shows that breathing of such an O_2-rich mixture for more than 10 minutes does not appreciably alter the hearing threshold, a fact which, as will be shown later, seems to point definitely to a prolonged cellular change as a result of O_2-lack.

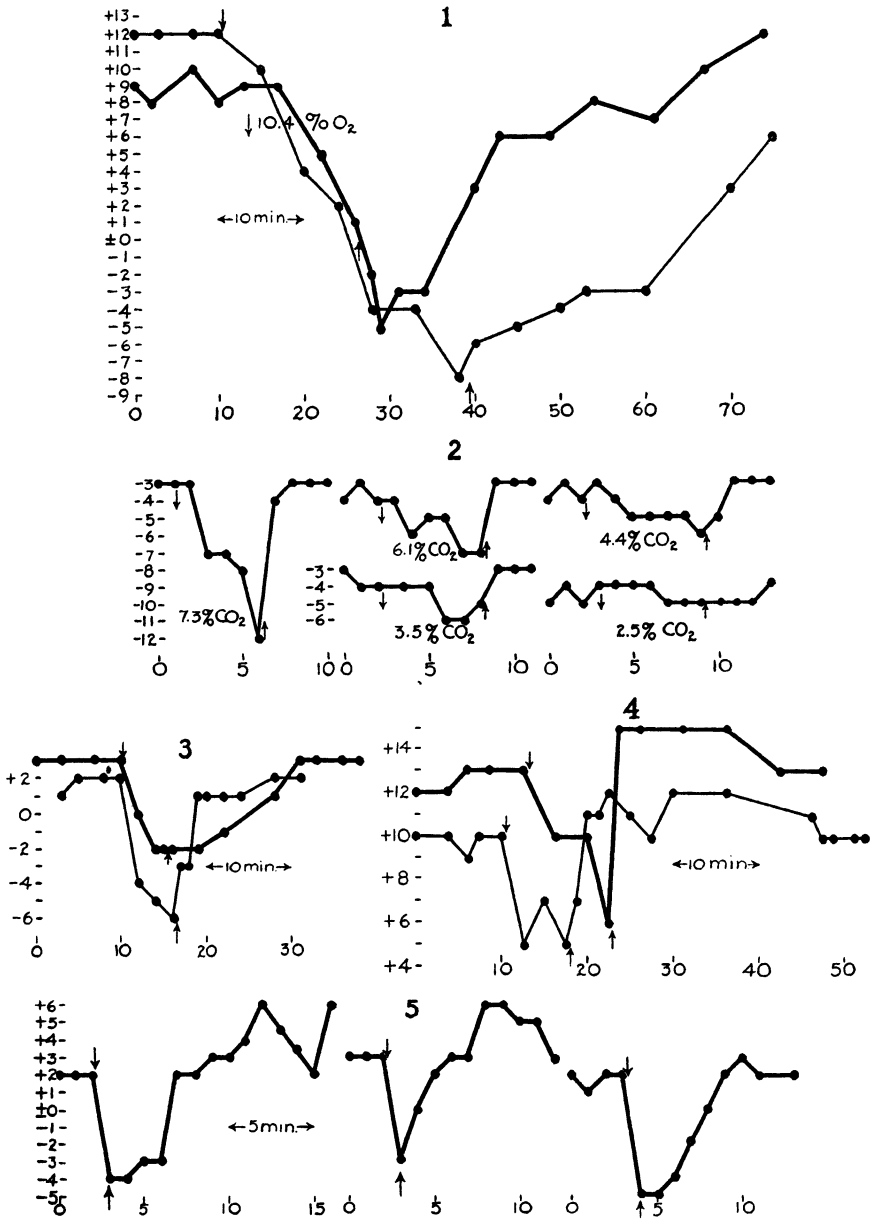

Fig. 1. In all figures: ordinate = auditory threshold in sensation units in percentage of the average human threshold for hearing. Abscissa = time in minutes. Between the arrows administration of N_2-air mixtures: In both experiments 10.4 per cent O_2.

Fig. 2. Between the arrows CO_2 as indicated on the graph. All experiments were done on the same person.

Fig. 3. Heavy line: 5.6 per cent CO_2. Thin line: 6.3 per cent CO_2.

Fig. 4. Heavy line: 7.05 per cent CO_2. Thin line: 6.9 per cent CO_2.

Fig. 5. Three experiments with hyperpnea (between the arrows) of 2 minutes each.

Oxygen in a concentration of 12 to 15 per cent inhaled for about 10 to 20 minutes sometimes produced a slight increase in hearing during the first few minutes, followed by a gradual decrease. The effects were slight but quite distinct, in view of the great constancy of the controls obtained before and after the O_2-lack period. They were readily reversible upon readministration of air. That we are here concerned with the effect of O_2-lack and not with other factors introduced by the breathing of a gas

TABLE 1

I. SUBJ.: ST. 5/21/34. SOUND: C1024

Time	Audiometer reading
A. Control period (air)	
minutes	
0	+8
2	+8
3	+9
6	+8
7	+9
B. Inhalation of 10.0 per cent O_2 for 30 minutes	
8	+6
14	+3
18	+3
24	+1
28	−2
30	−3
C. Control period (air) after O_2-lack	
2	−2
6	−1
11	−3
21	−2
29	+2
D. Inhalation of 50 per cent O_2 for 17 minutes	
minutes	
11	+3!!
17	+6
E. Control period (air)	
7	+6
12	+6
17	+4*
74	+7
75	+8
77	+7

from a Douglas bag was shown by the control experiments in which the threshold was not altered when ordinary air was inhaled.

The typical course in all experiments described so far was that during the period of O_2-lack hearing was gradually decreased and was restored by the inhalation of air with a rapidity depending on the concentration of O_2 and the duration of the O_2-lack period. It must, however, be mentioned that in some of our experiments an improvement in hearing above the ordinary threshold was noticed during the first minutes when air was again inhaled. The improvement in hearing did not amount to more than

two or three points ordinarily, but in a few experiments quite excessive improvements lasting for several minutes were observed.

Experiments with CO_2. Thirty-seven experiments with CO_2 varying from 2 to 8.4 per cent (5–22 minutes' duration of exposure) were performed. Figure 2 shows the records of five experiments performed on the same individual with varying CO_2 concentrations. It is evident that 2.5 per cent CO_2 is without effect on the hearing threshold and that the first slight effect is seen with 3.5 per cent CO_2. With increasing concentration the hearing becomes progressively less. The experiments with other subjects gave very similar results, the threshold being around 4 per cent for an experiment lasting on an average about 6 to 10 minutes. Obviously, the mechanism involved in hearing is far less sensitive to CO_2 than the respiratory mechanism, since the breathing of 2.5 per cent CO_2 shows considerable change in the pneumographic record. Figure 3 shows that in CO_2 concentrations of about 6 per cent the decrease in hearing may persist for several minutes after readmission of air but it may be said that the recovery was in all experiments considerably faster than in experiments with O_2 of about 10 per cent, and of similar duration. Figure 4 illustrates not only the decrease in hearing resulting from the inhalation of 7 per cent CO_2 but also a very considerable improvement in hearing immediately after the readministration of air. As can be seen from the graphs, this improvement lasts over a considerable length of time and is then gradually replaced by the ordinary hearing threshold.

Hyperpnea and hearing. Twenty-six experiments were performed in which the influence of hyperpnea on hearing was studied. The experimental subjects inhaled as deeply as possible for 3 to 6 minutes according to the rhythm of a metronome. In some experiments the frequency was 35 per minute, in others considerably higher, up to 90 per minute. The results were consistent throughout the whole series of experiments and showed that immediately following the period of hyperpnea hearing was greatly decreased. Readings were not taken during the period of hyperpnea because of the impossibility of concentrating and breathing violently at the same time. Figure 5 shows several typical experiments. It indicates that a decrease in hearing may last as long as 10 minutes after such a period of hyperpnea. Therefore, it is present not only during the apnea but also at a time at which breathing has become perfectly normal. Whereas the third curve in figure 5 may be taken as a representative of experiments which showed a decrease in hearing after hyperpnea and a gradual recovery afterwards to a normal hearing threshold, the other two experiments indicate that after the threshold has become normal it may be followed by a period of hyperacusis.

Most experiments were carried out with C 1024 because we found a greater constancy of the hearing threshold for this than for any other tone.

However, when tones between C 128 and C 4096 were used similar results were obtained.

DISCUSSION. Summarizing these experiments, it may be said that under conditions of O_2-lack, CO_2-excess, and CO_2-lack, hearing is gradually decreased depending on the duration of these periods and the degree of change involved. After restoration of normal conditions hearing returns to the normal threshold. In some cases prior to this a period of hyperacusis may be observed in all three conditions. The changes induced by CO_2 are more readily reversible than those with O_2-lack and hyperpnea. In experiments with O_2-lack changes in threshold (decrease in hearing) were observed as long as two hours after the experiment.

The question arises as to the nature of the decrease in hearing observed in all three groups of experiments. There is a possibility that diminished hearing is due not to a diminished excitability of the fundamental processes involved in hearing but to an inability of the experimental subject to "concentrate the attention." Unfortunately, we do not know what attention is nor what physiological processes are called into play when we direct our attention to a sensation and perception. We only know that this peculiar process makes the sensations more vivid and distinct. It is, therefore, at least theoretically possible that a decrease in "attention" gives results similar to those obtained when the excitability is decreased. We believe, however, that this interpretation of our results is ruled out for the following reasons: First, the long training of the experimental subjects which made it highly improbable that the diminution in hearing was obtained because they were unable to concentrate their attention on the experiment; second, it was found that not infrequently at the end of the O_2-lack or hyperpnea period a period of improved hearing was obtained. This certainly could not have been observed with a diminished attention; third, measurement of attention (Bourdon test), to be reported elsewhere, showed only slight disturbances in attention which never persisted after air had been readmitted.

Instead of assuming that alterations in attention are responsible for the effects on hearing, an assumption which is highly improbable because of the great constancy of the controls before and after the experiment, it seems more reasonable to interpret the variations as being due to changes in the nervous mechanism involved in the sensation itself. Such an interpretation seems still more justified since our observations on the effect of O_2-lack are paralleled by Schubert's observations (1934) on the motor effect of O_2-lack in animals. He found that under the influence of a decreased oxygen tension in the air animals showed a decreased motor excitability leading to coma. After readmission of air an increased motor excitability was observed, leading even to convulsions. In view of these facts, we believe that the effects of O_2-lack and variations in the CO_2 tension lead to alterations in the excitability of the fundamental nervous mechanism.

We may then ask: Are these changes due to alterations in the circulation, or are they of cellular origin? It is well known that the inhalation of CO_2 and hyperpnea results in changes in blood pressure. We found, however, that in experiments on healthy, young individuals changes in blood pressure during and following the exposure to O_2-lack and CO_2-excess, as well as during hyperpnea, were extremely small. The greatest changes were observed with CO_2 and amounted to about 10 mm. mercury (systolic blood pressure). The decrease in blood pressure during hyperpnea was practically negligible and not outside of the experimental error. These findings agree well with the measurements of Voit (1933) and Raab (1929). That small changes in blood pressure are not responsible for the effects on hearing is borne out by experiments in which a considerably greater increase in blood pressure was obtained after physical exercise (20–30 mm. Hg) without influencing the hearing threshold. Furthermore, it must be emphasized that not infrequently long after-effects on hearing were observed after hyperpnea and O_2-lack, although the blood pressure remained completely unchanged.

Whereas a change in blood pressure can be eliminated as a cause of the effects on hearing observed in our experiments, the vasomotor reactions due to changes in the O_2- and CO_2-tension of the blood require a more detailed consideration. Schmidt and Pierson (1934) and Schmidt (1934) have shown that these factors alter the blood supply of the medulla oblongata and of the hypothalamus. Furthermore, direct observations of the pial vessels by Cobb and Fremont-Smith (1931), Wolff and Lennox (1930) and Lennox and Gibbs (1932) lead to similar results. It must, therefore, be assumed that both O_2-lack and CO_2-excess produce vasodilatation and increased blood flow, whereas the reduction in CO_2-tension in hyperpnea is accompanied by a reduction in the blood supply of the brain. The reduction in hearing during O_2-lack occurs, of course, not because of the increased blood supply but in spite of it. Obviously the increased blood supply cannot fully compensate for the diminished O_2-tension and as a result, the O_2-supply of the brain is reduced, although to a lesser extent than was to be expected without the vasomotor adjustment. We, therefore, obtain a diminished excitability, particularly of the cortical elements involved in hearing, since they are more sensitive to O_2-lack than any other elements of the central nervous system (concerning the literature compare Gildea and Cobb, 1930).

The very marked persistence of the effects of O_2-lack on hearing is well in line with the observations of Gildea and Cobb following a temporary complete anoxia of the brain, and seems to point to the ganglion cells of the cortex as the site of the changes. This assumption is supported by histological studies of these authors, who found the most pronounced O_2-lack effects in lamina III and IV of the cortex. As far as our own

observations are concerned, the fact that the effects of O_2-lack on hearing are independent of the frequency of the sound used seems in the light of experiments of Pearcy (1929) to favor such an interpretation. So do those experiments in which 50 to 60 per cent O_2 was administered after a period of O_2-lack. The fact that even after a 5 or 10 minute period of inhalation of 50 per cent oxygen no appreciable change in threshold occurred, seems to indicate a cellular change which persists in spite of the complete oxygenation of the blood.

The decrease in hearing obtained under the influence of CO_2-excess is in agreement with other effects of CO_2 on the central nervous system. King, Garrey and Bryan (1932) have shown that the knee jerk is decreased in the intact animal. Obviously CO_2 acts simply on the basis of its acid properties since Fröhlich and Solé (1924) have found that by perfusion of the spinal cord with acid solutions reflex activity completely disappears.

The explanation of the reduction in hearing observed after hyperpnea seems to be more complex. We must here distinguish the effects of increased alkalinity on blood vessels and on neurons. The latter seem to show increased excitability due to increased conductivity (Broemser, 1925) and a shortening of the relatively refractory period (Strughold and Jörg, 1933). This leads to increased patellar reflexes in man and animals. On the other hand, Cobb and Schmidt and their co-workers found that hyperpnea leads to a decreased blood supply of the brain through vasoconstriction, which is not compensated for by the systemic blood pressure, since it remains either unchanged or drops slightly. The effects observed in our experiments are best understood by the not unreasonable assumption that the specific effects of decreased CO_2-tension in the blood are more than overcompensated by the vasoconstriction. We come, therefore, to the conclusion that the effects of hyperpnea on hearing are in the last analysis effects of O_2-lack.

In this respect observations of Cobb and Fremont-Smith (1931) in man are of great importance. They showed that, whereas CO_2-excess increases the pressure of the cerebro-spinal fluid, hyperpnea lowers it. In contrast to the quick restoration of the normal pressure level after readmission of air following the inhalation of CO_2, it was found that the pressure remained diminished for 7 minutes and more after hyperpnea was discontinued. This seems to indicate that the vasoconstriction caused by hyperpnea is only slowly reversible and accounts for the distinct after-effects of hyperpnea on hearing. It may, therefore, well be that all the effects of hyperpnea observed in our experiments can be explained fully on the basis of the vasomotor changes. It seems, however, not wise to make too sharp a distinction between the cellular effects of O_2-lack in our experiments with inhalation of low O_2-mixtures and the vasomotor effects of hyperpnea,

because it is to be expected that a sufficiently prolonged hyperpnea will result in cellular changes due to sustained vasoconstriction.

Comparing the results of our work with those of other investigators, it may be stated that Lewis (1918 and 1919) and Bagby (1921) were unable to observe any changes in hearing due to O_2-lack except immediately before collapse. The differences are probably due to the fact that these authors applied the tests in routine experiments, whereas our observations were performed on persons trained for several weeks or months prior to the main group of experiments described in this paper. Concerning CO_2-excess or CO_2-lack, no experimental work seems to have been reported in the literature except for some statements of Rosett (1924), who finds that during hyperpnea the sensitivity to pain and deep pressure was increased. But it is quite obvious, from his description, that this increased response on the part of the experimental subject was not due to a change in the excitability but to an alteration which concerned particularly "affective reactions" of the experimental subject. When weak stimuli were used a diminution in response (although without quantitative measurements) was observed by him.

The experiments of Brody and Dusser de Barenne (1932) on the excitability of the motor cortex show that it is difficult to obtain any effect with hyperventilation. On local application of strychnine, however, hyperventilation did produce increased excitability to electrical stimuli. Whether this effect is due to subcortical or cortical effects may be uncertain. In addition one must always take into account that the effect of hyperpnea on cortical excitability (motor or sensory) is due to the interaction of at least two factors: 1, the effect of increased OH-concentration causing increased excitability; 2, the depressing effect of O_2-lack due to vasoconstriction accompanying hyperpnea. The final results, therefore, may vary according to the special conditions and the quantitative reactivity of the tissue to these factors.

CONCLUSIONS

If air with oxygen content of about 10 per cent or less is inhaled for 10 to 30 minutes a decrease in the hearing threshold is observed which, dependent on the duration of the experiment, the concentration of the oxygen and the sensitivity of the experimental subject, may last up to several hours. CO_2 in concentrations of 4 to 8 per cent in air of normal O_2 content also causes a diminution in hearing which, however, is more quickly reversible. After a period of voluntary hyperpnea lasting from 3 to 6 minutes a considerable decrease in hearing is observed during the period of apnea and afterwards, until gradually the original threshold is obtained. In all three groups of experiments a supernormal phase may

temporarily be observed when normal air is readmitted. The changes in hearing seem to be due to chemical cellular alterations in the central nervous system itself.

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