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THE ACTION OF CERTAIN DRUGS ON RESPIRATION*

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The close affinity between physiology and pharmacology means that progress in one of these spheres often leads to advance in the other. In what follows an attempt is made to illustrate such interrelations in a special field and to show how the growth of our knowledge of the regulation of respiration during the past 25 years has enabled us to analyse more closely the action of different drugs on respiration. I hope I will be pardoned if I dwell mainly on studies in which I have myself been engaged.

Some New Facts

It may be useful first to recall some of the new physiological facts. The demonstration by Hering (1927) and others of the important role of the carotid sinus for the regulation of the arterial blood pressure raised the question whether the sinus is also in some way concerned with the regulation of respiration. Mainly thanks to Heymans and his collaborators (1930) it soon became evident that an increased pressure in the sinus may provoke inhibition and that a lowering of the pressure may stimulate respiration so long as the sinus nerves are intact, whereas denervation of the sinuses eliminates the effects. By this time it was known that a tonic influence is exercised from the sinus region on the blood pressure and the heart rate, this being proved by the rise in pressure and increase in heart rate after section of the sinus nerves. It seemed quite natural to assume that the effect of the pressure on respiration was analogous. A certain confirmation appeared to be afforded by observations that section of the depressor nerves, together with denervation of both sinuses, produced increased respiration.

The discovery made by J. F. and C. Heymans (1927) that asphyxial blood stimulates peripheral end-organs of the depressor nerves and thereby causes an increased activity of the respiratory centre, and that, similarly, acapnic blood induces diminution or suspension of breathing, made it highly desirable to investigate whether the carotid sinus could also be influenced by the chemical composition of the blood. The well-known experiments carried out by Heymans, Bouckaert, and Dautrebande (1930) proved this to be the case. They showed convincingly that oxygen want stimulates respiration almost exclusively by way of a reflex elicited in the sinus and to a less extent the aortic regions.

After their denervation the inhalation of a gas mixture poor in oxygen causes a depression of respiration. Carbon dioxide, on the other hand, acts directly on the centre as well as reflexly. Cyanides, lobeline, nicotine, and acetylcholine were also found to stimulate respiration by way of reflex. Thanks to further investigations by Bouckaert, Dautrebande, and Heymans (1931) it was possible to localize the chemical stimulation of the sinus region to the small carotid body. An analogous mechanism was demonstrated in the aorta by Comroe and Schmidt (1938).

The new results were at first received with a certain scepticism, as is shown by the following quotation from Haldane and Priestley (1935): "On the whole it seems that the reflex control of the breathing by chemical stimulation of the carotid nerve endings has not been established, at any rate as regards carbon dioxide. In respect of oxygen it has perhaps hardly been proved that the hyperpnoea is a carotid reflex apart from changes in circulation." There is in fact very little reason to connect the hyperpnoea during oxygen want with changes in circulation. Thus in the dog the arterial blood pressure remained constant when the animal breathed 5.2% oxygen, but respiration increased considerably (Euler and Liljestrand, 1936). After denervation of both sinuses the same gas mixture caused an elevation of the blood pressure, whereas respiration decreased and soon ceased. In the cat 8.25% oxygen led to a small rise in blood pressure and increased respiration. After denervation the effect of 8.25% oxygen was a rapid fall of the blood pressure and a decrease in respiration.

This new development made it doubtful whether the pressoreceptors have anything to do with the regulation of respiration. Euler and I (1937b) studied this question by perfusing both sinus regions by means of a Dale-Schuster pump. We found that an increase in the perfusion pressure often led to a reduction of ventilation, especially if the preceding pressure which had led to a stimulation of the chemoreceptors and over-ventilation was low. In other instances an increase in respiration resulted from high perfusion pressure, probably because sensory nerves within the sinus region were stimulated. No definite evidence was obtained of a direct inhibitory influence on breathing by the arterial blood pressure in the sinus region itself. Neither could we confirm the observation that denervation of the sinuses was followed by increased respiration. On the

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contrary, this operation regularly led to an increase in the alveolar carbon dioxide tension, which rose still more if the vagi were severed afterwards (Euler and Liljestrand, 1936). The effect was reduced, but not abolished, if the animals were breathing pure oxygen (Euler and Liljestrand, 1940). Part of the effect therefore must be due to oxygen want.

From these results it appeared that the chemoreceptors play a part in the regulation of respiration in normal anaesthetized animals. This was also clearly established by experiments by Euler, Liljestrand, and Zotterman (1939a) on the action potentials of the sinus nerve. These are of two kinds—great spikes, mainly appearing in bursts of impulses at each systole and elicited from the pressoreceptors, and much smaller potentials discharged continuously and partly due to chemical stimulation. It is possible to cut the branches of the sinus nerve from the sinus wall and thus to obtain the potentials from the chemical fibres practically isolated. The relation between the rate of impulses and the oxygen pressure in the inspired air was studied. Starting with 29% of oxygen in nitrogen, we found an increase of the impulse frequency already during air-breathing, indicating that the chemoreceptors begin to react at a rather high oxygen saturation of the haemoglobin. As the oxygen content of the inspired gas mixture went down, the number of potentials rose rapidly. Carbon dioxide elicited a corresponding effect already at an alveolar tension about 30 mm. Hg. It is interesting that De Castro, observing the carotid body under a low-power binocular microscope, found a great diminution of the organ during hyperpnoea due to carbon dioxide inhalation; during oxygen-breathing, however, the carotid body became somewhat larger than its normal size.

We confirmed the finding of Samaan and Stella (1935) that infusion of a cyanide solution was accompanied by a greatly increased number of small potentials in the sinus nerve, and we observed the same phenomenon after intravenous injection of lobeline or nicotine, which, as already mentioned, according to the Heymans school, exercise their action on respiration, mainly via the chemoreceptors. A typical difference, however, could be demonstrated between oxygen want or carbon dioxide accumulation and the alkaloids mentioned. Starting from the assumption that oxygen want and increased carbon dioxide tension stimulate the chemoreceptors by some common mechanism, presumably a change in the reaction within the cell to the acid side, we tried to influence it in the opposite direction by intravenous injection of moderate doses of ammonia. Even 0.5–2 ml. of a 0.5/N solution caused a complete temporary disappearance of the chemoreceptive impulses elicited by anoxaemia or by hypercapnia.

The same thing was found in respect of the action potentials during the infusion of cyanide. In this case pure oxygen could also counteract the cyanide, which supports the view that cyanides interfere with oxidation processes. The action potentials elicited by lobeline or nicotine, on the other hand, were not abolished by moderate doses of ammonia. We therefore concluded that these drugs act centrally to the point of stimulation involved in oxygen lack or carbon dioxide. This, in conjunction with the fact that a similar stimulating effect on the glomus is obtained also with other synaptotropic substances, such as acetylcholine, curarine, and potassium ions, and that they all paralyse the chemoreceptors in

considerable concentrations, led us to consider whether they could act on the carotid body in a way analogous to their action on sympathetic ganglia. I will return to this question later on.

Effect of Cyanides

The effects of cyanides have been studied in some detail (Euler and Liljestrand, 1937a). If a small amount is given by intravenous infusion an obvious stimulation of respiration results, and this is followed, immediately after stopping the infusion, by a level somewhat above the resting value. In the case of a more rapid infusion of the same concentration of cyanide several different stages can be seen. First, there is a rapid rise in amplitude as well as a moderate increase in the respiratory rate; characteristic "gasps" occur at fairly regular intervals. In a second stage the respiratory activity is lowered, though the gasps become more frequent. After the infusion has ceased the respiration soon increases again, the picture now being rather a reflected image of the first part of the curve. After some time a third stage, with deep regular respiration sets in.

A comparison with the effects of carbon dioxide excess and oxygen want, respectively, reveals that the first stage resembles closely the results obtained during oxygen want and less those after carbon dioxide excess. The frequent occurrence of gasps and the insignificant alteration of the expiratory position are typical of the action of cyanide as well as of oxygen want. The second stage is very similar to the situation during pronounced oxygen want, when the respiratory centre is beginning to fail. It is also characteristic that oxygen want and cyanide infusion increase each other's effects, as found already by Geppert (1889) and confirmed by us. The maximal ventilation that can be obtained with cyanide is, however, about 15% higher than that during oxygen want. Evidently, therefore, most of the primary effect during cyanide infusion is due to oxygen want, but a small part is due to some other factor. The first stage of cyanide action on respiration disappears almost completely after section of the sinus nerves, a result which is in harmony with the view that it is mainly caused by oxygen want. That the second stage is due to the effect of oxygen want on the centre seems to be quite evident.

With regard to the third stage, however, it persists after denervation of the sinus nerves. It seems probable that in this case increased acidity of the blood is the stimulus responsible for the effect, a considerable and rapid rise in the lactic acid content of the blood and a rise in the hydrogen-ion concentration of the arterial blood having been found in connexion with intravenous injection of cyanide by Gesell, Krueger, Gorham, and Bernthal (1930). This also gives a satisfactory explanation of the fact that the primary increase in ventilation is somewhat greater in the first stage of cyanide infusion than that found during oxygen want alone. The continuous moderate rise in ventilation during and after the infusion in the denervated animal accords well with this explanation.

Effect of Lobeline

As already mentioned, lobeline stimulates respiration over the chemoreceptor mechanism. In this way intense action can be secured before the paralysing effect on the centre or on the sinus nerves appears. Consequently the total increase in ventilation which can be secured with

lobeline is much greater than in the case of oxygen want, when the deleterious effect on the centre relatively soon counteracts the stimulation from the chemoreceptors. Thus the total ventilation in a cat under the influence of 3 mg. of lobeline rose from the basal value of 0.93 to 3.52 l. a minute, whereas the maximal value during continuous oxygen want, found just before the curve began to fall again, was only 1.85 l. The total increase in ventilation in the former case thus was 2.6, in the latter case only 0.92 l. a minute (Euler, Liljestrand, and Zotterman, 1939a, 1939b).

Effect of Adrenaline

When injected intravenously in moderate doses adrenaline has two quite different actions on respiration. The first of these accompanies the rise in blood pressure and consists in a diminution of the depth and rate of breathing, which sometimes goes so far that an apnoea results. In view of the great interest attaching to this substance, the apnoea has been the object of much work and speculation.

Thus several authors have assumed a direct depression of the respiratory centre, but Schmidt (1929) has advanced convincing evidence against this hypothesis—for example, by demonstrating that a dose injected into the vertebral artery, which gives a relatively smaller rise in blood pressure than when given intravenously, also depresses respiration less. Roberts (1921) assumed that adrenaline causes a constriction of the vessels of the medulla, so that the centre is paralysed owing to want of oxygen or to an accumulation of metabolites. His own observation that an apnoea can be produced if the blood pressure is quickly raised by compression of the abdominal aorta indicates other possibilities, and Schmidt's finding that the cerebral blood flow is augmented when adrenaline is injected intravenously clearly contradicts his view. Schmidt came to the conclusion that reflex inhibition seems to be a factor, as vagotomy usually decreases the effect, but he considered the most important cause to be increased blood supply to the centre. At that time, however, the part played by the sinus mechanism in the respiratory function was unknown, and in view of this new knowledge it became necessary to reinvestigate the matter.

Experiments on dogs and cats, performed by Heymans and Bouckaert (1930) and by Wright (1930), proved that the adrenaline apnoea is mainly of reflex origin. If both vagi were cut and the carotid sinuses denervated, the action was practically abolished, only a very small effect remaining. According to Heymans and Bouckaert, the adrenaline apnoea is due to a reflex inhibition of the respiratory centre, produced by the increase in the blood pressure in the cardio-aortic and sinus circulatory areas. This explanation squares with the view held by Heymans and his school that a direct inhibitory influence on respiration is exercised from the baro-receptors. As already pointed out, we found no support for such an assumption. It seemed to accord better with the known facts to assume that the increased arterial blood pressure should afford a better blood flow through the carotid and aortic bodies and thereby diminish the stimulation of the chemoreceptors. As a matter of fact, Winterstein (1934-5) had pointed out that the decrease in ventilation after adrenaline injection already begins before the blood pressure starts to rise—it might even be falling—though the blood flow has increased. He concluded that the effect on respiration cannot be due to

a reflex from the carotid sinus, but supposed that the explanation was to be sought either in the washing away of acid products or in a direct effect on the centre.

Gernandt, Liljestrand, and Zotterman (1945) found that the adrenaline apnoea could be prolonged if the animal was breathing oxygen; sometimes it also started a little later under these conditions. This seems to indicate a close connexion of the apnoea with the activity of the chemoreceptors. On the other hand, gas mixtures rich in carbon dioxide, as well as an injection of lobeline, could prevent the apnoea, which confirms that the centre is not paralysed. According to Heymans and Bouckaert and to Wright, only a very small decrease of respiration occurred after adrenaline if both vagi were cut and the sinuses were denervated. We further recorded the action potentials from the chemical fibres of the sinus nerve. There was a great reduction of impulses during adrenaline apnoea even during oxygen breathing. In this connexion the observation made by De Castro (1951) should be mentioned—namely, that the volume of the carotid body increased considerably after intravenous injection of adrenaline.

On recording the action potentials from the depressor nerve Gernandt (1946) found the same considerable reduction of small impulses after adrenaline as had been found earlier in the case of the sinus nerve. He also observed that if the chemoreceptors had been selectively eliminated by means of close intra-arterial injections of acetic acid, no apnoea occurred after adrenaline, though the pressoreceptors were still functioning. The same thing was seen by me in a cat in which the chemoreceptors of the carotid body had been eliminated by dissection. During oxygen want no increase in respiration was found and the blood pressure went down rapidly, but there was an excellent response of blood pressure to occlusion of the two common carotids, so that the pressoreceptors were intact. Adrenaline had hardly any immediate effect on respiration.

Our interpretation that the adrenaline apnoea is the result of a sudden elimination of the "chemoreceptor drive" (Bjurstedt, 1946) on respiration raised the question whether apnoea could be evoked by section of the sinus and vagus nerves. We found that section of the sinus nerves induces a reduction of respiration, and subsequent section of the vagi leads to slight apnoea. If the four buffer nerves are cut simultaneously an apnoea leading to the death of the animal results. The apnoea provokes oxygen want, and this causes a fall in the arterial blood pressure, as the depression of the vasomotor centre is not counteracted by the pressoreceptors. If the experiment was performed during oxygen breathing the usual rise in blood pressure due to the elimination of the inhibitory tone of the pressoreceptors occurred, and a short period of decreased respiration was observed. On the whole these experiences lend further support to the view that adrenaline apnoea is the consequence of a temporary elimination or reduction of the chemoreceptor activity.

The second effect of adrenaline on respiration appears when the blood pressure has again reached the normal level. A moderate increase in ventilation is then observed, which is probably due to the changed metabolism. As the respiratory quotient is usually somewhat increased a certain overventilation takes place. This seems to be sufficiently explained by the formation of lactic acid, which is a well-known consequence of the injection of adrenaline.

Effect of Acetylcholine

The last substance with which I propose to deal is acetylcholine. It has a complex action on respiration. As shown by Dautrebande and Maréchal (1933) and by Heymans, Bouckaert, Farber, and Hsu (1936), it stimulates the chemoreceptors. Schweitzer and Wright (1938) also demonstrated both stimulation and depression of respiration, which were to some extent independent of the chemoreceptors. In my experiments (Liljestrand, 1951) the effects of acetylcholine on the non-atropinized cat were compared with those of bleeding. It was found that small doses of acetylcholine stimulated respiration only indirectly owing to the oxygen want induced by the low blood pressure. With doses of 0.2 mg., however, there was also a direct stimulation of the chemoreceptors and a central inhibition as well as restriction of the amplitude of each respiration.

As is well known, atropinized cats stand much larger doses of acetylcholine, and these now cause a rise in blood pressure. A number of changes in respiration occur under these circumstances. After a brief expiratory apnoea, there is a short phase of increased breathing, followed by an apnoea of longer duration, which is interrupted by periodical respirations, and, finally, a period of regular breathing occurs again.

The initial apnoea is probably due to an inhibition of the respiratory centre, which is suddenly flushed by the drug. This view receives a certain support from the following observations: there is a simultaneous drop in the blood pressure, indicating an analogous effect on the vasomotor centre; after destruction of the carotid bodies the apnoea is prolonged and the blood pressure fall is more pronounced.

As has already been mentioned, the stimulating effect of acetylcholine is due to a reflex from the chemoreceptors. After intravenous injection of 0.7 ml. of 0.5/N ammonia hyperventilation due to oxygen want was greatly reduced and the blood pressure dropped suddenly. During the stimulating phase of acetylcholine the same dose of ammonia had no definite action on respiration, though a small drop in the blood pressure occurred. Similar results were found with carbaminoylcholine. These experiences tally well with the findings already quoted in respect of the action potentials.

The secondary apnoea is of a kind similar to that met with after adrenaline. If the centre is stimulated directly by carbon dioxide or indirectly by oxygen want the apnoea can be abolished. It comes a little later and is of somewhat greater duration than the adrenaline apnoea for the same rise in pressure, but this is to be expected as the result of the preceding period of stimulation. The action potentials in the chemical fibres of the sinus nerve disappear during the apnoea in the same way as after adrenaline. The periodical respiration following the apnoea is typical Cheyne-Stokes breathing resulting from overventilation and oxygen lack. It is abolished by oxygen.

Whether the increase in respiration after the periodicity is due to a direct stimulation of the centre—it is observed also after denervation—or to some indirect factor, has not been investigated.

The action of acetylcholine on the chemoreceptors is of special interest in respect of the question whether "drugs or changes in the blood which stimulate these nerve endings . . . produce their effects by liberation of

acetylcholine as the chemical intermediary" (Schweitzer and Wright). The distribution of the nervous structures and their relations to the epithelioid cells of the carotid body are rather complicated, as demonstrated by De Castro (1951). The synapse corresponds to the glomus cell and its nervous end-plate. If this is taken as the point of attack of acetylcholine and related substances, hypoxia might influence them, as well as the thin sensory fibres, directly. Gesell, Brassfield, and Hamilton (1942) have pointed out that increased acidity induces anticholinesterase activity; hence the shift of reaction in the cell caused by ammonia might give rise to such a rapid splitting of the acetylcholine formed that it does not reach the concentration necessary to activate the neurone. In this way acetylcholine would be the common mediator for different types of stimulating agents in the carotid and aortic bodies.

Hollinshead and Sawyer (1945) have determined the cholinesterase and pseudo-cholinesterase activity of the carotid body of the cat. They found that the true cholinesterase activity was much lower for the carotid than for the superior cervical ganglion and about the same as for the non-synaptic sensory ganglia. As a rule the glomus contained more pseudo-cholinesterase than true cholinesterase. These findings are difficult to interpret, but they do not seem to be irreconcilable with the hypothesis that acetylcholine is the chemical mediator in the chemoreceptor mechanism.

It seems desirable that other ways should be tried in order to find out whether the hypothesis is well founded or not. Experiments carried out with the object of comparing the effects of oxygen want on respiration before and after intravenous injections of eserine or atropine led to no definite result. Sometimes eserine seemed to increase and atropine to reduce the effects, but the differences were small and irregular. Such experiments will also be difficult to interpret, for both drugs may act on many different structures. As acetylcholine itself affects the respiratory centre as well as the chemoreceptors, the results will depend on several factors. There is also every probability that the so-called synapses in the carotid body will not react to the low concentrations of the drugs which can be obtained by intravenous injection without causing serious general disturbances.

It therefore occurred to me that it might be better to treat the carotid bodies locally by applying small pieces of cotton soaked with solutions of the two substances mentioned. This method gave quite definite results. After eserine treatment the respirations became deeper and the decrease after oxygen was somewhat more pronounced than before. Oxygen want or carbon dioxide accumulation now induced greater responses than normally. The eserine salicylate was washed away and atropine sulphate applied. A reduction of the resting respiration followed, hardly influenced at all by oxygen-breathing. Carbon dioxide gave much less response than before treatment, and oxygen want had the typical effect observed after denervation—a continuous decrease, soon leading to a respiratory standstill. The pressor reactions showed similar variations, the greatest effect being met with after eserine, the smallest after atropine. The explanation is presumably the varying role of the chemoreceptors when the carotids are clamped.

The results speak strongly in favour of the hypothesis that acetylcholine is the chemical mediator in the carotid bodies.

The experiments thus afford another example of the correlation between physiology and pharmacology. In this case it has been possible, by studying the actions of drugs, to gain some insight into the normal processes going on in the body.

Summary

The discovery that the chemoreceptors of the carotid and aortic bodies when stimulated by oxygen want or carbon dioxide excess induce increased breathing made it desirable to investigate their role with regard to the action of certain drugs.

It was found that cyanides stimulate respiration mainly via the chemoreceptors, but also, especially in later stages, directly on the centre, probably through formation of lactic acid.

Moderate doses of lobeline act exclusively on the chemoreceptors, but the point of attack is central to that of oxygen want or carbon dioxide excess.

An intravenous injection of adrenaline leads to decreased respiration or even apnoea; this is due to the sudden elimination of the "chemoreceptor drive."

The same holds true for acetylcholine after atropinization, though there are differences which can be explained from the fact that acetylcholine also stimulates the carotid and aortic bodies in a similar way to lobeline. Before atropinization the stimulating effect of acetylcholine is enhanced by the simultaneous lowering of the blood pressure, which leads to oxygen want.

Local application of eserine to the carotid bodies increases the respiratory response to oxygen deficiency and carbon dioxide accumulation; the sensitivity of the chemoreceptors to these stimuli as well as to lobeline is abolished by local treatment with atropine. These results indicate that acetylcholine is the chemical mediator within the carotid body.

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NEURAL CONTROL OF THE PITUITARY GLAND: II. THE ADENOHYPHYSIS

WITH SPECIAL REFERENCE TO THE SECRETION OF A.C.T.H.*

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As described previously, only two endocrine glands—the adrenal medulla and neurohypophysis—have a secretomotor nerve supply and are dependent on this supply for normal function. The adenohypophysis (anterior pituitary gland), thyroid, adrenal cortex, ovaries, and testes lack a well-defined innervation. It has been known for many years, however, that these latter glands are influenced by nervous processes—the evidence for this statement has been reviewed (Harris, 1948a)—but the mechanism whereby such an influence is exerted was uncertain. The position would be clarified if it could be found how the adenohypophysis is brought under neural control; for the thyroid, adrenal cortex, and gonads would then be indirectly under similar control via the action of the anterior pituitary eutrophic hormones. Some such sequence of events as illustrated in Fig. 1 may be envisaged. Stimuli arising in the external environment, such as changes in exposure to light or temperature or exposure to a variety of conditions grouped under the heading "stress," are reflected by changes in activity in various parts of the central nervous system. These changes, and those arising from mental and psychological upsets, may affect the secretory activity of the adenohypophysis by means of structures in the hypothalamus and pituitary stalk.

FIG. 1.—Diagram to illustrate a possible mechanism whereby the activity of the anterior pituitary gland, thyroid, adrenal cortex, and gonads may be modified by changes in the external environment or in the central nervous system (psychological or emotional upsets). It seems likely that such changes may affect anterior pituitary secretion via the intermediation of the thyrotrophic, adrenocorticotrophic, and gonadotrophic hormones may thus affect also the activity of the thyroid gland, adrenal cortex, and gonads.

These changes, and those arising from mental and psychological upsets, may affect the secretory activity of the adenohypophysis by means of structures in the hypothalamus and pituitary stalk.

Anatomical Links Between the Central Nervous System and the Adenohypophysis

Nervous

Three nervous pathways have been described as passing from the central nervous system to the adenohypophysis; branches from the cervical sympathetic

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