

THE ACTION OF VASO-CONSTRICTOR SUBSTANCES ON THE ARTERIES OF THE BRAIN.

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IN a previous communication(1) I have given reasons for believing that the apnoea which follows the intravenous injection of adrenalin in rabbits and cats is to be attributed to vaso-constriction in the respiratory centre. I have since found that Loewi and Meyer(2) had expressed the same view for more or less the same reasons. This view has received additional support from Mellanby and Huggett(3), who confirmed my results and showed further that the arrest of respiration did not occur if ergotoxin had previously been given, this fact indicating that the paralytic action of adrenalin was due to vaso-constriction and not to direct inhibition of the centre. The further demonstration by myself(4) that Cheyne-Stokes respiration when produced by adrenalin is associated with periodic opening and closing of the cerebral vessels seems to me to put this explanation beyond any doubt. But to many minds such a view is very difficult to accept and this for two reasons. First, the post-mortem perfusion of the brain with adrenalin has yielded widely different results in different hands; secondly, if a vaso-constrictor action of adrenalin on the brain were admitted it would be strong though not conclusive evidence that the cerebral vessels are under sympathetic control and this is now denied by the majority of physiologists. If, therefore, it can be shown that vaso-constrictor substances for which there is no *a priori* reason for excluding an action on the cerebral vessels produce the same changes in respiration as have been shown to follow adrenalin we shall be confirmed in our view that adrenalin has a cerebral vaso-constrictor effect since the only alternative is the very improbable coincidence that all vaso-constrictor substances directly inhibit the respiratory centre. In these pages I present the results of experiments performed with this object, the substances whose action has been investigated being pituitary extract, ergotoxin and barium chloride.

Pituitary extract. A number of investigations have been made upon the respiratory effect of pituitary extract with very different results. Mummery and Symes(5) noted a diminution in the amplitude. Houghton and Merrill(6) observed in the dog an increase in frequency

but owing to the limitation of their method they were unable to record any change in depth. A very full account of the effect both upon circulation and respiration in the rabbit is given by Paukow(7). Paukow using the Parke-Davis preparation showed the striking fact that with vagi intact there were always two periods of apnoea separated by a period of respiration, the first or "primary" apnoea which occurred immediately after the injection while the "secondary" apnoea which occurred during the recovery of blood-pressure from the profound fall which usually occurs in this animal. After atropine or after section of the vagi the primary apnoea, he said, did not occur. Paukow attributed the primary apnoea to a reflex inhibition of the centre set up by stimulation of afferent nerve-endings. The secondary apnoea he was unable to explain but suggested that it might be due to contraction of the bronchioles. Paukow further noticed that after the secondary apnoea the respiratory tracing often became spindle-shaped but he seems not to have realised that he was dealing with Cheyne-Stokes respiration. He thought that this effect might be partly the result of the anæsthetic. Fühner(8) approaching the subject from a pharmacological standpoint came to the same general conclusions but considered that the secondary apnoea only was characteristic of the specific principle of pituitrin, the primary apnoea being due to choline. In 1913 Fröhlich and Pick(9) studied the effect of various pituitary preparations upon tracheotomised but non-anæsthetised rabbits. They measured the volume of expired air and found considerable diminution accompanied by powerful expiratory efforts. This corresponded in point of time to Paukow's primary apnoea. It was abolished by atropine but, contrary to Paukow's result, not by section of both vagi. They believed that the effect was due to bronchial constriction. Paukow's secondary apnoea they attributed, following Loewi and Meyer's explanation of adrenalin apnoea mentioned above, to anæmia of the medulla by vaso-constriction. They supported this view by showing that this apnoea did not occur when pituitrin was given mixed with amyl nitrite so as to counterbalance the pressor effect. Paukow's secondary apnoea they termed "indirect" apnoea. Nice, Rock and Courtright(10) using cats and dogs found in general an increase in depth followed by shallowness. It appears, however, that the dose which they gave (usually the extract diluted 10 or 25 times) was too small to produce the characteristic effect upon blood-pressure. Weed and Cushing(11) on injecting the "hypophysin" preparation of Lucius, Meister and Brunig found an increase in the depth of respiration. Dixon and Halliburton(12) also found increase of respiration but they attributed

it to dyspnoea caused by contraction of the bronchioles. As the bronchial contraction took 30 seconds to be complete the effect on respiration did not occur at once. The only experiments upon the excised cerebral arteries are those of Cow⁽¹³⁾ who found no appreciable effect.

The following experiments were made upon rabbits and cats anæsthetised with urethane supplemented with a little C.E. mixture. The preparation used was the "pituitrin" of Messrs Parke-Davis and Co. It was given intravenously. Respiration was recorded as in previous experiments by connecting one limb of the Y-shaped trachea tube to a rubber tambour. In their work upon the bronchi Dixon and Halliburton have pointed out that this is not a good method of recording bronchial obstruction whether due to bronchial contraction or to vascular congestion such as they find is produced by adrenalin and other substances which increase systemic pressure. But since bronchial obstruction does not prevent respiration from affecting intra-tracheal pressure this method can be safely used to show whether there is apnoea or not. No doubt at the moment of obstruction the record does not accurately represent the change in strength of respiratory movements. I have, however, in all experiments watched the movements and found them to correspond with the tracings. Moreover, in one experiment (Fig. 1) I have taken a simultaneous tracing of the abdominal movements. The tracings are essentially the same.

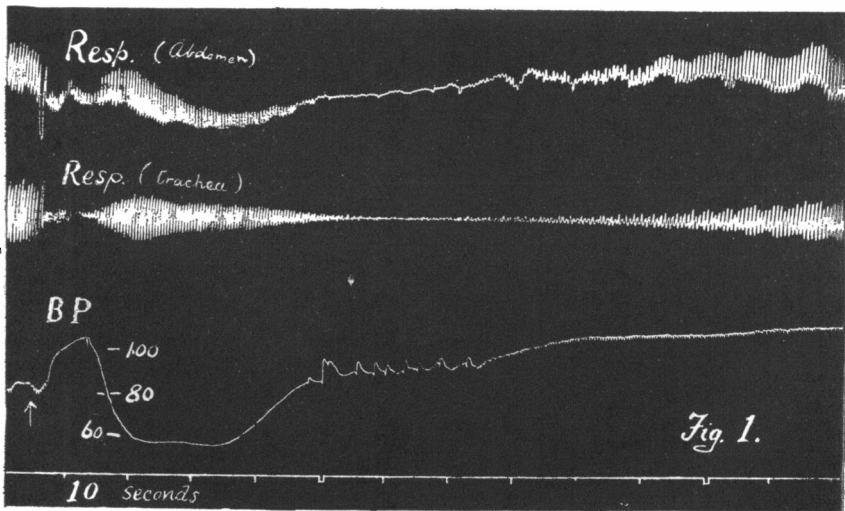


Fig. 1. Rabbit. Vagi intact. 1 c.c. pituitary intravenously. Typical effect.

We shall first deal with the rabbit. A typical effect of the injection of 1 c.c. is shown in Fig. 1. There is first an immediate diminution in the depth of respiration usually amounting to complete apnoea during which the chest is completely at rest. This lasts about 10 seconds and is usually accompanied by a transient rise of blood-pressure of variable degree. Rarely no rise occurs. Following this, the pressure undergoes a profound fall. During the fall respiration recommences progressively increasing in depth. Blood-pressure then slowly recovers, the tracing showing a much slower heart-beat. At the beginning of the rise respiration undergoes a progressive diminution in depth until a second apnoea sets in. This is more prolonged than the first apnoea and lasts sometimes until the blood-pressure reaches its summit which is often not much higher than its original level. Respiration is then gradually resumed. Besides these changes in depth there are usually changes in frequency. The respiration which follows the first apnoea is commonly at a much faster rate than the original but this alteration usually only occurs if the first apnoea is complete. It would appear that a new rhythm cannot be adopted unless the old rhythm is first completely suppressed. The respiratory rate following the second apnoea may be at the immediately previous rate or at the original rate or again at a totally new rate. Following the second apnoea Cheyne-Stokes respiration may occur, the extent to which it occurs depending as in the case of adrenalin upon individual susceptibility.

With vagi cut the appearances are in general the same. The first apnoea, however, tends to be less marked, a fact which may be associated with the slower rate of respiration. Further, the rate of respiration is usually unaltered throughout. An example is seen in Fig. 2 which shows in addition an unusual degree of periodic respiration.

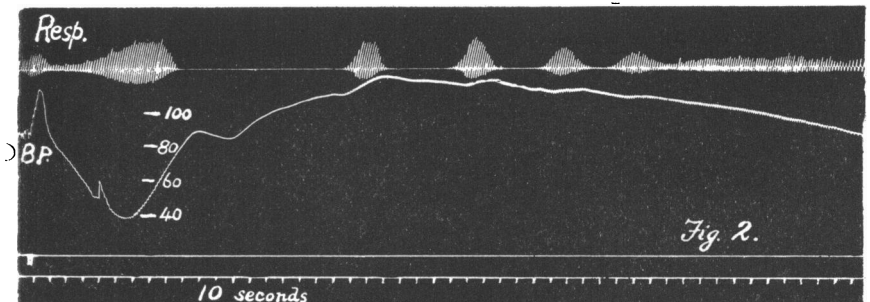


Fig. 2. Rabbit. Vagi cut. 1 c.c. pituitary. Well-marked Cheyne-Stokes respiration. Apart from the apnoeic periods there is no alteration in rate of breathing.

It will be seen that the results are more difficult to interpret than those obtained with adrenalin. Owing to the complex manner in which the cardio-vascular system is involved it seems at first sight difficult to correlate changes in respiration with those in the arterioles. It may be stated here that the first and second apnœa occur irrespective of gross changes in general blood-pressure. Fig. 3 shows that they occur when the

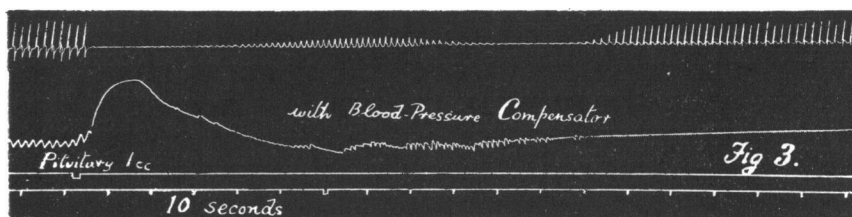


Fig. 3. Rabbit. 1 c.c. pituitary. Blood-pressure partially compensated.

general blood-pressure is largely counterbalanced by the use of the compensator previously described. At the same time it is important to know whether the great fall in pressure is cardiac or peripheral in origin. Paukow believed that it was cardiac. I have confirmed this by direct inspection of the heart. A large hole was made in the left side of the chest and the pericardium opened so that a good view of the heart could be obtained, the animal meanwhile breathing naturally with the right lung. It was easy to see that the fall in blood-pressure was accompanied by considerable embarrassment of the heart with enormous dilatation of the auricles. The blood-pressure therefore during this period gives no indication of the state of the arterioles.

As regards the Cheyne-Stokes respiration it is clear from Fig. 2 that there is an intimate relation between respiration and blood-pressure for the tracing shows quite clearly a fall in pressure preceding and during the development stage of each respiratory period and a rise in pressure during the stage of subsidence. The similarity in this respect between adrenalin and pituitrin is most striking. Unfortunately no record of cerebral pressure was taken in this experiment but the result, assuming that there is no variation in the action of the heart of which there is no evidence, shows that when the centre is reacting in this periodic manner it becomes active after and during vaso-dilatation and quiescent during vaso-constriction.

We have now to consider the first and second apnœic periods. It will be convenient to take the latter first. The second apnœa commences

as already stated when the blood-pressure is beginning to recover and terminates usually as it reaches its maximum. Now if the rabbit's ear be observed the following changes can easily be seen. During the preliminary rise and subsequent fall in pressure no visible change in the central artery occurs. But as the blood-pressure recovers the calibre of the artery becomes progressively smaller, sometimes to complete obliteration. The rise in pressure is therefore the resultant of a recovering heart-beat and gradual vaso-constriction. If the respiratory tracing be observed at the same time it will be seen that the vaso-constriction corresponds in point of time with the apnoea and further that the extent to which respiration is affected varies directly with the degree of obliteration of the artery. If, therefore, the changes in the arterioles of the ear are a guide to those occurring in the brain we may conclude that the second apnoea is due to medullary anæmia.

But in order that this conclusion should rest on something more than mere ocular demonstration I have contrived to confirm it by the following experiment. The ordinary blood-pressure record was taken from the central end of the right common carotid artery and the pressure in the Circle of Willis from the peripheral end of the same artery, the right external carotid having been tied. The left common carotid was also tied. Pituitrin (0.5 c.c.) was injected brainwards into the latter vessel. The result is shown in Fig. 4. As a record of changes in the cerebral arteries

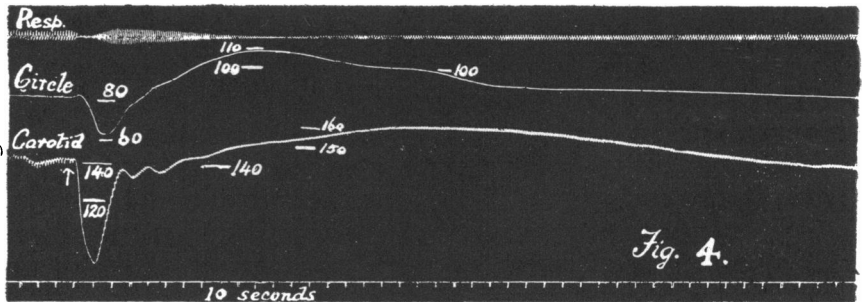


Fig. 4. Rabbit. Vagi cut. 1 c.c. pituitary injected brainwards. Description in text.

this experiment is imperfect inasmuch as the left external carotid had not been tied and therefore the Circle pressure was affected by vaso-constriction in the left side of the head outside the skull. As a matter of fact it is very doubtful whether an exclusive record from the cerebral vessels can be obtained owing to the anastomoses which these vessels make with those of the orbit and face. But accepting this limitation the

record shows an earlier and relatively higher rise in the Circle pressure than in the general systemic pressure.

The initial blood-pressure was 140 and the Circle pressure 80. At the arrow, 0.5 c.c. pituitrin was injected as stated. There is a sudden fall in blood-pressure and stoppage of respiration. As the pressure recovers, respiration is resumed for a time but after about 20 seconds it begins to diminish. At the same time the Circle pressure rises rapidly but the general pressure only very gradually so that when the second apnoea is fully developed the pressure in the Circle stands at 109 and the general pressure at 150. The difference between them, which was originally 60, is now 41. Expressed in another way, while the general pressure has only increased 7 p.c. the Circle pressure has increased 36 p.c. Clearly the arteries arising from the Circle have, owing to the stronger and earlier dose to which they have been subjected, undergone a relatively greater and more rapid constriction than have the arteries in the rest of the body. As we should expect, the effect passes off more rapidly in the brain. This is demonstrated by the subsequent course of events, for the Circle pressure falls while the general pressure continues to rise.

It might be thought that the greater rise in the Circle pressure was due to the fact that the brain cannot expand. But this is not so for if pituitrin be given intravenously so that it is distributed evenly throughout the body the Circle pressure fluctuates within a smaller range than does the systemic pressure. The point which Fig. 4 brings out is that the second apnoea is related not to the change in general pressure but exactly to the change in Circle pressure. The results shown in Figs. 2 and 4 taken together would seem to show that the second apnoea is due to constriction of the cerebral arterioles and that the subsequent Cheyne-Stokes respiration is due to rhythmic opening and closing of these vessels.

Incidentally this experiment illustrates another point. From the effects of intravenous injection it is not clear whether the delay in vasoconstriction is due to a real delay in the action of the drug or to a delay in the arrival of the drug at the arterioles owing to the suppressed action of the heart. The long interval of time which elapses even after injection into the carotid shows that in the rabbit pituitrin takes some time to develop its effect.

We may now consider the first apnoea. I have several times (*e.g.* in Fig. 4) obtained this apnoea with both vagi cut. This fact disposes of Paukow's idea of a vagal reflex, in itself a very unlikely hypothesis. Both Paukow and Fröhlich and Pick find that atropine abolishes the first apnoea. But I have found that even after injection of 10 mgms. of

atropine, a dose sufficient to paralyse the vagal fibres to the heart, this apnoea still occurs. It seemed possible that the positive effect which I obtained might be due not to pituitrin but to the too rapid injection of fluid. This was easily put to the test by injecting rapidly into the jugular vein 1 c.c. of warm Ringer solution. Respiration was unchanged. The explanation of the negative results of Fröhlich and Pick is, I think, to be found in the very slow rate of injection—on one occasion 1 c.c. in 60 seconds.

The primary apnoea has nothing to do with the bronchial constriction found by Fröhlich and Pick in their unanæsthetised animals. In the first place it has been shown by Dixon (unpublished observations) that the constrictor effect of pituitrin on the bronchioles is completely abolished after urethane. In the second place the apnoea produced under the circumstances of my experiments was always a true apnoea, in which all the respiratory muscles were either completely at rest or very much suppressed. There was no trace of the dyspnoea which invariably indicates bronchial obstruction.

That the first apnoea is central in origin is shown by the fact that when pituitrin is injected directly into the cerebral vessels as in Fig. 4 the apnoea ensues *immediately*, that is, before the drug has time to get into the general circulation. That it is caused by cerebral vaso-constriction is suggested by the fact that it usually occurs contemporaneously with an initial rise of blood-pressure as in Fig. 1.

The action of pituitrin on the cat calls for little comment. The simple rise in blood-pressure is accompanied by diminution in the depth of respiration. This is undoubtedly the typical effect. In the experiments already quoted of Nice, Rock and Courtright upon the cat and dog

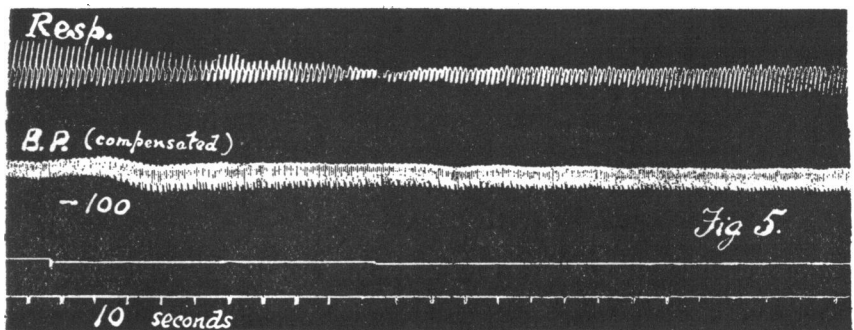


Fig. 5. Cat. Ergotoxin phosphate, 3 mgms. Blood-pressure compensated.

and in those of Weed and Cushing upon the dog the doses given were such that the typical rise of blood-pressure did not occur. This explains why these observers failed to obtain diminished respiration.

Ergotoxin. Fig. 5 shows the marked suppression of respiration which occurs in the cat when ergotoxin phosphate, 3 mgms., is given intravenously. (I am indebted to Dr Dixon for the ergotoxin used.) The respiratory effect was not due to the rise in pressure since this was completely neutralised by the use of the compensator.

Barium. Fig. 6 shows the complete respiratory pause following the

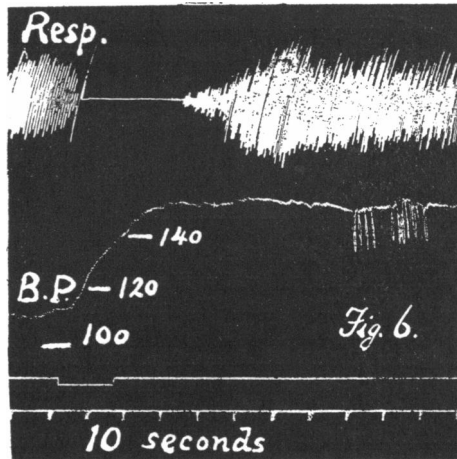


Fig. 6. Rabbit. Barium chloride, .01 gm.

injection of barium chloride, .01 gm. made up in Ringer solution. Barium is peculiar in that the respiratory effect is only of short duration whereas the raised blood-pressure continues for a very long time as is well known. This point requires further investigation. Two tentative explanations suggest themselves. The first is that the cerebral vaso-constriction passes off sooner than the vaso-constriction in the rest of the body. The second is that the vaso-constriction is only of moderate degree so that the medulla resumes its function when the hydrogen ion concentration of the blood has, owing to the apnoea, increased so as to counterbalance the diminished amount of blood supplying the centre.

SUMMARY.

1. The three vaso-constrictor substances tested, namely pituitrin, ergotoxin and barium chloride, all cause a diminution or complete stoppage

of respiration. Since this effect occurs when the blood-pressure is prevented from rising it must be referred to anæmia of the respiratory centre by cerebral vaso-constriction.

2. In the rabbit pituitrin causes two periods of apnoea. Of these the second is proved to be related to cerebral vaso-constriction. Reasons are given for believing that the first is due to a similar cause. The second apnoea is sometimes followed by Cheyne-Stokes respiration, the periods of which are related to changes in blood-pressure.

3. The fact that these substances all resemble adrenalin in their effect upon respiration and especially the close similarity which exists between pituitrin and adrenalin is confirmatory evidence for the view already expressed that adrenalin is vaso-constrictor to the brain.

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NOTE. After the above was in the Press a Paper by Bouckhaert (*Arch. Néerl. de Physiol.* 7. p. 285, 1922) came to my notice. Bouckhaert states that the first dose of adrenalin after ergotoxine causes a decrease of respiratory movement. This point then requires further investigation.