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THE CENTRAL DEPRESSOR ACTION OF ADRENALINE AND ITS INHIBITION BY ERGOTOXINE

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THE rise in blood pressure produced by the injection of moderate doses of adrenaline in the rabbit is generally followed by a more or less pronounced fall, which may last for several minutes. Thus van Leersum [1911] observed in the unanæsthetized rabbit that the secondary fall, after a dose of $\frac{1}{3}$ mg. of adrenaline injected into an ear-vein, exceeded 30 mm. Hg and lasted for a considerable time. This phenomenon has been interpreted as being due to a reflex stimulation of the vasodilator centres [Trendelenburg, 1929] and it has been suggested that the effect is analogous to the vasodilatation and the slowing of the heart after injections of adrenaline in the dog, due to reflex actions from the carotid sinus and the aortic arch, as shown by Heymans [1929]. The accumulation of tissue metabolites, especially those of an acid character due to a diminished blood supply to certain areas of the organism, has also been considered as a possible cause of the secondary fall. McGuigan & Mostroem [1912] found that the effect was increased after infusion of acid into the circulation and diminished after infusion of alkali. A great number of observations concerning the vasodilator or depressor effects of adrenaline, in different animals and under different conditions, have been reported, but only those dealing with a central action will be considered here.

Observations on rabbits showed that ergotoxine or ergotamine could abolish the normal secondary lowering of the blood pressure, even when given in doses too small to affect the pressor response to adrenaline. Preliminary experiments indicated that none of the suggested causes of the secondary effect, mentioned above, would offer a satisfactory explanation, the more so as they mostly apply to results obtained on

species other than the rabbit. An attempt has therefore been made to trace (1) the cause of the secondary fall in blood pressure after adrenaline in the rabbit, and (2) the mechanism of the abolition of this effect by small doses of sympathicolytic ergot alkaloids.

Experimental

The rabbits, mostly between 2·2 and 3·7 kg. in weight, were anæsthetized with urethane (6 c.c. 25 p.c. solution per kg.) or pernocton (0·6 c.c. 10 p.c. solution per kg.) intravenously, or ether. In some cases a combined anæsthesia of urethane and pernocton was given. The secondary fall appeared under all of the anæsthetics mentioned, as it does in the unanæsthetized animal. The blood pressure was recorded by means of a mercury manometer from the left carotid artery. Respiration was spontaneous unless otherwise stated.

The secondary fall in blood pressure after adrenaline

This frequently recorded phenomenon is shown in Fig. 1 *A*. The secondary fall varies in its extent, but has been absent only in a small minority of cases. The fall is generally well developed in the animal

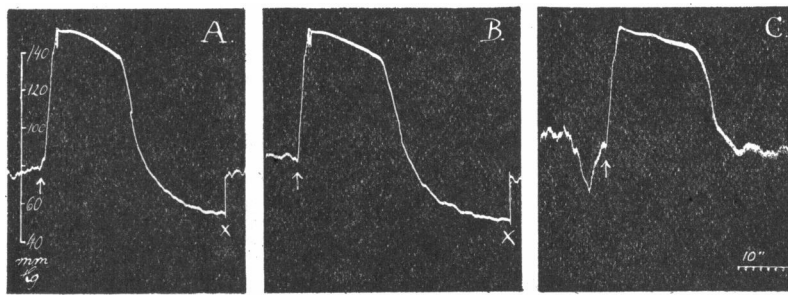

Fig. 1. Rabbit, blood pressure, urethane. *A*, 0·04 mg. adrenaline i.v. Between *A* and *B* both depressor nerves cut and carotid sinuses denervated. *B*, 0·04 mg. adrenaline i.v. *C*, ice on both vagi in the neck, 0·04 mg. adrenaline i.v. *X*, drum stopped.

under urethane after 0·005–0·04 mg. adrenaline. In two rabbits, rather deeply anæsthetized with pernocton and subjected to artificial respiration, the secondary fall was missing, the blood pressure remaining above the previous level for some 5 min. after the injection of adrenaline (Fig. 2 *A*). On the other hand, it was observed that moderate asphyxia, as brought about by letting the animals rebreathe through a length of tubing, would increase the secondary fall (Fig. 2 *B*).

As a rise in blood pressure is known to elicit vasodilatation and slowing of the heart by reflex actions through the buffer nerves, it became necessary to examine the effect of adrenaline after exclusion of these reflexes. For this purpose the depressor nerves on both sides were cut in the neck and both carotid sinuses were denervated. This was effected by isolating the external and the internal carotid arteries for a distance of about 5 mm. from the bifurcation, the tissue between the vessels being divided between ligatures. It was noted, however, that under urethane anæsthesia occlusion of the second common carotid, after denervation in the way described, caused in some cases a considerable rise in blood pressure, which could not be explained as a mechanical effect only. In these cases the same rise was obtained by clamping the

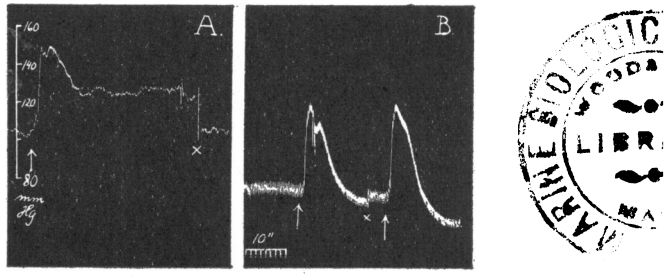

Fig. 2. *A*, rabbit, blood pressure, pernocton. Artificial respiration. Sinus and depressor nerves cut. 0·01 mg. adrenaline i.v. *B*, rabbit, blood pressure, urethane, sinus and depressor nerves cut. 0·02 mg. adrenaline i.v., before and after increase of respiratory dead space. *X*, drum stopped.

external carotid, and it is believed that this effect is reflex in origin and not merely mechanical, since the clamping of other vessels of the same size does not produce a similar rise. It could be shown, furthermore, that clamping the branches of the external carotid also caused a considerable rise in pressure, whereas occlusion of the internal carotid was without effect. By partial occlusion of the external carotid different degrees of rise in general blood pressure could be obtained. The site of the presumptive area of origin of these reflexes, peripheral to the carotid sinus, was not further investigated. In order to exclude the reflex changes in blood pressure, due to variations in pressure in this barosensitive region, the external carotids on both sides were tied in cases where this effect occurred. Variations in pressure in the common carotid were now either without any distinct action on the general blood pressure, or followed by insignificant changes only. Traction on the common carotid

after denervation of the sinus still produced a considerable fall in blood pressure, which effect could also be evoked by pinching or even light touching of the carotid artery in several cases. This effect is clearly not related to the sinus reflex proper. It seems that this effect is due merely to the stimulation of sensory nerves in the arterial wall. It has been pointed out by Florey & Marvin [1928] that the rabbit under urethane readily responds with a fall of blood pressure to stimuli of very various kinds, and this observation has been amply confirmed by the present writer. There is no evidence, however, that such changes in blood pressure as are brought about by the doses of adrenaline employed would cause any reflex change of the general blood pressure, after denervation of the carotid sinuses and cutting the depressor nerves in the manner described.

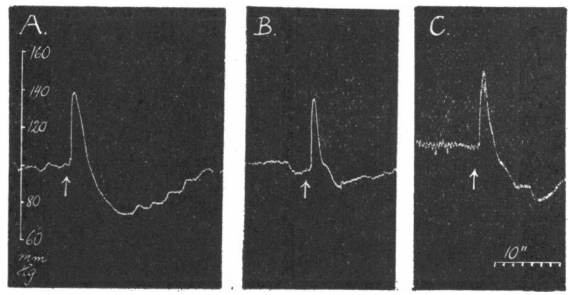

Fig. 3. Rabbit, blood pressure, urethane. *A*, 0·005 mg. adrenaline i.v. Between *A* and *B*, 5 mg. atropine sulphate. *B*, 0·005 mg. adrenaline i.v. *C*, about 1 hr. later, 0·005 mg. adrenaline i.v.

After exclusion of the barosensitive areas, including the tying of the external carotid arteries, the secondary fall after adrenaline still persisted (Fig. 1 *B*), though the effect in some cases seemed to have been diminished. It was thus clearly established that the effect in question was not due, at least not chiefly, to reflex actions originating in the barosensitive areas.

In order to determine whether the secondary fall is due to a central or a peripheral effect of adrenaline a search was made for possible nerve paths, transmitting impulses resulting in a fall in pressure. It was thus found that section of both vagi in the neck abolished the effect. This could be shown also when a temporary break was made in the nervous conduction by placing a piece of ice on the isolated vagi in the neck (Fig. 1 *C*). On removing the ice and allowing the nerve conduction to be restored the effect reappeared.

The secondary fall is therefore, as it appears, entirely dependent on impulses conducted through the vagi. Since it was found that injection

of atropine also prevents the effect (Fig. 3) afferent impulses in the vagi are not alone involved, if at all, and the effect must be due to an efferent function of the vagus fibres. This implies that the effect cannot be attributed to a diminution of the central vasomotor tone, but must be due to some actively depressor impulses transmitted by the vagi.

Effect of stimulation of the vagi below the heart. Actions of atropine, eserine and ergotoxine

Since the secondary fall after adrenaline, shown to be prevented by section of the vagi in the neck or by atropine may be due to a decreased output of the heart, or peripheral vasodilatation, or both, it seemed

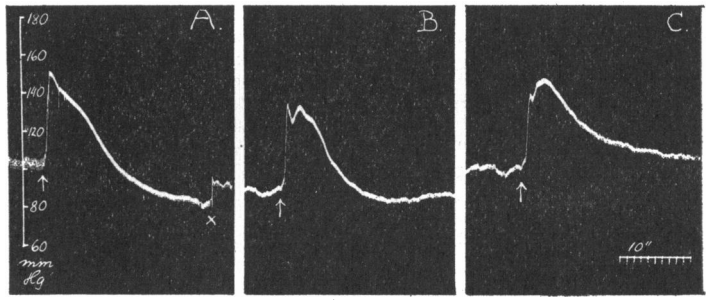

Fig. 4. Rabbit, blood pressure, pernocton. Sinus and depressor nerves cut. *A*, 0·01 mg. adrenaline i.v. Between *A* and *B* both vagi cut intrathoracically below the heart. *B*, 0·01 mg. adrenaline i.v. Between *B* and *C* both vagi cut in the neck. *C*, 0·01 mg. adrenaline i.v. *X*, drum stopped.

desirable to determine whether and to what extent the heart was involved. An attempt was made to cut the vagal branches to the heart in the chest, leaving the rest of the vagus intact, but this was found to be technically impracticable in the rabbit. Both vagi, therefore, were prepared on the œsophagus below the heart, with an open chest, and divided. This was found greatly to reduce the secondary fall after adrenaline, though division of the vagi in the neck decreased it yet further, or abolished it (Fig. 4). These results show that the effect in question is partly transmitted by the vagi below the heart and is partly due to an action transmitted by vagus fibres ending at a higher level, presumably in the heart. As to the former effect, it seemed reasonable to assume that it was due to vasodilator impulses carried by the vagi. Since the vagi may not improbably contain vasodilators for the splanchnic area and since the vascular bed of this region has a relatively large

significance in the rabbit, the blood pressure might readily be affected by vasodilator impulses carried to this area through the vagi.

The peripheral ends of the vagi, after division in the chest below the heart, were stimulated by faradization. In all cases a drop in blood pressure ensued, though the fall showed some variations in shape and extent. In two out of six cases the fall set in almost immediately and continued for the time of stimulation (20–40 sec.). After the stimulation had ended, the blood pressure returned to normal within a short time (Fig. 5 *A*). In the remaining cases the blood pressure fell more slowly, remained low for some time, and then recovered gradually (Fig. 5 *B*). In some instances a preliminary short rise preceded the fall. The drop in blood pressure during stimulation in some cases exceeded 35 mm. Hg. (In the cat the stimulation of the vagi below the heart causes, on the contrary, a small rise in blood pressure as observed by Brown & Garry [1932]. The same result was obtained in a single experiment on the cat by the present writer.)

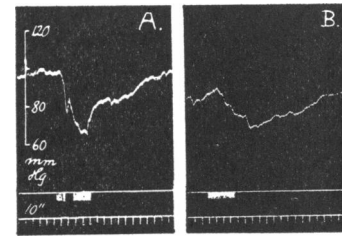

Fig. 5. Rabbit, blood pressure, pernocton. *A*, peripheral ends of vagi stimulated intrathoracically below the heart for 10 + 25 sec. *B*, another animal, same stimulation for 40 sec.

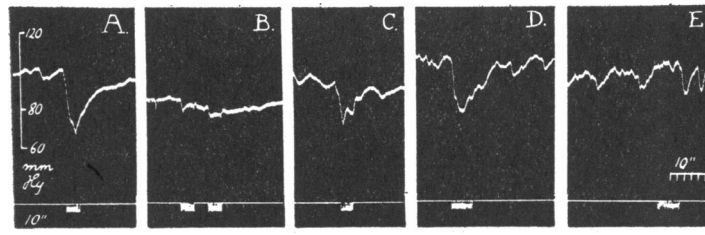

Fig. 6. Rabbit, blood pressure, pernocton. *A*, peripheral ends of vagi stimulated intrathoracically below the heart 20 sec. at 12.50. At 12.58 4 mg. atropine sulphate i.v. *B*, at 1.02 and 1.03 p.m. stimulation 20 sec. *C*, at 1.40 stimulation 20 sec. *D*, at 2.34 stimulation 25 sec. Between *D* and *E* both vagi tied below the diaphragm. *E*, at 2.45 stimulation 30 sec.

We have seen that the secondary fall in blood pressure after adrenaline was abolished by atropine (Fig. 3). It seemed, therefore, of interest to examine the action of atropine on the fall in blood pressure caused by stimulation of the peripheral ends of the intrathoracic vagi as described above. After vagus stimulation had been shown to produce a definite fall in blood pressure, 4 mg. of atropine were injected intravenously, and

caused a transient, moderate fall in blood pressure. As soon as the pressure had recovered to a steady level, the stimulation of the vagi was repeated and now no longer caused any significant fall. After about 1½ hr. the response to stimulation had returned, being now practically the same as before the administration of atropine (Fig. 6).

For the mechanism of this fall in blood pressure during vagus stimulation, several possibilities arise. A spread of current to sensory nerves, the stimulation of which generally causes a drop in blood pressure in the rabbit under urethane or pernocton, was ruled out by the facts that tying the vagus nerves below the diaphragm prevented the development of the fall, and that the effect was abolished by atropine. A diminution of the blood supply to the heart, as a result of contraction of the diaphragm, which was occasionally observed, could be excluded for the same reasons. The same argument might be put forward for any type of action not due to change in the activity of plain muscle innervated by the vagi. There seems to be no way of discriminating, however, between a true vasodilator effect and other effects on the distribution of the blood within the splanchnic area, arising from the activity of plain muscle, which might for one reason or other diminish the flow of blood to the heart. On the other hand, it is the general experience that atropine does not abolish the motor effects of vagus stimulation on the intestine of the rabbit. Reviewing the evidence, it seems fair to assume that the fall in blood pressure, during subcardial vagus stimulation in the rabbit, is due to vasodilatation in the splanchnic area. This would also account for the diminution of the secondary fall after adrenaline, when the vagi are divided below the heart, or atropine is administered.

The effect of centrally injected adrenaline on the blood pressure

Whereas adrenaline may increase the blood supply to the centres by raising the general blood pressure, and may thus remove a high vasomotor tone due to partial asphyxia [Nowak & Samaan, 1935], it may cause, under somewhat different conditions, a central depressant effect on the blood pressure which can hardly be explained in this way. Thus Dale & Richards [1927] observed that, while small intravenous doses of adrenaline would cause a moderate fall in blood pressure in the dog owing to a peripherally excited vasodilatation, similar doses, when injected into an artery supplying the centres, caused a much more powerful depressant action. In their experiment the dog's vagi were cut, the left subclavian artery tied centrally to the origin of the vertebral artery, all branches of the right subclavian artery except the vertebral

were tied, and a cannula was inserted in the central end of the right subclavian artery, enabling injections to be made through the right vertebral artery towards the centres. Both common carotids were tied. A rather spectacular fall in blood pressure followed the central injection of 0·005 mg. adrenaline by this route. Since adrenaline is known to elicit constriction of the cerebral vessels [Bouckaert & Jourdan, 1936] it seems likely that, in the experiment of Dale & Richards, the "abnormal" depressor effect was due to acute anoxia in the vasomotor centre, which would cause an instantaneous depression of the vasomotor tone.

Some similar experiments have been carried out in the present investigation in order to examine the central effects of adrenaline on the blood pressure of the rabbit. In a number of experiments on rabbits under various anæsthetics and in one experiment on the cat under chloralose, the adrenaline was injected through the internal carotid artery on one side, the second carotid being tied. A small dose, 0·001–0·002 mg., of adrenaline under such conditions regularly caused a transient pure fall in blood pressure, which was not followed by a rise after these amounts. The effect was greatly enhanced by cocaine (Fig. 7). It was tempting to assume that this effect of adrenaline was analogous to the delayed, secondary depressor effect observed after an intravenous injection of adrenaline. It could be shown, however, that this was not the case. Section of the vagi in the neck did not appreciably diminish this effect of the central injection of adrenaline and it was not abolished by atropine. The effect could therefore not be caused by a stimulation of the vasodilator or cardio-inhibitory centres (vagus centre), but must probably be due to a diminution of the vasomotor tone. Since the injection of adrenaline causes vasoconstriction and the observed effect is enhanced by cocaine, the central depression will obviously be best explained by assuming an acute anoxia in the vasomotor centre, causing a "shock"-like fall in blood pressure. The readiness with which this effect of adrenaline can be evoked under certain conditions appears to be of a certain interest for the production of sudden falls in blood pressure, and does not seem to have been explained earlier on these lines.

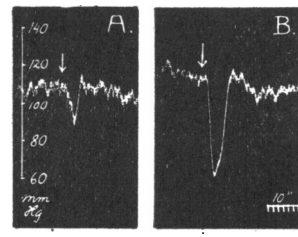

Fig. 7. Rabbit, blood pressure, ether. *A*, 0·002 mg. adrenaline into the internal carotid artery. *S*, same as *A* after 0·5 mg. cocaine hydrochloride injected the same way about 20 min. earlier.

The fact that anoxia gives rise to a fall of rapid onset in general blood pressure has been shown for the cat by Euler & Liljestrand [1936], who observed that the fall commences before the respiration is affected. The anoxia was produced by letting the animals breathe mixtures of oxygen and nitrogen. Hyperventilation did not occur since the carotid sinuses were denervated. In the present experiments anoxia was produced experimentally in the same way. Even if the anoxia was moderate, so as to evoke no marked change in the respiration of the animal deprived of its sinus innervation, a fall in blood pressure was observed (Fig. 8), which persisted after section of the vagi in the neck, though in some cases it appeared to be diminished. This may be explained as a mixed effect of the anoxia: partly due to a stimulation of the vagus centre and partly to a slight depression of the vasomotor centre. Peripheral effects due to accumulation of acid metabolites could not, however, be excluded in these experiments.

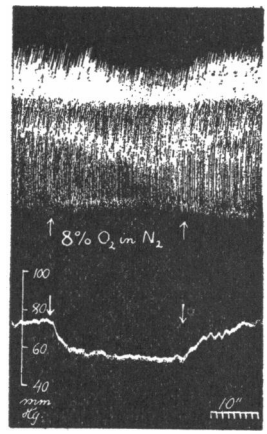

Fig. 8. Rabbit, ether. Upper curve, respiration; lower curve, blood pressure. Between arrows the rabbit was breathing a mixture of 8 p.c. oxygen in nitrogen. Sinus and depressor nerves cut.

Central anoxia was also produced in some experiments by injections of small doses of potassium cyanide directly towards the centres. These injections were also followed by a transient fall in blood pressure, much of the same type as those produced by adrenaline administered by the same route, and, like these, persisting after vagotomy. These experiments apparently support the explanation of the central depressant action of adrenaline suggested above.

It is interesting to note that, whereas a gradually developed anoxæmia, in the cat deprived of its sinus innervation, causes a fall in blood pressure, the same condition in the dog produces a rise in pressure, as observed by Euler & Liljestrand. In the rabbit I found a more complex action, the initial effect being a fall, which was in some cases followed by a transient rise in pressure which then was succeeded by a fatal fall. It seems, therefore, that the sensitiveness and the mode of reaction of the vasomotor centres to anoxia differs substantially in different species.

Abolition by ergotoxine of the secondary fall after adrenaline

As already mentioned, it was observed that intravenous injection of the sympathicolytic ergot alkaloids in doses of the order of 0·05–0·1 mg. per kg. rabbit suppressed the secondary fall after adrenaline, without causing any marked alteration of the primary, pressor effect (Fig. 9). In cases where the secondary fall was increased by moderate asphyxia (rebreathing), this effect was also abolished by ergotoxine or ergotamine. It could be shown further that this effect is not peripheral, since an amount known to be sufficient to abolish the secondary fall does not prevent the fall in blood pressure obtained after stimulation of the peripheral ends of the vagi below the heart. These results are in

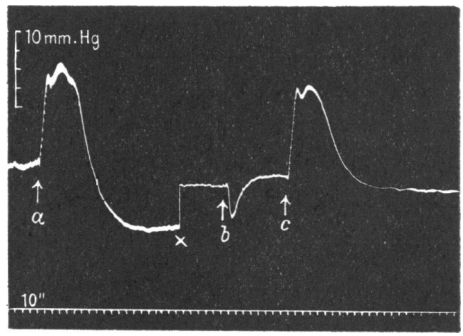

Fig. 9. Rabbit, blood pressure, urethane. *a*, 0·02 mg. adrenaline i.v. *b*, 0·2 mg. ergotoxine ethanesulphonate i.v. *c*, 0·02 mg. adrenaline i.v. *X*, drum stopped.

accordance with the early observations on the action of ergot by Dale [1906], who stated that "the cranial and sacral autonomic inhibitory nerves to the heart and arteries suffer no paralysis at any level". According to Rothlin [1923], who was the first to find that the depressor reflex is abolished by ergotamine, the excitability of the vagi is increased after ergotamine.

Using small doses of ergotamine (0·1–0·15 mg. per kg. body weight) Wright [1930] observed that the depressor and sinus reflexes in the vagotomized cat under chloralose were abolished, and concluded from these experiments and from the results of cerebral anæmia, which still produces a rise in pressure, that ergotamine exerts a paralysing effect on the afferent side of the vasomotor centre. With larger doses of ergotamine the pressor sinus reflexes as well were affected, and finally abolished. As pointed out by Heymans *et al.* [1930], the fact that cerebral anæmia still produces a rise in blood pressure

after a small dose of ergotamine may depend on the difference in type of stimulus. The last mentioned authors have also shown that ergotamine may abolish vasomotor reflexes by a central action, though apparently only pressor reflexes were studied. The effect of ergotoxine was also examined on the central depressant action of adrenaline, given by central arterial injection. It was found that this was diminished but not abolished by a dose of 0·005–0·01 mg. ergotoxine injected towards the centres, though scarcely affected by a dose of 0·15 mg. injected by a vein into the general circulation. This confirms the view that the secondary fall after intravenous adrenaline and the depressor effect of centripetal, arterial injection are not identical in their causation, as already suggested; small doses of ergotoxine apparently do not abolish the depression of the vasomotor centre evoked by anoxia.

Discussion

The secondary fall in blood pressure after adrenaline in the rabbit is evidently due to action on the centres, no evidence having been obtained either for a reflex action or a peripheral action. Brown [1916] produced evidence that adrenaline, injected into an isolated cerebral circulation, caused stimulation of the vagus centre. As to whether adrenaline has a direct action on the cells in the nerve centres or acts only through effects on the cerebral vessels, Nowak & Samaan [1935] have recently given reasons for believing that the central depressor effect sometimes observed in the dog is due to the latter cause, thus confirming the opinion held by Heymans [1933]. Nowak & Samaan, in experiments in which the head of the dog under observation was perfused by crossed circulation from another dog, found that adrenaline injected into the circulation of the donor would cause a general vasodilatation as shown by a fall in the blood pressure of the recipient, especially in those cases where the recipient vasomotor centre had an already restricted blood supply, and a consequent persistent increase in its tone, due to partial asphyxia. They argued that, in such circumstances, adrenaline injected into the circulation of the donor, increasing the blood supply of the isolated head by raising the pressure under which it was perfused, would remove the asphyxial stimulus from the vasomotor centre and thus cause vasodilatation and fall in blood pressure. While an increased perfusion pressure by itself would doubtless increase the blood supply to the centres, it appears less evident that adrenaline in all circumstances would produce this result. In view of the vasoconstrictor action of

adrenaline on the cerebral vessels [Bouckaert & Jourdan] it seems conceivable that adrenaline might cause its central effects also by diminishing the blood supply to the centres. According to Yamakita [1922] intravenously administered adrenaline causes a diminished blood flow through the centres, lasting for several minutes. Theoretically the following events may happen as a result of diminished blood supply: (1) stimulation by partial asphyxia of centres which act upon the blood pressure, and (2) depression of the same centres, due to a more severe anoxia. Since, in either case, centres with a depressor or a pressor effect may be affected, the final result will depend (1) on the centre predominantly affected, and (2) the degree of asphyxia or anoxia. In this connexion the question presents itself, whether, with regard to centres with a depressor effect, the actions are brought about by an influence on primary or secondary centres. If a vasodilator effect is transmitted through the vagi, as in the case of the secondary fall after adrenaline, it cannot at present be stated whether the effect originates at a primary centre, or arises at the vagus centre itself. The fact that cutting the vagi in the neck prevents the secondary fall after adrenaline does not exclude the former possibility, however, since the vagi may carry practically all the vasodilator fibres concerned in the rabbit.

The effect of a small dose of ergotoxine in my experiments is to annul the normal output of depressor impulses in the vagus, following the adrenaline rise of blood pressure, in the rabbit. This effect on the vagus centre might be due to a weak persistence in its vessels of the constrictor action of adrenaline, after its subsidence elsewhere: in that case the effect of ergotoxine might be due to a suppression of this vasoconstrictor remainder. On the other hand, on the analogy of the experiments of Wright, the effect of ergotoxine may be due to block of conduction at synapses correlated with the centres; in that case the secondary fall following the adrenaline rise would presumably be due to action, not on the vagus centre itself, but on some centre making synaptic connexions with it. My evidence, however, would not justify an attempt to choose among such possibilities.

Reviewing the evidence, it seems most likely that the secondary fall is due to an increased activity, excited directly or indirectly, of the vagus centre, caused by vasoconstriction. If, on the other hand, a stimulating action on the vasomotor centre in the rabbit is set up for the same reason, the effect on the centre sending out depressor impulses must outlast this, giving a fall of pressure as the late result.

SUMMARY AND CONCLUSIONS

The secondary fall in blood pressure after moderate intravenous doses of adrenaline in the rabbit persists after denervation of the carotid sinuses and cutting of the depressor nerves.

The effect is suppressed by division of the vagi in the neck and abolished by atropine.

The effect is explained as being caused by stimulation of centres governing vasodilator and cardio-inhibitory effects, due to restriction of the blood supply by vasoconstriction.

Stimulation of the peripheral ends of the vagi intrathoracically, below the heart, causes a fall in blood pressure in the rabbit, which is abolished by atropine, enhanced by eserine and not affected by small doses of ergotoxine.

Small intravenous doses of ergotoxine or ergotamine (0·05–0·1 mg. per kg. rabbit) suppress the secondary fall after adrenaline, probably by a central depressant action on the vagus centre.

Arterial injection of adrenaline or potassium cyanide to the centres produces a fall in blood pressure, which is not prevented by section of the vagi or by atropine. The same effect is brought about by severe anoxia and is explained as due to depression of the vasomotor tone. This effect is not abolished by small injections of ergotoxine into the general circulation, but centrally injected ergotoxine may suppress the effect on adrenaline directed to the centres, by antagonizing its action on the cerebral vessels.

I wish to express my thanks to Sir Henry Dale for his stimulating interest in the work.

REFERENCES

Bouckaert, J. J. & Jourdan, F. (1936). *Arch. int. Pharmacodyn.* **54**, 109.
Brown, E. D. (1916). *J. Pharmacol., Baltimore*, **8**, 195.
Brown, G. L. & Garry, R. C. (1932). *J. Physiol.* **75**, 213.
Dale, H. H. (1906). *Ibid.* **34**, 163.
Dale, H. H. & Richards, A. N. (1927). *Ibid.* **63**, 201.
Euler, U. S. v. & Liljestrand, G. (1936). *Skand. Arch. Physiol.* **74**, 101.
Florey, H. & Marvin, H. M. (1928). *J. Physiol.* **64**, 318.
Heymans, C. (1929). *Arch. int. Pharmacodyn.* **35**, 307.
Heymans, C. (1933). *Bull. Acad. Méd. Belg.* **13**, 289.
Heymans, C., Regniers, P. & Bouckaert, J. J. (1930). *Arch. int. Pharmacodyn.* **39**, 213.
Leersum, E. C. van (1911). *Pflügers Arch.* **142**, 377.
McGuigan, H. & Mostroem, H. T. (1912–13). *J. Pharmacol., Baltimore*, **4**, 277.
Nowak, S. & Samaan, A. (1935). *Arch. int. Pharmacodyn.* **51**, 463.
Rothlin, E. (1923). *Ibid.* **27**, 459.
Trendelenburg, P. (1929). *Die Hormone*, p. 264. Berlin: Springer.
Wright, Samson (1930). *J. Physiol.* **69**, 331.
Yamakita, M. (1922). *Tohoku J. exp. Med.* **3**, 496.