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THE ACTION OF ADRENALINE ON THE KNEE JERK

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In a previous paper [Schweitzer & Wright, 1937] we described the effects of central vagus stimulation on the knee jerk in cats under chloralose anæsthesia. The usual result obtained was an inhibition of the reflex, and it was suggested that the aortic fibres in the vagus nerve were responsible for the changes observed. Several investigators [Koch, 1931, 1932; Schweitzer, 1934, 1935] have demonstrated that the afferent impulses set up by raising the blood pressure in the carotid sinuses are also capable of inhibiting reflex activities of skeletal muscle. It was, therefore, thought of interest to study the effects of pressor doses of adrenaline on the knee jerk, as it is well known that the rise of blood pressure produced by this substance stimulates the vaso-sensory terminals and reflexly inhibits a number of functions such as the heart rate, respiration and the tonic discharge of the vaso-motor centre.

The only reference that we have been able to find to the action of adrenaline on muscular reflexes is a short note by Spychala [1932], who while investigating the Orbeli phenomenon compared the effects on the knee jerk of the injection of adrenaline with those of peripheral sympathetic nerve stimulation. He found that adrenaline usually produced some increase in the reflex response but occasionally noted an inhibition which occurred at the height of the rise of blood pressure. He seems to relate his results to the peripheral action of the sympathetic on skeletal muscle.

A preliminary report of our studies on the action of adrenaline on the knee jerk has already been made [Schweitzer & Wright, 1936].

Methods

The methods employed for eliciting and recording the knee jerk and for peripheral stimulation of the motor nerve to the quadriceps muscle were the same as those described in an earlier paper [Schweitzer & Wright, 1937]. As previously, the response of the quadriceps was studied both when free-weighted and after-loaded.

Results

Intravenous injection into cats under chloralose anæsthesia (0·065–0·08 g. per kg. body weight) of adrenaline in doses of 0·2–0·4 mg. (0·05–0·15 mg. per kg.) produces various effects on the knee jerk.

(1) The usual result obtained is a depression or abolition of the jerk often accompanied by some decrease in muscle tone (Fig. 1). The inhibition sets in after a latent period which is usually not shorter than 30 sec., but is often considerably longer and may extend to 3 or 4 min. The inhibition then progressively becomes more marked and reaches its maximum after 4–14 min. In some experiments the reflex may then remain in abeyance for as long as 10 min. Finally, recovery sets in gradually and is usually complete after 10–90 min.; not infrequently, however, complete recovery does not occur. The return of muscle tone usually precedes the full recovery of the knee jerk to its normal level.

Using the technique described a decrease in tone can, of course, be observed only when the limb is allowed to hang freely; it then shows itself by increased flexion at the knee joint. The degree of passive stretch of the quadriceps remains, however, unchanged, so that patellar stimulation presumably stretches the muscle to the same degree as previously. When the experiment is carried out with the leg supported, a decrease in tone leads to slackening of the quadriceps and to a corresponding diminution in the effectiveness of the stretching force exercised by the hammer blow on the tendon. A decrease in the extent of the knee jerk under such conditions must be due in part to the associated diminution in tone. Both experimental procedures do, however, give a measure of the extent to which adrenaline modifies proprioceptive reflexes.

(2) Very commonly there is, preceding the inhibition, an initial increase in the size of the response, the peak being gradually attained after about 3 min. The initial increase in tension may be considerable and amount to 40–100 p.c. of the initial value. The inhibition then gradually sets in as already described. In occasional experiments the initial stimu-

lation is the outstanding feature of the response and the secondary inhibition is slight or absent.

(3) Rarely a "triple reaction" may be obtained which consists essentially of reaction (2) preceded by a short initial depression. Fig. 2 illustrates one of these results and shows an initial rapidly developing short-lived depression, followed by a secondary stimulation and then by a final inhibition which in its turn is followed by the usual slow recovery.

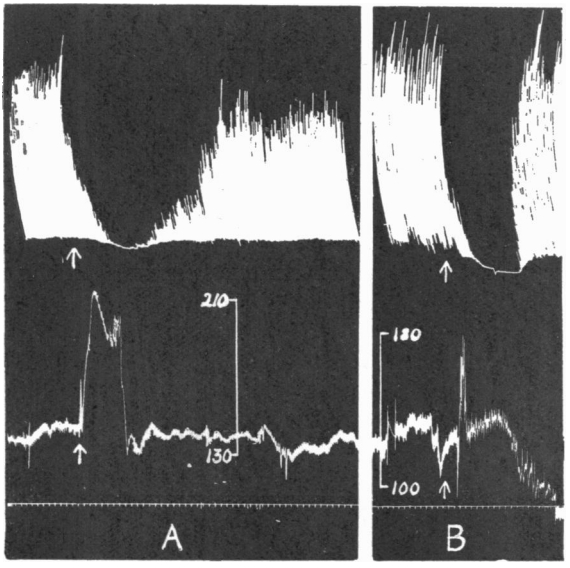

Fig. 1.

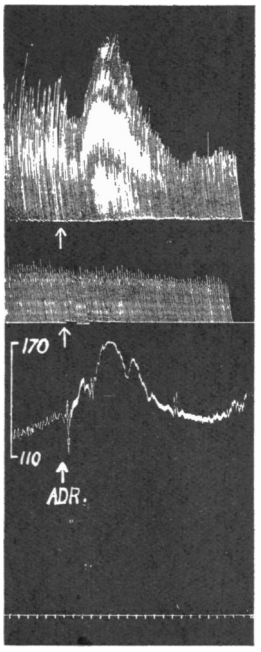

Fig. 2.

Fig. 1. Cat. Chloralose anæsthesia. Records from above downwards: knee jerk (free-weighted), blood pressure, time in 30 sec. A. Inject 0·4 mg. adrenaline. B. Carotid sinuses denervated and vagi cut. Inject 0·4 mg. adrenaline.

Fig. 2. Cat. Chloralose anæsthesia. Records from above downwards: knee jerk (after-loaded), quadriceps of other side stimulated through its motor nerve, blood pressure, time in 30 sec. Inject 0·4 mg. adrenaline.

(4) It can readily be shown that adrenaline also depresses other muscular activities. If the anæsthetic is light and the animal shows spontaneous movements these may be found to disappear after the injection of adrenaline at the same time as the knee jerk declines, and to return as the knee jerk recovers.

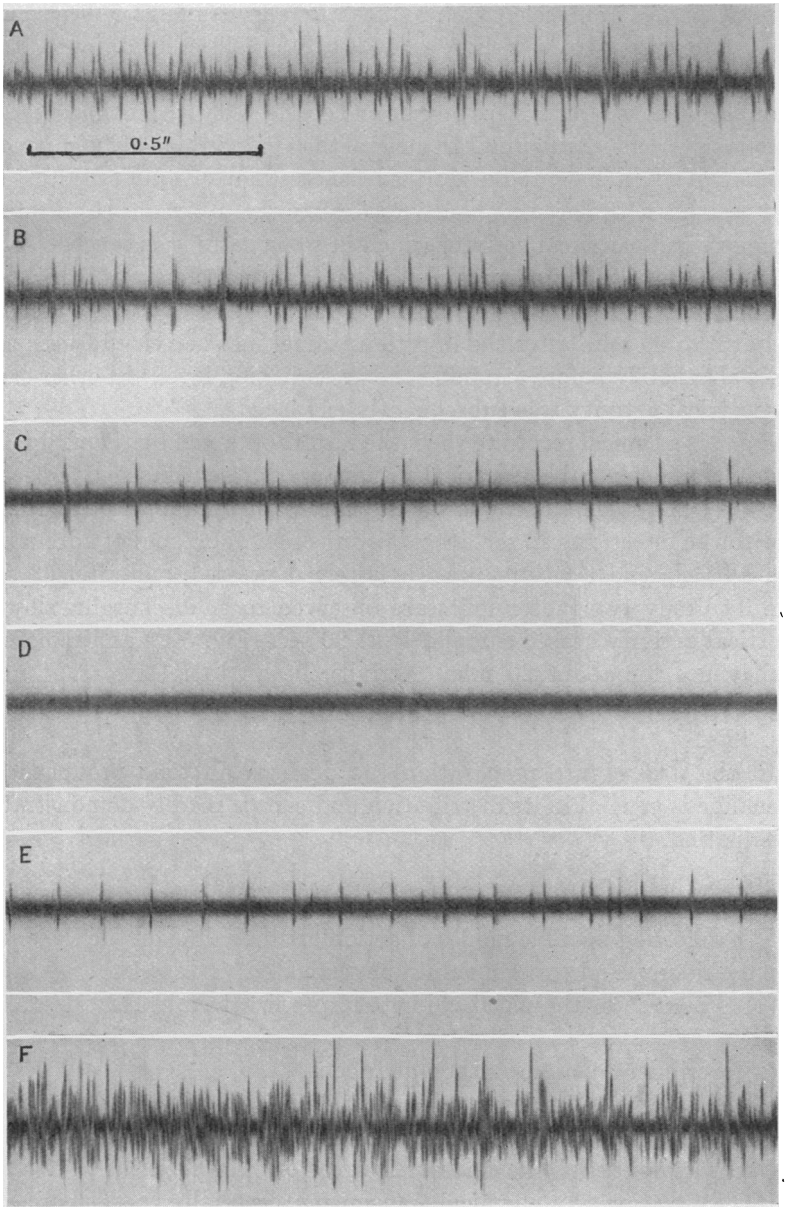

Fig. 3. Cat. Decerebrate. Records of action currents in quadriceps muscle (Adrian and Bronk concentric needle electrode and cathode ray oscillograph). A. Prior to injection. B. 22 sec. after injection of 0·2 mg. adrenaline. C. After 63 sec. D. After 90 sec. E. After 24 min. F. After 38 min. (From an experiment by W. Floyd and C. A. Keele.)

(5) Changes in muscle tone produced by adrenaline have been more fully studied by Floyd & Keele [1936] in the decerebrate animal by means of an Adrian and Bronk concentric needle electrode which is introduced into the quadriceps muscle and connected with an amplifier and cathode-ray oscillograph unit. In general they found that the intravenous injection of adrenaline produced: (i) a brief cessation of activity lasting for a few seconds which occurs about 15 sec. after the injection; (ii) a return of the original electrical activity which in some cases is enhanced; (iii) a decline in electrical activity which finally ceases completely at from 45 to 90 sec. after the injection; (iv) a slight gradual recovery to the original level at 3 to 40 min. after the injection; sometimes activity returns and ceases alternately before attaining the pre-injection level. In other cases the electrical activity was subsequently enhanced.

Fig. 3 is a typical record to show the results obtained by them. In this experiment considerable electrical activity was present in the quadriceps (Fig. 3 A), and was found to be steadily maintained for a period of 1 hour prior to the injection. 22 sec. after the injection of 0·2 mg. of adrenaline (Fig. 3 B) electrical activity was definitely depressed, and after 63 sec. (Fig. 3 C) only two motor units are observed to be discharging slowly. Electrical activity ceased completely at 90 sec. (Fig. 3 D) and remained in abeyance for about 20 min. Activity began to return at 24 min. (Fig. 3 E) and at 38 min. was more violent than prior to the injection (Fig. 3 F).

In the decerebrate preparation the decrease in tone produced by adrenaline is general in its distribution and can be readily demonstrated by palpation.

Mechanism of adrenaline action

The following possible modes of action of adrenaline on the knee jerk were considered and experimentally investigated.

(1) Presence of the usual chloretone preservative in the adrenaline solution.

(2) Peripheral action on the quadriceps.

(3) Coincident changes in respiration.

(4) Reflex action owing to the rise of blood pressure stimulating the vaso-sensory nerves in the sino-aortic areas or elsewhere.

(5) Liberation of a chemical transmitter, especially acetylcholine.

(6) Constriction of the blood vessels diminishing the blood flow through the central nervous system and directly or indirectly modifying the responses of the lumbar spinal centres.

(7) Rise of blood pressure acting directly on the central nervous system.

(8) Adrenaline acting directly on the neurones of the central nervous system.

(1) *Action of preservative*

The adrenaline solution employed contains 0·5 p.c. chloretone. The repeated injection of 1 c.c. of 0·5 p.c. chloretone has no effect whatever on the knee jerk. This is a larger amount than is present in the doses of adrenaline employed. The preservative, therefore, plays no part in producing the adrenaline reaction.

(2) *Peripheral action of adrenaline*

Previous workers have shown [Gruber, 1922, 1924] that in the mammal adrenaline may increase the response of skeletal muscle to peripheral motor nerve stimulation. It is, therefore, exceedingly improbable that the adrenaline inhibition of the knee jerk which has just been described can be attributed to a peripheral action of the drug on the muscle. It is possible, however, that the initial increase in the knee jerk often observed might be produced in this way. We carried out a number of experiments in which we compared simultaneously the effects of adrenaline on the knee jerk on the right side and on the peripherally stimulated quadriceps muscle on the left side (cf. Fig. 2). In none of our experiments was there any modification of the response of the peripherally stimulated muscle (apart from that attributable to fatigue) no matter what the type of alteration in the knee jerk happened to be. It is clear, therefore, that the peripheral action of adrenaline can be excluded as a significant factor in our results.

(3) *Changes in respiration*

No relationship can be established between the effects on the knee jerk and those on respiration. When the sinuses and vagi are intact it is found that the adrenaline apnœa passes off and breathing returns to normal before the inhibition of the knee jerk begins to set in. The breathing may be in the phase of secondary stimulation due to the direct action of adrenaline on the respiratory centre [Wright, 1930*b*] when the inhibition of the knee jerk is at its maximum.

(4) *Reflex action through the vaso-sensory nerves*

The changes in the knee jerk are likewise not closely related to those in blood pressure. Characteristically they lag behind the alterations in the blood pressure. Thus the rise of blood pressure attains its maximum

height before the inhibition of the knee jerk begins. Again the blood pressure commences to fall when the inhibition of the reflex is deepening. Frequently the blood pressure has returned to its pre-injection level before any indication of recovery of the knee jerk is noted.

The action of adrenaline was studied in animals with vagi cut and carotid sinuses denervated ("denervated" animals). It was found in such preparations that adrenaline still produces the usual characteristic inhibition of the knee jerk (Fig. 1 B). Floyd and Keele, who examined the question for us, similarly found in electrical studies on the quadriceps muscle of the decerebrate cat that the response to adrenaline was

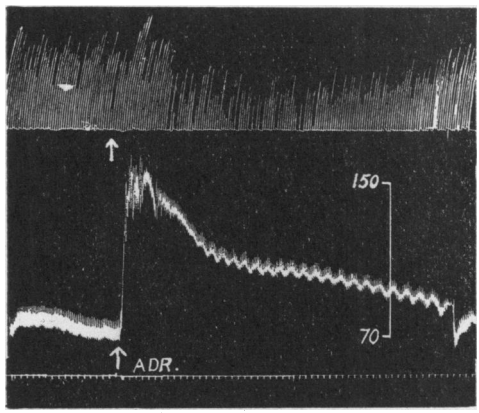

Fig. 4. Cat. Chloralose anæsthesia. Spinal cord divided in mid-thoracic region. Records from above downwards: knee jerk (after-loaded), blood pressure, time in 30 sec. Inject 0·4 mg. adrenaline.

unaffected by vaso-sensory denervation. The inhibition of the knee jerk is also obtainable after acute division of the spinal cord in the mid-thoracic region (Fig. 4). It can be concluded, therefore, that the effects of adrenaline are not essentially dependent on afferent impulses in the sino-aortic nerves. The experiments on the spinal animal also exclude the possibility that the afferent impulses which may be set up by blood pressure changes in the pulmonary circuit [Schwiegk, 1935; Schweitzer, 1936] are necessary for the responses obtained.

The role of other vaso-sensory nerves still remains to be considered. Gammon & Bronk [1935] showed that afferent impulses initiated by vascular distension may be set up in sensory nerve endings in the splanchnic area but offered no satisfactory proof that these were of functional significance. Heymans *et al.* [1936], however, produced

definite evidence that impulses set up by changes in mesenteric blood pressure can reflexly modify general vascular tone. They obtained similar results in the spinal animal but not following destruction of the medulla. They concluded that the medulla is an integral part of the reflex arc employed. Our experiments on the spinal animal demonstrate that vaso-sensory impulses which pass through the medulla, no matter what their origin, are not indispensable for the adrenaline effect on the knee jerk. It is possible, however, that the afferent impulses set up by adrenaline may pass directly from the splanchnic area to the lumbar spinal centres and produce inhibition there. To test this hypothesis experiments were performed in which animals were "denervated" and the splanchnic nerves which transmit the afferent impulses from the mesenteric vascular region were also divided. In such preparations adrenaline still produces its characteristic effects on the knee jerk. It may be concluded, therefore, that vaso-sensory impulses, no matter what their seat of origin, are not essential for the production of the adrenaline response.

Another point that may be mentioned which opposes the reflex hypothesis of the adrenaline action is that following central vagus stimulation the reflex inhibition of the knee jerk sets in almost immediately, while with adrenaline there is always a delay of at least 30 sec. and frequently of much longer duration.

It is useful to contrast with the foregoing results the analysis of the inhibition of the vaso-motor centre which is produced by adrenaline. Adrian *et al.* [1932] found that injection of 0·5–1 mg. of adrenaline intravenously in the rabbit arrested the efferent discharge in sympathetic fibres for 5 to 10 min. owing to an inhibition of the vaso-motor centre. This inhibitory action was almost completely abolished following section of the cardiac depressor nerves and tying the carotid arteries above and below the carotid sinus. This procedure does not, of course, completely denervate the vaso-sensory zones and it may be concluded, therefore, that the inhibitory action of adrenaline on the vaso-motor centre is wholly reflex in character.

(5) *Possible liberation of a chemical transmitter by adrenaline*

Feldberg & Schriever [1936] found that adrenaline in the eserinized animal causes the appearance of acetyl-choline in the cerebro-spinal fluid. We have shown [Schweitzer & Wright, 1936] that acetylcholine can markedly inhibit the knee jerk and it was, therefore, necessary to consider whether the action of adrenaline on the knee jerk was in part due to the mediation of this transmitter. A number of experiments were

performed in which animals were fully atropinized and then given an injection of 1 mg. eserine per kg. body weight. Under these conditions adrenaline still produces its characteristic inhibitory effects on the knee jerk but its action is not potentiated. There is, therefore, no reason to suppose that acetylcholine is concerned as an intermediary in the adrenaline reaction.

(6) *and* (7) *Role of vaso-constriction and direct action of rise of blood pressure*

The next possibilities that have to be considered are whether the rise of blood pressure or the vaso-constriction produced by adrenaline are the responsible factors. The following observations bear on the elucidation of this question:

(i) It has already been mentioned that there is no direct time relationship between the changes in the blood pressure and in the knee jerk.

(ii) In some experiments, where the rise of blood pressure produced by adrenaline has been small and very transient, a marked inhibition of the knee jerk has yet been obtained (Fig. 1 B).

(iii) In animals with vagi previously divided, occlusion of both common carotid arteries produces a marked sudden rise of blood pressure which equals in extent and acuteness that produced by an appropriate injection of adrenaline. In the experiment illustrated by Fig. 5, clipping the carotid arteries caused the blood pressure to rise from 190 to 260 mm., but the knee jerk showed only a negligible modification. A subsequent injection of 0·4 mg. adrenaline which raised the blood pressure equally rapidly to 260 mm. produced, after an initial stimulation, the characteristic and long-lasting abolition of the knee jerk, followed by a slow recovery. This experiment shows particularly well how the blood pressure may fall to below its pre-injection level long before the inhibition of the knee jerk becomes maximal. Such experiments exclude the possibility of the rise of blood pressure *per se* being responsible for the results.

In one experiment, however, carotid occlusion did produce a marked decrease in the knee jerk. The same result was still obtained after the suprarenal glands were removed to exclude the possibility of adrenaline being discharged into the circulation. It has, however, been shown previously [Schweitzer & Wright, 1937] that cerebral anæmia depresses the knee jerk, probably by causing the medullary centres to discharge inhibitory impulses to the lumbar cord [Montgomery & Luckhardt, 1930]. The exceptional result with carotid occlusion can probably be explained on such lines.

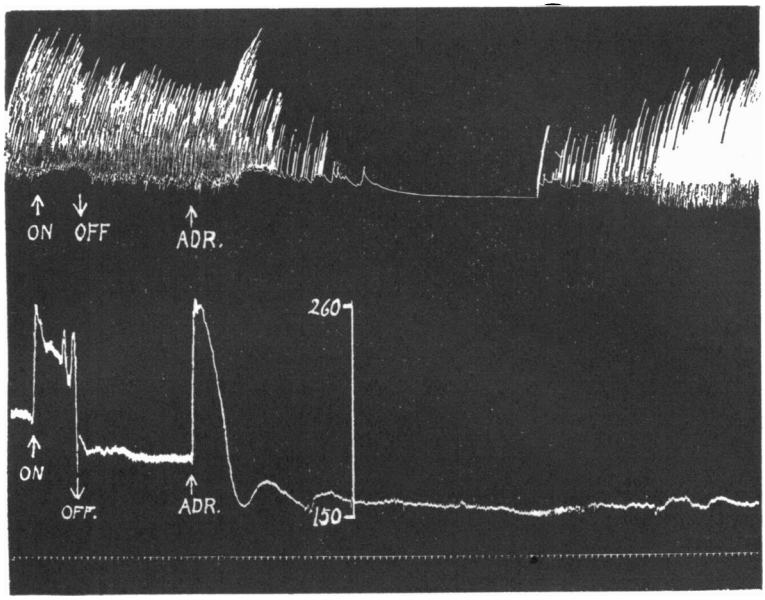

Fig. 5. Cat. Light chloralose anæsthesia (0·065 g. per kg.). Both vagi cut. Left carotid sinus denervated. Suprarenals excluded. Records from above downwards: knee jerk (after-loaded), blood pressure, time in min. At first arrow: clip right carotid artery. At second arrow: remove clip. At third arrow: inject 0·4 mg. adrenaline. The irregularities in the knee jerk are mainly due to the light anæsthesia.

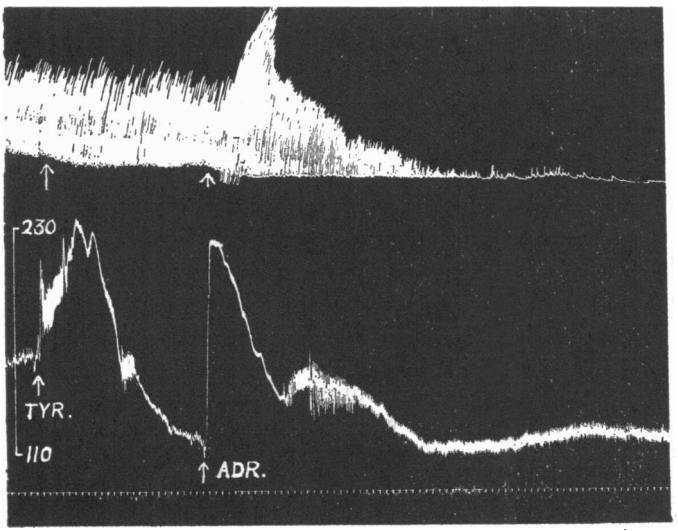

Fig. 6. Cat. Chloralose anæsthesia. Records from above downwards: knee jerk (after-loaded), blood pressure, time in min. Inject successively 10 mg. tyramine, 0·4 mg. adrenaline.

(iv) The effects of other pressor drugs were compared with those of adrenaline. Fig. 6 shows that the injection of 10 mg. tyramine may raise the blood pressure to 250 mm. without affecting the knee jerk at all, while the subsequent injection of adrenaline which produced an equal rise of blood pressure caused the characteristic inhibition. When very large doses of tyramine are employed, e.g. about 100 mg., they produce as a rule a gradual but lasting depression of the knee jerk which is sometimes completely abolished. Respiration may then fail and death ensues. These results are doubtless due to a direct poisonous action of large doses of the drug.

Similar negative results have been obtained with large pressor doses of pituitrin (5 units).

(v) In some experiments, when adrenaline is injected after the carotid arteries have been clipped, it may produce no further elevation of the blood pressure but still gives rise to the typical inhibition of the knee jerk.

In these experiments the important fact to consider is not the degree of general vaso-constriction but the extent to which it affects the blood vessels of the central nervous system. We are not aware of any work on the changes produced by adrenaline in the spinal blood vessels which are those that particularly concern us, but for the moment it would presumably be safe to suppose that they are of the same nature as those taking place in the cerebral blood vessels. Forbes & Wolff [1928] found in six experiments that when adrenaline was injected intravenously in large pressor doses pure constriction of the cerebral vessels did not occur; in four cases constriction took place following an initial dilatation, and in two a pure dilatation occurred. Fig. 14 of their paper shows that the maximal decrease in vessel diameter was 33 p.c. and that the diameter of the pial vessels returned to normal at about the same rate as the blood pressure. In our experiments it has been clear that there is a long time lag between the restoration of the blood pressure and the recovery of the knee jerk. Furthermore, our previously reported observations on the effects of anæmia and anoxia showed clearly that to produce a complete abolition of the knee jerk such as occurs so frequently with adrenaline, it is necessary for the oxygen supply of the central nervous system to be completely cut off for some minutes. It is obvious from the account of Forbes & Wolff that such a state of affairs does not occur following injections of adrenaline.

These experiments and theoretical considerations taken together demonstrate that neither the rise of blood pressure nor the vaso-constriction set up by adrenaline plays any significant part in producing its effects on the knee jerk.

(8) *Direct action of adrenaline on the central nervous system*

The last possibility to be considered is that adrenaline acts directly on the components of the central nervous system. This view is supported by the following observation. It is well known that an increase in the amount of adrenaline injected, once a certain dose has been reached, does not produce a corresponding increase in the rise of blood pressure. Fig. 7 shows an experiment in which the successive injections of 0·05, 0·2, 0·4 mg. adrenaline raised the blood pressure to approximately equal levels, i.e. to about 200 mm. The effect on the knee jerk, however, was proportional to the dose of adrenaline employed: it was negligible with 0·05 mg.; there was a slight depression following the initial stimulation with 0·2 mg.; with 0·4 mg. there was complete inhibition following the initial stimulation, followed by a very gradual process of recovery.

Action of ergotoxin. Ergotoxin paralyses certain of the motor actions of adrenaline through its effects on peripheral nerve endings [Dale, 1906]. It was, therefore, thought of interest to see whether it had any influence on the central actions of adrenaline which have been described in this paper. The problem is complicated by the fact that ergotoxin itself directly modifies the knee jerk in a variable and often marked manner. It is commonly found that the dose of ergotoxin which is necessary to delay or reverse the pressor action of adrenaline, itself depresses or even abolishes the knee jerk permanently. Different preparations of the drug were found to differ among themselves in respect of this action. There is evidence too from other sources [Wright, 1930*a*; Heymans *et al.* 1930] that ergotoxin depresses the medullary centres such as the vaso-motor and the respiratory. In a few experiments, however, we were successful in reversing the vascular action of adrenaline by means of ergotoxin without adversely affecting the knee jerk to a serious extent. In such cases the injection of 0·4–1 mg. adrenaline failed to produce the characteristic effects on the knee jerk. We do not wish to stress these results unduly but they suggest the possibility that under some circumstances ergotoxin may antagonize the central as well as certain of the peripheral actions of adrenaline.

Action of drugs which potentiate the peripheral action of adrenaline. According to Bacq [1936] cocaine, pyrogallol and thyroxine sensitize certain organs to sympathetic stimulation and to the injection of adrenaline. We have carried out experiments with all these substances but in our hands they produced no modification of the adrenaline action on the knee jerk.

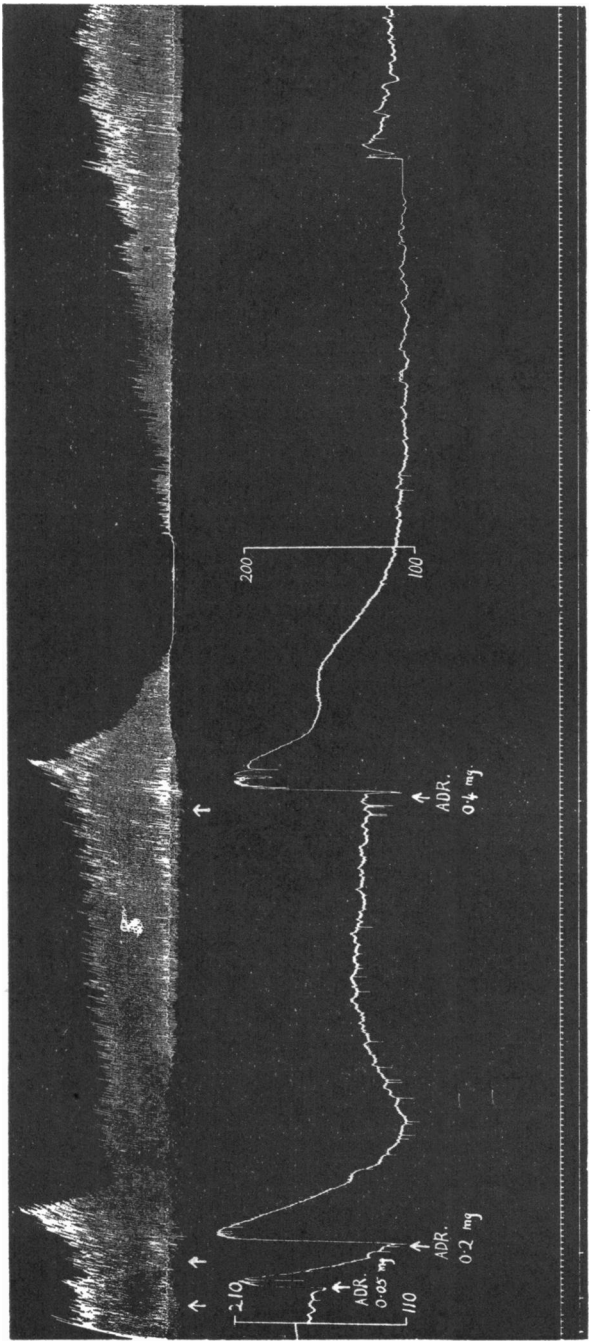

Fig. 7. Cat. Chloralose anæsthesia (0·07 g. per kg.). Both vagi cut. Records from above downwards: knee jerk (after-loaded), blood pressure, time in min., signal line. Inject successively 0·05, 0·2, 0·4 mg. adrenaline.

Discussion

The facts reported demonstrate that adrenaline acts directly on the elements of the central nervous system and more especially on the lumbar spinal somatic centres. The effects of adrenaline on the knee jerk cannot be reproduced by other procedures which cause a similar degree of vaso-constriction or an equal rise of blood pressure. It is certain, therefore, that the vascular changes produced by adrenaline acting either directly or reflexly are not the main factors responsible for producing the alterations in the knee jerk. This conclusion is strengthened by the fact that the knee jerk changes are not significantly modified when adrenaline is injected following denervation of the sino-aortic areas and exclusion of the mesenteric and pulmonary vascular afferents. Even when the more refined method is employed of studying the action currents due to muscle tone in the quadriceps in the decerebrate animal, it cannot be shown that vaso-sensory denervation alters the adrenaline response. These results surprised us in view of the evidence already quoted that afferent impulses from the carotid sinuses and experimental stimulation of the central end of the vagus may produce a considerable degree of inhibition of muscle tone and skeletal reflex activity. Our observations, however, do not absolutely exclude the possibility that vaso-sensory impulses play a minor part during the adrenaline reaction in the intact animal.

We have come all the more unwillingly to these conclusions because the research arose from the theory that injection of adrenaline would inhibit skeletal muscle activities exclusively reflexly from the vaso-sensory zones.

Although the regular response to adrenaline is inhibition, we must admit that initial stimulation occurs with sufficient frequency to merit consideration as a normal component of the reaction. We have not been able to discover the factors which determine the type of response that is to be obtained. In our small number of experiments on the spinal animal initial stimulation has not occurred and the possibility exists that adrenaline may act differently on the spinal and higher centres.

Emphasis has been laid on the remarkably prolonged nature of the adrenaline action on the central nervous system. As we have mentioned, in some experiments 90 min. may elapse before the pre-injection condition is restored. In this connexion it is of interest to draw attention to the experiments of Palme [1936], who found that painting the exterior of the carotid sinus with a solution of 1/1000 adrenaline produced a reflex fall of blood pressure which lasted for 40–60 min. This

is another piece of evidence that adrenaline may act on nervous elements other than the post-ganglionic terminals of the sympathetic and that its action in such cases may be very prolonged. It has been shown that the destruction of adrenaline in the body is effected by specific enzymes, but it does not yet seem to have been determined whether these substances are found in nervous tissues or in what concentrations (Blaschko). Such information might throw considerable light on the prolonged duration of the central action of adrenaline.

It is premature to speculate at the moment about the exact way in which adrenaline modifies the behaviour of somatic centres. It would be of interest to know whether in appropriate concentrations it can modify the oxidative or other metabolic processes of slices of spinal cord *in vitro*.

We do not wish at present to suggest that our experiments have other than a purely pharmacological significance, as the doses of adrenaline that we have to employ to produce our results are far greater than are ever supposed to be secreted in the body; but if one were tempted to consider the results from the physiological standpoint, it is obvious that they are contrary to the generally accepted idea of the emergency function of the adrenal gland, unless we suppose that "passive resistance" is the most appropriate response to certain situations of danger. Nor do we wish to suggest that adrenaline is concerned as a transmitter in skeletal muscle reflexes, though it may possibly modify the formation or removal of any transmitter that may be concerned, or to use Sherrington's terminology, it may influence the central excitatory or inhibitory states.

Summary

1. The action of adrenaline on the knee jerk has been studied in cats under chloralose anæsthesia. Intravenous injection of 0·2–0·4 mg. adrenaline usually produces a diminution or abolition of the knee jerk accompanied by a decrease in muscle tone. Recovery sets in gradually and is complete in 10–90 min. Initial stimulation often precedes the inhibition or there may be a "triple response" consisting successively of depression, stimulation and depression. Floyd & Keele have demonstrated that adrenaline abolishes the action currents due to muscle tone in the quadriceps of the decerebrate cat.

2. The effects described are not due to the chloretone preservative nor to the peripheral action of adrenaline on the quadriceps muscle itself.

3. The adrenaline inhibition is still obtained following denervation of the sino-aortic pulmonary and mesenteric vascular areas or division of the spinal cord in the mid-thoracic region.

4. The adrenaline effects are not reproduced when a similar degree of vaso-constriction and rise of blood pressure is brought about in other ways, such as by occlusion of the carotid arteries (in animals with vagi cut), or by injection of tyramine or pituitrin.

5. Increasing doses of adrenaline, though causing equal rises of blood pressure, produce a progressively greater degree of inhibition of the knee jerk.

6. The action of adrenaline is not potentiated by eserine, cocaine, pyrogallol or thyroxine. It is sometimes antagonized by ergotoxin.

7. It is concluded that adrenaline acts on the knee jerk by a direct effect on the elements of the nervous system. The exact nature of this central action is not known.

8. The significance of these results is discussed.

REFERENCES

Adrian, E. A., Bronk, D. W. & Phillips, G. (1932). *J. Physiol.* **74**, 115.

Bacq, Z. M. (1936). *Arch. int. Physiol.* **42**, 340; *C. R. Soc. Biol.*, Paris, **122**, 112.

Blaschko, H. Private communication.

Dale, H. (1906). *J. Physiol.* **34**, 163.

Feldberg, W. & Schriever, H. (1936). *Ibid.* **86**, 277.

Floyd, W. F. & Keele, C. A. (1936). *Ibid.* **87**, 93*P*.

Forbes, H. S. & Wolff, H. G. (1928). *Arch. Neurol. Psychiat.*, Lond., **19**, 1057.

Gammon, G. D. & Bronk, D. W. (1935). *Amer. J. Physiol.* **114**, 77.

Gruber, C. M. (1922). *Ibid.* **61**, 475; **62**, 438.

Gruber, C. M. (1924). *J. Pharmacol.*, Baltimore, **23**, 335.

Heymans, C., Bouckaert, J. J., Farber, S. & Hsu, F. Y. (1936). *C. R. Soc. Biol.*, Paris, **112**, 115.

Heymans, C., Regniers, P. & Bouckaert, J. J. (1930). *Arch. int. Pharmacodyn.* **39**, 213.

Koch, Eb. (1931). *Die Reflektorische Selbsteuerung des Kreislaufes*, p. 171. Dresden: Steinkopff.

Koch, Eb. (1932). *Klin. Wschr.* p. 225; *Z. Kreislaufforsch.* **24**, 251.

Montgomery, M. F. & Luckhardt, A. B. (1930). *Amer. J. Physiol.* **91**, 210.

Palme, F. (1936). *Z. Kreislaufforsch.* **28**, 173.

Schweitzer, A. (1934). *Ibid.* **26**, 601; *Pflügers Arch.* **235**, 110.

Schweitzer, A. (1935). *Klin. Wschr.* p. 665.

Schweitzer, A. (1936). *J. Physiol.* **87**, 46 *P*.

Schweitzer, A. & Wright, Samson (1936). *Ibid.* **87**, 92*P*.

Schweitzer, A. & Wright, Samson (1937). *Ibid.* **88**, 459.

Schwiegk, H. (1935). *Pflügers Arch.* **236**, 206.

Spychala, V. (1932). *Z. ges. exp. Med.* **83**, 192.

Wright, Samson (1930 *a*). *J. Physiol.* **69**, 331.

Wright, Samson (1930 *b*). *Ibid.* **69**, 493.