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THE PRESSOR AND DEPRESSOR EFFECTS OF CERTAIN SYMPATHOMIMETIC AMINES

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Amphetamine and its *dextro*-isomer are widely used in obesity, in patients who are often liable to suffer from hypertension. Methyl-amphetamine (methedrine) and related substances are also frequently given in repeated doses for their blood-pressure raising effect. As the pharmacological action of these agents becomes weaker on repeated administration, it appeared of interest to reinvestigate and compare their effects.

According to Beyer (1946), the diversity of the response to these agents is not adequately accounted for by Gaddum and Kwiatowski's (1938) theory, which explains the action of ephedrine as being due to its power to inhibit the destruction of adrenaline by amine oxidase. The pressor effects of aromatic alkylamines under various experimental conditions were therefore compared with the action of adrenaline and with each other.

METHODS

Cats were anaesthetized with pentobarbitone intravenously or intraperitoneally, or with ether. Blood pressure was recorded by a mercury manometer connected with a cannula in the carotid artery. All drugs were injected into the external jugular vein. Respiration was recorded by means of a tambour attached to the thoracic or abdominal wall.

RESULTS

A slight increase of blood pressure after an injection of ephedrine, racemic or *d*-amphetamine sulphate, or methedrine could be observed with doses of 0.002 mg./kg. and upwards. The rise was usually maximal with 1 mg./kg. In different animals the response varied greatly both in intensity and duration. After 0.2 mg./kg. dexedrine, the pressor effect lasted for eight minutes in one animal, but it took up to fifty minutes in other cats before the original level was reached.

This individual variation was also present in spinal animals. Within the range of pressor responses no definite quantitative difference was observed between the various amines which were tested.

Curtis (1929), in his studies on ephedrine and related substances, has pointed out that the diminished response to repeated injections makes it impossible to compare quantitatively the effect of these substances in the same animal. It was found, however, that some comparison could be made when small amounts of two agents were injected alternately at short intervals. When using this method for racemic amphetamine and its *dextro*-isomer, we observed a gradually diminishing pressor effect as if the same substance had been injected all the time (Fig. 1).

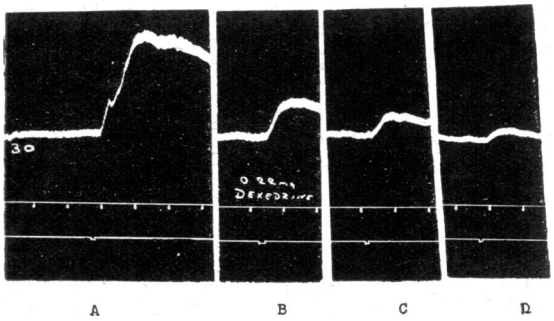

FIG. 1.—Blood pressure effect of alternate doses of 0.1 mg./kg. racemic (A and C) and *dextro*- (B and D) amphetamine sulphate in a spinal cat. Time: minutes.

The small effect of repeated doses of the amines was followed, when injections were continued, by a fall of blood pressure, except with ephedrine, which never caused such an inversion. The amount of the sympathomimetic amine required for the production of such tolerance again varied individually. Usually 1 to 3 mg./kg. were necessary, given either in one or two doses or by injecting smaller amounts repeatedly (Fig. 2). After some hours tolerance to a fresh injection disappeared and

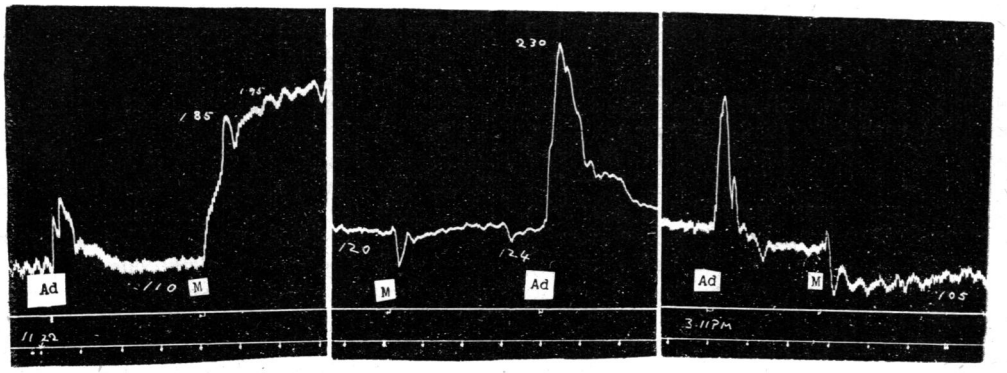

FIG. 2.—Blood pressure effect of repeated doses of 1 mg./kg. methedrine (M) in a cat (pentobarbitone). The pressor effect is marked in A, but reversed in B and C almost 4 hours later; 0.5 ml. adrenaline 1/100,000 (Ad) is pressor throughout. Time: minutes.

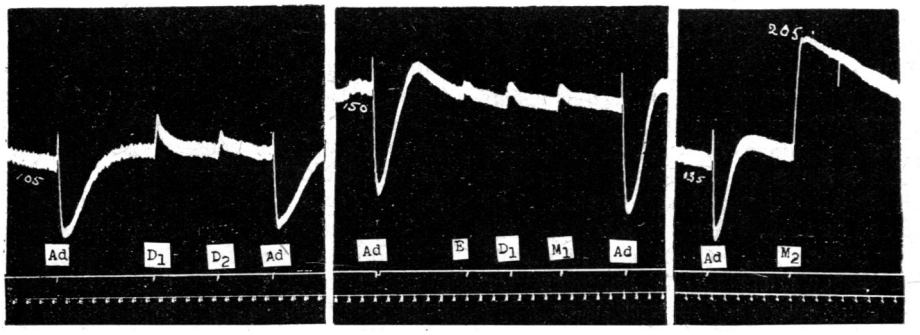

FIG. 3.—Pressor effect of *dextro*-amphetamine sulphate, ephedrine, and methedrine, and depressor effect of adrenaline in a cat (ether). Knee jerk abolished throughout. Time: minutes. Ad = 0.5 ml. adrenaline 1/100,000. D_1 = 0.0017 mg./kg. *d*-amphetamine sulphate. D_2 = 0.00085 mg./kg. *d*-amphetamine sulphate. E = 0.0018 mg./kg. ephedrine. M_1 = 0.0018 mg./kg. methedrine. M_2 = 0.3 mg./kg. methedrine.

a pressor response occurred again. When large doses of the drugs had been given, however, an inverted response was observed even when several hours had been allowed to elapse after the first series of injections. Atropine had no influence on the decreased or inverted responses.

In producing this tolerance to repeated doses the various amines were interchangeable; for example, ephedrine would prevent a rise of blood pressure in response to a later injection of amphetamine or methedrine and *vice versa*. The inverted response after repeated injections was not influenced by atropine, and it was obtained in the decapitated cat.

While the blood pressure effects of ephedrine, racemic amphetamine, dexedrine, and methedrine were very much alike, adrenaline acted differently under our experimental conditions. Under pentobarbitone anaesthesia its pressor action persisted even when large amounts of other amines had been given (Fig. 2).

When, under ether anaesthesia, the response to adrenaline became depressor the other amines retained their pressor effect for their initial doses. This applied both to small and large amounts of the substances (Fig. 3).

The pulse rate in the anaesthetized animals remained substantially unchanged during these depressor responses.

DISCUSSION

Both aliphatic amines and aromatic alkylamines have a decreased blood pressure effect when injected repeatedly (tachyphylaxis). Tainter (1929) has described this for ephedrine, and Ahlquist (1943) has shown it for various aliphatic substances with a sympathomimetic action. Elmes and Jefferson (1942) injected ephedrine into the anaesthetized cat

at hourly intervals and found the pressor effect to decrease gradually; Burn (1946) observed a similar effect with methedrine. Detrick *et al.* (1937), confirming the observation for amphetamine, found in dogs great variability of the pressor response. Pinkston *et al.* (1939) and Pinkston and Pinkston (1939) state that after an initial dose of 1 mg./kg. the magnitude of the response varied directly with the dosage up to 6 to 8 mg./kg. Clinical studies by Myerson *et al.* (1936) and Reifenstein and Davidoff (1938) stress the irregularity of pressor responses to amphetamine in man.

Our experiments show that in the anaesthetized cat 0.002 mg./kg. of these amines will usually produce a very slight rise of blood pressure. The pressor effect becomes sustained after 0.2 to 0.5 mg./kg. and maximal with 1 mg./kg. It may last for almost an hour after a large dose in one cat and for a few minutes only in another. We did not find that the depth of anaesthesia had much influence on this variability.

The strength of pressor action of various agents can be compared in the same animal when small doses are given. Though tachyphylaxis develops, one may find a larger or smaller pressor action when the respective substances are injected at short intervals of one another, but an exact comparison could not be made. Alles (1939) and Hauschild 1940) found that racemic amphetamine and its *dextro*-isomer had the same pressor effect, while Swanson *et al.* (1943) considered the *laevo*-isomer to be more powerful in its pressor action. Our own observations did not show any appreciable difference between the various forms of amphetamine.

That the differences of blood-pressure effects between various animals are not due to a varied sensitivity of the central nervous system and, particularly, that they are not secondary to the action on the respiratory centre was shown in the decapitated cat. Here, as well as when atropine had been given, the same individual differences were observed and tachyphylaxis developed in the same way as in the intact animal.

Several stages could be observed as the animals became gradually saturated with the drugs:

1. The pressor effect became smaller and was eventually absent as if an inert substance had been injected.
2. A momentary drop of blood pressure was immediately followed by a short elevation resulting in a biphasic tracing.
3. The blood pressure fell and returned to its original level sometimes quickly and sometimes very slowly.

However, ephedrine never led to a drop in blood pressure, though the diminution and eventual disappearance of the pressor effect developed as readily as in experiments with amphetamine and methedrine.

The depressor effect was explained by Ahlquist (1943, 1944) and Jackson (1944) as being due to myocardial depression. In flow meter studies on the dog's hind leg, Ahlquist (1945) found that the depressor response was partly due to peripheral vaso-dilatation, and that it was similar to the dilatation after adrenaline. From our observations of the pulse rate during the depressor phase, there was no evidence of a direct effect on the heart. As the depression is not influenced by atropine and as it is also present in the spinal cat, it appears to be due to a vaso-dilator action in the periphery.

The pressor action of aliphatic amines can be blocked by repeating doses or by ephedrine (Ahlquist, 1945). The same applies to the sympathomimetic effect of aromatic alkyl-amines. Hence, once ephedrine, amphetamine, dexedrine, or methedrine have been given in fair doses, further injections will not cause a rise of blood pressure and may, apart from ephedrine, even produce a depressor effect which lasts for a considerable time.

The effect of the amines tested was in our experiments quite different from that of adrenaline. Under pentobarbitone or in the spinal cat the adrenaline response remained pressor. Likewise when under ether anaesthesia adrenaline acted as a depressor, ephedrine, amphetamine, dexedrine and methedrine had their usual pressor effect until tachyphylaxis developed. These differences between adrenaline and the other sympathomimetic amines when given to the same animal at short intervals of each other made it clear that under the given experimental conditions their mechanisms of action are not identical.

It appears difficult to reconcile these results with the theory of Gaddum and Kwiatowski (1938) according to which adrenaline is the substance through which ephedrine acts. If this were true the action of adrenaline and the other sympathomimetic amines would be more or less alike. Tainter (1929, 1933), Aström (1948), and others have shown differences in the effect of ephedrine and other pressor amines.

Tainter (1929) concluded that ephedrine and adrenaline did not have the same seat of pressor action. The opposite responses to the group of sympathomimetic amines on the one hand and to adrenaline on the other shown in our experiments make it likely that their modes of action are different.

Beyer (1946) suggested that the action of sympathomimetic amines might be explained by their effect on the formation of adenosinetriphosphate as influenced by various breakdown products of metabolism and by their influence on the efficiency with which energy is used. This would allow more flexibility than would be permissible if the action of all sympathomimetic amines were mediated through one common agent, adrenaline. It would allow for differences between the effect of adrenaline and the other amines described in this paper. The observation by Govier *et al.* (1945) that certain concentrations of amines lead to an increase of oxidations while larger amounts produce an inhibition of oxygen uptake might help to explain their diminishing pressor effect and the eventual reversal to a depressor action.

We are indebted to Messrs. Menley and James, Ltd., for a supply of dexedrine.

SUMMARY

1. In the anaesthetized and in the spinal cat racemic amphetamine and its *d*-isomer are equally potent in their effect on the blood pressure.

2. Ephedrine differs from amphetamine, its isomers, and methedrine in that on repeated doses it does not cause a fall of blood pressure.

3. As the various amines are interchangeable in blocking the pressor effect an injection of methedrine may result in a drop of blood pressure when either ephedrine, amphetamine, or methedrine itself has been given beforehand in fair dosage.

4. None of these effects is influenced by atropine.

5. The pressor effect of adrenaline persists independently of the changes in the action of the other amines. When, under ether, adrenaline is depressor the other amines have a pressor effect. Under pentobarbitone and in the spinal cat adrenaline still raises the blood pressure when, through repeated injections, ephedrine has lost its effect and amphetamine and methedrine have become depressor agents.

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