CAN ADRENALINE POTENTIATE THE ACTION OF NORADRENALINE?

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IT is known that ephedrine in low concentrations sensitises the frog heart and perfused frog's blood vessels to both adrenaline and noradrenaline, whilst in high concentrations it is antagonistic to both amines[1]. Since the synergism and antagonism run quite parallel, it is possible that, in these excitor responses, adrenaline and noradrenaline utilise the same receptor substances. When added to adrenaline, noradrenaline either has no effect or a simple additive action on the adrenaline response. It is suggested, therefore, that it may compete with adrenaline for the receptor substance, but the combination is slow and its high activity prevents its use in concentrations of 100 to 1000 times that of adrenaline[2,3]; such concentrations of certain other sympathomimetic amines (e.g., ephedrine) would antagonise the adrenaline effects.

The present investigation was undertaken to study this interaction further, and to note if adrenaline could in fact sensitise tissue *in vivo* to noradrenaline. It has already been reported[4] that the action of intravenous doses of noradrenaline on the non-pregnant uterus of a cat under chloralose anæsthesia may be potentiated by intravenous doses of adrenaline.

METHODS

Spinal cats prepared by the method of Burn, Hutcheon and Parker[5] were used throughout. In the first series of experiments, contractions of the right nictitating membrane were recorded as well as blood pressure records from the left carotid artery. A three-way cannula was inserted into the right carotid artery[6], and drugs were injected by this route. In the second series, contractions of the right nictitating membrane were recorded as well as blood pressure records from the left carotid artery. One branch of the splenic vein and the right femoral vein were cannulated and drugs were injected by these routes. In the third series with female cats, contractions of the left horn of the non-pregnant uterus were recorded using thread, pulleys, and a frontal writing lever. Drugs were given through cannulæ inserted in the right femoral vein and the right femoral artery.

RESULTS

Intra-carotid doses of adrenaline were found to sensitise the nictitating membrane of the cat to intra-carotid doses of noradrenaline (Fig. 1). These observations were positive in 4 out of 5 cats tested. It will be noted that the ratio of equi-active dose of noradrenaline to that of

adrenaline is about 4, a value usually obtained when intravenous doses of the amines are given.

In the second series of 4 cats, equi-active intravenous doses of adrenaline and noradrenaline were used. Following a very large intraportal dose of methylene blue (to partially inactivate the amine oxidase in the

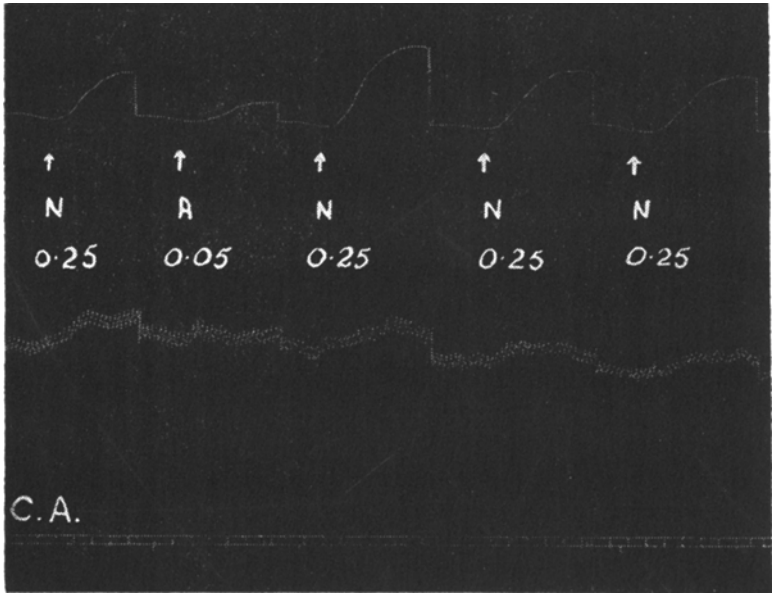

FIG. 1. Spinal Cat, 2 kg. Upper record, contractions of the right nictitating membrane; lower record, blood pressure recorded from the left carotid artery. Injections of adrenaline (A) and noradrenaline (N) into the right carotid artery. Doses in μg. Time in 10 sec. Note that a small dose of adrenaline sensitises the membrane to doses of noradrenaline.

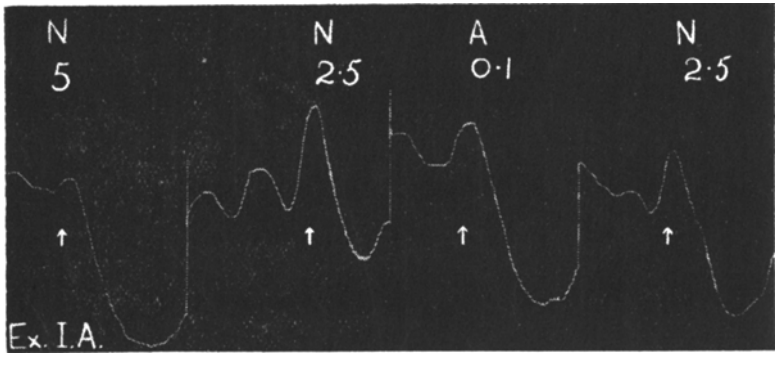

FIG. 3. Spinal Cat, 1·8 kg. Record of movement of left horn of non-pregnant uterus. Injections of adrenaline (A) and noradrenaline (N) into right external iliac artery. Doses in μg. Time in 10 sec. Noradrenaline (2·5 μg.) is potentiated by previous dose of adrenaline (0·1 μg.).

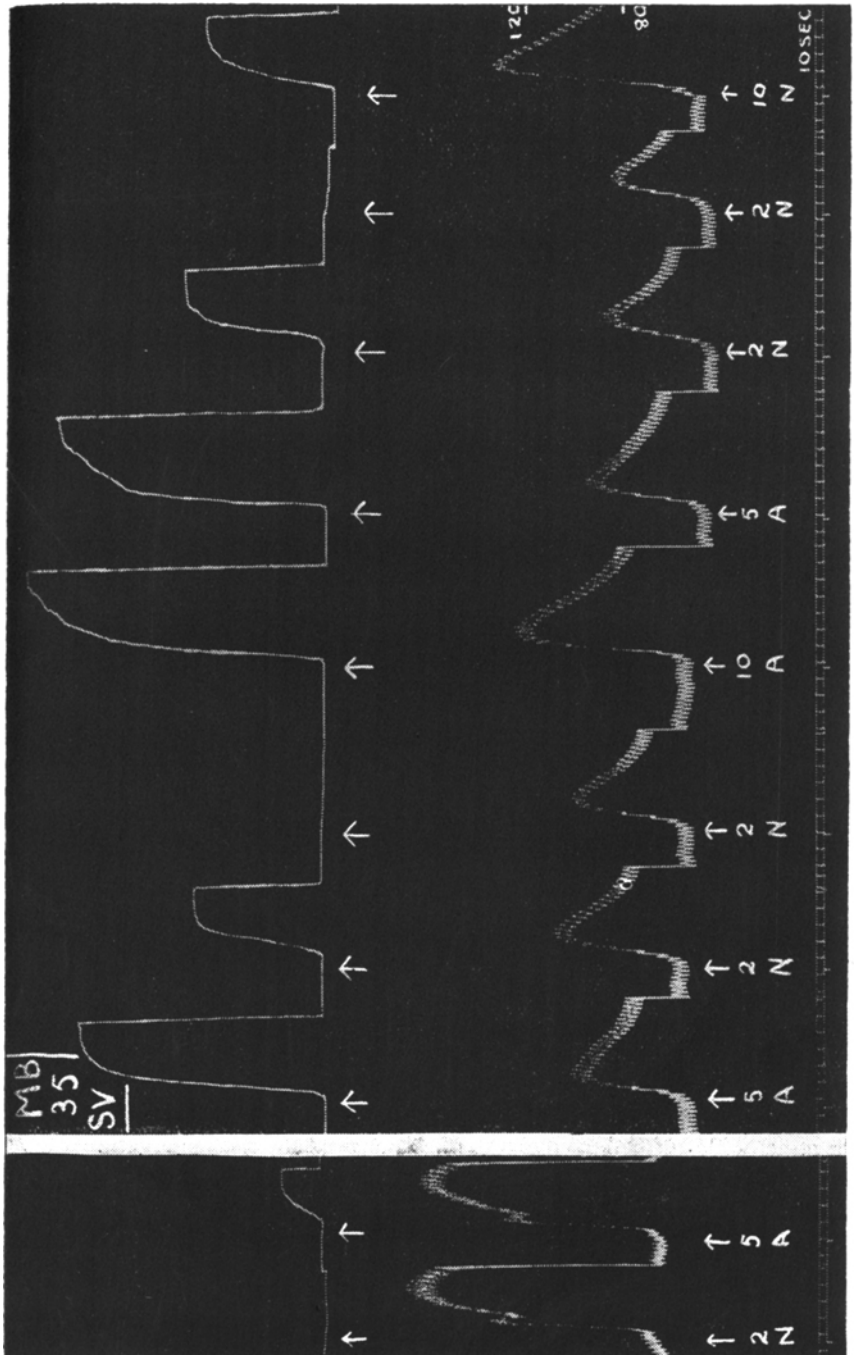

FIG. 2. Spinal Cat, 3·9 kg. Records as in Fig. 1. Injections of adrenaline (A) and noradrenaline (N) into the right femoral vein. Between the two tracings, 35 ml. 0·002 M methylene blue given intraportally. Doses in μg. Time in 10 sec. Noradrenaline effect on membrane is potentiated by previous dose of adrenaline.

nictitating membrane and in the liver), the effect of these doses on the blood pressure was depressed, but there was potentiation on the membrane (Fig. 2). It will be seen that adrenaline sensitises the nictitating membrane to doses of noradrenaline, and the effect may be repeated. It is known that both amines are readily and rapidly destroyed by amine oxidase, so that this is probably true sensitisation and not simply enzyme inhibition by adrenaline.

In the third series on 3 female cats, intra-arterial doses of adrenaline sensitised the uterus to intra-arterial doses of noradrenaline (Fig. 3). Similarly adrenaline by intravenous route produced the same action on intravenous noradrenaline (Fig. 4).

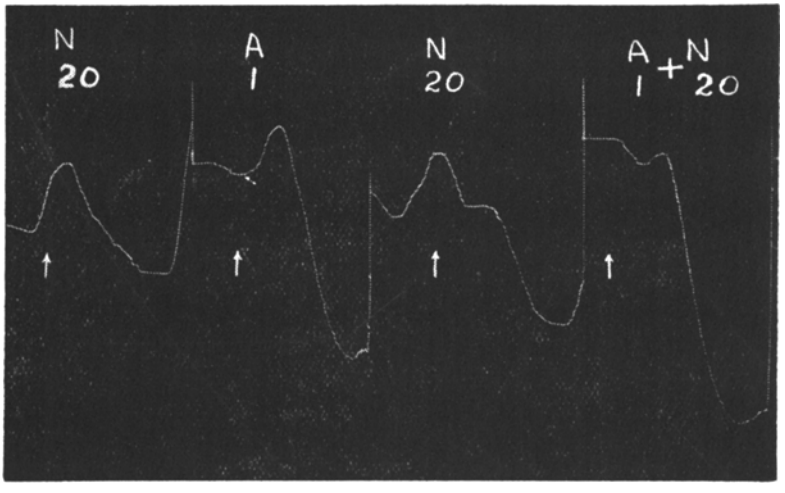

FIG. 4. Spinal Cat, 2 kg. Record as in Fig. 3. Drugs given by femoral vein. Doses in μg. Time in 10 sec. Note that adrenaline (A) sensitises the uterus to doses of noradrenaline (N).

DISCUSSION

These four results, together with that reported earlier on the non-pregnant uterus, illustrate that there may be sensitisation of tissues *in vivo* to noradrenaline by active doses of adrenaline. It is a little difficult to understand the mechanism by which this sensitisation can be produced. The first observation that may be part of the explanation is that amine oxidase (the enzyme system responsible for the inactivation of these amines) has a preference for noradrenaline as compared with adrenaline[7]. If adrenaline temporarily reduced the activity of this enzyme, then the first subsequent dose of noradrenaline would be potentiated. This is well seen in the experiments using intraportal doses of methylene blue. The second observation is that in life a mixture of adrenaline and noradrenaline is liberated from the adrenal medulla and other adrenergic nerve endings when these fibres are stimulated, so that it may be advantageous for one amine to facilitate or potentiate the action

of the other. It is certainly of interest that the observations recorded here refer both to excitor and inhibitor actions.

SUMMARY

Intra-arterial and intravenous doses of adrenaline may, under certain circumstances, sensitise the nictitating membrane and non-pregnant uterus of a spinal cat to corresponding doses of noradrenaline.

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