RESEARCH PAPERS

ANTAGONISM OF GUANETHIDINE BY DEXAMPHETAMINE AND OTHER RELATED SYMPATHOMIMETIC AMINES

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Dexamphetamine and certain other indirectly acting sympathomimetic amines prevent or reverse the sympathetic nerve blocking action of guanethidine in anaesthetised cats and dogs. Noradrenaline and dopamine do not antagonise the blocking action of guanethidine. These observations are discussed in relation to the mode of action of guanethidine and to a possible clinical significance of these findings.

WILSON and Long (1960) reported that bretylium did not reduce the blood pressure in hypertensive patients who were being treated with amphetamine to reduce obesity. In other patients, whose hypertension was successfully treated with bretylium, they found that amphetamine antagonised the hypotensive action of bretylium. Laurence and Rosenheim (1960) found in two patients that methylamphetamine abolished the postural hypotension due to treatment with guanethidine. Recently, Day (1962) has investigated the effect of a number of sympathomimetic drugs in antagonising the sympathetic nerve-blocking activity of guanethidine, bretylium and xylocholine. He found that when the responses of the rabbit's isolated ileum and of the cat's nictitating membrane to sympathetic nerve stimulation had been abolished by these sympathetic nerve blocking drugs the responses could be restored by dexamphetamine, ephedrine, mephentermine and other related sympathomimetic amines, whereas adrenaline, noradrenaline and phenylephrine did not restore responses.

We now wish to report further observations on the antagonism of guanethidine by dexamphetamine and related drugs.

METHODS

Dogs and cats were anaesthetised with chloralose (80–100 mg./kg.) sometimes with an adjuvant dose of pentobarbitone (5–10 mg./kg.). The blood pressure was recorded, usually from a femoral artery, with a mercury manometer. Drugs were injected or infused into a suitable vein.

Sympathetic responses were elicited either directly, by stimulating the cervical sympathetic nerve and recording the contractions of the nictitating membrane, or reflexly, by bilateral occlusion of the carotid arteries or by electrical stimulation of the central end of a divided vagus nerve, and recording the effects on the blood pressure.

RESULTS

Experiments on Dogs

The reflex pressor response to occlusion of the common carotid arteries was abolished after injection of guanethidine (Fig. 1). This phenomenon

has been observed previously by Maxwell, Plummer, Schneider, Povalski and Daniel (1960), Page and Dustan (1959) and McCubbin (1961). Fig. 1 also shows that at the same time as the response to sympathetic nerve stimulation was blocked the response to injection of noradrenaline was

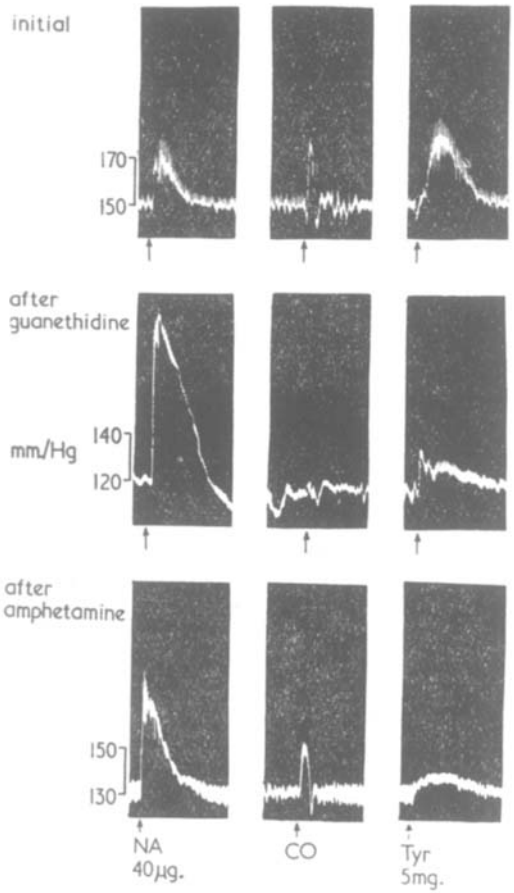

FIG. 1. Dog 12·0 kg., blood pressure recorded from femoral artery. Responses to noradrenaline 40 μg. (NA), bilateral carotid occlusion for 20 sec. (CO) and tyramine 5 mg. (Tyr.). Upper series of tracings: control observations. Middle series: after guanethidine 12 mg./kg. Lower series: after 1 mg./kg. dexamphetamine.

enhanced, confirming the findings of Maxwell and others (1960) and McCubbin (1961). These effects of guanethidine are very persistent; Maxwell and others (1960) and Page and Dustan (1959) using dogs found that the effects of a single, large dose of guanethidine were still present from 5 to 20 days later. However, as Fig. 1 shows, after the injection of a small dose of dexamphetamine the pressor response to occlusion of the carotid arteries was restored and the sensitivity to noradrenaline was reduced. Maxwell, Plummer, Povalski and Schneider (1960) found that guanethidine

antagonised the response to tyramine (and related compounds), and we have also observed this effect (Fig. 1). The injection of dexamphetamine, which caused the restoration of the pressor response provoked by occlusion of the common carotid arteries, did not restore the response to tyramine.

In other experiments it was observed that the sympathetically mediated pressor responses to stimulation of the central end of the vagus nerve were abolished by guanethidine (10 mg./kg.) and then partly restored after dexamphetamine (1 mg./kg.).

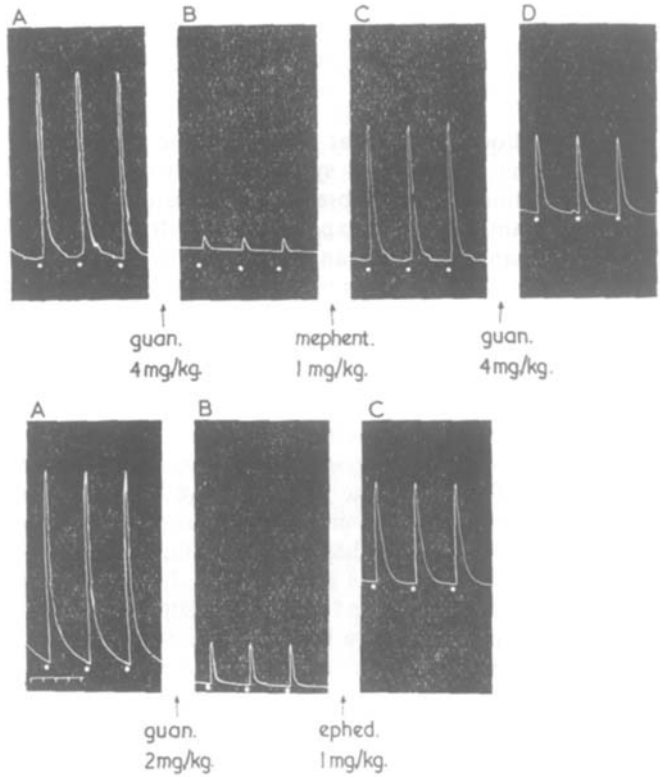

FIG. 2. Contractions of cat nictitating membrane to cervical sympathetic nerve stimulation. Stimulation at white dots with supramaximal voltage pulses of 2 msec. duration at 20/sec. applied for 10 sec. in upper records and for 20 sec. in lower records at 3 min. intervals. Upper and lower records are from two separate experiments. In the experiment shown in the upper records guanethidine (guan.) reduced the contraction, and mephentermine (mephent.) partly restored them. A second dose of guanethidine then had a lesser effect. The experiment in the lower series of records shows the block produced by guanethidine and the restoration of responses by ephedrine (ephed.).

We have investigated the effects of dexamphetamine alone on reflexly induced, sympathetic pressor responses in the anaesthetised dog. It was thought possible that the action of dexamphetamine in reversing guanethidine blockade might be due to a sensitisation of effector organs to the effects of sympathetic nerve stimulation. However, the results obtained

were not consistent with this view. Thus, when the blood pressure had returned to normal after an injection of dexamphetamine (1·6 mg./kg.) the reflex pressor responses to bilateral carotid artery occlusion and to central vagal stimulation were considerably reduced, whilst the sensitivity to noradrenaline was enhanced. It should be noted that these effects of dexamphetamine are qualitatively the same as the effects of guanethidine. When guanethidine was given after dexamphetamine there was no further blockade of the sympathetically induced responses. This observation is in accord with the findings of Day (1962) that dexamphetamine not only reverses a guanethidine blockade, but if given first will prevent its appearance.

Experiments on Cats

Day (1962) has shown in the cat that after the contractions of the nictitating membrane to cervical sympathetic nerve stimulation are blocked by guanethidine they can subsequently be restored by dexamphetamine or by related amines. The experiments illustrated in Fig. 2 show that mephentermine and ephedrine antagonise the action of guanethidine in blocking the response of the cat's nictitating membrane to sympathetic nerve stimulation. After mephentermine the same dose of guanethidine which previously produced a 94 per cent reduction in response to nerve stimulation now produced only a 45 per cent reduction.

Prolonged administration of guanethidine. Experiments in which the acute sympathetic nerve blocking action of guanethidine is reversed up to 4 hr. later by injection of dexamphetamine, are subject to the criticism that any delayed actions of guanethidine may not have had sufficient time to develop. One delayed action of guanethidine is the depletion of the noradrenaline content of tissues (Sheppard and Zimmerman, 1959; Cass, Kuntzman and Brodie, 1960; Cass and Spriggs, 1961). In this respect guanethidine resembles reserpine and it has been suggested that guanethidine may owe its sympathetic nerve blocking activity to the depletion of the noradrenaline stores. Therefore experiments were carried out on cats chronically treated with guanethidine.

The records illustrated in Fig. 3 are from an experiment on a cat which had been injected with large doses of guanethidine (12·5 mg./kg./day) for 7 days. The response of the nictitating membrane to stimulation of the cervical sympathetic nerve was a contraction of 3 mm. (on the kymograph). The reflex increase in blood pressure produced by occluding both the common carotid arteries was 40 mm. Hg. This cat was very sensitive to noradrenaline, 5 μg. injected intravenously produced a 100 mm. rise in blood pressure. An intravenous injection of 0·5 mg./kg. of dexamphetamine sulphate increased the blood pressure and contracted the nictitating membrane. These responses were smaller than those produced by the same dose of dexamphetamine in normal cats, but the initial effect of dexamphetamine on blood pressure was greater than that usually seen in guanethidine-treated animals (Maxwell, Mull and Plummer, 1959). However, the pressor response to dexamphetamine differed from that usually seen in normal cats in that the blood pressure did not return to the

pre-injection level during the next 2 hr. It appeared therefore that in addition to producing a pressor response, dexamphetamine had reversed the hypotension caused by guanethidine. Thus, before dexamphetamine, the mean blood pressure was 92 mm. but 2 hr. after the amine it was 104 mm. This reversal of the hypotension is even more impressive when it is considered that the blood pressure usually declines progressively during such experiments. That the sustained increase in blood pressure was, in fact, due to reversal of guanethidine-induced hypotension is borne out by the observation that the responses of the nictitating membrane to sympathetic nerve stimulation gradually increased, until finally the contraction of the nictitating membrane was 43 mm. (on the kymograph). The pressor response to occlusion of both common carotid arteries was increased by 50 per cent, whilst the response to noradrenaline was decreased by 20 per cent. Later in this experiment a further dose of 0·5 mg./kg. of dexamphetamine produced no more improvement of the responses of the nictitating membrane or of the carotid sinus pressor reflex. At this stage a further dose of guanethidine (12·5 mg./kg.) was given (which in normal cats rapidly and completely abolished sympathetic responses); it depressed but failed to abolish the contractions of the nictitating membrane or the pressor response to carotid occlusion. This experiment shows that dexamphetamine can reverse the effects of prolonged guanethidine treatment as effectively as it reverses the effects of an acute dose.

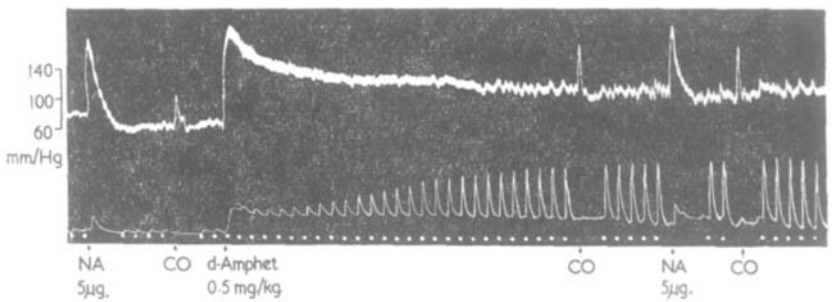

FIG. 3. Cat 3·2 kg., injected with 12·5 mg./kg./day guanethidine for 7 days. Upper record, blood pressure from left femoral artery. Lower record, contractions of right nictitating membrane. At white dots, right cervical sympathetic nerve stimulated with 5 V, 2 msec. pulses at 20/sec. for 8 sec. At NA, intravenous injections of 5 µg. noradrenaline bitartrate, at d-Amphet., 1·6 mg. of dexamphetamine sulphate, and at CO, both common carotid arteries were occluded for 30 sec.

Comparison with reserpine. In reserpine treated cats endogenous stores of noradrenaline are reduced. This leads to a failure of the responses to sympathetic nerve stimulation and of the effect on the blood pressure of tyramine, an amine which has been shown to produce its normal pressor action by releasing noradrenaline (Burn and Rand, 1958). When an infusion of noradrenaline, or one of its precursors, such as dopamine, is given, the responses to sympathetic stimulation and to tyramine are partly restored as a result of restoration of the noradrenaline

content of the tissues (Burn and Rand, 1958; Pennefather and Rand, 1960). In cats treated chronically with guanethidine some degree of noradrenaline depletion would be expected (Cass, Kuntzman and Brodie, 1960), but infusions of noradrenaline or of dopamine did not appreciably restore responses to sympathetic nerve stimulation although they did slightly increase the responses of the nictitating membrane to tyramine. These results are shown in Fig. 4 in an experiment on a cat which had been pre-

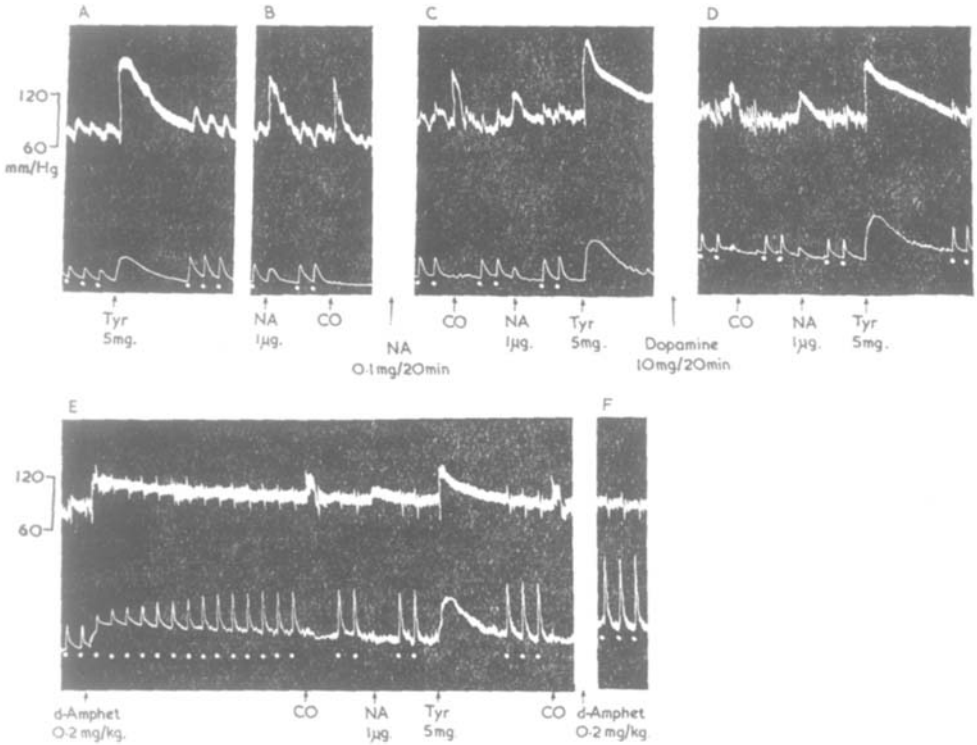

FIG. 4. Cat 2·2 kg., injected with 12·5 mg./kg./day of guanethidine for 4 days. Blood pressure from left carotid artery. At white dots, right cervical sympathetic nerve stimulated with 10 V, 2 msec. pulses at 20/sec. for 8 sec. At Tyr, tyramine hydrochloride, at NA, noradrenaline, at d-Amphet., dexamphetamine sulphate, given intravenously in the doses stated in the figure. At CO, right carotid artery occluded for 1 min.

treated with guanethidine (12·5 mg./kg./day) for 4 days; the responses of the nictitating membrane to cervical sympathetic stimulation and to tyramine (2 mg./kg.) were considerably depressed. After an infusion of noradrenaline the response of the nictitating membrane to tyramine was increased, but the responses to sympathetic nerve stimulation were not. Later, an infusion of dopamine further increased the response of the nictitating membrane to tyramine but did not increase responses to nerve stimulation. However, dexamphetamine increased the responses to sympathetic nerve stimulation, but decreased the responses to tyramine.

Our explanation of these results is that the decreased responses to sympathetic nerve stimulation after guanethidine treatment were not due solely to depletion of noradrenaline stores, although some degree of depletion may have accounted for the reduced responses to tyramine and for the ability of noradrenaline and dopamine to increase the response of the nictitating membrane to tyramine.

Discussion

Mode of Action of Guanethidine

Guanethidine has the property in common with bretylium and with reserpine of impairing the responses to sympathetic nerve stimulation. In addition guanethidine and reserpine prevent the action of sympathomimetic amines whose effects are mediated through release of noradrenaline. Tyramine and dexamphetamine serve as examples of this type of sympathomimetic amine.

However, there are marked differences between the actions of guanethidine and bretylium on the one hand and those of reserpine on the other. Thus, reserpine produces its effects mainly as a result of depletion of the transmitter substance (noradrenaline) from sympathetic nerve endings (Bein, 1953; Muscholl and Vogt, 1953; Burn and Rand, 1958; Burn, Leach, Rand and Thompson, 1959). When the store is replenished by an infusion of noradrenaline the responses to sympathetic nerve stimulation and to indirectly acting sympathomimetic amines are restored (Burn and Rand, 1958; Pennefather and Rand, 1960). The impairment in responses to sympathetic nerve stimulation induced by bretylium and by guanethidine are not reversed by noradrenaline (McCubbin, Kaneko and Page, 1961; Day, 1962). However, the blocking action of these agents is convincingly reversed by the injection of a small dose of dexamphetamine or of a related compound. For these reasons we suggest that the depletion of noradrenaline by guanethidine is not its main action and is not responsible for its hypotensive action.

There are minor differences between the actions of guanethidine and of bretylium. Thus, bretylium does not block the action of indirectly acting sympathomimetic amines such as tyramine (Boura and Green, 1959; Huković, 1960; Burn and Rand, 1960), and does not cause a significant depletion of noradrenaline stores (Cass and Spriggs, 1961).

However, Day (1962) has shown that dexamphetamine and related amines antagonise the sympathetic nerve blocking action of guanethidine and of bretylium, but not the block produced by reserpine. Therefore, from a practical as well as from a theoretical point of view, the action of bretylium and guanethidine may be classed together as quite distinct from the action of reserpine.

The action of guanethidine in potentiating noradrenaline at the time when sympathetic nerve responses are blocked, and the subsequent decrease in response to noradrenaline when sympathetic nerve responses are restored by dexamphetamine, suggest that there is a relationship between the functioning of the sympathetic nerves and the sensitivity of

tissues to noradrenaline. The potentiation of noradrenaline by guanethidine may be related to the potentiation of noradrenaline by denervation. After surgical section of the nerve the onset of supersensitivity occurs after degeneration of the distal portion of the nerve, but guanethidine "denervates" at the end of the nervous apparatus and so the supersensitivity is immediate in onset. Similar considerations apply to the hypersensitivity to noradrenaline produced by bretylium.

Antagonism of Guanethidine by Dexamphetamine

The exaggerated response to injected noradrenaline after guanethidine is decreased by dexamphetamine; therefore it is unlikely that the explanation for the restoration of responses to sympathetic stimulation by dexamphetamine is due to an increased sensitivity of the effector organs to the sympathetic nerve transmitter. Another explanation for the antagonism is that dexamphetamine may increase the amount of transmitter liberated by the nerves, but this explanation is unlikely because after dexamphetamine, given alone, the pressor responses to occlusion of the common carotid arteries and to central vagus nerve stimulation were impaired at the same time as the response to noradrenaline was potentiated and the response to tyramine reduced; these effects of dexamphetamine are, in fact, the same as the actions of guanethidine.

Day (1962) has proposed a mechanism to explain the way in which dexamphetamine antagonises the sympathetic nerve blocking action of guanethidine. He drew attention to the fact that dexamphetamine and guanethidine have a number of properties in common. Both possess sympathomimetic activity which depends on the presence of a store of noradrenaline at the sympathetic nerve ending, and both diminish the response to sympathetic nerve stimulation. Dexamphetamine is much less potent than guanethidine in diminishing the response to sympathetic stimulation. If dexamphetamine and guanethidine were acting at the same site, then the less potent blocking drug dexamphetamine may displace the more potent drug guanethidine. Day has recently made observations which show that the antagonism of guanethidine by dexamphetamine is probably competitive in nature.

The Use of Dexamphetamine to Terminate a Guanethidine or Bretylium Induced Hypotension

The intestinal absorption of bretylium is irregular and sometimes the blood pressure may fall precipitously (Dollery, Emslie-Smith and McMichael, 1960). Dexamphetamine could be used as an antidote for overdosage with either bretylium or guanethidine.

In experimental animals and in patients who have been treated with bretylium or guanethidine there is a marked hypersensitivity to noradrenaline (Laurence and Rosenheim, 1960). On this account and because of its transient action, noradrenaline is not a suitable drug for overcoming the hypotension.

There is no hypersensitivity to the pressor action of dexamphetamine after bretylium and guanethidine; instead dexamphetamine produces a

persistent increase in blood pressure of slow onset. The possession of a reliable and rapidly acting antagonist of bretylium and guanethidine, such as dexamphetamine which has the added advantage of being active by mouth, may extend their use to patients with occlusive vascular disease in whom unpredictable falls in blood pressure are dangerous (Dollery and others, 1960).

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