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CARDIOVASCULAR INTERACTIONS BETWEEN ACUTELY ADMINISTERED RESERPINE AND MEPHENTERMINE

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Although it is well established that chronic administration of reserpine depletes the noradrenaline stores of peripheral organs (Carlsson, Rosengren, Bertler & Nilsson, 1957; Burn & Rand, 1958a) and reduces the cardiovascular responses to certain of the sympathomimetic amines (Carlsson *et al.*, 1957; Burn & Rand, 1958b), the early influence of acutely administered reserpine on indirectly acting amines has not been well defined. Schmitt & Schmitt (1958a,b) showed that the responses to phenethylamine, tyramine and ephedrine on the blood pressure and nictitating membrane were augmented after acutely administered reserpine. This observation has been confirmed by several investigators (Nakamura & Shimamoto, 1960; Schmitt & Schmitt, 1960; Nasmyth, 1962; Walaszek & Burford, 1963). The augmented response to indirectly acting sympathomimetic amines seen after acutely administered reserpine has been attributed to an increased release of catechol amines from tissue stores (Yelnosky, Kirkpatrick & Govier, 1962; Ross, Wenger, Ludden & Stone, 1963). Harrison, Chidsey & Braunwald (1963) presented evidence for this view, showing that the quantity of noradrenaline released from the heart by tyramine was greatly enhanced after reserpine.

" Reserpine reversal," a pressor response to the administration of reserpine after an indirectly acting sympathomimetic amine, was reported by Schmitt & Schmitt (1957) using ephedrine. Valdecasas, Salva & Cuenca (1958) obtained similar results with amphetamine; Chessin, Dubnick, Leeson & Scott (1959) with methylamphetamine; and Yelnosky *et al.* (1962) with an amphetamine derivative. It has been suggested that the pressor response to reserpine after indirectly acting sympathomimetic amines is also due to an enhanced release of catechol amines from the tissue stores (Schmitt & Schmitt, 1961; Yelnosky *et al.*, 1962).

Mephentermine also releases catechol amines (Chidsey, Harrison & Braunwald, 1962; Swaine, Perlmutter & Ellis, 1964) and the pressor response to it is potentiated after an acute injection of reserpine (Breese & Nash, 1964). " Reserpine reversal " after a previous dose of mephentermine has also been observed. The purpose of the present study was to examine further the interrelationships of mephentermine and acutely administered reserpine on the cardiovascular responses and catechol amine stores of the dog.

METHODS

General techniques. Mongrel dogs of either sex were anaesthetized with sodium pentobarbitone and vagotomized or atropinized (0.5 mg/kg). A Harvard respirator was used to maintain those animals in which a midline thoracotomy was performed. Ventricular contractile force was measured with a Walton-Brodie strain-gauge arch (Boniface, Brodie & Walton, 1953) sutured to the right ventricle; heart rate was calculated from the electrocardiogram; and carotid blood pressure was measured with a Statham pressure transducer or a mercury manometer. Spinal animals were prepared under pentobarbitone anaesthesia by sectioning the spinal cord at the second cervical vertebra. Animals were treated with reserpine (1 mg/kg) either 24 hr (subcutaneously) or 7 min (intravenously) before administration of mephentermine. Noradrenaline content of the left ventricular tissue was measured by the method of Shore & Olin (1958). Solutions of mephentermine sulphate, atropine sulphate, cocaine hydrochloride and noradrenaline bitartrate were made in 0.9% saline. Reserpine was dissolved in 20% ascorbic acid solution. Doses of reserpine and noradrenaline are expressed as free base; all other drug doses are expressed as salt. Either Student's *t*-test or analysis of variance was used for analysis of data. A probability value of <0.05 was considered significant.

Dose/response curves. A dose/response curve of the blood pressure effects of mephentermine was established by giving to individual dogs single doses of mephentermine at one of the following levels: 0.03, 0.1, 0.3 and 1.0 mg/kg. In these same animals, 7 to 10 min after the dose of mephentermine, a single dose of reserpine (1 mg/kg) was administered to show the effects of the different doses of mephentermine on the responses to reserpine. In separate groups of spinal and anaesthetized animals, a dose/response curve was obtained for mephentermine after reserpine by giving reserpine (1 mg/kg) 7 min before various doses of mephentermine—0.01, 0.03, 0.1 and 0.3 mg/kg.

Adrenalectomized dogs. Reserpine (1 mg/kg) was administered 7 min before mephentermine (0.3 mg/kg) in acutely adrenalectomized animals and blood pressure responses were compared with those obtained in nonadrenalectomized dogs which had received these same doses. The same procedure was used for experiments in which reserpine (1 mg/kg) was given after mephentermine (1 mg/kg).

Open-chest dogs. In eighteen animals bilateral vagotomy was performed, the chest was opened, and blood pressure, heart rate, and contractile force were recorded. Responses to mephentermine (1 mg/kg) were compared with those in animals which had previously received reserpine (1 mg/kg) 7 min or 24 hr before the injection of mephentermine.

Duration studies. Reserpine (1 mg/kg) was given to dogs 1 or 4 hr before mephentermine (0.3 mg/kg) to see whether its effects were still augmented at these time periods. For the mephentermine-reserpine sequence, the same general procedure was followed except that reserpine (1 mg/kg) was administered 0.5 and 2 hr after mephentermine (1 mg/kg).

Noradrenaline sensitivity studies. The effect that cocaine (2 mg/kg), reserpine (1 mg/kg) and mephentermine (0.3 or 1.0 mg/kg) had on responses to noradrenaline was tested by giving two control doses of 0.5 μg/kg of noradrenaline before and again 7 min after these agents; the responses were compared statistically as paired data. Responses to noradrenaline were similarly tested before and after complete tachyphylaxis had been obtained to mephentermine by repeated doses of 1 mg/kg. Cocaine was given after tachyphylaxis to mephentermine and sensitivity to noradrenaline again tested. To test further for changes in sensitivity to noradrenaline, noradrenaline (0.5 μg/kg) was administered before and after the reserpine-mephentermine sequence in several animals.

Interactions of reserpine with cocaine or mephentermine on pressor responses. Reserpine (1 mg/kg) was administered 15 min before or 15 min after either cocaine (2 mg/kg) or mephentermine (0.3 mg/kg). At these doses, cocaine potentiated noradrenaline and mephentermine did not.

Noradrenaline in cardiac tissue. The effect of mephentermine, reserpine, and the reserpine-mephentermine sequence on noradrenaline in the heart was studied by measuring the noradrenaline content of the left ventricular tissue 20 min after drug injection in one series of experiments and 60 min after drug injecton in a second series. In the latter case, mephentermine was administered every 10 min until complete tachyphylaxis of the blood pressure response was obtained. Control animals received the same amounts of reserpine vehicle and atropine as experimental animals. The dose of both reserpine and mephentermine was 1 mg/kg.

RESULTS

Pressor response to mephentermine after reserpine. The pressor response to mephentermine (0.3 mg/kg) administered to intact dogs 7 min after reserpine was markedly potentiated. A typical example of such a response in an intact animal is shown in Fig. 1. The blood pressure rise in six dogs was 165±7.7 mm Hg (mean and standard error). Mephentermine alone produced a rise of 29±3.0 mm Hg; a typical response is shown in Fig. 1. This augmented hypertensive response lasted from 15 to 45 min in contrast to 4 to 6 min for mephentermine alone. Further injections of mephentermine gave much reduced responses and by the third or fourth dose complete tachyphylaxis had occurred and the *depressor* response characteristic of mephentermine after tachyphylaxis was seen. A tracing from an adrenalectomized animal is also shown in Fig. 1. The mean pressor response for four dogs was 152±8.3 mm Hg. This response did not differ from that in non-adrenalectomized dogs, indicating that the adrenal glands do not significantly contribute to the augmented response to mephentermine after reserpine.

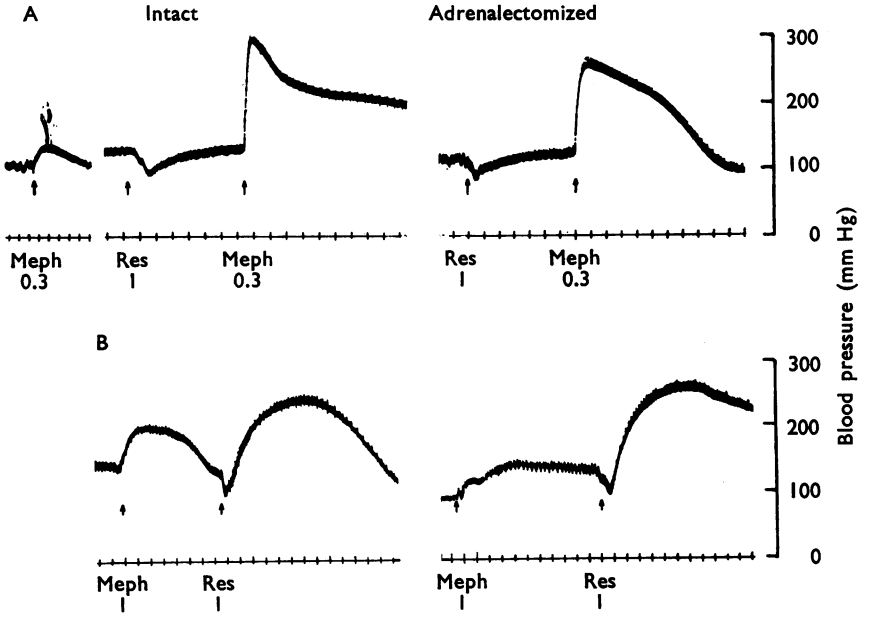

Fig. 1. Responses to mephentermine (0.3 mg/kg) alone and after reserpine (1 mg/kg) in anaesthetized (intact) and acutely adrenalectomized dogs are shown in line A. Responses to reserpine (1 mg/kg) after mephentermine (1 mg/kg) in anaesthetized and acutely adrenalectomized dogs are shown in line B. A typical response to reserpine without prior treatment with mephentermine is indicated in line A. Responses in the five panels were obtained in separate animals. Drugs were administered at the arrows. Time in minutes.

" *Reserpine reversal* " *after mephentermine.* A typical response obtained when reserpine was given *after* mephentermine is shown in Fig. 1. At 7 to 10 min after mephentermine (1 mg/kg), reserpine produced a pressor response, which in six dogs gave a mean of 93±6.3 mm Hg. A second dose of reserpine gave no pressor response. The pressor response to reserpine was also present in acutely adrenalectomized dogs (Fig. 1). The mean pressor

rise for four animals was 90±12.7 mm Hg and did not differ significantly from the mean response in non-adrenalectomized animals. Furthermore, adrenalectomy did not alter the magnitude of the response to mephentermine alone, emphasizing that mephentermine does not owe its activity to adrenal release of catechol amines.

Comparison of mephentermine in control and reserpine-treated dogs. Fig. 2 presents a comparison of control responses to mephentermine (1 mg/kg) with responses at 7 min or

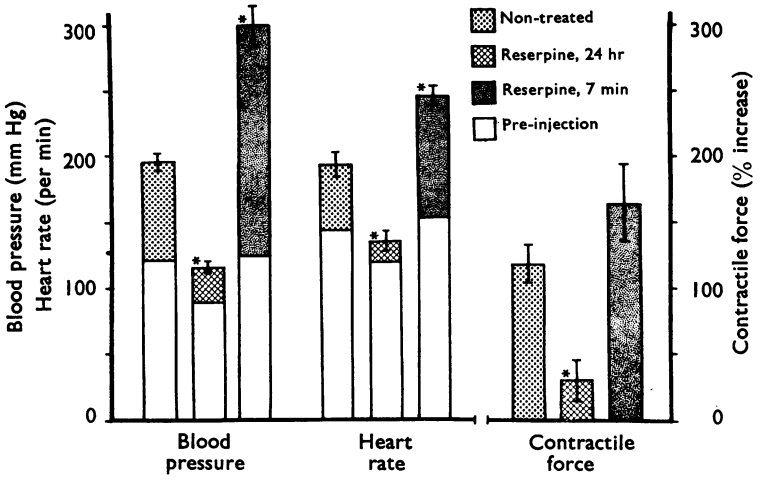

Fig. 2. Comparison of responses to mephentermine (1 mg/kg) in seven control dogs and in animals having received reserpine at 7 min (seven dogs) or at 24 hr (four dogs) before mephentermine. Contractile force values, expressed as percentages of controls are indicated on the right-hand scale. Blood pressure and heart rate values are indicated on the left-hand scale. Standard errors are shown by the central vertical lines. *$P<0.05$.

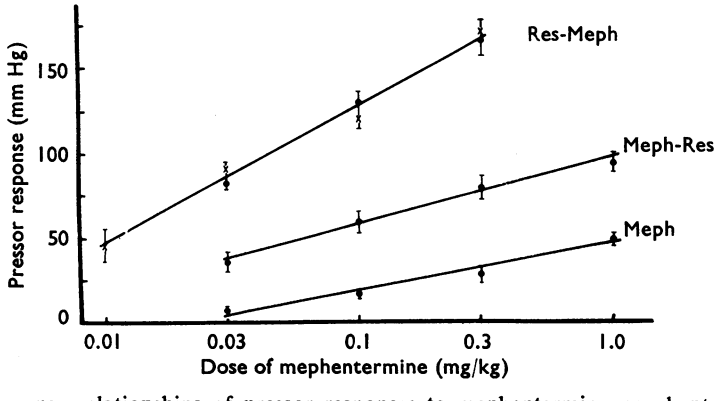

Fig. 3. Dose/response relationships of pressor responses to mephentermine, mephentermine-reserpine sequence, and reserpine-mephentermine sequence are compared. Mephentermine was administered either 7 to 10 min before or 7 min after the acutely administered reserpine (1 mg/kg). Each point represents not less than five dogs. Standard errors are shown by the vertical lines. X=spinal dogs; ●=intact dogs. The line for the reserpine-mephentermine sequence, and the corresponding standard errors, were based on the values for both spinal and intact dogs.

at 24 hr after treatment with reserpine. All responses to mephentermine were significantly reduced by reserpine given 24 hr previously. This reduction indicates the importance of stored noradrenaline to mephentermine activity. In contrast, mephentermine administered 7 min after reserpine greatly augmented the blood pressure and heart rate responses. The increase in contractile force does not show a significant difference from the control response to mephentermine. This lack of a significant increase might be due to a direct cardiac depressant effect of either mephentermine or reserpine.

Dose/response relationships. The dose/response relationships of the pressor responses to mephentermine after reserpine, to reserpine after mephentermine, and to mephentermine alone are shown in Fig. 3. The reserpine-mephentermine sequence was tested in both anaesthetized and spinal animals; no difference between them was observed. Thus, central stimulation from higher centres does not contribute significantly to this augmented response.

Duration studies. Table 1 shows the effect of drug sequence and time interval on responses to mephentermine and reserpine. The potentiated response of mephentermine after reserpine decreased significantly over a 4-hr period from the response observed at 7 min, but the response at 4 hr was still considerably greater than that produced by mephentermine alone. The response of reserpine after mephentermine was reduced at 30 min from the response at 7 min, but was not further reduced at 2 hr.

TABLE 1

EFFECT OF DRUG SEQUENCE AND TIME INTERVAL ON RESPONSES TO MEPHENTERMINE AND RESERPINE

Reserpine-mephentermine refers to the administration of mephentermine (0·3 mg/kg) after reserpine (1 mg/kg). Mephentermine-reserpine refers to reserpine (1 mg/kg) administered after mephentermine (1 mg/kg). Pressure responses are means and standard errors. * Response significantly different from the response at 7 min ($P<0·05$)

Drug sequence	Interval between drugs	No. of dogs	Pressor response to second drug (mm Hg)
Reserpine-mephentermine	7 min	6	165 ±7·7
Reserpine-mephentermine	1 hr	4	143 ±8·7
Reserpine-mephentermine	4 hr	4	102 ±9·6*
Mephentermine-reserpine	7 min	6	93·3±6·3
Mephentermine-reserpine	0·5 hr	4	68·5±4·9*
Mephentermine-reserpine	2 hr	6	70·8±6·7*

Noradrenaline in cardiac tissue. The effect of mephentermine, reserpine, and the combination of reserpine and mephentermine on noradrenaline stores was determined for the left ventricle (Table 2). In experiment I, in which the hearts were removed 20 min after drug injection, neither mephentermine- nor reserpine-treated animals differed significantly from controls. However, the reserpine-mephentermine combination significantly reduced noradrenaline levels.

In experiment II, in which the hearts were removed 60 min after drug injection, mephentermine-treated animals again did not differ from control animals despite the repeated administration of mephentermine to produce tachyphylaxis. The animals treated with reserpine, as well as those treated with both reserpine and mephentermine, differed significantly from controls. Like the reserpine-mephentermine sequence at 20 min, the

TABLE 2

EFFECT OF MEPHENTERMINE AND RESERPINE ON THE NORADRENALINE CONTENT OF THE DOG LEFT VENTRICLE

In Experiment I dogs received single doses of 1 mg/kg of the listed drugs. In Experiment II, the dose of reserpine was 1 mg/kg and mephentermine (1 mg/kg) was repeated until complete tachyphylaxis had developed (four doses). Hearts were removed for assay either 20 or 60 min after the first drug injection. Heart noradrenalines are means and standard errors. * The reserpine-mephentermine combination reduced the noradrenaline level significantly more than the sum of the responses to reserpine and mephentermine alone ($P<0.05$). N.S., Not significant

Treatment	No. of dogs	Heart noradrenaline (μg/g)	Significance (P)
Experiment I: 20 min duration			
Control	10	1·38±0·12	—
Mephentermine	10	1·40±0·08	N.S.
Reserpine	10	1·24±0·15	N.S.
Reserpine-mephentermine	10	0·91±0·07*	<0·01
Experiment II: 60 min duration			
Control	10	1·53±0·09	—
Mephentermine	7	1·41±0·18	N.S.
Reserpine	7	1·19±0·18	<0·05
Reserpine-mephentermine	7	0·79±0·11*	<0·01

reserpine-mephentermine combination at 60 min reduced the noradrenaline content significantly more than the sums of the effects of reserpine and mephentermine alone.

When the reserpine-mephentermine sequence was given, the degree of depletion after 60 min, even with mephentermine given to tachyphylaxis, was only slightly greater than the depletion seen at 20 min.

Effect of cocaine, reserpine, and mephentermine on sensitivity to noradrenaline. Table 3 shows the means of the blood pressure responses obtained to noradrenaline (0.5 μg/kg) given before and after the reserpine-mephentermine sequence. No potentiation of noradrenaline was seen. In view of the report by Trendelenburg & Crout (1964) that mephentermine will enhance the effect of noradrenaline on the guinea-pig atrial pacemaker and prevent uptake of noradrenaline into the tissue, a study in the dog of the effect of

TABLE 3

EFFECT OF COCAINE, RESERPINE AND MEPHENTERMINE ON THE PRESSOR RESPONSE TO NORADRENALINE

In the reserpine-mephentermine sequence, reserpine (1 mg/kg) was followed in 7 min by various doses of mephentermine. Pressor responses to noradrenaline (0·5 μg/kg) are means and standard errors. (T) Indicates that the dose of mephentermine was given in divided 1-mg/kg doses until complete tachyphylaxis had developed. P values are based on comparisons of paired values. N.S., Not significant

Treatment	Dose (mg/kg)	No. of dogs	Pressor response to noradrenaline (mm Hg)		Significance (P)
			Before	After	
Reserpine-mephentermine	0·3	4	60·0±4·0	63·0± 4·2	N.S.
Reserpine-mephentermine	0·1	4	55·0±7·3	47·5± 7·1	N.S.
Reserpine-mephentermine	0·03	4	62·5±8·5	59·0± 9·9	N.S.
Cocaine	2·0	4	47·0±2·2	100·5± 6·8	<0·005
Reserpine	1·0	11	45·4±2·4	42·4± 3·6	N.S.
Mephentermine	0·3	6	48·5±3·3	49·0± 3·7	N.S.
Mephentermine	1·0	5	48·8±1·9	64·0± 5·2	<0·05
Mephentermine	3–4(T)	5	48·8±1·9	82·4± 6·6	<0·01
Mephentermine(T)-cocaine	2·0	5	82·4±6·6	100·4±12·0	<0·05

TABLE 4

INTERACTION OF RESERPINE WITH COCAINE OR MEPHENTERMINE ON PRESSOR RESPONSES

The dose of mephentermine was 0·3 mg/kg; the dose of cocaine was 2 mg/kg; and the dose of reserpine was 1 mg/kg. The pressor responses are means and standard errors

Drug sequence	No. of dogs	Pressor response to second drug (mm Hg)
Reserpine-cocaine	5	35·2±5·8
Cocaine-reserpine	4	−5·5±3·8
Reserpine-mephentermine	4	122·8±9·8
Mephentermine-reserpine	5	54·4±8·4

mephentermine on sensitivity to noradrenaline was particularly important. Mephentermine in a dose of 0.3 mg/kg did not increase the sensitivity to noradrenaline, whereas 1 mg/kg of mephentermine potentiated noradrenaline responses significantly. The sensitivity to noradrenaline was further increased by giving mephentermine in repeated doses to produce tachyphylaxis. Cocaine (2 mg/kg) increased the sensitivity of noradrenaline greatly, much more than after tachyphylaxis to mephentermine. When cocaine was given after tachyphylaxis to mephentermine there was always a further increase in the sensitivity to noradrenaline.

Many of the published observations on sensitivity to noradrenaline after reserpine have been complicated by the administration of other agents. In this study, reserpine alone did not increase the sensitivity to noradrenaline tested 7 min later.

Interactions of reserpine with cocaine or mephentermine. The mean pressor responses of cocaine or mephentermine after reserpine, of reserpine after cocaine, and of reserpine after mephentermine are shown in Table 4. These results show that the combination of reserpine and mephentermine (0.3 mg/kg) produced much greater responses than the combination of reserpine and cocaine (2 mg/kg).

DISCUSSION

In these studies acutely administered reserpine potentiated the cardiovascular responses to mephentermine, and mephentermine reversed the blood pressure response to acutely administered reserpine. The possibility that the reserpine-mephentermine combination facilitated the release of noradrenaline was confirmed by analysis of the left ventricular muscle. Since the adrenal medullae did not contribute significantly to the augmented circulatory responses of the mephentermine-reserpine or reserpine-mephentermine sequences, these responses can be attributed to a rapid release of noradrenaline from nerve endings.

The greater response to reserpine-mephentermine compared with the mephentermine-reserpine combination (Fig. 3) may be explained by the rapid release of noradrenaline, which would produce a greater response than the same amount released more slowly. The slower rise of blood pressure after the mephentermine-reserpine sequence (Fig. 1) suggests that a smaller noradrenaline gradient developed, and may indicate that reserpine must first act before stored noradrenaline is made available for release.

Since analysis of cardiac tissue for noradrenaline after tachyphylaxis to mephentermine

showed insignificant depletion (Table 2), neither tachyphylaxis nor the increased noradrenaline sensitivity to mephentermine could be attributed to catechol amine depletion. Alternatively, mephentermine tachyphylaxis may be due to an accumulation of the drug at the neuronal membrane resulting in a cocaine-like inhibition of its own releasing activity.

The ability of cocaine to prevent noradrenaline uptake is believed by many to be the mechanism for its potentiation of noradrenaline (Muscholl, 1961). Trendelenburg & Crout (1964) suggested that mephentermine has a cocaine-like action and our results showing that doses of 1 mg/kg will potentiate responses to noradrenaline agree with this view. However, doses below 1 mg/kg did not alter responses to noradrenaline, indicating a lack of cocaine-like activity at lower doses. Furthermore, if mephentermine were acting by inhibiting an uptake mechanism of noradrenaline, then, in combination with reserpine, cocaine at a dose that potentiated noradrenaline would be expected to give greater responses than mephentermine in a dose that did not potentiate noradrenaline. Such a comparison of cocaine and mephentermine (Tables 3 and 4) demonstrated a lack of correlation between noradrenaline potentiation and potentiated responses due to an interaction with reserpine. Thus, the possibility seems remote that the potentiated responses seen in this study could be based on an inhibition of noradrenaline uptake.

Reserpine acts by inhibiting catechol amine storage (Carlsson, Hillarp & Waldeck, 1963). The observation that noradrenaline in the heart is rapidly reduced by the reserpine-mephentermine sequence at 20 min without further reduction at 60 min (Table 2) suggests that reserpine may act rapidly on a portion of the storage mechanism while acting more slowly on another portion. The slower release could be explained if the dissociation of a noradrenaline complex in the storage granules were a rate-limiting step in the liberation of the amine.

Accordingly, the augmented pressor responses seen in this study may be explained in the following way. Reserpine may rapidly affect the noradrenaline storage process permitting a gradient of " freed " noradrenaline to become available behind a limiting membrane. Upon mephentermine administration, this " freed " noradrenaline is rapidly released to the receptor due to an action of mephentermine in increasing membrane permeability. In the reverse sequence, reserpine after mephentermine, the gradient of " freed " noradrenaline produced by reserpine is somewhat less since mephentermine has already increased membrane permeability. As the dose of mephentermine is increased, a progressively larger response is produced to the fixed dose of reserpine because of the increasing membrane effect of mephentermine.

SUMMARY

1. In anaesthetized dogs, acutely administered reserpine potentiated the pressor responses to subsequent doses of mephentermine and itself produced a pressor response after mephentermine.

2. Dose/response curves were plotted for mephentermine after reserpine and for reserpine after mephentermine. The slope of the reserpine-mephentermine dose/response curve was steeper than either the mephentermine-reserpine curve or the mephentermine curve.

3. Adrenal secretion or central nervous stimulation were not factors in these augmented pressor responses since the responses were unaffected by adrenalectomy and spinal section.

4. Studies on interrelations of reserpine with cocaine and mephentermine revealed a lack of correlation between potentiated pressor responses and increased sensitivity to noradrenaline. Sensitivity to noradrenaline was not increased after acutely administered reserpine.

5. Analysis of cardiac tissue confirmed that the reserpine-mephentermine sequence facilitated the release of noradrenaline from tissue stores, even though repeated doses of mephentermine alone given to the point of tachyphylaxis did not significantly reduce noradrenaline levels.

6. The hypothesis is proposed that reserpine rapidly affected the noradrenaline storage process permitting a gradient of freed noradrenaline to become available behind a limiting membrane which mephentermine then released by an action on membrane permeability.

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