SYMPATHOMIMETIC ACTIONS OF RESERPINE ADMINISTERED DURING TREATMENT WITH DOPAMINE IN THE DOG

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Abstract—Reserpine injected intravenously during infusion with dopamine brought about sympathomimetic effects, but a second injection of reserpine after 120 minutes did not elicit such effects. This pressor effect was eliminated by phenoxybenzamine and this positive chronotropic effect by propranolol. Reserpine induced similar but weak sympathomimetic effects after cocaine, while it induced no changes in blood pressure and heart rate after infusion with noradrenaline. Meanwhile, pressor response to dopamine was potentiated 24 hours after reserpine and was further potentiated after additional infusion with noradrenaline. The sympathomimetic actions induced by the concurrent administration of reserpine and dopamine may be attributable to a facilitation of those indirect mechanisms, principally of endogenous catecholamine release.

Dopamine when given with reserpine is reportedly ineffective in producing hypertension in dogs (1). Tyramine was also thought to be a sympathomimetic amine lacking in interactive action with reserpine, presumably because of its rapid metabolism, however, it has been shown that reserpine does induce a hypertensive response in dogs if given during infusion with tyramine (2).

Tyramine is an indirectly-acting amine and its effect in releasing catecholamines is well documented. It has also been proposed that dopamine is an indirectly-acting amine though it has direct sympathomimetic actions (3, 4).

Such being the case we investigated interaction of dopamine with reserpine by the method of infusion.

MATERIALS AND METHODS

Mongrel dogs of either sex, weighing between 6 to 18 kg, were anesthetized with pentobarbital sodium 35 mg/kg i.p. or 10 mg/kg i.p. in reserpine-pretreated dogs. Supplemental injections of the anesthetics were given i.v. in one-eighth the original dose to the extent required to maintain constant anesthesia.

Systemic arterial pressure was measured in mmHg with either a mercury manometer or a pressure transducer (Toyo, LPU-05-360-0-III) by inserting a cannula into the femoral artery. The ECG was obtained from standard limb leads and heart rate was integrated with a cardiotachometer coupler to give a continuous record. Both blood pressure and heart
rate were recorded on a polygraph (Sanei, PG-602).

The animals were bilaterally vagotomized 20 min before the experiment.

Intravenous administration of drugs was given through a polyethylene tube introduced into the left femoral vein. Intravenous infusion of drugs was given through a polyethylene tube inserted into the right caudal femoral vein, using a constant infusion apparatus (Natsume, KN-202). The infusion volume was constant at 0.28 ml/min, and infusion dose of dopamine was 15 μg/kg/min while that of noradrenaline was 0.8 μg/kg/min.

The drugs used were dopamine hydrochloride (Nutritional Biochemicals), noradrenaline hydrochloride (Sankyo), phenoxybenzamine hydrochloride (Tokyokasei Industries), propranolol (Sumitomo Chemical), cocaine hydrochloride (Takeda Chemicals Industries) and reserpine (Inverni & Della Bella).

Dopamine was dissolved as 1% solution in 1/100 N hydrochloric acid, diluted with saline before administration, and used within a week. Phenoxybenzamine and reserpine were dissolved respectively according to the method described by Nickerson & Goodman (5) and by Orlans et al. (6). Other drugs were dissolved in saline or distilled water.

The dosages of all drugs are expressed in terms of the salt. Details of dosages and time schedule are given in appropriate places under figures.

The mean value and standard error of the mean in blood pressure and heart rate were determined for each group of animals at each time interval, and the significance of difference was estimated using Student’s t test (P<0.05).

RESULTS

Effects of reserpine administered acutely during infusion with dopamine

The results are shown in Fig. 1. The continuous infusion with dopamine (15 μg/kg/min) in 8 dogs, in which mean blood pressure and heart rate were 135.1±2.5 mmHg and 136.9±8.0 beats/min respectively, exhibited a sustained rise in blood pressure and a progressive increase in heart rate, accompanied with an initial transient and slight fall and decrease.

Reserpine (1 mg/kg) administered i.v. in 3 dogs, in which mean blood pressure and heart rate were 110.0±10.0 mmHg and 141.7±17.6 beats/min respectively, brought about a slight rise in blood pressure and an increase in heart rate, following a slight fall and decrease.

Reserpine (1 mg/kg) administered i.v. at the same time as the start of infusion with dopamine (15 μg/kg/min) in 11 dogs, in which mean blood pressure and heart rate were 138.0±5.9 mmHg and 143.2±9.4 beats/min respectively, induced an immediate and remarkable rise in blood pressure which was maximal at 10 min and lasted for 60 min, and an immediate and marked increase in heart rate which was maximal at 15 min and lasted for over 120 min.

The same or twice the dose of reserpine (1, 2 mg/kg) was administered 120 min after the first administration in dogs in which infusion with dopamine was continuous. Reserpine brought about only a transient and slight rise in blood pressure as well as a transient and
Slight decrease in heart rate, as seen in Fig. 1.

Reserpine administered simultaneously with dopamine 30 min after intravenous administration of phenoxybenzamine (10 mg/kg) in 4 dogs induced slight depressor and moderate positive chronotropic effects, and propranolol (0.2 mg/kg) administered additionally 15 min later abolished the positive chronotropic effect of reserpine. Thus, the pressor response to reserpine was eliminated by phenoxybenzamine and the positive chronotropic effect by propranolol.

**Effects of reserpine administered acutely after cocaine**

Cocaine (4 mg/kg) produced almost no changes in blood pressure and a slight decrease in heart rate which was maximal at 20 min and lasted for 120 min, accompanied by a slight initial increase in 4 dogs, in which mean blood pressure was 144.0±7.7 mmHg and heart rate was 165.0±2.0 beats/min. Responses to reserpine (1 mg/kg) administered 20 min after cocaine in 4 dogs, in which mean blood pressure was 110.3±11.4 mmHg and heart rate was 129.3±17.0 beats/min, appeared to be similar to but weaker than those seen in dopamine-infused dogs (Fig. 2).
FIG. 2. Pressor and positive chronotropic effects of reserpine administered after cocaine. ○—○ Cocaine 4 mg/kg (n=4); ●—● Reserpine 1 mg/kg after cocaine 4 mg/kg (n=4). Cocaine was injected i.v. 15 min before reserpine. Each point shows mean values ± S.E.M.. * denotes a significant change in blood pressure or heart rate from cocaine according to t-test (P<0.05).

Effects of reserpine administered acutely after infusion with noradrenaline

Reserpine (1 mg/kg) administered acutely after 30 min infusion with noradrenaline

FIG. 3. Effect of reserpine after noradrenaline infusion. ○—○ Reserpine 1 mg/kg (n=3); ●—● Reserpine 1 mg/kg after noradrenaline infusion. Noradrenaline 3 μg/kg/min was infused i.v. for 30 min before reserpine. Each point shows mean values ± S.E.M..
(3 μg/kg/min) in 3 dogs, in which mean blood pressure and heart rate was 112.3±11.3 mmHg and 158.3±23.7 beats/min respectively, induced no significant changes in blood pressure and heart rate as compared with changes observed without the infusion.

**Influence of reserpine on blood pressure response to dopamine**

Dopamine injected i.v. in 17 dogs, in which blood pressure was 103.8±8.0 mmHg, elicited purely a depressor response in small doses (1–10 μg/kg), biphasic responses, i.e., an initial rise followed with a fall in intermediate doses (20–50 μg/kg), and purely a pressor response in large doses (100–200 μg/kg).

Dopamine injected 24 hr after s.c. administration of reserpine (1 mg/kg) induced a potentiated pressor response followed by a slight fall in blood pressure in 8 reserpine-treated dogs in which blood pressure was 82.3±0.9 mmHg. The pressor response to dopamine was further potentiated and the depressor response disappeared after additional infusion with noradrenaline (0.8 μg/kg/min) for 1 hr.

For statistical analysis, the changes in blood pressure are expressed as peak change (mmHg) and dimensions of change (cm²) determined by measuring the recorded change below or above the control level, and biphasic changes as a sum of pressor and depressor components. As shown in Fig. 4, the pressor responses to dopamine were potentiated by reserpine and were further potentiated after additional infusion with noradrenaline.

![Fig. 4. Potentiation of dose-dependent pressor responses to dopamine by pretreatment with reserpine and additional infusion with noradrenaline. The left panel shows changes in blood pressure in mmHg and the right panel in dimension recorded on paper. ——— Control responses to dopamine (n=7); ———— Responses to dopamine in reserpine treated (n=8); ———— Responses to dopamine after noradrenaline infusion in reserpine treated (n=8). Each point shows mean values ± S.E.M.](image)

**DISCUSSION**

Reserpine, when injected i.v. into animals treated with certain sympathomimetic amines, induces a hypertensive response or so called reserpine reversal. This phenomenon has been reviewed by Schmitt and Schmitt (7) who proposed that indirectly-acting amines such as amphetamine, ephedrine and N-methylated derivative were active while directly-acting amines including dopamine were ineffective. However, it is presumed that reserpine and dopamine do not interact under the condition of a single dose of dopamine since dopamine...
is rapidly metabolized. In fact, it was demonstrated in the present study that reserpine brings about reserpine reversal in both blood pressure and heart rate when is administered during infusion with dopamine. These hypertensive and positive chronotropic effects of reserpine were eliminated by alpha and beta adrenergic blocking agents.

Regarding the mechanisms involved in the reserpine reversal by dopamine, it may be considered that reserpine reduces the uptake of dopamine into the nervous tissues and enhances the direct effect of dopamine on the adrenergic receptors. However, Schmitt and Schmitt (7) hold the view that only neuronal storage sites are implicated in the hypertensive effect of reserpine and the effect is mediated by facilitated releases of catecholamines. In fact, Takasaki (8) observed that ephedrine and methamphetamine induced a potent hypertensive response to reserpine after first injection of reserpine but the second injection of reserpine no longer elicited the hypertension, and he postulated that this abolishment in hypertensive response to secondarily administered reserpine could not be explained by the direct effect of amine on the receptor and may be due to the reduction in the facilitated release of endogenous catecholamine by the second administration. A similar abolishment in the sympathomimetic responses to reserpine was likewise observed herein by dopamine and reserpine when reserpine was administered secondarily. We proposed earlier that dopamine action was due in part to the receptor but was principally an indirectly-acting amine since the pressor responses to dopamine were abolished by repeated administration of ephedrine (4). Therefore, the sympathomimetic responses to reserpine induced by dopamine are presumably due to the facilitated catecholamine release from its store sites, as proposed with other indirectly-acting amines.

However, as dopamine inhibits noradrenaline re-uptake, blocks monoamine oxidase by being a preferential substrate and acts as a precursor for noradrenaline synthesis (9, 10, 11), the possibility that another indirect mechanism may be involved in the reserpine reversal induced by dopamine cannot be dismissed. In our present studies on dogs, reserpine reversal occurred after cocaine though its potency was weaker than that in dopamine-infused animals. Cocaine was reported to cause a pressor response to reserpine in spinal cats and an accelerated release of noradrenaline by reserpine could not be detected after cocaine in pithed rats (7), whereas cocaine and reserpine are proposed to prevent uptake of catecholamine from the interstitial spaces into the nerve terminal or at the granular membrane (12). Dopamine is also reported to reduce the uptake (11, 13). Therefore the reduction in the noradrenaline uptake by both dopamine and reserpine might be partially involved in producing the phenomenon of reserpine reversal by dopamine. It is also possible that, as dopamine inhibits monoamine oxidase by being a preferential substrate (14) and is the biochemical precursor of noradrenaline, an intravenous infusion of dopamine results in a repletion of noradrenaline in the sympathetic nerve terminal. However, the repletion itself does not appear to be directly involved in the reserpine reversal since the reversal did not occur after the repletion was induced by noradrenaline infusion for 30 min.

It is thus most likely that dopamine and reserpine elicit a facilitation of indirect mechanisms, principally of catecholamine release, though the involvement of a direct mechanism
DOPAMINE REVERSES RESERPINE ACTION

cannot be ruled out. In the meantime, the result in the reserpine-treated animals has been proposed to confirm a concept of direct and indirect effect of sympathomimetic amines. However, Luchelli-Fortis and Langer (15) have recently cast doubt on the pharmacological significance of the reserpine-induced depletion of noradrenaline store as a reliable criterion for the classification of the mechanism of action of sympathomimetic amines, and they have proposed that the failure of reserpine pretreatment to reduce responses to sympathomimetic amines does not exclude the possibility that amines might release endogenous noradrenaline. Concerning dopamine, pressor response to dopamine was potentiated 24 hr after reserpine and was further potentiated after additional infusion with noradrenaline in dogs, while the response was eliminated and reversed to depressor response after repeated treatment with ephedrine as previously mentioned (4), notwithstanding that reserpine has been well documented as a potent endogenous catecholamine depletor. In cats, pressor response to dopamine was likewise slightly potentiated after reserpine (3). If indirect mechanisms including a facilitated release of endogenous catecholamine are still involved between dopamine and reserpine, sympathomimetic actions of dopamine remain after reserpine and the actions in the reserpine-treated animals cannot be necessarily attributed to direct effect of dopamine on the receptor.

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REFERENCES