THE EFFECT OF COCAINE ON THE PRESSOR RESPONSE TO SYMPATHOMIMETIC AMINES BEFORE AND AFTER ACUTE RESERPINIZATION IN DOGS

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The effect of cocaine on the pressor response to some sympathomimetic amines before and after the acute reserpinization in dogs, anesthetized with pentobarbital sodium (i. v) in combination with morphine hydrochloride (s. c) and atropine sulfate (s. c), was investigated.

Administration of cocaine suppressed the pressor effect of ephedrine and related compounds; but administration of reserpine considerably removed the suppressive action of cocaine, though some difference was found according to the stage. However, the suppressive action of cocaine on tyramine was more intense than other drugs. In experiments in which no ephedrine-like compounds in the control dose were administered before cocaine, blood pressure rose after reserpine was restored, especially in the case of tyramine.

It is well known since the early reports of Holzbauer et al. and Bertler et al. that reserpine depletes catecholamines from the storage site of various tissues. On the other hand, cocaine is said to inhibit the release or uptake of norepinephrine at its storage site (e. g. early reports of Mac Millan and Whitby et al.), along with the suppression on the entrance of the ephedrine-like compounds into the storage site (Farrant). In the previous experiments (Takasaki), a marked and prolonged pressor response elicited by reserpine following the administration of ephedrine and methamphetamine were recognized. Moreover, this reserpine hypertension was greatly reduced by the administration of cocaine.

In the present paper, changes due to cocaine administration, and the combined effect of cocaine and reserpine on the pressor response caused by some sympathomimetic amines is systematically and comparatively studied in many cases. The mechanism of action of the drugs at adrenergic terminal is also discussed.

METHODS

Forty three mongrel dogs of both sexes ranging in body weight from 5 to 15 kg were used.

Blood pressure was recorded on a smoked drum by means of a kymograph.
and mercury manometer connected to a cannula via a rubber tube filled with saline. An arterial cannula filled with heparine solution was inserted into the common carotid artery. The statistical significance of the difference was checked by Student's test.

The dogs were anesthetized by the intravenous injection of 15 mg/kg pentobarbital sodium 30 min after premedication of subcutaneous injection of 1 mg/kg atropine sulfate along with 10 mg/kg morphine hydrochloride.

All drugs, with the exception of reserpine, were diluted in saline and administered to the femoral vein. The following three experiments, using cocaine conducted:

1) Control dose of sympathomimetic amines (amines) was administered first. When the effect almost disappeared, reserpine 1 mg/kg was treated, followed by cocaine 5 mg/kg 1/2-1 hr later. The same dose of amines was injected 5 min after cocaine.

2) After observing the action of the amines, cocaine 5 mg/kg was given; followed by the administration of reserpine 1 mg/kg 5 min later; and then the same dose of amines as before 1/2-1 hr later.

3) At first cocaine 5 mg/kg was administered; followed by amines 5 min later; reserpine 1 mg/kg; and the same dose of amines as before 1/2-1 hr later, in this order.

RESULTS

After observation on the effect of 0.1-1 mg/kg ephedrine, methamphetamine, tyramine and pheniprazine, 5 mg/kg cocaine was administered, followed by the same dose of the first drug. Pressor effect was markedly eliminated or inhibited (e.g. ephedrine and tyramine, Fig. 4 A and B).

In a similar experiment, the pressor effect of 1-5 μg/kg epinephrine and norepinephrine was markedly increased after cocaine (e.g. norepinephrine, Fig. 4 C).

The usual hypotensive effect of 50 mg/kg pyrogallol was changed to a mild pressor effect after cocaine.

Amines, reserpine and cocaine were then administered in 3 different orders,

Fig. 1. Average blood pressure changes caused by sympathomimetic amines after cocaine and/or reserpine using different procedures.

- Ephedrine 0.5 mg/kg.
- Pheniprazine 0.5 mg/kg.
- Methamphetamine 0.5 mg/kg.
- Tyramine 0.5 mg/kg.

Cont: Control. C: After cocaine 5 mg/kg. R: After reserpine 1 mg/kg. Ordinate: Scale in percentage. From left column: Control response and after cocaine; control response, and after reserpine and cocaine; control response, and after cocaine and reserpine; after cocaine and after reserpine.
to observe the pressor effects. The experimental results with ephedrine and related compounds are shown in Fig. 1.

Experiments based on the order of administration of amines, reserpine, cocaine and amines.

The potentiation of pressor effects of ephedrine and related compounds after reserpine and cocaine were considerably milder than that after reserpine alone (e.g. ephedrine, Fig. 2 A). However, reserpine suppressed the inhibitory effect of cocaine on the pressor effect of ephedrine and related compounds instead of the marked inhibition of the pressor effect seen upon administration of cocaine alone. Following the second dose of methamphetamine, however, a tendency towards tachyphylaxis was demonstrated. In the majority, the magnitude of the pressor response was frequently even smaller after reserpine and cocaine than that after reserpine alone.

In an experiment with tyramine, the pressor effect was inhibited to a considerable degree after reserpine and cocaine. The degree of rise was about 1/2 that seen upon administration of reserpine alone. Despite the administration of reserpine, cocaine caused an intense inhibitory effect on tyramine action as compared with other drugs. However, the duration of the pressor response was prolonged after cocaine (Fig. 2 B).

In contrast to the substances of the ephedrine series, the pressor effect of 1-5 µg/kg of epinephrine and norepinephrine was markedly potentiated after reserpine and cocaine (Fig. 2 C).

Experiments based on the order of administration of amines, cocaine, reserpine and amines.

In animals in which cocaine was administered before reserpine, the pressor effect of ephedrine and related drugs after reserpine was markedly eliminated and no substantial rise took place.

The pressor effects caused by ephedrine and pheniprazine were slightly more suppressed than that seen after reserpine alone; while that of tyramine was suppressed to less than 50% of the effect of the control (Fig. 3 A and B). The tendency towards tachyphylaxis was even more intense following administration of methamphetamine.

The pressor effect of 1-5 µg/kg epinephrine and norepinephrine was
somewhat milder than that after reserpine and cocaine.

Experiments based on the order of administration of cocaine, amines, reserpine and amines.

Following administration of cocaine, the pressor effect of ephedrine-like compounds was markedly eliminated and scarcely any rise occurred in many cases. However, through subsequent reserpine administration the inhibitory effect of cocaine was reversed or abolished and the augmentation of the pressor effect of ephedrine-like compounds appeared (Fig. 4 A).

With tyramine in particular the intensifying action recovered considerably after reserpine (Fig. 4 B).

Administration of 1–5 μg/kg of epinephrine and norepinephrine caused an augmentation of the pressor effect after cocaine, but such intensifying action became considerably milder and almost no enhancement of response was achieved after reserpine (Fig. 4 C).

DISCUSSION

In the present experiment, cocaine action was quite characteristic, and the pressor effect of ephedrine and related compounds was markedly inhibited by cocaine. However, administration of reserpine before or following cocaine suppressed cocaine action. Reserpine thus weakens the inhibitory action of cocaine.
Cocaine is said to inhibit the release or uptake of norepinephrine at its storage site (Mac Millan, Whitby et al., and others). The cocaine has an inhibiting effect on the entrance of the ephedrine and related compounds in the storage site through a membrane or simultaneous inhibition on accumulation (Farrant). For this reason, norepinephrine release by ephedrine and related compounds probably occurs less efficiently after cocaine. The action of cocaine is probably exerted on terminal cell membrane and storage membrane (Schumann et al., Hertting et al., Philippu et al., Lindmar et al.). Furthermore, loosening of the blocking action of cocaine by reserpine suggests the action of cocaine and reserpine on the same terminal cell membrane, with which the entrance of ephedrine and related substances into the storage site after reserpine becomes easy. Norepinephrine release also becomes easy. Such blocking action of cocaine might be exerted most intensely on the action of tyramine. This would suggest that tyramine acts on the storage site in the considerably superficial softly bound form at the terminal. In other words, cocaine probably exerts a blocking action of the storage site at the cell membrane and/or in the neighboring site. Reserpine may act on a portion near the cell membrane to open it and make the release of active form of norepinephrine easier. However, as discussed in the previous reports (Takasaki), reserpine alone has no effect to cause such release actively. The action of reserpine is probably passive.

In the present experiment, on the other hand, the intensity of pressor effect of ephedrine and related substances administered after reserpine varied according to the time of administration of cocaine. In the series in which the control dose of ephedrine and related substances was administered first, pressor response following cocaine and reserpine was not considerably potentiated. On the contrary, administration of cocaine at first, followed by ephedrine and related substances, and followed later by reserpine resulted in a considerably pronounced augmentation.

The following explanations might be possible for this: In the series in which the control dose of ephedrine and related substances was administered before reserpine, a constant amount of ephedrine and related substances is accumulated in the terminal cell; so that the second administration limits the entrance into the terminal cell and no intense release of norepinephrine occurs. Pressor response is also not pronounced. In animals in which cocaine was administered at first, subsequent entrance of ephedrine and related substances into the terminal cell is extremely limited. Subsequent administration of reserpine loosens the action of cocaine and the second dose of ephedrine-like compounds enters the terminal cell quite easily. The release of norepinephrine occurs intensely and pressor response could be markedly potentiated. The entrance of ephedrine and related substances into the terminal cell through administration of cocaine is loosened by reserpine, but the intensity of pressor response after reserpine depends upon the prior entrance and accumulation of ephedrine-like compounds. For this reason, the action of cocaine on tyramine is characteristic. When a control dose was administered, the inhibiting action of cocaine occurs more intensely than with other drugs despite reserpine administration. This might be explained by the fact that tyramine releases only quite superficially localized free form of norepine-
phrine alone in a very short time. Cocaine then exerts its action close to the cell membrane. When cocaine was administered at first, without administration of the control dose, the pressor response to ephedrine-like substances was markedly inhibited, but the intensity of the pressor response was restored through reserpine administration, suggesting the facilitation of the entrance of these drugs into the storage site by reserpine. The more pronounced recovery of pressor response by tyramine than other drugs might be due to the fact that the entrance of tyramine into the storage site is prevented by cocaine. Even if a small amount entered, the action of tyramine is so short in duration (Chidsey et al. and Musacchio et al.), that no accumulation occurs as in other drugs. After suppression of cocaine action by reserpine, the entrance of tyramine into the storage site for release might be larger than other drugs which accumulate in it. This condition might be the same as the state in which no cocaine was administered at all before tyramine.

The action of pyrogallol causes a fall in blood pressure in a normal state. However, after cocaine pyrogallol produced a slight rise of pressure. It is most likely that cocaine blocks the entrance of circulating catecholamines into storage site. Additionally, catechol-O-methyltransferase was inhibited by pyrogallol (Axelrod et al., Bacq et al. and Hertting et al.). Therefore, undestructable catecholamines increase in the out side of storage site, they excite the receptors, and cause a pressor response.

REFERENCES

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