SPECIES DIFFERENCES IN ANTAGONISTIC EFFECT OF MORPHINE AGAINST DEPRESSOR RESPONSE TO DOPAMINE

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Abstract—Species differences in antagonistic effect of morphine against depressor response to dopamine, determined by the minimum level of blood pressure attained, were observed in dogs, cats and rabbits. A depressor response to dopamine after α-adrenergic blockade was eliminated by morphine in cats, but potentiated in dogs. The response to dopamine after repeated injections of ephedrine was potentiated by morphine both in cats and dogs. Without pretreatment in rabbits, the response to dopamine was diminished by morphine. It thus appears that species difference is considerable regarding antagonism of morphine to dopamine in blood pressure responses.

It has been proposed that the depressor response to dopamine administered after α-adrenergic blockade was blocked by morphine in cats (1). However, the blocking effect of morphine has not been studied in different species of animals, despite the fact that the species difference in central actions of morphine is well known, i.e., dogs and rabbits are sedated by morphine while cats are stimulated rather than sedated (2).

The present study was an attempt to determine whether or not there were species differences regarding the counteractive effect of morphine on dopamine in blood pressure responses.

MATERIALS AND METHODS

Mongrel dogs weighing 7–18 kg, cats, 2.3–2.8 kg and rabbits, 1.8–2.3 kg of both sexes were anesthetized with pentobarbital sodium (35 mg/kg, i.p.).

Systemic arterial pressure was recorded by means of a mercury manometer connected to a cannula in the femoral artery of dogs or the carotid artery of cats and rabbits. The vagus nerves were cut in the cervical region.

Drugs used were: pentobarbital sodium; dopamine hydrochloride; ephedrine hydrochloride; phenoxybenzamine hydrochloride; morphine hydrochloride, and all doses refer to the salts. Phenoxybenzamine hydrochloride was dissolved in propyleneglycol (3). Dopamine hydrochloride was dissolved in 0.01 N HCl, and diluted with saline before in-

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Dopamine (30–100 μg/kg), phenoxybenzamine (4–7 mg/kg) or morphine (5–15 mg/kg) was administered i.v. through a catheter inserted into the right femoral vein, and morphine was injected very slowly.

Four to six injections of ephedrine 5 mg/kg i.v. were given at 30 min intervals.

Studies related to the antagonism were begun 20 to 30 min after phenoxybenzamine and 15 to 20 min after morphine, and experiments with the latter were carried out under artificial respiration.

Depressor responses to dopamine were determined by the minimum level of blood pressure attained, and changes in blood pressure were expressed as percentage increase or decrease from control level which was observed after α-blockade or repeated administration of ephedrine.

**RESULTS**

Influence of morphine on depressor response to dopamine administered after phenoxybenzamine

**Cats:** In seven cats, mean blood pressure after phenoxybenzamine (7 mg/kg) was 82 ± 5.1 mmHg. Dopamine (50 μg/kg) caused a depressor response (19 ± 2.0 mmHg). Morphine (10 mg/kg) caused a fall of blood pressure (26 ± 3.4 mmHg) up to the dotted line in Fig. 1, after which the same dose of dopamine produced a slight rise of the pressure (2 ± 4.7 mmHg). This pressor effect was, however, not statistically significant.

**Dogs:** In six dogs, mean blood pressure after phenoxybenzamine (4 mg/kg) was 92 ± 7.5 mmHg. Dopamine (30 μg/kg) exhibited a depressor response (28 ± 5.0 mmHg).

After administration of morphine (5–10 mg/kg), which caused hypotension (12 ± 3.7 mmHg) to the dotted line in Fig. 2, the same dose of dopamine brought about a further depressor response (26 ± 4.2 mmHg).

**Influence of morphine on depressor response to dopamine administered without previous treatment in rabbits**

In six experiments, mean systemic blood pressure was 80 ± 6.0 mmHg. Dopamine (10 μg/kg) produced a fall of blood pressure (24 ± 4.8 mmHg). After morphine (15 mg/kg) which tended to cause a slight rise of the pressure (2 ± 7.8 mmHg) up to the dotted line in Fig. 3, the same dose of dopamine produced a diminished fall of the pressure (11 ± 3.5 mmHg), but this decline in the response to dopamine was not...
statistically significant.

When dopamine was given in a dose of 50 μg/kg, similar results were obtained as in Fig. 3.

**Influence of morphine on depressor response to dopamine administered after repeated administration of ephedrine**

**Cats:** In five cats, blood pressure after repeated ephedrine (total 20 mg/kg) was 121 ± 18.3 mmHg. Dopamine (50 μg/kg) caused a fall of blood pressure (20 ± 3.8 mmHg) preceded by a transient and slight rise. The same dose of dopamine induced a further fall of the pressure (5 ± 2.9 mmHg) after administration of morphine (15 mg/kg) which caused a fall of systemic pressure (35 ± 9.4 mmHg) up to the dotted line in Fig. 1.

**Dogs:** In five dogs, mean blood pressure after repeated ephedrine (total 30 mg/kg) was 153 ± 18.4 mmHg. Dopamine (100 μg/kg) elicited a fall of the pressure (48 ± 8.5 mmHg) accompanied with or without a slight and transient initial rise. The same dose of dopamine decreased the blood pressure (26 ± 1.4 mmHg) after injection of morphine (10–15 mg/kg) which produced a fall of pressure (59 ± 17.5 mmHg) to the dotted line in Fig. 2.

**DISCUSSION**

The effects of dopamine on blood pressure vary to a certain extent depending on species of animals. A pure depressor response is elicited with small doses of dopamine, a biphasic response with intermediate doses and a pure pressor response with large doses in dogs and cats, while dopamine in rabbits induced purely a fall of blood pressure in all
doses. The pressor component of blood pressure responses to dopamine is, however, converted to a depressor response when the animals are treated previously with α-blocking agents. These depressor responses to dopamine, induced after α-blocking agents or without previous treatment, are not affected by β-adrenergic blocking agents, ganglion blocking agents, anticholinergics and antihistaminics (4, 5).

However, the responses are eliminated by haloperidol in dogs (6). Bulbocapnine is also reported to reduce the depressor response to dopamine (7, 8), though it does not block the relaxing effect of dopamine in isolated aorta. The dopamine-induced renal and mesenteric vasodilations are inhibited by phenothiazines and haloperidol (9, 10, 11) in dogs. These results support the concept that dopaminergic specific receptors are present in the circulatory system.

In the present study, the depressor response to dopamine, determined by the minimum level of blood pressure attained, was blocked by morphine in cats, tended to be diminished in rabbits, and was potentiated to some extent in dogs.

The pressor response to dopamine is also proposed to be reversed even after repeated administration of ephedrine, and this depressor response to dopamine in ephedrine-treated dogs is not affected by β-adrenergic blockade, ganglion blockade, anticholinergics, antihistaminics and haloperidol (12). The depressor response to dopamine induced after ephedrine was slightly potentiated by morphine in both cats and dogs in this present investigation.

It has been thus demonstrated that the counteraction of morphine on dopamine in the circulatory system varies considerably depending on the species of animal.

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