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HYPOTENSION PRODUCED BY INTRAVENOUS APOMORPHINE IN THE ANAESTHETIZED DOG IS NOT CENTRALLY MEDIATED

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1 Intravenous administration of apomorphine (1.25 to 20 μg/kg) in the anaesthetized dog produced a dose-dependent decrease in blood pressure which was antagonized by haloperidol but not influenced by propranolol or atropine.

2 Intracarotid administration of apomorphine produced a systemic hypotension which was significantly smaller than that seen with intravenous injection.

3 Doses of apomorphine that caused a decrease in blood pressure on intravenous injection, had no effect on blood pressure or caused retching accompanied by an increase in blood pressure on intravertebral or intracisternal administration. The animals showed a marked hypotension on intravertebral or intracisternal injection of clonidine.

4 From these results it is concluded that the hypotension seen with intravenous apomorphine cannot be explained by a central site of action.

Introduction

The fall in blood pressure seen with intravenous apomorphine in the cat has been ascribed to an action on central dopamine receptors (Barnett & Fiore, 1971). Antonaccio & Robson (1974) assumed that in the dog too, the haloperidol-sensitive hypotension produced by intravenous apomorphine is mediated by central dopamine receptors. However, in the dog peripheral effects of apomorphine exist that can decrease vascular resistance and which are sensitive to haloperidol: vasodilatation in the renal and mesenteric vascular bed (Goldberg, 1972; Crumly, Pinder, Hinshaw & Goldberg, 1976), vasodilatation in the femoral vasculature (Buylaert, Willems & Bogaert, 1977; Laubie, Schmitt & Falq, 1977) and inhibition of transmission in orthosympathetic ganglia (Willems & Bogaert, 1975).

In view of the present interest in central dopaminergic control of blood pressure (Stumpe, Higuchi, Kolloch, Krück & Vetter, 1977) we restudied the hypotension after intravenous apomorphine in the anaesthetized dog and tried to evaluate whether the hypotensive effect can be explained by a central mechanism.

Methods

Mongrel dogs of either sex, ranging in weight between 14 and 28 kg, were anaesthetized with intravenous sodium pentobarbitone (30 mg/kg), additional small doses being given as needed. Blood pressure, measured in the left brachial artery by a Statham pressure transducer, and heart rate, derived from the ECG, were displayed on a Beckman Dynograph type R recorder. Intravenous injections were given via the right cephalic vein. Injections in the cisterna magna were given via a needle introduced by suboccipital puncture. Injections into the common carotid artery were given through a catheter introduced via the arteria thyroidea superior. For injection of drugs into the left vertebral artery a catheter was introduced via the left axillary artery, with its tip in the subclavian artery just before the origin of the vertebral artery, and a ligature was then placed on the subclavian artery around the catheter just past the origin of the vertebral artery (Van Zwieten, 1975). A continuous infusion of 0.9% w/v NaCl solution (saline, 0.2 ml/min) ensured patency of the intra-arterial catheters, and the infusion rate was accelerated to 5 ml/min for 15 s after the injection of drugs. Drugs were always administered in a bolus injection of 0.2 ml. Injections were given at intervals of at least 20 minutes. For statistical analysis of the results a paired t test was used. Significance was assumed when $P \leqslant 0.05$. In the text, mean values $\pm$ standard error of the mean are given.

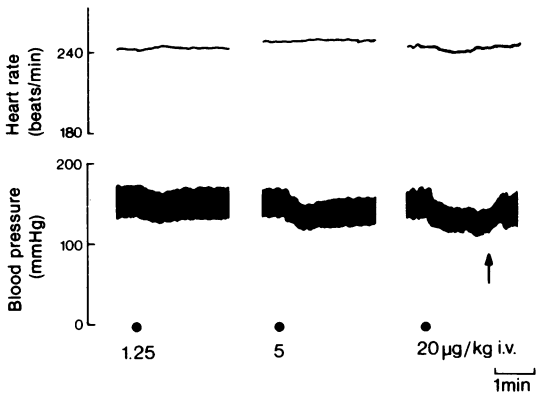

Figure 1 Blood pressure and heart rate responses to intravenous injections of apomorphine in an anaesthetized dog. The arrow indicates the moment the dog started retching.

Drugs

The following drugs were used: acetylcholine chloride (Hoffman-La Roche), (±)-apomorphine hydrochloride, atropine sulphate (Boehringer-Sohn), clonidine hydrochloride (Boehringer-Sohn), haloperidol (Janssen Pharmaceutica), and (±)-propranolol (ICI). Drug solutions were prepared in saline on the day of the experiment and stored in ice. Haloperidol was prepared as previously described (Willems, 1973).

Results

Effects of intravenous apomorphine on blood pressure and heart rate

Within the dose range studied (1.25 to 20 µg/kg), apomorphine injected intravenously produced a dose-dependent decrease in blood pressure (Figure 1). In 6 animals the mean decrease in blood pressure for 1.25, 5 and 20 µg/kg of apomorphine was 9 ± 1, 20 ± 2 and 22 ± 3 mmHg. With doses up to 5 µg/kg, the decrease in blood pressure was accompanied by a slight increase in heart rate. With doses higher than 5 µg/kg, increases, decreases or biphasic changes in heart rate occurred. With the higher doses (> 5 µg/kg) of apomorphine, retching occurred in some dogs approximately 1 to 2 min after the start of the hypotension. The retching lasted several minutes and was accompanied by an increase in blood pressure that temporarily interrupted the hypotensive effect of apomorphine (Figure 1).

Influence of haloperidol, atropine and propranolol on the hypotensive effect of intravenous apomorphine

In 4 dogs, apomorphine (1.25 µg/kg) was injected before and 5 min after haloperidol (4 µg/kg i.v.). The decrease in blood pressure of 8 ± 1 mmHg was reduced to 1 ± 1 mmHg ($P < 0.01$) by haloperidol and the increase in heart rate was abolished. The hypotension after administration of a higher dose of apomorphine (20 µg/kg) was not influenced by 4 µg/kg of haloperidol but 128 µg/kg of haloperidol reduced it from 25 ± 1 mmHg to 6 ± 2 mmHg ($P < 0.01$) ($n = 4$). Even this dose of haloperidol had no lasting effect on blood pressure and did not antagonize the hypotension seen with intravenous acetylcholine (0.4 µg/kg) ($n = 4$).

Atropine (1 mg/kg i.v.) and propranolol (0.5 mg/kg i.v.) had no influence on the decrease in blood pressure produced by apomorphine, even when low doses of apomorphine (1.25 µg/kg) were used ($n = 4$). The slight increase in heart rate of 12 ± 2 beats/min occurring with this dose of apomorphine was abolished by propranolol.

Comparison between intravenous and intravertebral injection of apomorphine (Figure 2)

In 7 dogs intravenous injection of apomorphine (2.5 µg/kg) produced a hypotension of 11 ± 2 mmHg. When in these animals the same dose of apomorphine was injected into the vertebral artery there was no change in blood pressure in 2 dogs and a decrease of 4 mmHg in 1 dog; in the 4 remaining dogs, blood pressure increased when retching occurred, i.e. 1 to 2 min after the injection. Lower doses of apomorphine injected into the vertebral artery had no influence on blood pressure.

At the end of these experiments clonidine was given. Intravenous injection of clonidine (1 µg/kg) produced a small increase in blood pressure in all 7 animals, followed in 4 of these by a decrease of 6 ± 2 mmHg. Intravertebral injection of the same dose of clonidine caused a decrease in blood pressure of 28 ± 3 mmHg in the 7 dogs.

Comparison between intravenous and intracarotid injection of apomorphine

In 5 animals, 1.25 µg/kg of apomorphine injected intravenously caused a fall in blood pressure of 11 ± 2 mmHg. When the same dose was injected into the common carotid artery the decrease in blood pressure was 6 ± 1 mmHg ($P < 0.05$).

Comparison between intravenous and intracisternal injection of apomorphine

Two to three min after apomorphine (1.25 µg/kg) was injected into the cisterna magna in 4 dogs, retching and an increase in blood pressure of 17 ± 2 mmHg occurred; 1.25 µg/kg of apomorphine given intra-

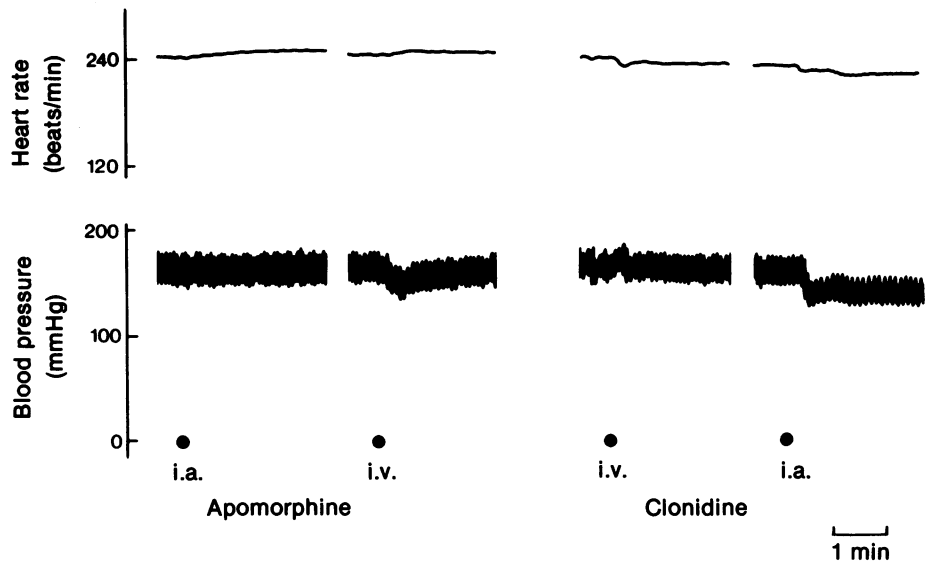

Figure 2 Blood pressure and heart rate responses to injections of apomorphine (2.5 μg/kg) and clonidine (1 μg/kg) into the cephalic vein (i.v.) and into the vertebral artery (i.a.) of an anaesthetized dog.

venously in the 4 dogs produced a hypotension of 9 ± 1 mmHg. Intracisternal injection of clonidine (1 μg/kg) in these dogs caused a decrease in blood pressure of 23 ± 7 mmHg.

Discussion

The observation by Antonaccio & Robson (1974) that intravenous injection of apomorphine in the anaesthetized dog produces a haloperidol-sensitive decrease in blood pressure is confirmed by our results. Moreover, we show that the hypotensive effect of apomorphine is dose-related and that it is not blocked by propranolol or atropine. The hypotension caused by the lower doses of apomorphine is accompanied by a slight tachycardia which is probably of reflex origin since it is antagonized by propranolol and absent after inhibition of the hypotensive effect of apomorphine by haloperidol. The bradycardia observed in some animals with higher doses of intravenous apomorphine can be explained by increased vagal activity (Fadhel, 1967) or decreased sympathetic tone, either due to ganglionic inhibition (Willems, 1973) or to presynaptic inhibition of transmitter release (Long, Heintz, Cannon & Kim, 1975).

The main object of the present study was to know whether the hypotension seen with intravenous apomorphine is centrally mediated as assumed by Antonaccio & Robson (1974). This problem was approached by comparing the effects of injections directed towards the central nervous system with the effects of intravenous injections (Van Zwieten, 1975). The immediate fall in blood pressure observed with intravenous administration of apomorphine was not seen with intravertebral injections while in the same animal the hypotension after intravertebral clonidine was much larger than after intravenous injection. The effects after intracisternal and intracarotid injections also failed to suggest a central hypotensive action of apomorphine.

From the results obtained we conclude that the fall in blood pressure after intravenous apomorphine cannot be explained by a central mechanism.

In view of the interest in a possible role for central dopamine receptors in blood pressure regulation (Stumpe, Higuchi, Kolloch, Krück & Vetter, 1977), it is important to realize that the hypotension seen with intravenous injections of apomorphine in the anaesthetized dog, is not a good indicator for central dopamine receptor stimulation.

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