Br. J. Pharmac. (1969), 37, 367–370.

Interaction between (±)-amphetamine and atropine on the rat cardiovascular system

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1. The effects of atropine on the pithed rat blood pressure after (±)-amphetamine depend on the pattern of the cardiovascular responses to the latter.

2. If the pressor response to amphetamine is followed by oscillations of blood pressure and a reduction in pulse pressure or by a fall in blood pressure terminating in circulatory failure, atropine increases blood pressure, but if it is not followed by these patterns, atropine decreases blood pressure.

3. The fall in blood pressure produced by atropine after amphetamine might be due to weak alpha-adrenoceptor blockade.

While studying the effects of (±)-amphetamine on the blood pressure of the pithed rat, an interaction with atropine was observed which appeared to depend on the pattern of the cardiovascular responses to amphetamine.

Methods

Male rats (250–350 g) were given atropine (1 mg/kg intraperitoneally), anaesthetized with ether and then pithed (Gillespie & Muir, 1967). Blood pressure was recorded from one carotid artery. One femoral vein was cannulated for the administration of drugs. Drug interactions were investigated further using the isolated rat heart (Langendorff technique) and isolated rat femoral artery (De la Lande & Rand, 1965). Both were perfused (the former at 1·4 ml./min ; the latter at 4 ml./min) with Krebs bicarbonate solution using a Watson Marlow constant flow pump.

The drugs used were (±)-amphetamine sulphate (kindly supplied by Smith Kline and French Laboratories), atropine sulphate, (−)-noradrenaline bitartrate and vasopressin. With the exception of vasopressin, all doses are expressed in terms of the bases.

Results

Pithed rat blood pressure

In all experiments (twenty), (±)-amphetamine 50 μg increased the blood pressure. In ten experiments, intravenous injections of amphetamine produced pressor

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responses which were followed by a smooth return of blood pressure to control levels (Fig. 1). Intravenous injection of atropine 400 μg did not affect the blood pressure when given before amphetamine (Fig. 1). However, after a minimum of three and up to a maximum of eight successive doses of amphetamine, injection of atropine decreased the blood pressure by 6 to 26 mm Hg (Fig. 1). Subsequent administration of up to three successive doses of atropine 400 μg produced similar responses with no need for further injections of amphetamine, but the time taken for the effect to wear off was not determined.

In the other ten experiments, however, recovery of the blood pressure response to amphetamine was followed by either slow oscillations of pressure with a periodicity of about 1 min and a reduction in pulse pressure (Fig. 2) or a fall in blood pressure terminating in circulatory failure. These patterns occurred most often (seven experiments) after one or two doses of amphetamine, but on three occasions appeared only after three to five successive doses. On these latter, the resting blood pressure was

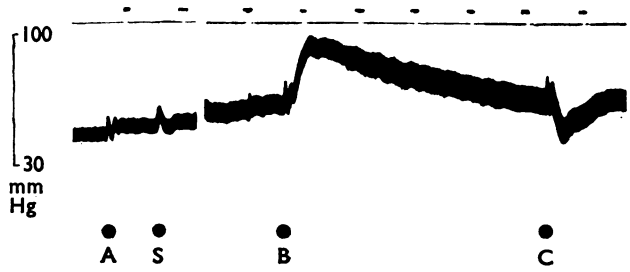

FIG. 1. Interaction of (±)-amphetamine and atropine on the pithed rat blood pressure. Time marks, 1 min. At A, atropine 400 μg had no effect on blood pressure. At B, (±)-amphetamine 50 μg increased blood pressure but did not induce oscillations of pressure or reduce pulse pressure. After (±)-amphetamine, atropine 400 μg (C) decreased blood pressure. At S, 0·3 ml. 0·9% NaCl solution given.

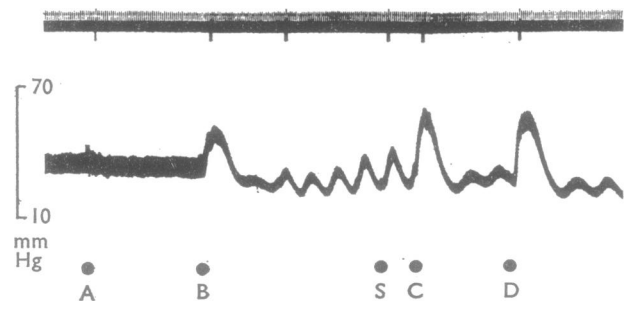

FIG. 2. Interaction of (±)-amphetamine and atropine on the pithed rat blood pressure. Time marks, 5 sec. At A, atropine 300 μg had no effect on blood pressure. At B, (±)-amphetamine 50 μg increased blood pressure, induced slow oscillations of pressure and reduced pulse pressure. Atropine 100 μg (C) and 150 μg (D) after (±)-amphetamine increased blood pressure, reduced the size of the oscillations and temporarily improved the pulse pressure. At S, 0·3 ml. 0·9% NaCl solution given.

maintained or increased after the initial doses of amphetamine and the patterns did not appear until the resting pressure began to fall after the drug. As in the other experiments atropine (100–400 μg) had no effect on the blood pressure when given before amphetamine (Fig. 2). When given after amphetamine, atropine increased the blood pressure by 13 to 50 mm Hg, temporarily reduced the size of the oscillations and temporarily improved the pulse pressure (Fig. 2). Subsequent administration of up to three successive doses of atropine produced similar pressor responses with no need for further injections of amphetamine, but the time taken for the effect to wear off was not determined.

Isolated rat heart

In most cases, (±)-amphetamine, in single doses of 5–50 μg or perfused in concentrations of 5–40 μg/ml., produced no significant changes in the rate or amplitude of the heart beat. Atropine, in single doses of 50–500 μg, slightly increased the amplitude of the heart beat and no differences were found when it was given before or after amphetamine.

Isolated rat femoral artery

The perfusion of (±)-amphetamine 20–100 μg/ml. increased the perfusion pressure. Atropine 400 μg given before amphetamine had either no effect on the perfusion pressure or caused a slight rise. During perfusion with amphetamine, the same dose decreased the perfusion pressure. Similar effects were observed with atropine 400 μg given before or during perfusion with noradrenaline 0·1–1 μg/ml. When the artery was perfused with vasopressin 0·0005–0·004 units/ml., however, atropine 400 μg increased the perfusion pressure still further.

Discussion

We do not know why some rats showed signs of circulatory instability after amphetamine or why there should be a correlation between the effects of atropine on blood pressure and the pattern of the cardiovascular responses to amphetamine. One possible mechanism for a pressor response after atropine is that blockade of muscarinic receptors facilitates the release of catecholamines by amphetamine, as Lindmar, Löffelholz & Muscholl (1968) found using acetylcholine on isolated hearts. However, we found no interaction between amphetamine and atropine on isolated hearts and since the effects of atropine on blood pressure were brief and all animals were pre-dosed with atropine, an explanation based on muscarinic blockade seems unlikely. An explanation for the depressor effect of atropine might be based on the interaction between atropine and amphetamine which we found in isolated rat arteries. Since atropine also interacted with noradrenaline but not with vasopressin, and since Bussell (1940) found a similar interaction between atropine and adrenaline on the perfused dog hind leg, the vasodilatation might be due to weak alpha-adrenoceptor blockade.

The technical assistance of Mr J. E. Thomson and Mr J. McCormick is gratefully acknowledged.

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(*Received August* 7, 1969)