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Cardiovascular effects of (−)-cathinone in the anaesthetized dog: comparison with (+)-amphetamine

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World health authorities have been concerned for many years with the problem of 'Khat' obtained from the plant *Catha edulis*, Forsk (League of Nations 1936). Earlier chemical studies resulted in the isolation of several alkaloidal fractions believed to represent the active principles of the drug (for references see Halbach 1972). However, the powerful central nervous system (c.n.s.) stimulating actions of the fresh plant material observed in man and mice could not be explained on the basis of the content and relatively weaker biological effects of the alkaloidal fractions (Brucke 1941). Chemical studies of the plant were, therefore, reinstituted. The United Nations Narcotics Laboratory (1979) has reported isolation of more than 20 substances from the plant. Among these (−)-cathinone appears to be the major component repsonsible for its (c.n.s.) activity.

The chemical structure of cathinone differs from that of amphetamine only in the keto group substitution on the beta carbon of amphetamine. In the present investigation we have compared the effects of (−)-cathinone, the natural isomer, with (+)-amphetamine on cardiac contractile force (CCF), blood pressure (BP), and heart rate (HR) in the anaesthetized dog. (−)-Cathinone hydrochloride received from United Nations Narcotics Laboratory, Vienne and (+)-amphetamine sulphate obtained from National Institute on Drug Abuse, Rockville, Maryland were used in this study.

Male mongrel dogs, 16–26 kg, were anaesthetized with sodium pentobarbitone, 30 mg kg^{-1} i.v., and maintained under light surgical anaesthesia with 2–3 mg kg^{-1} i.v. as needed. Through a midline neck incision tracheotomy was performed and the trachea, the left carotid artery, and the right external jugular vein were cannulated. Both vagus nerves were islolated. Dogs were respired with room air via a Harvard respiratory pump. A thoracotomy was performed, and after incision of the pericardium, a Walton-Brodie strain gauge arch was sutured to the right ventricle, as previously described (McDonald & Goldberg 1963). All dogs were bilaterally vagotomized. Carotid blood pressure was recorded with a Bell and Howell transducer, type 4-327-0010. HR was measured by a Beckman tachometer with input from intracutaneous EKG needles using standard leads. Carotid blood pressure, HR, and CCF were recorded simultaneously on a Beckman type R-611 dynograph. The animals were allowed to stabilize for 15–20 min before drug administration. All drugs were injected into the external jugular vein in 2–3 ml of 0·9% NaCl (saline).

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(−)-Noradrenaline, 0·125 and 0·25 μg kg^{-1}, was injected i.v. in each animal to determine responsiveness to the standard catecholamine. (−)-Cathinone or (+)-amphetamine (10 μg kg^{-1}) was injected first in alternate animals. Following the first injection, the drugs were given in the following sequence (μg kg^{-1}): Drug 2, 10; Drug 2, 30; Drug 1, 30; Drug 1, 100; Drug 2, 100. Sufficient time (15–30 min) elapsed between injections to allow the return of all parameters to the baseline.

Tyramine, 30 μg kg^{-1}, was used as a standard indirectly-acting amine. Methylphenidate, which blocks the neuronal uptake process, was used to determine the direct or indirect sympathomimetic activity of the drugs under study (Meyer & Goldberg 1966). The various drugs were repeated 5–10 min after the administration of methylphenidate, 5 mg kg^{-1} i.v.

All parameters were measured as change from the baseline. Results are expressed as mean ± s.e. Student's *t*-test for paired data was used to assess statistical differences between amphetamine and (−)-cathinone at each dose level.

(−)-Cathinone and (+)-amphetamine caused almost identical dose-related increases in HR, BP, and CCF; 10 μg kg^{-1} appeared to be the threshold dose of both compounds. Doses higher than 100 μg kg^{-1} were not used since this dose caused prolonged and excessive increases in HR and BP and also tended to induce cardiac arrhythmias (Fig. 1 upper panel).

The effects of (−)-cathinone and (+)-amphetamine were compared in 8 experiments. The results are summarized in Table 1. The effects of 10, 30, and 100 μg kg^{-1} of (−)-cathinone and amphetamine on HR and CCF were statistically indistinguishable. However, 100 μg kg^{-1} of (+)-amphetamine produced a significantly greater increase in BP than the same dose of (−)-cathinone.

In 6 of the above experiments, effects of (−)-cathinone and (+)-amphetamine, 100 μg kg^{-1}, were studied after administration of methylphenidate, 5 mg kg^{-1} i.v. This dose of methylphenidate potentiated the effects of noradrenaline, 0·125 μg kg^{-1}, on HR, BP, and CCF, whereas the effects of tyramine, 30 μg kg^{-1}, were completely abolished as previously reported (Meyer & Goldberg 1966). The effects of the highest dose of (−)-cathinone and (+)-amphetamine, like tyramine, were eliminated by pretreatment with methylphenidate. A representative experiment is shown in Fig. 1.

The above results demonstrate a marked similarity

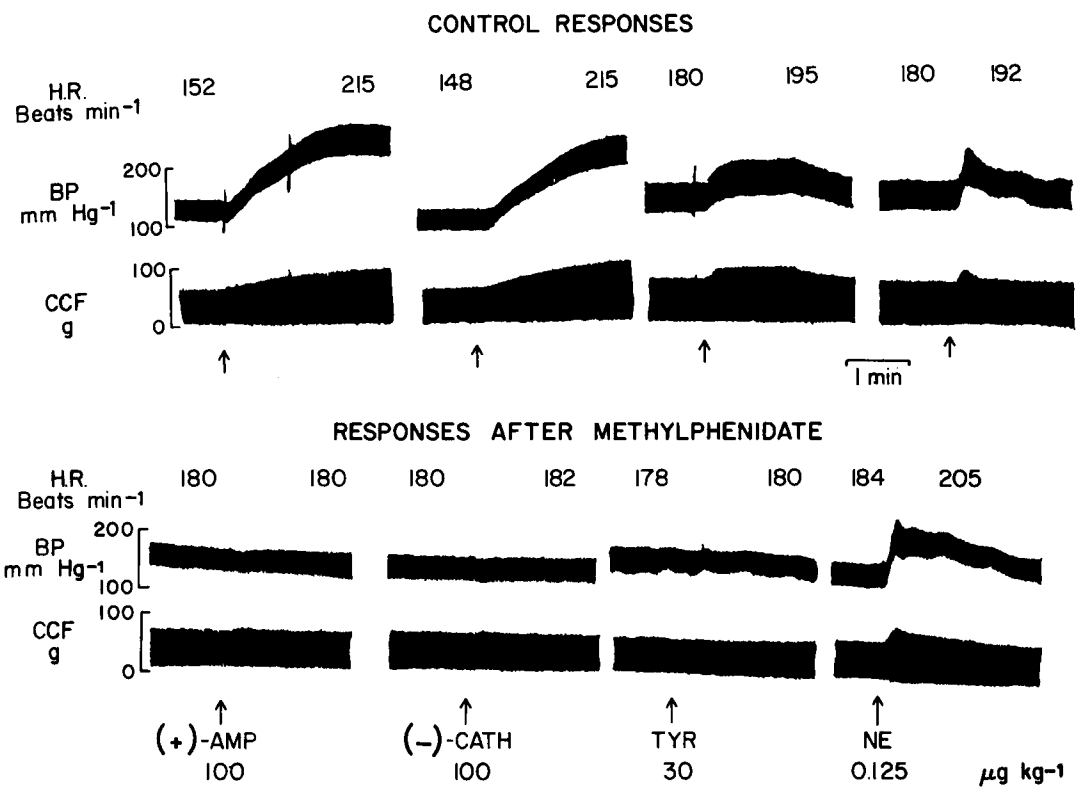

FIG. 1. Effect of (+)-amphetamine (+)-AMP, (−)-cathinone (−)-CATH), tyramine (Tyr), and noradrenaline (NA) before (upper panel) and after (lower panel) methylphenidate on heart rate (HR), carotid blood pressure (BP), and cardiac contractile force (CCF) in a pentobarbitone-anaesthetized dog.

Table 1. Increase over baseline of heart rate (HR), blood pressure (BP), and cardiac contractile force (CCF). Mean ± s.e. (n = 8)†

Dose	HR beats min^{-1}		BP mm Hg		CCF (g)	
μg kg^{-1}	(−)-Cath	(+)-Amph	(−)-Cath	(+)-Amph	(−)-Cath	(+)-Amph
10	6 ± 1·5	6 ± 1·6	6·5 ± 1·7	6 ± 1·6	9 ± 2·6	9 ± 3
30	16 ± 1·7	17 ± 2·6	20 ± 3·8	24 ± 4	16 ± 2·6	17 ± 3
100	36 ± 5	40 ± 4·5	47 ± 12	61 ± 12*	37 ± 7	48 ± 8

*$P < 0·05$

† Basal values for the various parameters were: HR, 166 ± 5·4 beats min^{-1}; BP, 165 ± 9·5 mm Hg; CCF, 131 ± 10·1 g.

between the cardiovascular effects of (+)-amphetamine and (−)-cathinone. The two compounds appear to be equipotent in raising BP and in producing positive inotropic and chronotropic effects in the heart. It is further shown that, like (+)-amphetamine, (−)-cathinone is an indirectly-acting sympathomimetic amine. The cardiovascular complications of overdose or abuse of cathinone may, therefore, be expected to be similar to those of amphetamine. Although most reports, including the present study, have noted the sympathomimetic actions of (−)-cathinone, a recent study by Maitai (1981) recorded an interesting difference between ephedrine and cathinone. Whereas, high doses of ephedrine produced cardiodepressant effects on the chick embryo heart blocked by atropine, the cardiodepressant effect of cathinone in the same preparation was resistant to atropine. The reason for this difference is not understood.

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The influence of ethanol on the synthesis of prostaglandin-like material by resident rat peritoneal cells from exogenous arachidonic acid

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During the course of initial investigations into the effect of different parameters on the uptake and metabolism of arachidonic acid (AA) in rat peritoneal cells it was found that if ethanol was added to the AA solution before mixing with the cell suspension (but not after) there was a stimulation of prostaglandin-like (PGL) synthesis and a change in the cell membrane as shown by trypan blue uptake. This phenomenon was investigated further and the results of the experiments are presented in this communication.

Resident rat peritoneal cells were isolated from a 0·9% NaCl (saline) wash of a Wistar rat peritoneum by centrifugation at 4 °C and 500 *g* for 10 min. The different cell samples were pooled and the number of viable cells measured using trypan blue exclusion. The cells were recentrifuged and a final suspension of 5×10^6 viable cells ml^{-1} was prepared in saline. AA (10 μl volume) and 1 ml of the cell suspension were added to 1 ml plastic reaction vials, vortex mixed and incubated for 20 min at 37 °C in a water bath. After the incubation period a few drops of the medium were taken to measure cell viability and the rest of the cells centrifuged at 8000 *g* for 30 s. PGL activity in the supernatant was assayed by superperfusion of rat stomach strips as described by Vane (1964) and modified by Bult & Bonta (1976). PGE_2 was used as a reference compound and the activity of PGL material in the supernatant is given as equivalent to ngPGE_2/20 min/5×10^6 cells.

The level of PGL material in the medium of saline incubated cells was below the limit of detection of the bioassay used (10–100 pg PGE_2/50 μl sample). There was significant formation of PGL material if the cells were incubated with 10 μg ml^{-1} AA, however, if the stock solution (100 μg/10 μl) was diluted 1/10 with saline (to give a concentration of 10 μg/10 μl) there was less activity (6·7 ± 0·6 ng PGE_2) than if it was diluted in ethanol (27·2 ± 2 ng PGE_2). Addition of 10 μl of ethanol to incubation tubes after the cells and saline diluted AA had been mixed (to give the same final concentration of ethanol) did not stimulate PGL formation to any great extent (7·7 ± 0·5 ng PGE_2). Control incubations of AA in saline had no PGL activity after 20 min. Cells incubated with AA diluted in ethanol showed permeability changes as shown by trypan blue uptake (0% viable) whilst cells incubated with saline diluted AA showed no alteration (93 ± 6% viable). Addition of ethanol after mixing the cells and saline siluted AA resulted in a small decrease in viability (86 ± 4%) (Fig. 1). When different volumes of ethanol were added to 10 μg (10 μl volumes) AA before mixing with the cell suspension, a dose-dependent increase in PGL formation and decrease in cell viability was seen. If the ethanol was added after mixing, no effect of ethanol was observed (Fig. 2).

These experiments showed that the initial concentration of ethanol in the solution used to dissolve the AA was important, not the end concentration in the incubation mixture. They also excluded the possibility that ethanol stimulated cell metabolism in general as the same effect would then have been expected when the ethanol was added after the cells and AA had been mixed. Similarly, the permeability changes would appear to be due to the AA and not the ethanol.

In order to investigate the effect of ethanol at different AA concentrations 10 μl volumes of an ethanolic solution of AA (for each concentration) were added to the 1 ml reaction tubes and the ethanol evaporated off. Saline or ethanol (10 μl) was then added and the tubes left for 10 min, with occasional vortex mixing, to allow the AA to redissolve. If the AA was presented in ethanol there was a log/linear increase in PGL synthesis over the range 1–50 μg ml^{-1} AA but at 100 μg ml^{-1} there was a decrease in formation to 20% of the 10 μg ml^{-1} level (Fig. 3). No PGL activity could be detected using 10 ng or 100 ng AA. Permeability changes were seen in all cells incubated with greater than 1 μg ml^{-1} AA. If saline was the solvent there was a similar log/linear increase which was seen over the range 1–100 μg ml^{-1} AA with an absolute increase of half the ethanol group at each AA concentration (up to 50 μg ml^{-1} AA). There was little change in cell permeability up to 10 μg ml^{-1}, but at higher concentrations viability decreased rapidly to less than 10% at 50 μg ml^{-1}. AA samples treated as above but incubated without cells

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