Br. J. Pharmac. Chemother. (1966), **28**, 73–83.

MECHANISM OF CARDIOVASCULAR ACTIONS OF 1-(1-PHENYLCYCLOHEXYL)PIPERIDINE HYDROCHLORIDE (PHENCYCLIDINE)

BY

K. F. ILETT, B. JARROTT, STELLA R. O'DONNELL AND JANET C. WANSTALL*

From the Department of Physiology, University of Queensland, Brisbane, Australia
(*Received June* 20, 1966)

1-(1-phenylcyclohexyl)piperidine hydrochloride (phencyclidine) is primarily a central nervous system depressant and produces anaesthesia in humans sufficient for both minor and major surgery to be performed (Greifenstein, De Vault, Yoshitake & Gajewski, 1958 ; Johnstone, Evans & Baigel, 1959 ; Collins, Goroscope & Rovenstine, 1960 ; Camilleri, 1962). However, phencyclidine is also psychotomimetic (Greifenstein *et al.*, 1958 ; Johnstone *et al.*, 1959 ; Meyer, Greifenstein & De Vault, 1959) and a pressor agent in man (Greifenstein *et al.*, 1958 ; Johnstone et al., 1959) and in animals (Chen, Ensor, Russell & Bohner, 1959).

Phencyclidine produced a transient but marked pressor response in anaesthetized dogs (Chen *et al.*, 1959 ; Domino, 1964) which was not blocked by hexamethonium or by an adrenergic blocking drug (Chen *et al.*, 1959). Enhancement of the pressor responses to adrenaline (Chen *et al.*, 1959 ; Domino, 1964), dimethylphenylpiperazine (Chen *et al.*, 1959), noradrenaline and 5-hydroxytryptamine (Domino, 1964) have also been reported. The aim of this study was to investigate further the mechanism of the hypertensive action of this cyclohexylamine derivative and the interaction of phencyclidine with other drugs on the cardiovascular system. Since this study started a report has appeared in which the effects of phencyclidine on the blood pressure of dogs are compared with those of cocaine and desoxyephedrine (Chen, Ensor & Bohner, 1965).

METHODS

Blood pressure of anaesthetized and spinal cats

Cats of either sex, weighing 1.8 to 4.2 kg, were premedicated with atropine sulphate (1 mg/kg intraperitoneally). They were then either anaesthetized with ether followed by intravenous chloralose (80 mg/kg in a 10% (v/v) aqueous solution of polyethylene glycol) or intravenous pentobarbitone (40 mg/kg), or were made spinal under ether anaesthesia by the anterior approach of Zarro & Di Palma (1964). Blood pressure was recorded from the left carotid artery with a mercury manometer. Drugs were injected into the left femoral vein. When drug infusions were given, the right femoral vein was cannulated with polyethylene tubing attached to a continuous slow injector (Palmer). Heparin (1,000 u./kg) was administered intravenously as an anticoagulant. In some experiments respiration was recorded using a tambour (Burn, 1952), or heart rate was recorded from the electrocardiogram.

* Present address: Department of Human Physiology and Pharmacology, University of Adelaide, South Australia.

Adrenalectomy

Acute bilateral adrenalectomy was performed under chloralose anaesthesia *via* a midline incision. The adrenolumbar vein and artery were tied off and the gland carefully freed.

Pretreatment with reserpine

Reserpine (3 mg/ml.) dissolved in 20% (w/v) ascorbic acid solution was administered 24 hr before the experiment in a dose of 3 mg/kg as described by Trendelenburg, Muskus, Fleming & Gomez Alonso de la Sierra (1962a). The animals were made spinal before recording blood pressure.

Blood presure of anaesthetized and pithed rats

Rats of either sex, weighing 180 to 220 g, were anaesthetized with urethane (1 ml./100 g of a 12% w/v solution, intraperitoneally) or were pithed, under ether anaesthesia, by passing a long steel needle through the orbit and down the spinal cord. Blood pressure was recorded from a carotid artery using a mercury manometer and drugs were injected into a jugular vein. Heparin (1000 u./kg) was administered intravenously as an anticoagulant.

Adrenalectomy

Acute, bilateral adrenalectomy was carried out in anaesthetized rats by the method of Zarrow, Yochim, McCarthy & Sanborn (1964).

Pretreatment with reserpine

Rats of either sex, weighing 180 to 220 g, were anaesthetized with urethane (1 ml./100 g of a 12% as described by Gillis & Nash (1961). The animals were pithed before recording blood pressure.

Isolated heart tissue

Atria from freshly killed young guinea-pigs were suspended in a 10 ml. organ bath containing oxygenated Ringer-Locke solution at 29 to 30° C. Contractions were recorded on a smoked drum using a Starling heart lever (magnification 10×). Counts of the rate of beating were made immediately before the addition and at 1 min intervals after the addition of a drug. The drug was left in contact with the atria for 3 min.

Papillary muscles, from the right ventricles of cats anaesthetized with ether, were mounted on muscle holders and placed in 2.5 ml. chambers containing oxygenated Krebs-Ringer bicarbonate solution at 37.5° C. A tension of 1 to 2 g was applied to the muscles and they were stimulated with supramaximal, rectangular pulses of 2 msec duration at a frequency of 90 shocks/min. Recordings were made for 10 sec every min using an isometric transducer. Test drugs were added after 60 to 90 min of stimulation when the muscle was failing. The drug was left in contact until a maximal response was observed, and then washed out.

Isolated perfused central artery of rabbit ear

The isolated central artery of the rabbit ear was perfused as described by De La Lande & Rand (1965).

Drugs

The following drugs were used: acetylcholine chloride, adrenaline acid tartrate, atropine sulphate, choline phenyl ether bromide (TM1), cocaine hydrochloride, dimethylphenylpiperazinium iodide (DMPP), hexamethonium bromide, isoprenaline sulphate, nicotine acid tartrate, noradrenaline acid tartrate, phencyclidine hydrochloride (Sernylan), phenoxybenzamine hydrochloride, piperoxan (933F), reserpine, tetraethylammonium bromide, tolazoline hydrochloride, tyramine hydrochloride.

All doses are expressed as weight of salt with the exception of reserpine which is expressed as the weight of base.

RESULTS

Effect of phencyclidine on blood pressure

In both anaesthetized and spinal cats phencyclidine (0.5–1.0 mg/kg) produced an immediate rise in blood pressure which lasted 10 to 15 min. A second dose administered immediately after the effects of the first dose had worn off showed tachyphylaxis. With further doses of phencyclidine the tachyphylaxis continued until after 8 to 10 doses the response usually became depressor. If consecutive doses were separated by intervals of 30 min tachyphylaxis did not occur. Thus in most experiments doses of 0.5 or 1 mg/kg of phencyclidine were administered at 30 min intervals.

An intravenous injection of phencyclidine (1 mg/kg) produced a mean rise in blood pressure of 58.0 ± 7.4 (s.e. of mean) mm Hg in five anaesthetized cats and a mean rise in blood pressure of 59.5 ± 6.9 mm Hg in eleven spinal cats. The responses to phencyclidine in these two groups of animals are not significantly different ($t = 0.15$, $P = 0.8$–0.9).

In two experiments a spinal cat was set up for the simultaneous recording of electrocardiogram and blood pressure. The pressor responses to phencyclidine (0.5 and 1.0 mg/kg) were accompanied by a bradycardia of 15 beats/min.

In anaesthetized cats a cessation of respiration frequently accompanied the pressor response to the first dose of phencyclidine. This was most noticeable when pentobarbitone had been used as the anaesthetic. The respiratory depression caused by doses of phencyclidine of 1 mg/kg or less was reversible but above this dose the depression was irreversible.

In six anaesthetized rats tachyphylaxis to successive doses of phencyclidine (0.125 mg/kg) was not observed. This dose produced a mean blood pressure rise of 18.0 ± 1.2 mm Hg. A pressor response to phencyclidine (0.25–5.0 mg/kg) was also observed in three pithed rats.

Effect of ganglion blocking agents

In both cats anaesthetized with chloralose and spinal cats hexamethonium (1 mg/kg) abolished the pressor response to dimethylphenylpiperazinium iodide (DMPP) but not to phencyclidine. In anaesthetized cats nicotine, administered in three doses of 3.5 mg over 20 min, did not affect the rise in blood pressure produced by phencyclidine.

In anaesthetized rats tetraethylammonium bromide and hexamethonium, in doses which considerably reduced the pressor effect of the ganglion stimulant choline phenyl ether bromide (TM1), did not reduce the response to phencyclidine.

Effect of α-adrenergic blocking agents

In both anaesthetized and spinal cats phenoxybenzamine (5 mg/kg) blocked or reversed the blood pressure rise produced by adrenaline and markedly reduced, and in two experiments completely blocked, the response to phencyclidine. Piperoxan (933F) caused a marked reduction but not complete blockade of the response to phencyclidine in spinal cats and pithed rats.

Effect of adrenalectomy

The rise in blood pressure produced by phencyclidine in cats and rats was not affected by acute, bilateral adrenalectomy. In two adrenalectomized cats a dose of 1 mg/kg of

phencyclidine caused initial rises in blood pressure of 65 and 90 mm Hg. In another cat a dose of 0.75 mg/kg produced an initial rise of 40 mm Hg. Tachyphylaxis to consecutive doses of phencyclidine still occurred. In six adrenalectomized rats 0.125 mg/kg of phencyclidine produced a mean rise in blood pressure of 19.5 ± 1.5 mm Hg. Tachyphylaxis to consecutive doses was not observed. In six anaesthetized control rats the mean pressor response to this dose of phencyclidine was 18.0 ± 1.3 mm. Hg. The difference between these two results is not statistically significant ($t = 0.79$, $P = 0.4$—0.5).

Effect of reserpine

In seven spinal cats pretreated with reserpine, phencyclidine (1 mg/kg) produced a mean rise in blood pressure of 45 ± 9 mm Hg. The magnitude of this response is not significantly different from that in untreated spinal cats ($t = 1.28$, $P = 0.2$–0.3). In all experiments tyramine (0.5 mg/kg) was administered intravenously to confirm that the noradrenaline stores were depleted. If phencyclidine was administered at 15 min intervals marked tachyphylaxis in the response was exhibited, but when tachyphylaxis had occurred a pressor response to noradrenaline was still elicited (Fig. 1). If doses of phencyclidine (1 mg/kg) were administered at 30 min intervals tachyphylaxis did not occur.

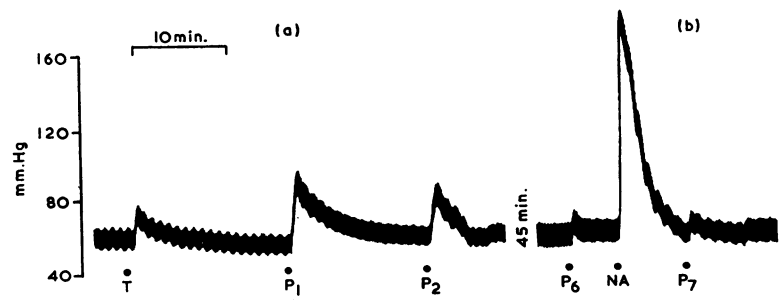

Fig. 1. Blood pressure of spinal cat (2 kg) pretreated with reserpine. At T, tyramine (0.5 mg/kg); at P_1, P_2, P_6 and P_7 phencyclidine (1 mg/kg) and at NA, noradrenaline (2.5 μg/kg) were administered intravenously. Between (a) and (b) three doses of phencyclidine (1 mg/kg) were administered at 15 min intervals to elicit tachyphylaxis to phencyclidine.

In two experiments a slow intravenous infusion of noradrenaline (40 μg/min for 20 min) was given immediately after a pressor response to phencyclidine (1 mg/kg) had been obtained. Five min after stopping the infusion a second dose of phencyclidine (1 mg/kg) was administered. The pressor response was reduced. A further dose of phencyclidine administered 30 min later still produced a much decreased response.

The pressor response to phencyclidine in rats was not abolished by pretreatment of the animals with reserpine. In three anaesthetized rats, phencyclidine (0.25 mg/kg) produced a mean pressor response of 29.0 ± 2.1 mm Hg. This same dose produced a rise of 25 mm Hg and 30 mm Hg in two rats pretreated with reserpine. Repeated doses of phencyclidine administered at 40 min intervals did not cause tachyphylaxis. The hypertensive effect in the reserpinized rats was reduced by intravenous administration of 25 mg/kg tolazoline.

Effect of cocaine

In three spinal cats cocaine (10 mg/kg), administered intramuscularly in four divided doses, markedly reduced the response to a 1 mg/kg dose of phencyclidine (Fig. 2). In two experiments cocaine (0.5 mg/kg) administered intravenously before phencyclidine completely abolished the pressor response to 0.5 mg/kg phencyclidine.

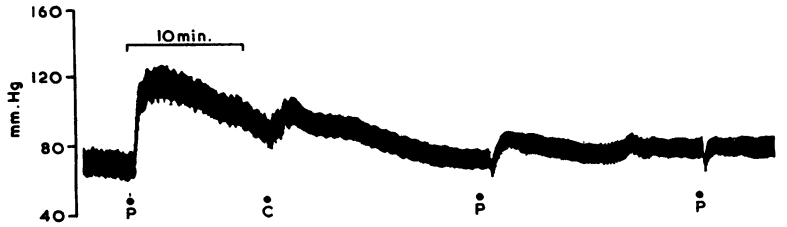

Fig. 2. Blood pressure of spinal cat (4 kg). An intramuscular injection of cocaine (10 mg/kg in four divided doses) administered at C markedly reduced the response to an intravenous injection of phencyclidine (1 mg/kg) administered at P.

Effect of phencyclidine on blood pressure responses to adrenaline and noradrenaline

A single dose of phencyclidine (1 mg/kg) in anaesthetized and spinal cats potentiated the pressor responses to adrenaline and noradrenaline (Figs. 3a & 3b). The responses were increased both in size and duration and were still potentiated 1 hr after administration of the phencyclidine. This potentiation also occurred in adrenalectomized cats and in anaesthetized, pithed and adrenalectomized rats.

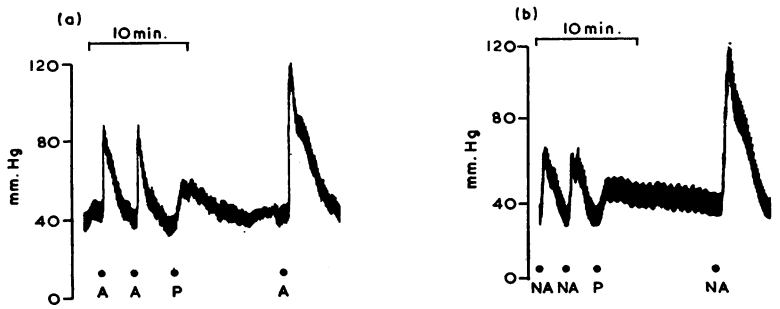

Fig. 3. (a) Blood pressure of spinal cat (4 kg). Shows potentiation of pressor response to adrenaline (A, 5 μg/kg) after phencyclidine (P, 1 mg/kg). (b) Blood pressure of spinal cat (3.5 kg). Shows potentiation of pressor response to noradrenaline (NA, 2 μg/kg) after phencyclidine (P, 1 mg/kg).

Effect on blood pressure response to tyramine

Phencyclidine (0.5 mg/kg) given immediately before tyramine (1 mg/kg) resulted in a 50% reduction in the tyramine response (Fig. 4). Fifteen min later the pressor response to tyramine had returned to the control height. Day & Rand (1963) showed that this dose of tyramine administered at 15 min intervals did not show tachyphylaxis on the blood pressure of spinal cats. Therefore, the reduction of the tyramine response by phencyclidine was not due to tachyphylaxis.

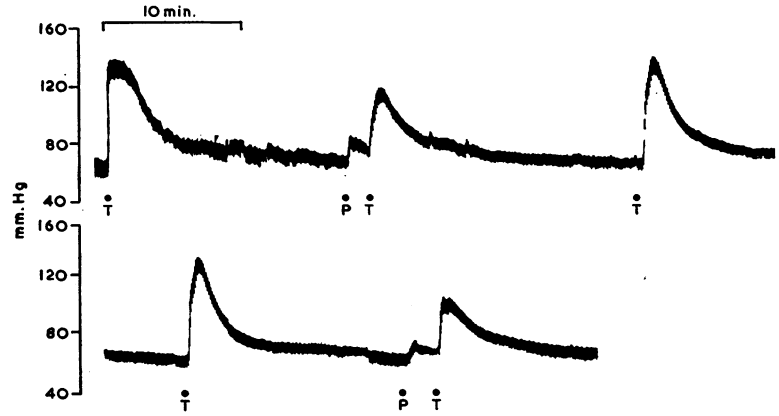

Fig. 4. Blood pressure of spinal cat (4 kg). The records are continuous. Phencyclidine (0.5 mg/kg), administered at P, reduced the response to tyramine (T, 1 mg/kg) administered immediately afterwards.

Effect on isolated heart tissue

Doses of phencyclidine (5 and 10 μg/ml. bath fluid) administered to the isolated, electrically stimulated cat papillary muscle caused a marked depression of the force of contraction. Phencyclidine (2.5–50 μg/ml. bath fluid) produced a marked decrease in the rate of contraction of isolated guinea-pig atria (Table 1). This decrease in rate could not be blocked by atropine and large doses of phencyclidine (10–50 μg/ml.) produced a very prolonged depression of atrial rate even after the tissue had been washed several times.

TABLE 1

EFFECT OF PHENCYCLIDINE ON RATE OF CONTRACTION OF ISOLATED GUINEA-PIG ATRIA

Doses of phencyclidine were added to a 10 ml. bath and left in contact for 3 min. Values are means with standard errors of the percentage decrease in rate. Numbers of experiments are in parentheses

Dose of phencyclidine (μg)	Percentage decrease in rate
5	0 (5)
25	9·1±1·8 (5)
50	19·8±3·7 (5)
100	29·2±2·5 (5)
200	35·8±2·7 (5)
*500	45·0±2·8 (3)

* This dose of phencyclidine in two experiments caused atria to cease beating completely.

Effect on isolated artery

High doses (0.5–1.5 mg) of phencyclidine were required to produce vasoconstriction on isolated preparations of the central artery of the rabbit ear. This effect was partially reduced by 3 μg phenoxybenzamine (Fig. 5). Marked potentiation of the constriction produced by noradrenaline, histamine and periarterial electrical stimulation was observed after these doses of phencyclidine.

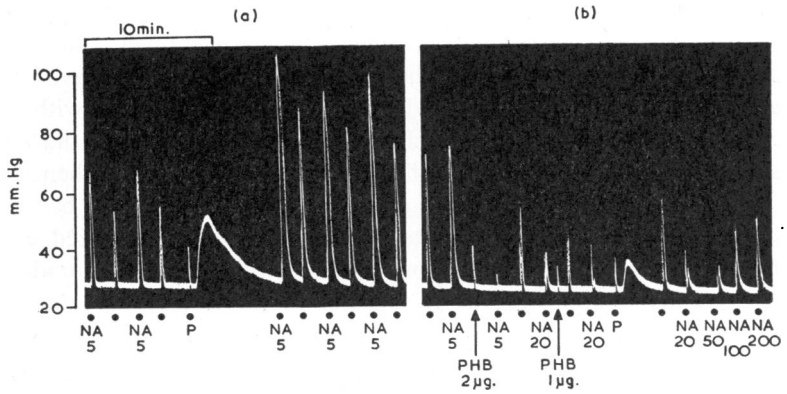

Fig. 5. Isolated central artery of rabbit ear perfused with Krebs solution at 37° C. Perfusion rate 7 ml./min. Constriction recorded by increase in perfusion pressure. At NA, noradrenaline was injected (numerals indicate doses in ng). At unlabelled dots, histamine (200 ng) and at P, phencyclidine (1.5 mg) were injected. Between (a) and (b) 15 min elapsed during which noradrenaline (5 ng) and histamine (200 ng) were injected alternately at 2 min intervals. After injection of phenoxybenzamine (2 μg and 1 μg) at PHB the responses to noradrenaline, histamine and phencyclidine were markedly reduced.

DISCUSSION

Phencyclidine has previously been reported to produce a rise in blood pressure when administered intravenously to anaesthetized dogs (Chen *et al.*, 1959). A pressor response has now been shown to occur in anaesthetized cats and rats and also in spinal cats and pithed rats. Large doses of phencyclidine in cats caused a fall in blood pressure accompanied by a bradycardia. This has previously been observed to occur in anaesthetized dogs (Chen *et al.*, 1959).

Phencyclidine decreased the rate of beating of isolated guinea-pig atria and had a negative inotropic effect on the isolated cat papillary muscle. In addition, in spinal cats, doses of phencyclidine that were pressor always caused bradycardia. Thus, the actions of phencyclidine on heart and blood pressure appear to be independent. The increase in blood pressure cannot be attributed to an increase in cardiac output since phencyclidine caused depression of isolated preparations of heart tissue.

Chen *et al.* (1959) found that the pressor response to phencyclidine in anaesthetized dogs was not affected by ganglion blockade. This has been confirmed in cats and in rats. Since it has been shown that some ganglion stimulants are not antagonized by competitive ganglion blockers but are antagonized by depolarizing ganglion blockers (Franko, Ward & Alphin, 1963) ganglia were blocked by both types of agent. However, phencyclidine still elevated the blood pressure. Also, the pressor response in cats and rats was not abolished by adrenalectomy. Thus phencyclidine does not stimulate sympathetic ganglia nor discharge catecholamines from the adrenal medulla.

The pressor response to phencyclidine was markedly reduced by a number of α-adrenergic blocking agents in both cats and rats, as was the constrictor action on the isolated artery of the rabbit ear. Phenoxybenzamine, piperoxan and tolazoline all caused

a reduction of the pressor response and this is in contrast to the findings of Chen and his co-workers who found that the response to phencyclidine was unaffected by adrenergic blockade (Chen *et al.*, 1959). Recently, the same group of workers have claimed that phencyclidine is a sympathomimetic drug which would seem at variance with their earlier results (Chen *et al.*, 1965). That phencyclidine could act directly on the α-adrenergic receptors appeared to be supported by the finding that the response to phencyclidine was not affected by prior reserpinization of the animals. Chen *et al.* (1965) have also found this in dogs. Furthermore, the response to phencyclidine in reserpinized cats was not increased after the administration of a slow intravenous infusion of noradrenaline but was decreased. Thus it appeared, at this stage, that phencyclidine did not act on catecholamine stores.

However, the pressor response to phencyclidine was abolished by cocaine. Cocaine has been shown to abolish or reduce the pressor action of tyramine (Tainter & Chang, 1927) and ephedrine (Tainter, 1929) and Trendelenburg, Muskus, Fleming & Gomez Alonso de la Sierra (1962b) have shown that cocaine can antagonize the indirect actions of all sympathomimetic amines whether they are purely indirect, like tyramine, or are mixed, like ephedrine. Thus, the findings with phencyclidine in reserpine pretreated animals and after cocaine appeared contradictory. Nevertheless, the effects of reserpine and cocaine on the pressor response to phencyclidine did parallel effects which have been reported for reserpine and cocaine on the pressor response to ephedrine: cocaine prevented the vasopressor action of ephedrine (Tainter, 1929) whereas reserpine pretreatment did not (Moore & Moran, 1962 ; Goodman & Gilman, 1965).

Chen *et al.* (1965) have found that the pressor action of phencyclidine is reversed in anaesthetized dogs after pretreatment with the catecholamine-releasing agent, 3-phenoxypropylguanidine, and this would also suggest that phencyclidine is able in some way to act on noradrenaline stores. If doses of phencyclidine were administered to cats more frequently than every 30 min tachyphylaxis was observed. When tachyphylaxis to phencyclidine had occurred the circulatory system was still responsive to adrenaline and noradrenaline. Thus, the tachyphylaxis to phencyclidine might be due to depletion of endogenous catecholamine stores rather than to a saturation of the α-receptors.

It is known that pretreatment of animals with reserpine can cause supersensitivity of the vascular smooth muscle to directly acting amines (Burn & Rand, 1958 ; Fleming & Trendelenburg, 1961). If phencyclidine is able to act on both the α-adrenergic receptors and also indirectly on the catecholamine stores, then the cardiovascular system of the reserpine-treated animals may have been supersensitive to the direct actions of phencyclidine, so that the loss of any indirect component was obscured. Trendelenburg *et al.* (1962a) have shown that reserpine does not reduce the maximal response to ephedrine on blood pressure, although that to tyramine is reduced, but the dose-response curves to both ephedrine and tyramine are markedly shifted to a higher dose range. The shift in the dose-response curve is a measure of the indirect component, and the height of the maximal response is a measure of the direct component of the sympathomimetic effect. Therefore, a study of the nature of the dose-response curves to phencyclidine in reserpinized animals should reveal a shift to a higher dose range if phencyclidine is not acting solely on the α-adrenergic receptors.

Potentiation of the pressor actions of noradrenaline and adrenaline has been shown for a large number of drugs, including cocaine (Roszkowski & Koelle, 1960) and ephedrine (Jang, 1940; Roszkowski & Koelle, 1960). It has been shown that many drugs that potentiate catecholamines can block the uptake of noradrenaline by the adrenergic nerve terminals *in vivo* (Hertting, Axelrod & Whitby, 1961) and it is now realized that uptake of noradrenaline into tissues is an important means of inactivating noradrenaline. Thus drugs that inhibit uptake will potentiate the actions of noradrenaline released endogenously by nerve impulses, and of noradrenaline administered exogenously, since the concentration of noradrenaline reaching the adrenergic receptors is much higher (Iversen, 1965). Phencyclidine has been shown to potentiate the pressor effects of adrenaline and noradrenaline and the vasoconstrictor effects of noradrenaline, and of periarterial electrical stimulation, on the isolated central artery of the rabbit ear. It is possible that this potentiation of the actions of noradrenaline and adrenaline by phencyclidine is caused by the ability of phencyclidine to block the uptake of noradrenaline into the stores of the adrenergic nerve terminal. Although no direct evidence for this view is available at present, there is indirect evidence from the observation that phencyclidine caused a transient but marked reduction of the pressor activity of tyramine. Its action and potency were similar to those previously observed for cocaine by Bartlet (1962). It has been postulated that cocaine inhibits tyramine by blocking its uptake into the adrenergic store resulting in the inability of tyramine to release endogenous noradrenaline (Furchgott, Kirkepar, Riekar & Schwab, 1963).

Thus, the pressor action of phencyclidine appears mainly to be due to a direct sympathomimetic action on the α-adrenergic receptors, but part of its action is associated with the catecholamine stores, presumably in the adrenergic nerves, or some other peripheral site except the adrenal medulla. Phencyclidine can potentiate the actions of circulating catecholamines and may be able to prevent the uptake of catecholamines into the adrenergic nerve terminals. Thus the indirect actions of phencyclidine may be due to potentiation of the actions of circulating catecholamines or to release of noradrenaline from a peripheral store.

SUMMARY

1. Phencyclidine caused a rise in blood pressure in anaesthetized cats and rats and in spinal cats and pithed rats. This pressor response was not blocked by ganglion blocking agents, reserpine pretreatment, or bilateral adrenalectomy but was blocked by α-adrenergic blocking agents and cocaine. Tachyphylaxis to the rise in blood pressure produced by phencyclidine was observed in cats but not in rats.

2. Phencyclidine had negative inotropic effects on the isolated cat papillary muscle and negative chronotropic effects on the isolated guinea-pig atria. In spinal cats pressor doses of phencyclidine reduced the heart rate.

3. The pressor responses to adrenaline and noradrenaline, and the vasoconstriction produced by noradrenaline and periarterial electrical stimulation on the isolated central artery of the rabbit ear were potentiated by phencyclidine. The pressor response to tyramine was reduced by phencyclidine.

4. It is concluded that phencyclidine has both direct and indirect sympathomimetic characteristics in that it can act directly on the α-adrenergic receptors, but part of its

action is concerned with the catecholamine stores. Effects on the heart do not contribute to the pressor effects since phencyclidine appears to be a direct myocardial depressant. It is suggested that phencyclidine might inhibit the uptake of catecholamines into the noradrenaline stores at the adrenergic nerve terminals.

We are grateful to Dr. H. O. J. Collier, Parke-Davis and Company, England, for supplies of phencyclidine and to Burroughs Wellcome, Imperial Chemical Industries, Smith Kline and French Laboratories and Parke-Davis and Company for their generous gifts of other drugs used in this investigation. We are indebted to Professor R. H. Thorp, Department of Pharmacology, University of Sydney, and Dr. I. S. De La Lande, Department of Human Physiology and Pharmacology, University of Adelaide, for allowing us to carry out some of the experiments in their laboratories. We would also like to thank Miss Sandra Whyte for technical assistance.

REFERENCES

BARTLET, A. L. (1962). Some cocaine-like actions of 3-phenoxypropylguanidine. *Br. J. Pharmac. Chemother.*, **18**, 475–489.

BURN, J. H. (1952). *Practical Pharmacology*, pp. 35–37. Oxford: Blackwell Scientific Publications.

BURN, J. H. & RAND, M. J. (1958). The action of sympathomimetic amines in animals treated with reserpine. *J. Physiol.*, **144**, 314–336.

CAMILLERI, J. G. (1962). The use of phencyclidine (CI-395) in obstetric procedures. *Anaesthesia*, **17**, 422–426.

CHEN, G., ENSOR, C. R. & BOHNER, B. (1965). An investigation on the sympathomimetic properties of phencyclidine by comparison with cocaine and desoxyephedrine. *J. Pharmac. exp. Ther.*, **149**, 71–78.

CHEN, G., ENSOR, C. R., RUSSELL, D. & BOHNER, B. (1959). The pharmacology of 1-(1-phenylcyclohexyl)-piperidine HCl. *J. Pharmac. exp. Ther.*, **127**, 241–250.

COLLINS, V. J., GOROSCOPE, G. A. & ROVENSTINE, E. A. (1960). Intravenous nonbarbiturate, non-narcotic analgesics: Preliminary studies, 1, cyclohexylamines. *Anaesthesia and Analgesia*, **39**, 302–306.

DAY, M. D. & RAND, M. J. (1963). Tachyphylaxis to some sympathomimetic amines in relation to monoamine oxidase. *Br. J. Pharmac. Chemother.*, **21**, 84–96.

DE LA LANDE, I. S. & RAND, M. J. (1965). A simple isolated nerve-blood vessel preparation. *Aust. J. exp. Biol. med. Sci.*, **43**, 639–656.

DOMINO, E. F. (1964). Neurobiology of Phencyclidine (Sernyl), a drug with an unusual spectrum of pharmacological activity. *Int. Rev. Neurobiol.*, **6**, 303–347.

FLEMING, W. W. & TRENDELENBURG, U. (1961). The development of supersensitivity to norepinephrine after pre-treatment with reserpine. *J. Pharmac. exp. Ther.*, **133**, 41–51.

FRANKO, B. V., WARD, J. W. & ALPHIN, R. S. (1963). Pharmacologic studies of N-benzyl-3-pyrrolidyl acetate methobromide (AHR-602), a ganglion stimulating agent. *J. Pharmac. exp. Ther.*, **139**, 25–30.

FURCHGOTT, R. F., KIRKEPAR, S. M., RIEKER, M. & SCHWAB, A. (1963). Actions and interactions of norepinephrine, tyramine and cocaine on aortic strips of rabbit and left atria of guinea-pig and cat. *J. Pharmac. exp. Ther.*, **142**, 39–58.

GILLIS, C. N. & NASH, C. W. (1961). The initial pressor actions of bretylium tosylate and guanethidine sulphate and their relation to release of catecholamines. *J. Pharmac. exp. Ther.*, **134**, 1–7.

GOODMAN, L. S. & GILMAN, A. (1965). *The Pharmacological Basis of Therapeutics.* 3rd ed., p. 505. New York: The MacMillan Company.

GREIFENSTEIN, F. E., DE VAULT, M., YOSHITAKE, J. & GAJEWSKI, J. E. (1958). A study of 1-aryl cyclo hexyl amine for anaesthesia. *Anaesthesia and Analgesia*, **37**, 283–294.

HERTTING, G., AXELROD, J. & WHITBY, L. G. (1961). Effect of drugs on the uptake and metabolism of H3-norepinephrine. *J. Pharmac. exp. Ther.*, **134**, 146–153.

IVERSEN, L. L. (1965). Inhibition of noradrenaline uptake by drugs. *J. Pharm. Pharmac.*, **17**, 62–64.

JANG, C. S. (1940). Interaction of sympathomimetic substances on adrenergic transmission. *J. Pharmac. exp. Ther.*, **70**, 347–361.

JOHNSTONE, M. W., EVANS, V. & BAIGEL, S. (1959). Sernyl (CI-395) in clinical anaesthesia. *Br. J. Anaesth.*, **31**, 433–439.

MOORE, J. E. & MORAN, N. C. (1962). Cardiac contractile force responses to ephedrine and other sympathomimetic amines in dogs after pre-treatment with reserpine. *J. Pharmac. exp. Ther.*, **136**, 89–96.

MEYER, J. S., GREIFENSTEIN, F. & DE VAULT (1959). A new drug causing symptoms of sensory deprivation: Neurological electroencephalographic and pharmacological effects of sernyl. *J. nerv. ment. Dis.*, **129**, 54–61.

ROSZKOWSKI, A. P. & KOELLE, G. B. (1960). Enhancement of inhibitory and excitatory effects of catecholamines. *J. Pharmac. exp. Ther.*, **128**, 227–232.

TAINTER, M. L. (1929). Comparative effects of ephedrine and epinephrine on blood pressure, pulse and respiration with reference to their alteration by cocaine. *J. Pharmac. exp. Ther.*, **36**, 569–594.

TAINTER, M. L. & CHANG, D. K. (1927). The antagonism of the pressor action of tyramine by cocaine *J. Pharmac. exp. Ther.*, **30**, 193–207.

TRENDELENBURG, U., MUSKUS, A., FLEMING, W. W. & GOMEZ ALONSO DE LA SIERRA, B. (1962a). Modification by reserpine of the action of sympathomimetic amines in spinal cats; a classification of sympathomimetic amines. *J. Pharmac. exp. Ther.*, **138**, 170–180.

TRENDELENBURG, U., MUSKUS, A., FLEMING, W. W. & GOMEZ ALONSO DE LA SIERRA, B. (1962b). Effect of cocaine, denervation and decentralisation on the response of the nictitating membrane to various sympathomimetic amines. *J. Pharmac. exp. Ther.*, **138**, 181–193.

ZARRO, V. J. & DI PALMA, J. R. (1964). A preparation of the spinal cat by an anterior approach. *J. Pharm. Pharmac.*, **16**, 427–428.

ZARROW, M. X., YOCHIM, J. M., MCCARTHY, J. M. & SANBORN, R. C. (1964). *Experimental Endocrinology*, pp. 194–195. New York: Academic Press.