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Influence of Dopamine-β-Hydroxylase Inhibition on the Cardiovascular and Respiratory Actions of Dopamine in Rats

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In rats pretreated with clorgyline, a MAO-type A inhibitor, intracerebroventricularly (i.c.v.) dopamine caused a fall in blood pressure and heart rate, and a depression followed by stimulation of the respiratory frequency. Inhibition of dopamine-β-hydroxylase with U-14624 was used to ascertain the nature of the dopamine effects. U-14624 reduced the brain noradrenaline concentration and increased the brain dopamine/noradrenaline ratio. U-14624 partially blocked the cardiovascular effects of i.c.v. dopamine 30 and 100 μg; the respiratory depressant effect was also partially inhibited, and the stimulant effect was abolished. U-14624 did not inhibit completely the conversion of exogenous dopamine into noradrenaline. It is concluded that central noradrenergic mechanisms mediate most of the cardiovascular and respiratory effects of dopamine, although the involvement of dopaminergic receptors cannot be totally excluded.

The cardiovascular actions of dopaminergic drugs are eliciting considerable interest with the aim to find new mechanisms to treat the hypertensive disease and cardiac arrhythmias. Several dopamine receptor agonists have been shown to decrease heart rate and blood pressure in different species (2, 4, 14, 21, 26, 29). Dopamine itself is known to reduce blood pressure and heart rate (1, 8, 11). The mechanisms, however, remain elusive and several sites in the central and peripheral nervous system are being proposed to account for these actions (4, 5). In a previous study dopamine, injected intracerebroventricullarly (i.c.v.) in normotensive anesthetized rats, was shown to reduce blood pressure and heart rate (22). Since the hypotensive effect was enhanced by clorgyline, a monoamine oxidase type A

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inhibitor, and antagonized by the central blockade of α-adrenoceptors it was proposed that dopamine centrally affected cardiovascular regulation, either after conversion into noradrenaline, or through a direct stimulation of central α-adrenoceptors. The purpose of the present report is to further clarify this issue by studying the influence that the inhibition of the dopamine-β-hydroxylase (DBH) with U-14624 (1-phenyl-3-[2-thyazolil]-2-thiourea) may have on the cardiovascular action of exogenous dopamine. Controversial results have been obtained by using disulfiram (8) and FLA 63 (bis-[1-methyl-4-homopiperazinyl-thiocarbonyl]-disulphide (30), but brain catecholamines levels are not reported in these studies

The action of dopamine on the central respiratory activity has received less attention. MEDIAVILLA *et al.* (18) found that intracerebroventricular dopamine stimulated respiration and proposed that the effect was accounted for by direct stimulation of dopamine receptors at the central level. The present study will also serve to analyze whether the respiratory action of dopamine is direct or is the consequence of its previous conversion into noradrenaline.

Materials and Methods

The experiments were performed on 125 Sprague-Dawley normotensive rats of either sex, weighing 250-450 g. The animals were anesthetized with thiopental (50 mg/kg i.p.) which allowed cannulation of the trachea and catheterization of a carotid artery and a femoral vein. Subsequently urethane (375 mg/kg) was injected intravenously, divided into two equal doses, separated by 30 min. Each experiment was initiated 30 min after the last dose of urethane. For i.c.v. injections, intact rats were placed in a stereotaxic frame (David Kopf) and a needle attached to a Hamilton syringe was guided into the right lateral cerebral ventricle. Dopamine was injected in a volume of 10 μl. Blood pressure and cardiac frequency were recorded continuously through appropriate transducers; respiratory frequency was recorded through a Harvard thermistor attached to the tracheal cannula connected to an appropriate preamplifier. All measurements were recorded on a Harvard recorder. Body temperature was monitored with a rectal probe connected to an analogue thermometer and maintained constant at 37.0 ± 0.2° C.

Assay of brain catecholamines. Animals were sacrificed by decapitation. Brains were quickly removed and dissected on dry ice, brain stem sectioned 2 mm below the obex, the meninges and cerebellum removed, and the remainder stored at —30° C until assayed. Catecholamines were measured using modifications of the fluorimetric methods of SHORE and OLIN (25) and BROWNLEE and SPRIGGS (3).

Drugs. For i.c.v. administration, dopamine HCl (Sigma) was diluted in saline to a constant volume of 10 μl. For intravenous infusion, dopamine was diluted in 1 ml of saline and injected at a constant rate for 10 min. Clorgyline (May & Baker) was diluted in saline and injected i.v. slowly at the dose of 1 mg/kg; clorgyline was always administered 40 min before dopamine. Each rat received a single dose of dopamine, the effects being observed for 2 hr. The dopamine-β-hydroxylase inhibitor U-14624 (Aldrich) was suspended in a solution of 1 % Tween-80 in saline, and injected i.p. at the dose of 100 mg/kg, 14 to 20 h before the administration of either dopamine or saline.

Analysis of results. For each animal, the cardiovascular and respiratory responses were expressed as the percent change in relation to its corresponding pre-drug value. Results are given as

means ± S.E.M. *t* test were used for statistical evaluation of the results. A p value <0.05 was considered to indicate a significant difference.

Results

Cardiovascular effects of i.c.v. dopamine. All the groups were pretreated with clorgyline to potentiate the dopamine effects (16, 22). Control values of mean blood pressure are shown in table I. In the control group of 10 rats, i.c.v. saline induced a slight reduction in blood pressure of about 10% (fig. 1). Dopamine was injected in 4 groups of 10 rats each; two of them received, respectively, 30 and 100 μg intravenously, and the other two received identical doses in a lateral ventricle. I.v. dopamine induced a marked and dose-dependent rise in blood pressure wich lasted for about 30 min, and a late and slight reduction of about 10%, 75 min after injection. In contrast, 30 μg of i.c.v. dopamine produced an immediate decrease in blood pressure which attained the lowest level (—40%) in 30 min, and persisted for the 2 h of the experiment. 100 μg of i.c.v. dopamine slightly increased the blood pressure in some rats during the first 5 min, but afterwards it consistently caused a progressive hypotension which reached the lowest level of —35% in 60 min. I.c.v. dopamine, 30 and 100 μg, also reduced slightly but significantly the heart rate (table II).

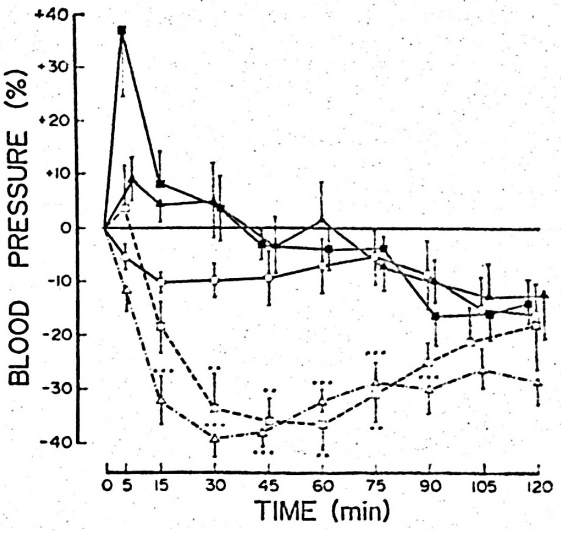

Fig. 1. *Time course of the percent changes in blood pressure (means ± SEM) induced by i.v. and i.c.v. injections of dopamine in clorgyline-pretreated rats.*
○ = Saline i.c.v. △ = Dopamine 30 μg i.c.v. □ = Dopamine 100 μg i.c.v. ▲ = Dopamine 30 μg i.v. ■ = Dopamine 100 μg i.v.

Table I. *Control values of mean blood pressure and respiratory frecuency (mean±SEM).*

	Mean blood pressure (mmHg)	Respiratory frequency (min^{-1})
Clorgyline + saline i.c.v.	80.6±3.9	70.1±4.6
Clorgyline + DA 30 μg i.v.	108.3±4.2	68.5±4.8
Clorgyline + DA 100 μg i.v.	110.2±2.9	69.3±3.8
Clorgyline + DA 30 μg i.c.v.	114.5±6.6	67.0±7.1
Clorgyline + DA 100 μg i.c.v.	117.2±5.8	68.8±7.6
U-14624+Clorgyline+ saline i.c.v.	105.1±4.6	66.3±3.6
U-14624+Clorgyline+ DA 30 μg i.c.v.	104.4±6.3	62.8±3.1
U-14624+Clorgyline+ DA 100 μg i.c.v.	107.1±4.6	69.8±5.3

The effect of a constant dose of U-14624 on the hypotension induced by the two doses of i.c.v. dopamine in clorgyline-pretreated rats was tested in 2 groups of 10 rats each (fig. 2). U-14624 regularly inhibited the hypotensive effect of 30 μg dopamine in about 50% for the whole period of the experiment. However, re-

Table II. *Effects of i.c.v. injection of dopamine on cardiac rate under several experimental conditions (mean ± SEM).*

	Control (beats/min)	% change after injection			
		15 min	30 min	60 min	120 min
Clorgyline + saline i.c.v.	348.0±16.1	+4.2±3.8	+6.9± 5.3	+7.6± 5.0	—10.1±4.9
Clorgyline + DA 30 μg i.c.v.	338.0±15.7	—10.4±2.2 *	—9.5± 3.9 *	—5.7± 3.9	—0.4±3.9
Clorgyline + DA 100 μg i.c.v.	350.0±17.9	—5.0±7.4 *	—13.2±12.3 *	—9.8±11.5 *	+1.6±4.4
U-14624+Clorgyline+ saline i.c.v.	337.4±18.2	—0.2±1.9	+1.0± 2.4	+3.4± 5.2	+2.5±4.3
U-14624+Clorgyline+ DA 30 μg i.c.v.	343.8±11.5	—4.5±2.8	—4.0± 4.2	—1.8± 4.1	+0.2±3.8
U-14624+Clorgyline+ DA 100 μg i.c.v.	346.0±16.6	—2.9±5.2	—2.0± 4.9	+0.8± 5.3	+12.8±6.7

* Different from Clorgyline + saline, $p < 0.05$.

garding the dose of 100 μg of dopamine, U-14624 was less effective; it failed to prevent the descending course of the hypotension although it shortened the time of maximal depression and accelerated the recovery period. Changes in heart rate were also partially inhibited (table II).

Respiratory effects of i.c.v. dopamine. Control values are shown in table I. Intravenous dopamine did not modify consistently the respiratory frequency. On the other hand, both doses of i.c.v. dopamine induced a consistent response characterized by a biphasic pattern (fig. 3): a depression which reached the maximum at 30 min and returned to the baseline at 60 min, followed by a dose-dependent and persistent stimulation; by the end of the second hour this stimulation had attained a plateau level of +23% after 30 μg, and it was still increasing after the dose of 100 μg.

U-14624 was able to antagonize the respiratory action of i.c.v. dopamine during both phases, the depressant and the stimulatory. It fully inhibited the effects of dopamine 30 μg, so that the respiratory time course was not different from that induced in the saline group. As for the dose of 100 μg of dopamine, U-14624 partially inhibited the depressant effect and completely prevented the development of the excitatory activity during the second hour.

Brain concentrations of dopamine and noradrenaline. Dopamine (DA) and noradrenaline (NA) were assayed in groups of rats different from those used in the recording studies, but the treatments and drug intervals were similar. Values of the treated rats were expressed as the percent change related to the values obtained in the control untreated animals, processed concurrently in the same assay. Control values of NA were in the range of 350-470 μg/g of tissue, and DA values were 580-680 μg/g of tissue.

The injection of saline (n = 18) in the cerebral ventricles did not modify the levels of either DA or NA (fig. 4). As expected, clorgyline (n = 15) elevated

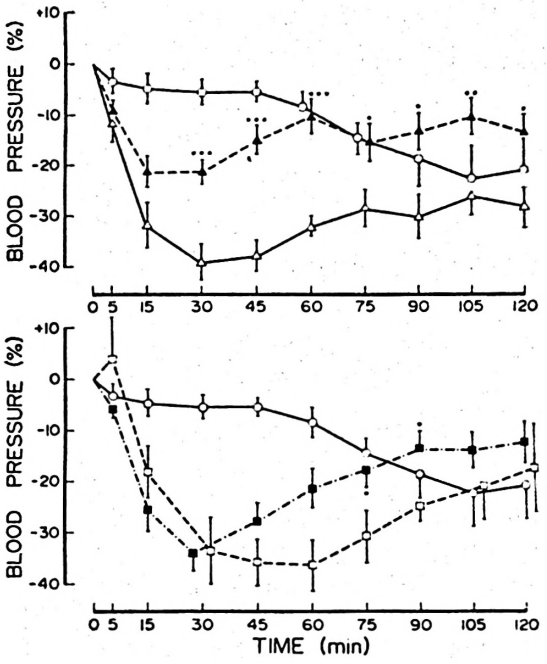

Fig. 2. *Influence of U-14624 upon the vasodepressor effect of i.c.v. 30 and 100 μg of dopamine in anesthetized rats pretreated with clorgyline (means ± SEM).*
○ = U-14624 + clorgyline i.v. + saline i.c.v. △ = Clorgyline i.v. + saline i.c.v. ▲ = U-14624 + clorgyline i.v. + dopamine 30 μg i.c.v. □ = Clorgyline i.v. + dopamine 100 μg i.c.v. ■ = U-14624 + clorgyline i.v. + dopamine 100 μg i.c.v.

significantly ($p < 0.05$) the concentrations of both catecholamines, but the DA/NA ratio was not changed. The inhibition of DBH (n = 16) induced a 50 % fall in the concentration of NA which was matched by a 50 % increment in DA concentration, thereby increasing the DA/NA ratio; changes in NA and DA were significant ($p < 0.01$). When the MAO inhibition was added to the DBH inhibition (n = 8), the reduction in noradrenaline concentration was maintained at the same level (50 %), but the concentration of dopamine was significantly enhanced from +50 % up to +200 % ($p \pm 0.01$).

The injection of 30 μg of i.c.v. dopamine in the MAO-inhibited rats (n = 11) caused an important increase in the concentration of NA ($p < 0.01$ in relation to saline), thus showing that a fraction of the injected dopamine was converted into noradrenaline. When both enzymes,

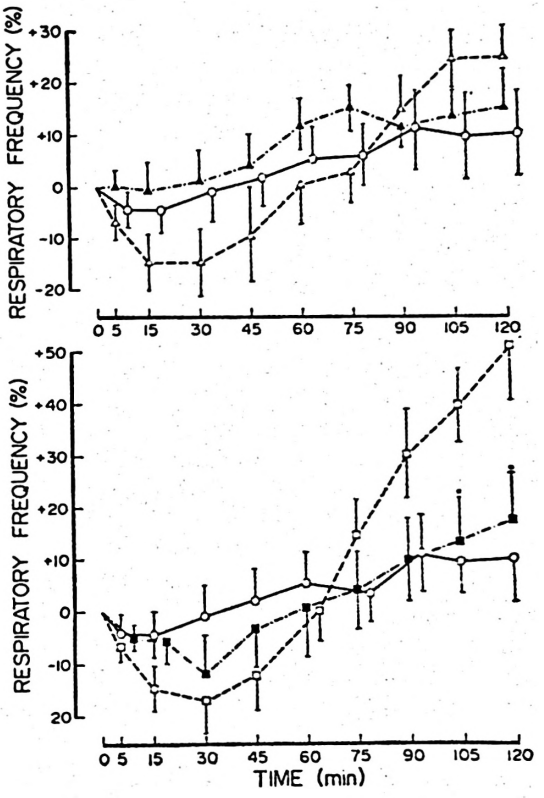

Fig. 3. *Influence of U-14624 upon the time course of the respiratory responses to i.c.v. 30 and 100 μg of dopamine in anesthetized rats pretreated with clorgyline.*
Values indicate the percent changes in relation to the control period (means ± SEM). ○ = U-14624 + clorgyline i.v. + saline i.c.v. △ = Clorgyline i.v. + dopamine 30 μg i.c.v. ▲ = U-14624 + clorgyline i.v. + dopamine 30 μg i.c.v. □ = Clorgyline i.v. + dopamine 100 μg i.c.v. ■ = U-14624 + clorgyline i.v. + dopamine 100 μg i.c.v.

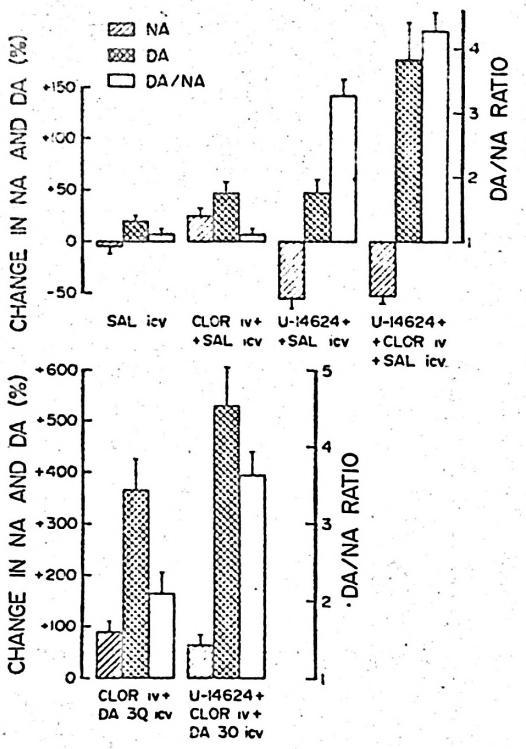

Fig. 4. *Percent changes in the concentrations of noradrenaline (NA) and dopamine (DA), and in the DA/NA ratio of the total brain of rats subjected to different drug treatments.*
Notice the difference of scales for NA and DA changes, between the upper and the lower values.

MAO and DBH, were inhibited (n = 14), i.c.v. dopamine (30 μg) was still able to increase NA; however, the increase in NA was smaller, and the increase in DA higher than those occurred in the group which did not receive the DBH inhibitor, so that the DA/NA ratio was significantly elevated ($p < 0.001$). It is therefore evident that the dose of U-14624 which was able to deplete the brain NA to a half of the control level, could not fully prevent the conversion of exogenous dopamine into noradrenaline.

Discussion

Cardiovascular actions. The present results confirm previous studies showing that dopamine administered in the cerebral ventricles reduces the blood pressure and heart rate of normotensive anesthetized rats through a central mechanism, and support the contention that this action is mediated, at least partially, by a noradrenergic mechanism (22). The severe hypotension and the moderate bradycardia induced by i.c.v. dopamine were in contrast with the hypertension and tachycardia evoked after intravenous infusion. The moderate reduction in heart rat induced by i.c.v. dopamine may not express the total bradycardiac effect of the drug, since the fall in blood pressure probably elicited some reflex tachycardia.

Clorgyline is considered to inhibit MAO-type A selectively (20) which is the predominant form of the enzyme in rats (10); and according to the *in vitro* studies (28) it is also the most active in oxidizing brain dopamine. In our experiments, the selected dose of clorgyline was able to increase significantly the brain concentrations of DA and NA in the control group. This increment was markedly elevated after i.c.v. administration of dopamine. U-14624 has been shown to inhibit brain DBH in rats and mice to a greater extent than in adrenergic terminals (13). In our studies, the inhibition of brain DBH by the selected dose of U-14624 was clearly demonstrated because NA concentration dropped to 50 %. DBH inhibition did not modify the control values of blood pressure and cardiac frequency, but it partially prevented the hypotensive and bradycardic responses to i.c.v. dopamine; this inhibition was more evident at the dose of 30 μg of dopamine than at the dose of 100 μg. These results suggest that the dopamine effects are accounted for, at least in part, by the noradrenaline derived from dopamine, because: a) DBH inhibition prevented the

full development of the hypotensive effect of exogenous dopamine; b) this antagonism was induced even in the presence of a higher DA/NA ratio. A second alternative to be considered is that the dopamine hypotension was caused by the displacement induced by high concentrations of the exogenous dopamine on the noradrenaline neuronal stores; the noradrenaline released would activate NA receptors to induce hypotension. In this case, the antagonism of U-14624 could be explained because the drug would partially deplete the noradrenaline stores so that less amine would be available for release. Our results confirm previous studies by DAY and ROACH (8) who showed that disulfiram, another DBH inhibitor, prevented the hypotensive (but not the hypertensive) effects of i.c.v. dopamine in cats.

DBH inhibition was not able to prevent completely the cardiovascular effects of exogenous dopamine. This seems to indicate that dopamine itself is also able to influence directly on blood pressure regulation. Although this possibility can not be discarded, it is important to realize that DBH inhibition was not complete either, since noradrenaline concentration was still partially increased after giving 30 μg of dopamine; indeed this increment should be higher after 100 μg of dopamine. It is then possible that the hypotensive effects observed under conditions of DBH inhibition might be due to a residual elevation of noradrenaline derived from the exogenous dopamine. In any case, the validity of our catecholamines values is limited by the fact that they correspond to total brain, and not to the areas more specifically involved in cardiovascular regulation. These areas are characterized by having a higher noradrenergic activity (7); therefore they may show a higher selectivity to DBH inhibition, which can not be evaluated by measuring the concentration of catecholamines in the whole brain.

Respiratory actions. Some discrepancy exists regarding the dopaminergic influence on the central respiratory rhythmicity. Most studies have been performed with drugs that stimulate dopaminergic receptors. Intracisternal apomorphine (10-100 μg) was shown to reduce respiratory frequency for one hour, whereas after i.v. injection (3-300 μg) it induced a biphasic response: a reduction for 30 min followed by stimulation (2). Reduction of frequency by apomorphine (1-10 mg/kg, s.c.) was also reported in anesthetized rats to which the cervical vagal and sympathetic trunks were sectioned (9). On the other hand, a dose-dependent stimulation of frequency was observed by LUNDBERG *et al.* (15) who used apomorphine (0.3-9.0 mg/kg, i.p.) in rats anesthetized with halothane; this stimulation was antagonized by haloperidol. Bromocriptine (5 mg/kg, i.v.) induced in rats, anesthetized with thiopental and urethane, a 15 min depression followed by prolonged stimulation (21); the stimulation was totally prevented by the i.c.v. administration of the α-blocking drug phentolamine. MEDIAVILLA *et al.* (18) showed that i.c.v. dopamine induced a short-lasting depression of frequency followed by stimulation, which was enhanced after MAO inhibition with clorgyline and deprenyl.

In our experiments this biphasic effect was confirmed: i.c.v. 30 μg and 100 μg of dopamine caused a 20 % fall in respiratory frequency for more than 30 min, followed by a persistent and dose-dependent increase. Inhibition of DBH partially prevented the depressant effect and blocked the late stimulant response to dopamine. These findings would suggest that part of the respiratory responses to dopamine are due to its transformation in noradrenaline. This is in agreement with previous studies in which it was shown that amphetamine stimulated respiration through an α-adrenergic mechanism (17). However, a direct effect of dopamine itself can not be discarded, because: 1) dop-

aminergic drugs like apomorphine affect respiration, and 2) the late respiratory stimulation obtained by i.c.v. dopamine was not inhibited by i.c.v. phentolamine (18).

It is important to emphasize the pattern of the respiratory response to dopamine and other dopaminomimetic drugs which is emerging as the most common from several studies: an immediate depression followed by stimulation. This pattern may be the expression, as demonstrated in other neural organizations, of a sequential activation of different types of dopaminergic receptors — pre and postsynaptic — and noradrenergic receptors, with differential sensitivities to the drugs. Looking at the respiratory responses observed in the present study, dopamine could primarily activate presynaptic dopaminergic receptors, which are known to be more sensitive than the postsynaptic to dopaminergic stimulation (24); this presynaptic action is frequently responsible for the early inhibition of several behavioral responses. At a later stage, when more molecules of dopamine become in contact with deeper structures, other dopaminergic and/or noradrenergic receptors could be activated to elicit the stimulatory responses. The early depressant effect could also be explained by the rapid conversion of dopamine into noradrenaline, which has been shown in microiontophoretic studies to inhibit some respiratory units (6).

Our experiments do not allow to define the level at which dopamine influenced respiration. The scarcity of dopaminergic fibers and receptors at the pontomedullary level (19, 27) would argue against a direct effect of dopamine on the respiratory center. But some dopamine has been found in the nucleus tractus solitarii (23), and dopaminergic drugs are known to be very active upon the chemoreceptor trigger zone of the area postrema, which in turn activates the vomiting center and disrupts the pattern of the respiratory activity (12, 16). On the other hand, the persistent stimulation of the respiratory frequency observed during the second phase could be the respiratory expression of a generalized behavioral activation of dopaminergic and noradrenergic systems located at more rostral areas in the central nervous system. Further work is needed to establish the level at which these different responses are taking place.

Note added in proof:

A biphasic respiratory response induced by i.c.v. apomorphine in halothane-anesthetized rats has been also reported by HEDNER *et al.* (*Eur. J. Pharmacol.*, 81, 603-615, 1982), while this paper was in press.

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Resumen

La dopamina administrada por vía intracerebroventricular (i.c.v.) produce en ratas pretratadas con clorgilina, un inhibidor de la MAO tipo A, hipotensión y bradicardia, y depresión de la frecuencia respiratoria seguida de estimulación. Para determinar la naturaleza de estos efectos se utilizó un inhibidor de la dopamina-β-hidroxilasa, el U-14624. Este fármaco redujo la concentración cerebral de noradrenalina y elevó la relación dopamina/noradrenalina en el cerebro. El U-14624 antagonizó parcialmente los efectos cardiovasculares de dopamina i.c.v., 30 y 100 μg; inhibió parcialmente el efecto depresor de la frecuencia respiratoria y suprimió el efecto estimulador. No pudo bloquear por completo la conversión de la dopamina exógena en noradrenalina. Se sugiere que la mayoría de los efectos cardiovasculares y respiratorios de la dopamina administrada i.c.v. se realizan a través de mecanismos noradrenérgicos centrales, pero no se descarta la implicación parcial de receptores dopaminérgicos en estas acciones.

References

1. BAUM, T. and SHROPSHIRE, A. T.: *Neuropharmacology*, **12**, 49-56, 1973.
2. BOLME, P., FUXE, K., HÖKFELT, T. and GOLDSTEIN, M.: *Adv. Biochem. Psychopharmac.*, **16**, 281-290, 1977.
3. BROWNLEE, G. and SPRINGGS, T. L. B.: *J. Pharm. Pharmac.*, **17**, 429-432, 1965.
4. CAVERO, I., LEFEVRE-BORG, F. and GOMENI, R.: *J. Pharmacol. Exp. Ther.*, **218**, 515-524, 1981.
5. CAVERO, I., LEFEVRE-BORG, F. and GOMENI, R.: *J. Pharmacol. Exp. Ther.*, **219**, 510-519, 1981.
6. CHAMPAGNAT, J., DENAVIT-SAUBIE, M., HENRY, J. L. and LEVIEL, V.: *Brain Res.*, **160**, 57-68, 1979.
7. CONWAY, E. L., LOUIS, W. J. and JARROT, B.: *Neuropharmacology*, **18**, 279-286, 1979.
8. DAY, M. D. and ROACH, A. G.: *Br. J. Pharmac.*, **58**, 505-515, 1976.
9. FARBER, J. P. and MALTBY, M. A.: *Neuropharmacology*, **19**, 63-68, 1980.
10. GARRICK, N. A. and MURPHY, D. L.: *Psychopharmacology*, **72**, 27-33, 1980.
11. HEISE, A. and KRONEBERG, G.: *Naunyn-Schmiedebergs Arch. Pharmac.*, **279**, 285-300, 1973.
12. JIMÉNEZ-VARGAS, J., ASIRON, M. and VOLTAS, J.: *Rev. esp. Fisiol.*, **22**, 173-184, 1966.
13. JOHNSON, G. A., BOUKMA, S. J. and KIM, E. G.: *J. Pharmacol. Exp. Ther.*, **171**, 80-87, 1970.
14. LOKHANDWALA, M. F. and BUCKLEY, J. P.: *Life Sci.*, **20**, 507-516, 1977.
15. LUNDBERG, D., BREESE, G. R. and MUELLER, R. A.: *Eur. J. Pharmacol.*, **54**, 153-159, 1979.
16. MCCARTHY, L. E. and BORISON, H. L.: *Am. J. Physiol.*, **226**, 738-743, 1974.
17. MEDIAVILLA, A., FERIA, M., FERNÁNDEZ, J. F., CAGIGAS, P., PAZOS, A. and FLÓREZ, J.: *Neuropharmacology*, **18**, 133-142, 1979.
18. MEDIAVILLA, A., PAZOS, A. and FLÓREZ, J.: *Arch. Farmacol. Toxicol.*, **7**, 73-76, 1981.
19. MOORE, R. Y. and BLOOM, F. E.: *Ann. Rev. Neurosci.*, **1**, 129-169, 1978.
20. NEFF, N. H., YANG, H. Y. and FUENTES, J. A.: *Adv. Biochem. Psychopharmacol.*, **12**, 49-57, 1974.
21. PADRÓN, F. and FLÓREZ, J.: *Arch. Farmac. Tox.*, **4**, 211-220, 1978.
22. PAZOS, A., MEDIAVILLA, A. and FLÓREZ, J.: *Neuropharmacology*, **31**, 317-322, 1982.
23. SAAVEDRA, J. M., KVETNANSKY, R. and KOPIN, I. J.: *Brain Res.*, **160**, 271-280, 1979.
24. SEEMAN, P.: *Pharmacol. Rev.*, **32**, 229-313, 1980.
25. SHORE, P. A. and OLIN, J. S.: *J. Pharmacol. Exp. Ther.*, **122**, 295-300, 1958.
26. SVED, A. F. and FERNSTROM, J. D.: *J. Pharm. Pharmacol.*, **31**, 814-817, 1979.
27. SWANSON, L. W. and HARTMAN, B. K.: *J. Comp. Neurol.*, **163**, 467-506, 1975.
28. URWYLLER, S. and VON WARTBURG, J. P.: *Biochem. Pharmacol.*, **29**, 3067-3073, 1980.
29. YEN, T. T., STAMM, N. B. and CLEMENS, J. A.: *Life Sci.*, **25**, 209-216, 1979.
30. ZANDBERG, P., DE JONG, W. and DE WIED, D.: *Eur. J. Pharmacol.*, **55**, 43-56, 1979.