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## BEHAVIORAL AND BIOCHEMICAL EFFECTS OF XYLAZINE: POSSIBLE INTERACTIONS BETWEEN CENTRAL NORADRENERGIC-DOPAMINERGIC SYSTEMS\*

### EFEITOS COMPORTAMENTAIS E BIOQUÍMICOS DA XILAZINA: POSSÍVEIS INTERAÇÕES ENTRE OS SISTEMAS NORADRENÉRGICO E DOPAMINÉRGICO CENTRAIS

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#### SUMMARY

Behavioral and biochemical effects of xylazine were studied both in rats and mice. The results showed that xylazine: a) decreased the general activity of rats and mice observed in an open field; b) was unable to produce catatonia and suppressed haloperidol-induced catatonia in mice; c) increased apomorphine-induced stereotyped behavior in rats; and d) increased brain noradrenaline without effect on brain dopamine levels. These results were discussed in the light of a possible interference of xylazine with brain noradrenergic system and, thus, with the dynamic interaction between noradrenergic-dopaminergic neurons within the Central Nervous System.

**UNITERMS:** Xylazine; Behavior, animal; Stereotyping; Catatonia

#### INTRODUCTION

Xylazine (Rompun, Bay 1470, 2-(2,6-dimethyl-phenylamino)-5-6-dihydro-4H-1, 3-thiazine) is a drug widely used in veterinary not only for its sedative and nonnarcotic-analgesic restraining properties, but also for its muscle relaxant effects in a large number of animal species (SPINOSA; SPINOSA<sup>28</sup>, 1991). It has been suggested that xylazine is an alpha<sub>2</sub>-adrenergic agonist (BERTHELSEN; PETTINGER<sup>4</sup>, 1977; KOBINGER; PICHLER<sup>14</sup>, 1983; TRANQUILLI; THURMON<sup>31</sup>, 1984) similar to clonidine.

Several different receptors and synaptic mechanisms may be influenced by the direct and indirect actions of xylazine and/or clonidine namely, beta-adrenergic (MAGGI et al.<sup>20</sup>, 1980), cholinergic (KRONEBERG et al.<sup>15</sup>, 1967; SCHIMITT et al.<sup>22</sup>, 1974; TIMMERMANS; van ZWIETEN<sup>30</sup>, 1982), serotonergic (TIMMERMANS; van ZWIETEN<sup>30</sup>, 1982), dopaminergic (ANTELMAN; CAGGIULA<sup>1</sup>, 1977; GOLDBERG; ROBERTSON<sup>7</sup>, 1983) and opioid receptors (FARSANG et al.<sup>6</sup>, 1980).

Although xylazine has been used clinically for over 20 years, its effects on Central Nervous System are not totally known. The present study was undertaken to characterize some behavioral and biochemical effects of xylazine and its

involvement with central catecholaminergic system.

#### MATERIAL AND METHOD

##### Animals

Male Wistar rats, 250-330 g, and male Swiss Webster mice, 25-35 g, from our colony, were used. Seven days before the beginning of the experiments, the rats were randomly housed (groups of three or individually) in wire mesh cages (16 x 30 x 19 cm) and mice (groups of twenty) in plastic cages (17 x 27 x 14 cm), at 21-23°C on a 12-hr light-dark cycle (lights on 7:30 a.m.) with free access to food and water, except at the observation periods. Each animal was used once.

##### Drugs

Xylazine (Rompun, Bayer of Brazil) and haloperidol (Haldol, Janssen Pharmaceutica) were obtained in commercially available ampoules. Apomorphine hydrochloride (Sandoz) dissolved in distilled water was also used. Drugs were administered i.p., except apomorphine was administered s.c., in volume no greater than 2.0 ml/kg of body weight. All doses refer to the salt.

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#### EXPERIMENT 1 - OPEN FIELD STUDIES

Two open fields were constructed based on that described by BROADHURST<sup>5</sup> (1960): one for rats (97 cm diameter) and other for mice (40 cm diameter). Hand-operated counters and stop-watches were employed in both apparatus to score ambulation frequency (number of floor units entered), rearing frequency (number of times the animal stood on hind legs) and immobility duration (total seconds of lack of movement).

Both mice and rats were divided at random into three experimental and one control groups with 10 animals each. Experimental animals were treated with xylazine (1, 10 or 30 mg/kg); control animals received the same volume of NaCl 0.9%. Fifteen minutes after treatments, the animals were individually placed in the center of the open field arena for behavioral observations that lasted 3 minutes; this procedure was repeated 30, 60, 120 and 180 minutes after drug or control solution injections. The open field was cleaned with water-alcohol (5%) solution before placing subjects in order to eliminate possible biasing effects of odor clues left by previous subjects. To minimize possible circadian influences on animal's open field behavior, experimental and control animals were intermixed; observations were performed between 1.30 and 5.30 p.m. An analysis of variance followed by Duncan's test (SPIEGEL<sup>27</sup>, 1972) was applied to analyse the open field data, since the Bartlett's test (JOHNSON; LEONE<sup>11</sup>, 1964) showed the presence of homocedasticity among open field data. The probability level of  $p < 0.05$  was considered the critical criterion for all statistical evaluations.

#### EXPERIMENT 2 - CATATONIA STUDIES

Eighteen mice were divided at random into 3 equal groups. Mice of one group received 8 mg/kg of haloperidol and 30 minutes later 10 ml/kg of NaCl 0.9%; mice of the 2<sup>nd</sup> group received 10 ml/kg of NaCl 0.9% and 30 minutes later, 30 mg/kg of xylazine, finally animals of the 3<sup>rd</sup> group received 8 mg/kg of haloperidol and 30 minutes later, 30 mg/kg of xylazine. Catatonia was measured 15, 45, 75 and 105 minutes after the last injection through animal's immobility duration (total sec of lack of movement). For this, mice were individually tested for their permanence on the upright position, with their forepaws flatted against one horizontal bar placed 4.5 cm above the bench. Each mouse was tested three times for catatonia at each time interval and the sum of 3 immobilities in each time was used to perform the statistical analysis. Thus, an analysis of variance followed by Duncan's test (SPIEGEL<sup>27</sup>, 1972) was used to investigate possible differences among the catatonia durations. The level of significance to show differences was also  $p < 0.05$ .

#### EXPERIMENT 3 - STEREOTYPY STUDIES

Rats were divided at random into one experimental (23 animals) and one control (22 animals) groups. Experimental animals received 10 mg/kg xylazine and 15 minutes later, a s.c. injection of apomorphine. Animals of the control group received the same volume of NaCl 0.9%, 15 minutes before apomorphine administration.

Animals were observed individually for stereotyped behavior in wire-mesh cages. Stereotypy was quantified every 10 minutes, for 3<sup>h</sup> after apomorphine treatment using a scoring system proposed elsewhere (SETLER et al.<sup>23</sup>, 1976). Briefly, scores varying from 0 (asleep or stationary) to 6 (continual licking and/or gnawing in cage grids) were assigned to each animal, by an observer who was unaware of the drug treatment. This rating is not subjective; an excellent inter-observer agreement has been noted elsewhere (SOUZA; PALERMO NETO<sup>25</sup>, 1982) between scores from two different observers (Pearson's correlation,  $R = 0.98$ ). Four doses of apomorphine (0.1, 1.0, 3.0 and 10.0 mg/kg) were used. The median of the total sum of the stereotypy scores obtained 180 minutes after each apomorphine dose was used to construct the dose-response curve. Data of the experimental groups were compared to those of the control group using the Mann-Whitney U test (SIEGEL<sup>24</sup>, 1975). Differences were considered significant when  $p < 0.05$ .

#### EXPERIMENT 4 - BIOCHEMICAL STUDIES

Mice were randomly divided into 2 experimental (19 animals) and 2 control (17 animals) groups. The experiment was done in two replications: one for dopamine and other for noradrenaline determinations. In each replication, experimental animals received 30 mg/kg of xylazine 15 minutes before sacrifice and control animals, at the same time, an identical volume of NaCl 0.9%. Immediately after decapitation, the mice brains were removed, washed in cold NaCl 0.9% solution, being dried and weighed for biochemical evaluation. Dopamine was isolated and determined through the method of ATACK<sup>6</sup> (1973). Noradrenaline isolation was performed according to ATACK and MAGNUSSON<sup>3</sup> (1978), being quantified by the method of KEHR et al.<sup>13</sup> (1976). Student's t test (SPIEGEL<sup>27</sup>, 1972) was used to analyse the biochemical data. Results were considered significant when  $p < 0.05$ .

## RESULTS

### OPEN FIELD STUDIES

Results of the open field studies are outlined in Tab. 1 and 2 for rats and mice respectively. As it can be seen, xylazine treatment decreased, in both species, ambulation and rearing frequencies and increased immobility duration in a dose-dependent way ( $p < 0.05$ ). These effects had longer duration for mice; indeed, both ambulation and rearing frequencies were still decreased in mice 60 minutes after 1 mg/kg xylazine administration. Rats that received 1 mg/kg were not differ from controls 30 minutes after treatment.

### CATATONIA STUDIES

Tab. 3 shows the effects of xylazine on mice's catatonia. As expected, haloperidol treatment was able to induce catatonia; however, this behavior was not produced by xylazine administration *per se*. It was also found that xylazine treatment completely suppressed haloperidol effects in mice.

### STEREOTYPY STUDIES

Fig. 1 shows the complete dose-response curves constructed to xylazine effects on apomorphine-induced stereotyped behavior in rats. Thus, it was not only feasible to construct dose-response curves to apomorphine using the proposed stereotypy scores, but also to study quantitatively the xylazine effects, since this drug was able to cause a significant leftward displacement of the control dose-response curve. Indeed stereotypy score were higher ( $p < 0.05$ ) for all apomorphine doses employed, in rats treated with xylazine. The higher score observed in xylazine-treatment rats was a consequence of increased duration and intensity of this behavior.

### BIOCHEMICAL STUDIES

Tab. 4 shows the effects of xylazine treatment on dopamine and noradrenaline whole brain levels in mice. Thus, xylazine administration had no effects on dopamine brain levels, but significantly increased those of noradrenaline ( $p < 0.05$ ).

## DISCUSSION

General activity has been related to the central catecholaminergic system, whereas catatonia and stereotypy are related to central dopaminergic systems (MASON<sup>21</sup>, 1984). These behaviors were used, in present work, to study xylazine effects. Thus, xylazine decreased then open field behavior of rats and mice in a dose-dependent way. This result is in agreement with previous research on the sedative effects

**TABLE 1**

Effects of xylazine administration on open field behavior of rats. Data are means  $\pm$  SD; \*  $p < 0.05$ , Anova and Duncan's test. São Paulo, 1987.

parameter	observation (min)	NaCl 0.9%	xylazine dose (mg/kg)		
			1	10	30
ambulation frequency (number)	15	34 $\pm$ 16	22 $\pm$ 4*	3 $\pm$ 3*	1 $\pm$ 3*
	30	17 $\pm$ 10	10 $\pm$ 6	2 $\pm$ 5*	2 $\pm$ 6*
	60	22 $\pm$ 11	15 $\pm$ 11	10 $\pm$ 7*	4 $\pm$ 6*
	120	14 $\pm$ 9	24 $\pm$ 8	23 $\pm$ 12	5 $\pm$ 4
	180	25 $\pm$ 6	16 $\pm$ 11	21 $\pm$ 10	5 $\pm$ 5*
rearing frequency (number)	15	13 $\pm$ 5	9 $\pm$ 2*	1 $\pm$ 1*	0 $\pm$ 0*
	30	5 $\pm$ 5	5 $\pm$ 4	1 $\pm$ 3	0 $\pm$ 1*
	60	9 $\pm$ 6	5 $\pm$ 5	3 $\pm$ 3*	1 $\pm$ 1*
	120	5 $\pm$ 3	11 $\pm$ 3*	8 $\pm$ 5	1 $\pm$ 2
	180	11 $\pm$ 3	6 $\pm$ 6	9 $\pm$ 5	2 $\pm$ 2*
immobility duration (sec)	15	6 $\pm$ 9	36 $\pm$ 33*	168 $\pm$ 15	178 $\pm$ 4*
	30	19 $\pm$ 14	54 $\pm$ 14*	164 $\pm$ 38*	164 $\pm$ 27*
	60	12 $\pm$ 9	39 $\pm$ 29	73 $\pm$ 28*	160 $\pm$ 24*
	120	34 $\pm$ 20	14 $\pm$ 10	20 $\pm$ 13	90 $\pm$ 46*
	180	18 $\pm$ 8	40 $\pm$ 19	27 $\pm$ 21	82 $\pm$ 47*

**TABLE 2**

Effects of xylazine administration on open field behavior of mice. Data are means  $\pm$  SD; \*  $p < 0.05$ , Anova and Duncan's test. São Paulo, 1987.

parameter	observation (min)	NaCl 0.9%	xylazine dose (mg/kg)		
			1	10	30
ambulation frequency (number)	15	75 $\pm$ 21	43 $\pm$ 16*	24 $\pm$ 16*	22 $\pm$ 21*
	30	47 $\pm$ 21	32 $\pm$ 15*	7 $\pm$ 4*	18 $\pm$ 14*
	60	46 $\pm$ 22	25 $\pm$ 15*	14 $\pm$ 13*	12 $\pm$ 13*
	120	41 $\pm$ 23	27 $\pm$ 13	72 $\pm$ 15*	12 $\pm$ 10*
	180	30 $\pm$ 22	29 $\pm$ 12	55 $\pm$ 34	37 $\pm$ 21
rearing frequency (number)	15	17 $\pm$ 8	7 $\pm$ 5*	2 $\pm$ 2*	2 $\pm$ 3*
	30	13 $\pm$ 10	6 $\pm$ 8*	0 $\pm$ 0*	1 $\pm$ 2*
	60	14 $\pm$ 8	6 $\pm$ 7*	0 $\pm$ 0*	1 $\pm$ 1*
	120	10 $\pm$ 8	6 $\pm$ 6	9 $\pm$ 8	1 $\pm$ 1*
	180	5 $\pm$ 6	5 $\pm$ 4	10 $\pm$ 7	5 $\pm$ 6
immobility duration (sec)	15	1 $\pm$ 2	38 $\pm$ 31*	107 $\pm$ 56	97 $\pm$ 42*
	30	12 $\pm$ 17	50 $\pm$ 46*	138 $\pm$ 21*	113 $\pm$ 44*
	60	16 $\pm$ 49	49 $\pm$ 51	129 $\pm$ 32*	128 $\pm$ 44*
	120	13 $\pm$ 18	35 $\pm$ 33	14 $\pm$ 16	118 $\pm$ 47*
	180	36 $\pm$ 47	28 $\pm$ 34	24 $\pm$ 46	50 $\pm$ 60

of xylazine (HSU<sup>10</sup>, 1981; HATCH et al.<sup>8</sup>, 1982) and some qualitative observations performed with different methodologies in several animal species (HOFFMAN<sup>9</sup>, 1974; LEWIS et al.<sup>18</sup>, 1983; KALPRAVIDH et al.<sup>12</sup>, 1984).

**TABLE 3**

Effects of xylazine administration on haloperidol-induced catatonia in mice. Data are means  $\pm$  SD (in min). São Paulo, 1987.

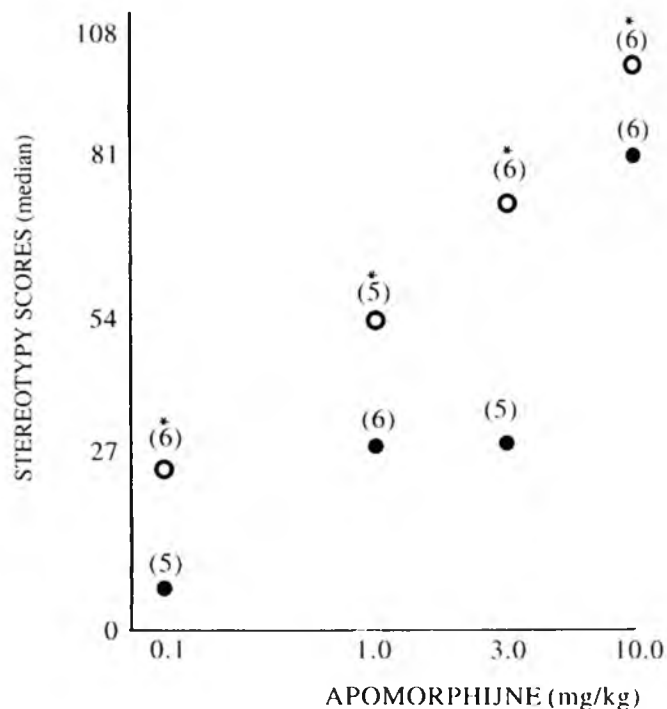
haloperidol (mg/kg)	xylazine (mg/kg)	observation moments (min)			
		15	45	75	105
8	-	15.7 $\pm$ 4.9	15.1 $\pm$ 5.4	15.1 $\pm$ 6.4	12.3 $\pm$ 6.1
-	30	0	0	0	0
8	30	0	0	0	0

**TABLE 4**

Effects of xylazine treatment on dopamine and noradrenaline brain levels of mice. Data are means  $\pm$  SD; number in brackets represent number of animals used; \*  $p < 0.05$ , Student's t test. São Paulo, 1977.

group	brain levels (ug/g)	
	dopamine	noradrenaline
control	0.96 $\pm$ 0.26 (9)	1.77 $\pm$ 0.55 (8)
experimental	0.91 $\pm$ 0.20 (10)	2.35 $\pm$ 0.49 (9)

The participation of noradrenaline on xylazine effects on open field behavior seems to be plausible. In fact, other  $\alpha_2$  adrenoceptor agonist, clonidine, is able not only to decrease rat's general activity but also to induce sedation (LAVERY; TAILOR<sup>17</sup>, 1969; TILSON et al.<sup>29</sup>, 1977). In addition,  $\alpha_2$  adrenoceptor agonist decreases noradrenaline release from noradrenergic neurons (McAFFEE et al.<sup>19</sup>, 1981; TRANQUILLI; THURMON<sup>31</sup>, 1984), without altering dopamine levels; similar effects on catecholaminergic neurotransmitter levels were observed in the present work. The higher dose of xylazine did not induce catatonia *per se* (as haloperidol, a dopaminergic blocker); xylazine, contrary, induced flaccidity and no rigidity. A similar effect was observed with clonidine (KULKARNI<sup>16</sup>, 1981). The anticatatonic effect of xylazine may result from muscle relaxation by action on  $\alpha_2$  adrenergic receptors or be due to some other mechanism not yet understood. On the other hand, xylazine increased apomorphine-induced stereotypy, suggesting that is possible to exist a balance between central noradrenergic-dopaminergic systems on central xylazine



**FIGURE 1**

Effects of xylazine administration (10 mg/kg - open circles) on apomorphine - induced stereotyped behavior in rats. Data show the median of the sum of the stereotypy scores observed after each apomorphine dose; number of animals tested at each apomorphine dose is showed in brackets. An asterisk on top of circles means a statistically significance from control data (full circles)  $p < 0.05$  (Mann-Whitney U Test).

effects. In fact, phenoxybenzamine and phentolamine ( $\alpha$ -adrenoceptor antagonist) also displaced to the left the control apomorphine dose-response curve (SOUZA; PALERMO NETO<sup>26</sup>, 1982) like observed with xylazine.

The results presently reported reinforce the suggestion that xylazine acts on  $\alpha_2$  adrenergic receptors and alters the normal balance between central noradrenergic and dopaminergic systems.

## RESUMO

Alguns efeitos comportamentais e bioquímicos da xilazina foram estudados em ratos e camundongos. Os resultados mostraram que a xilazina: a) diminuiu a atividade geral de ratos e camundongos observados em campo-aberto; b) foi incapaz de produzir catatonia e suprimiu este comportamento induzido pelo haloperidol em camundongos; c) potencializou o comportamento estereotipado induzido pela apomorfina em ratos; d) aumentou os níveis cerebrais de noradrenalina, porém não alterou aqueles de dopamina. Estes resultados foram discutidos considerando-se ação da xilazina em sistemas noradrenérgicos centrais e da interação entre sistemas noradrenérgicos e dopaminérgicos centrais.

**UNITERMOS:** Xilazina; Comportamento animal; Estereotipagem; Catatonia.

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