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BRIEF COMMUNICATION

Increased Disrupting Effects of Haloperidol on a Conditioned Avoidance Response After 6-Hydroxydopamine Treatment

JAIME M. MONTI[1,2] AND MARTA RUIZ

Laboratorio de Psicofarmacología, Departamento de Farmacología y Terapéutica
Hospital de Clínicas Piso 1, Montevideo, Uruguay

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MONTI, J. M. AND M. RUIZ. *Increased disrupting effects of haloperidol on a conditioned avoidance response after 6-hydroxydopamine treatment.* PHARMAC. BIOCHEM. BEHAV. 3(5) 943–945, 1975. – The influence of prior catecholamine depletion was studied on the behavioral depressant effects of haloperidol using a conditioned avoidance response. The butyrophenone disrupting effects on the avoidance behavior were significantly increased by 6-hydroxydopamine pretreatment.

6-OHDA Haloperidol Behavior disruption Conditioned avoidance

IT has been pointed out that haloperidol-induced depression of the CNS could be related to blockade of catecholamine (CA) receptors [1]. Our own findings showing that dihydroxyphenylalanine (dopa) prevents, while a-methyl-p-tyrosine (a-MT) potentiates the disruption of a conditioned avoidance response (CAR) after haloperidol administration [5,7], are in agreement with this assumption. These data suggest that dopa would be acting through a competitive mechanism, while a-MT would be inhibiting a compensatory CA-increased turnover. We reasoned that the disrupting actions of the butyrophenone derivative would be increased if the compound was administered to animals with a functional deficit of the CA system caused by selective destruction of central sympathetic fibers.

METHOD

To test this hypothesis we trained groups of 5 male albino rats (Wistar, 180–200 g) to 100 percent CAR in a chamber with an electrified grid floor and a safety area provided by a pole attached to the top of the chamber. The conditioned stimulus (CS) was the sound of a buzzer; the unconditioned stimulus (US) was a shock delivered through the grid floor of the chamber (current 0.6 mA). The CS and US were delivered for periods of 15 sec or until the rat climbed the pole. The CS/US interval was 15 sec. After reaching the criterion, the animals were separated into 2 groups and drug administration was started. Haloperidol (aqueous solution prepared with distilled water) was studied at 2 dose levels: 75 and 150 μg/kg given by IP. During control sessions, animals received corresponding volumes of solvent.

Sessions began 60 min after solvent or drug injection and each rat was tested for 10 trials.

During a second stage the rats were anesthetized with sodium pentobarbital (30 mg/kg) and fixed to a stereotaxic apparatus. In order to damage both noradrenergic (NA) and dopaminergic (DA) systems [2,9], the animals received 250 μg of 6-hydroxydopamine (6-OHDA) by intraventricular route, 30 min after the IP injection of 40 mg/kg phenelzine. Seven days later a second dose of 250 μg was given without phenelzine. Control animals received 2 intraventricular injections of the vehicle (25 μg of isotonic saline solution containing 1 mg/ml ascorbic acid).

Animals were allowed 20 days to recover. After they regained previous levels of CAR, placebo and haloperidol treatments were repeated as above. The basic data, consisting of totals CR and UR responses emitted were expressed as percent avoidances. Differences in mean

[1] On sabbatical leave. Present address: Depto. de Psicobiologia Escola Paulista de Medicina, São Paulo, Brazil.

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percentages were tested for significance at the 0.05 level by applying a *t*-test for correlated means.

At the end of the experiments the animals were sacrified, their brains removed and smears from cerebral cortex, hypothalamus and caudate nucleus were treated according to the techniques of Olson and Ungerstedt [6] and Lidbrink and Jonsson [4] to compare the number, intensity of fluorescence and size of CA nerve terminals.

RESULTS AND DISCUSSION

After haloperidol injection no differences in spontaneous activity could be detected by direct observation between control and 6-OHDA treated animals. Both groups showed a decrease of ongoing activity, looking drowsy and indifferent to their environment.

In the behavioral test, haloperidol blocked the CR in a dose-response related manner (Table 1), while the UR was not modified.

Previous intraventricular administration of the vehicle did not significantly influence the haloperidol induced depression of conditioned behavior (Table 1). Conversely, pretreatment with 6-OHDA resulted in a greater depression of the CR, although significance was attained only after the highest dose of haloperidol (Table 1). The UR was decreased also, amounting 65 percent of pretreatment values.

Smears of cerebral cortex, hypothalamus and caudate nucleus from 6-OHDA treated animals showed, when compared to controls, a marked decrease of the number of fluorescence intensity of CA terminals. As previously shown by Lindrink and Jonsson [4], these changes reflect true decreases of central NA and DA concentrations. In agreement with the findings of Taylor and Laverty [8] the CAR regained pretreatment levels after 6-OHDA treatment, the decrease of CA notwithstanding. However, treatment with 6-OHDA resulted in an increased sensitivity to the disrupting effects of haloperidol on the conditioned behavior. This is consistent with the results of Cooper *et al.* [3] who found that rats depleted of NA and DA displayed significantly lower levels of continuously reinforced bar press performance following haloperidol.

Finally, our results give further support to the present hypotheses relating haloperidol's actions on the CNS to an inhibition of the CA system. Thus, the depressive effects of the compound on the CAR were significantly potentiated in animals with a lesioned although possibly in part compensated CA system.

TABLE 1

EFFECTS OF HALOPERIDOL ON CONDITIONED AVOIDANCE RESPONSES IN CONTROL AND 6-OHDA TREATED RATS

Groups	Placebo	Haloperidol	
		75 μg/kg	150 μg/kg
Control			
pre	96.7 ± 2.1	90.0 ± 4.5	62.0 ± 5.8
post	100.0	85.0 ± 7.2	57.0 ± 3.4
6-OHDA			
pre	98.0 ± 2.0	86.0 ± 9.8	58.0 ± 13.2
post	98.0 ± 2.0	74.0 ± 8.1	24.0 ± 8.1*

*Differences in mean values were tested by applying the *t*-test for correlated means: $p<0.01$.

Numbers represent percent CR based on 10 trials for each animal (N = 5 for each group).

Mean values and standard errors are given. In both groups comparisons were done with values obtained prior to intraventricular injection.

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