Brazilian J Med Biol Res (1989) 22: 741-743 *SHORT COMMUNICATION*

STRIATAL DOPAMINE RECEPTOR SUPERSENSITIVITY AFTER LONG-TERM HALOPERIDOL TREATMENT OF HYPOPHYSECTOMIZED RATS

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Dopamine (DA) receptor sensitivity was studied after long-term treatment with haloperidol (0.5 and 3.0 mg/kg, *ip*, single daily dose) or saline in hypophysectomized and intact rats. Haloperidol treatment for seven days produced a 25 to 125% increase in [^{3}H]-spiroperidol binding to striatal DA receptors in a dose-dependent fashion. The increase in binding sites (B_{max}) was similar in both hypophysectomized and intact rats when compared to controls. The present results show that hypophysectomy does not effect the supersensitivity of striatal DA receptors induced by long-term haloperidol treatment.

Key words: hypophysectomy, haloperidol, supersensitivity, dopamine receptors.

Long-term interruption of dopaminergic transmission in the central nervous system by surgical or pharmacological means leads to an increase in the sensitivity of dopamine (DA) receptors (1,2). The prolonged administration of neuroleptics results in DA receptor hypersensitivity (3-8). The systemic administration of prolactin (PRL) to male rats increases the density of striatal DA receptors (9,10), an effect which may account for the supersensitivity of striatal DA receptors produced by haloperidol since the latter drug increases PRL secretion from the pituitary (9-11). However, there is some controversy regarding the action of PRL on the striatal DA receptors given the lack of effect of PRL on nigrostriatal DA neuronal activity (12,13).

In the present study we investigate the effects of hypophysectomy in rats on the supersensitivity of striatal DA receptors induced by long-term treatment with haloperidol.

A total of 144 male Wistar rats were used. Seven days before the experiment the rats were housed individually in wire mesh cages at 22 ± 2°C and exposed to a 12-h light-dark cycle with lights on from 7:00 to 19:00 h. Food and water were available *ad libitum*. Seventy-two rats were hypophysectomized using the parapharyngeal approach. The completeness of this operation was confirmed by the lack of postoperative weight gain and by direct examination of the sella turcica when the animals were killed after the experiment. Plasma PRL levels were not measured in the hypophysectomized rats.

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The intact and hypophysectomized rats were randomly and equally divided into experimental and control groups. The experimental group was treated with haloperidol (0.5 and 3.0 mg/kg) and the control group with saline, *ip*, daily for 7 consecutive days.

The animals were then decapitated 72 h after the last haloperidol or saline injection in order to permit partial elimination of the drug from the body. Striatal membranes were prepared as described by Burt et al. (14). The binding reaction was performed in duplicate in a final volume of 2.2 ml containing 0.025 g of striatal membranes; concentrations of [^{3}H]-spiroperidol (specific activity, 25 Ci/mmol) from 0.25 to 4 nM were used routinely for the saturation curves. Nonspecific binding was determined in a second set of duplicate tubes containing 1 μM d-butaclamol (15).

Table 1 - *Effect of long-term treatment with haloperidol (0.5 and 3.0 mg/kg,* ip, *on specific [^{3}H]-spiroperidol binding in rat striatum.*

Data are reported as the mean ± SEM for two experiments involving 6 animals per group. *P < 0.01 compared to the saline (control) group. **P < 0.01 compared to the saline + hypophysectomy (control) group.

Treatment	B_{max} (pmol/g)	% Change compared to control
Saline (control)	5.6 ± 0.5	–
Saline + hypophysectomy (control)	5.2 ± 0.4	–
Haloperidol (0.5 mg/kg)	7.0 ± 0.6*	25
Haloperidol (0.5 mg/kg) + hypophysectomy	7.9 ± 0.9**	51
Haloperidol (3.0 mg/kg)	11.6 ± 2.2*	101
Haloperidol (3.0 mg/kg) + hypophysectomy	11.9 ± 1.1**	126

Binding data were plotted by the Scatchard method and regression analysis was performed by the least squares method to determine the maximum density (B_{max}) and the dissociation constant (K_d) of the striatal DA receptors. The differences in [^{3}H]-spiroperidol binding were tested for significance by the Student *t*-test.

Rats treated with haloperidol (0.5 and 3.0 mg/kg, *ip*) for 7 days showed a 25 to 126% increase in [^{3}H]-spiroperidol binding to striatal DA receptors in a dose-dependent fashion. Scatchard analysis indicated that enhanced binding was due to an increase in the number of binding sites (B_{max}) when compared to controls. No change in affinity constant (K_d) was observed (data not shown). The increase in binding sites (B_{max}) was similar in hypophysectomized and intact rats (Table 1).

The present results show that hypophysectomy did not alter the supersensitivity of striatal DA receptors induced by long-term haloperidol treatment. Thus, it seems reasonable to assume that this effect depends on the presence of hormones from sources other than the pituitary gland.

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