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ENHANCEMENT OF APOMORPHINE-INDUCED INHIBITION OF STRIATAL DOPAMINE-TURNOVER FOLLOWING CHRONIC HALOPERIDOL

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Abstract—Following chronic treatment with haloperidol, there was no change in dopamine concentration or turnover in the rat striatum. However, the threshold dose of apomorphine to inhibit dopamine turnover was reduced. These data provide neurochemical evidence for super-sensitivity of dopamine receptors after chronic treatment with neuroleptics.

Chronic treatment of rats with neuroleptics has been shown to produce an increased sensitivity to the behavioral effects of drugs which stimulate dopamine receptors [1–5]. However, previous investigations have been limited to the observation of an enhanced stereotypy induced by apomorphine or amphetamine in rats treated chronically with neuroleptics. We have recently shown [6–7] that the supposed increased sensitivity of dopamine receptors can be demonstrated neurochemically by enhanced inhibition of striatal dopamine turnover after injection of apomorphine. The dose of apomorphine required to inhibit striatal dopamine turnover was considerably reduced and there was considerable increase in apomorphine-induced aggression in morphine-dependent rats. We used the same approach in the present experiment and found that rats treated chronically with haloperidol also exhibit an enhanced responsiveness to the effects of apomorphine on striatal dopamine turnover.

MATERIALS AND METHODS

Male Long-Evans rats (275–325 g) were injected intraperitoneally, twice daily, with gradually increasing doses of haloperidol for 17 days as described previously [1]. A starting dose of 2·5 mg/kg was increased to the terminal dose of 20 mg/kg day. The drug was discontinued 7 days before measuring the effect of apomorphine. All animals were housed in a room in which ambient temperature of 22° was thermostatically controlled and room lights were turned off between 8 pm and 8 am. Animals were sacrificed during the early afternoon.

The effects of apomorphine on dopamine turnover were evaluated indirectly be measuring the rate of dopamine disappearance from the corpus striatum after the administration of alpha-methyl-*p*-tyrosine methylester hydrochloride (MPT). The animals were deprived of food for 18–24 hr and injected intraperitoneally with apomorphine; MPT (300 mg/kg) was administered 30 min later. Half of the rats were sacrificed immediately by decapitation and the remaining animals were sacrificed 2 hr later. This time period was selected from an earlier study of a time–response relationship in which dopamine depletion was linear for approximately 3 hr after MPT. The corpus striatia (approx. wt 110 mg) were rapidly dissected and homogenized in 0·4 N perchloric acid. All of the manipulations were carried out in ice-chilled glassware. The homogenates were centrifuged at 10,000 rev/min for 10 min. The supernatants were transferred into 50-ml beakers and the pH was adjusted to 8·5 with Tris buffer (pH 9·5). The extracts were then passed through alumina columns. The adsorbed dopamine was eluted with 0·2 N acetic acid. Dopamine in the acetic acid eluate was oxidized and determined spectrofluorometrically [8–9]. The dopamine turnover was calculated from the rate of striatal dopamine depletion observed after the administration of MPT, according to the method of Costa and Neff [10].

Table 1. Effect of chronic haloperidol treatment on striatal dopamine*

	Controls	Chronic haloperidol†	P‡
Striatal dopamine (nmoles/g)	43·7 ± 2·69	39·9 ± 4·81	>0·05
Dopamine turnover (nmoles/g/hr)	11·7 ± 1·31	12·3 ± 1·65	>0·05

* Values are mean ± S.E. of four animals in each group.
† Seven days after last administration of haloperidol.
‡ Student's *t*-test.

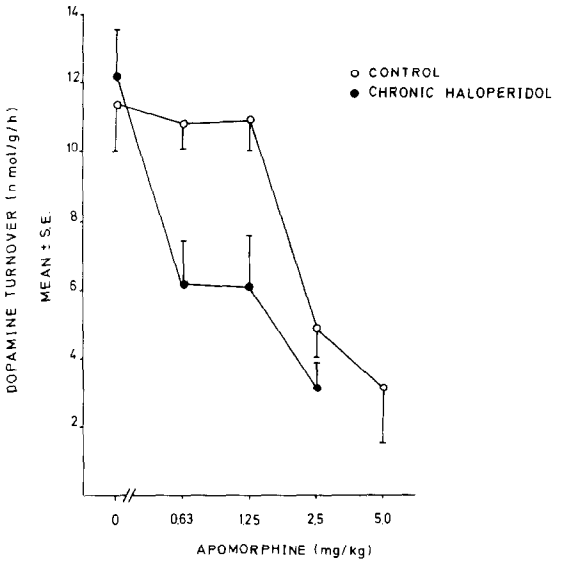

Fig. 1. Effect of apomorphine on striatal dopamine turnover. Chronic treatment with haloperidol discontinued 7 days before sacrifice. Each point in mean (± S.E.) from four subjects.

RESULTS AND DISCUSSION

As has been shown previously [11], chronic treatment with haloperidol did not alter either the steady state level of dopamine or the striatal turnover of dopamine after the drug was discontinued (Table 1). However, after chronic treatment with haloperidol, the activity of apomorphine was enhanced since it effectively decreased the turnover of dopamine in the haloperidol-treated rats at doses which were without effect in drug-naive rats (Fig. 1).

Since it has been suggested that apomorphine decreases dopamine turnover by stimulating directly the striatal dopamine receptors [12–13], it may be reasoned that the enhanced inhibition of dopamine turnover results from an increased sensitivity of these receptors. This increase in receptor sensitivity results from prolonged blockade of the same receptors by haloperidol. Our interpretation is consistent with the behavioral data obtained in the previous study [1]. After chronic treatment with haloperidol the action of drugs which are believed to directly stimulate dopaminergic systems was enhanced.

The enhancement of receptor sensitivity in dopaminergic systems is not limited to neuroleptics as a similar enhancement was previously shown in rats which have been chronically treated with morphine [6–7, 14] or methadone [18]. Both of these drugs are believed to reduce the activity of dopamine receptors [11, 14–17].

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