Increased Effect of Apomorphine on Homovanillic Acid in Rats Terminated From Chronic Haloperidol*

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Summary

Rats who were administered apomorphine seven days after termination of chronic treatment with haloperidol had significantly (59%) lower level of brain HVA than saline control rats. This finding is consistent with the behavioral evidence suggesting supersensitivity of post-synaptic dopamine receptors after termination of chronic haloperidol.

Introduction

After termination of chronic administration of neuroleptic drugs, rats, mice, and guinea pigs exhibit behavioral evidence of dopamine receptor supersensitivity when administered direct or indirectly acting dopamine agonists such as apomorphine or amphetamine (Smith and Davis, 1975; Smith and Davis, 1976; Tarsy and Baldessarini, 1974; Rubovits et al., 1974; Gianutsos et al., 1974). We now report biochemical evidence that rats withdrawn from chronic haloperidol show an increased response to apomorphine, specifically a greater decrease in homovanillic acid (HVA) compared to saline controls.

Method

In all experiments, Sprague-Dawley rats, initial weights 225—300 gms, were used. Rats were housed in group cages under standard laboratory conditions, maintained at 72±1 °F with a 12 hour light-dark cycle. Rats

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were injected 5 days a week, for 7 weeks with one of the following drug regimens: 1) chronic haloperidol rats—increasing doses of haloperidol beginning at 1 mg/kg/day in week 1 and rising to 2.5 mg/rat/day using commercial haldol vials; or 2) saline controls—normal saline 0.5 ml/day. Because food and water intake differed between groups during chronic drug administration, food and water available for rats' consumption was controlled so that all groups received the same amount of food and water during the period of chronic drug administration, this amount to be determined by the lowest intake group. Seven days after termination of chronic haloperidol administration (the time that peak behavioral supersensitivity occurred in our previous studies [Smith and Davis, 1975; Smith and Davis, 1976]), rats received probenecid 200 mg/kg i.p. and 2 hours later apomorphine 1 mg/kg i.p. Forty-five minutes after apomorphine, rats were sacrificed by decapitation, brains were placed on glass over dry ice, and the striatum (caudate, putamen, globus pallidus) was dissected out. Striatum was dissected by the procedures of Glowinski and Iversen (1966) (mean weight 126 ± 3 mg). Tissue was homogenized in 1 N methanolic or ethanolic HCl, and analyzed for HVA content by selective ion monitoring using the specific gas chromatographic-mass spectrometric methods previously described in detail (Narasimhachari, 1974; Narasimhachari et al., 1974; Narasimhachari et al., 1975). HVA standards were interspersed frequently with brain samples and the mean of two duplicate determinations at the same m/e ion peak were used for analysis. In addition, for many samples, quantitative determinations of HVA were checked at two or more m/e ion peaks with the same derivative.

Results and Discussion

Rats who had been terminated from chronic haloperidol 7 days earlier had 59% lower HVA levels 45 min after 1 mg/kg apomorphine than saline controls (mean ± s.e.m. — Haloperidol rats [(N = 11)] — 406 ± 58 ng/gm; Saline controls [(N = 9)] — 984 ± 179 ng/gm; t = 2.90, df = 18, p < .01).

Changes in the levels of HVA after probenecid may reflect changes in dopamine release, metabolism, and turnover (Andén et al., 1964; Werdinius, 1967; Tamerkin et al., 1975). The reduction in HVA produced by apomorphine may be due to compensatory changes in pre-synaptic dopamine neurons mediated by a feedback loop inhibition when apomorphine stimulates the post-synaptic receptor (Ross, 1967; Kehr et al., 1972). If post-synaptic dopamine receptors are supersensitive after termination of chronic neuroleptic administration, as the behavioral evidence suggests (Smith and Davis, 1975; Smith and Davis, 1976; Tarsy and Baldessarini, 1974; Rubovits et al., 1974; Gianutsos et al., 1974), then apomorphine administered to these rats would be expected to cause a greater decrease in HVA than in saline controls. Recent reports by other groups (Burt et al., 1977;