Lithium effects on haloperidol-induced pre- and postsynaptic dopamine receptor supersensitivity†

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Low doses of apomorphine inhibit dopamine (DA) release from the dopaminergic nerve terminals in the central nervous system (cns) (Nowycky & Roth 1978). Inhibition of DA release is due to stimulation of presynaptic dopaminergic receptors (or autoreceptors) on the dopaminergic nerve terminals. This activation of presynaptic receptors is thought to be the mechanism whereby low doses of apomorphine decrease locomotor activity in rats (Schwartz et al 1978). However high doses of apomorphine cause increase in locomotor activity and stereotype behaviour by acting on postsynpatic receptors. It has been suggested that chronic dopamine receptor blockade causes increased postsynaptic dopamine receptor sensitivity (Allikments et al 1979). On the other hand long-term treatment with lithium prevents the development of postsynaptic dopamine receptor supersensitivity induced by chronic haloperidol treatment (Pert et al 1978).

In the last decade, several studies have suggested that presynaptic DA receptors play an important physiological role in the control of DA synthesis and release (Kehr et al 1972; Nowycky & Roth 1978). In this study, we selected low dose apomorphine-induced inhibition of locomotor activity in order to determine chronic haloperidol-induced presynaptic DA receptor supersensitivity. Recently Gallager et al (1978) showed electrophysiologically that chronic haloperidol treatment causes supersensitivity in the presynaptic DA receptor and this effect is blocked by chronic lithium administration. The purpose of this study is to produce supportive evidence in a behavioural model that chronic haloperidol treatment does cause presynaptic DA receptor supersensitivity and that this effect can be blocked by chronic administration of lithium.

Male Sprague-Dawley rats (200–220 g) were housed five rats per cage under a 12 h light-12 h dark cycle and were allowed free access to food and water. The rats were divided into four treatment groups: (1) chronic NaCl, 0·9% (1 cc kg^{-1}), (2) chronic lithium chloride, 2 mequiv kg^{-1} (1 cc kg^{-1}), (3) chronic haloperidol, 1 mg kg^{-1} and (4) chronic lithium chloride, 2 mequiv kg^{-1} and chronic haloperidol, 1 mg kg^{-1}. Drugs were administered daily by intraperitoneal injection for 34 days. On day 35, daily injection of drugs was terminated. The effect of apomorphine or (0·9% NaCl) saline on the locomotor activity of each individual rat was quantified six days after drug termination. Behavioural experiments were done in a diffusely illuminated room maintained at a constant temperature (21 ± 2 °C). Following a subcutaneous injection of saline or apomorphine the rat was put into a Plexiglas cage (24 × 20 × 45 cm) sitting on top of an selective activity meter (Columbus Instrument, Model S). Locomotor activity was quantified by movement of the rat in an electromagnetic field generated by the activity meter. Spontaneous activity was recorded for 30 min following injection.

Fig. 1 shows the effects of low doses of apomorphine on locomotor activity in rats treated chronically with different drugs. Significant inhibition of locomotor activity was observed only at the 0·016 mg kg^{-1} dose of apomorphine for both chronic saline- and chronic lithium-treated groups. When compared with saline-treated controls, apomorphine-induced sedation was significant at the $P < 0.01$ level for chronic saline and chronic lithium. These data support previous reports that low doses of apomorphine-induced sedation.

After chronic administration of haloperidol to the animals, apomorphine at 0·004 and 0·008 mg kg^{-1} induced a significant inhibition of locomotor activity

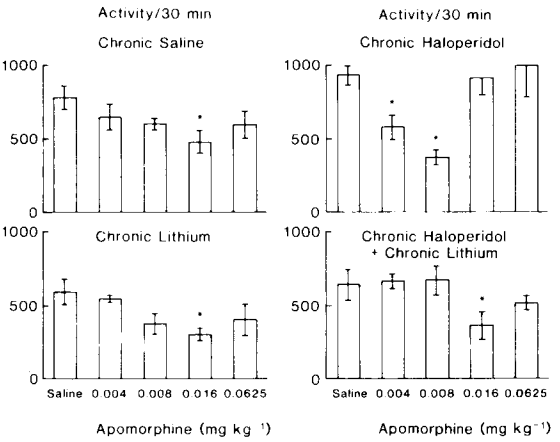

FIG. 1. The effects of apomorphine on locomotor activity in the rat. The rats were treated for 34 days with saline, haloperidol (1 mg kg^{-1} day^{-1}), lithium chloride (2 mequiv kg^{-1} day^{-1}) or lithium chloride with haloperidol. Six days after termination of chronic treatment the effects on locomotor activity of apomorphine (0·004–0·0625 mg kg^{-1}) or saline were determined in each group. The height of each column represents the mean ± s.e.m. of 5 animals. The data was analysed by using two-way ANOVA. Differences between the means were compared using the least significant differences method (* $P < 0.01$).

† This work was supported in part by NIH Research Grant GM-22365.

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when compared with rats injected acutely with saline. Since the apomorphine-induced sedation is considered to be mediated by presynaptic dopamine receptors, these data are evidence for the development of presynaptic supersensitivity following chronic haloperidol. Higher doses of apomorphine elevated locomotor activity to presedative levels indicating an activation of supersensitive postsynaptic dopamine receptors. In addition 2 out of 5 rats displayed obvious stereotypic behaviour.

Combined injection of haloperidol and lithium daily for 34 days reversed the pre- and postsynaptic supersensitive responses to apomorphine. Apomorphine at 0·004 and 0·008 mg kg^{-1} did not induce significant inhibition of locomotor activity as was seen in rats treated chronically with only haloperidol (Fig. 1). This supports previous electrophysiological data suggesting that lithium blocks the development of presynaptic dopamine receptor supersensitivity.

The higher doses of apomorphine did not produce increases in locomotor activity in chronic haloperidol plus lithium treated rats (Fig. 1). On the contrary apomorphine (0·016 mg kg^{-1}) induced sedation that was analogous to the responses seen in the control groups.

In conclusion lithium appears to block the development of supersensitivity in both pre- and postsynaptic dopamine receptors. The chronic lithium regimen has been demonstrated to result in plasma lithium concentrations in the therapeutic range of lithium in man (Allikments et al 1979). Therefore the stabilization of pre- and postsynaptic receptors by lithium may represent an important mechanism in the clinical pharmacotherapy of manic-depressive disorders and tardive dyskinesia.

February 1, 1980

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In vivo alteration of calcium turnover induced by reserpine in rat tissues

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Alterations of calcium storage and/or turnover have been reported in heart and vascular smooth muscles after reserpine pre-treatment (Hudgins & Harris 1970; Carrier & Jurevics 1973; Tenner & Carrier 1978). These alterations have been studied in isolated organs and have been related to catecholamine depletion caused by reserpine in these tissues. We wondered whether alterations in calcium turnover after reserpine pre-treatment could be demonstrated in vivo and if they would be limited to cardiovascular tissues, since catecholamines influence parathormone secretion (Vora et al 1979; Mayer et al 1979; Brown et al 1978). We report here that reserpine pre-treatment impairs calcium turnover not only in heart and aorta but also in bone of intact rats.

Male Sprague-Dawley rats (300–350 g) were randomly separated into control and treated groups. The treated rats received reserpine daily (intraeosophogeal 0·3 mg kg^{-1} gum acacia suspension 5 ml kg^{-1}) for three days. Control rats received the same volume of gum suspension. The body weight and temperature of treated rats were not different from those of controls and there was no obvious alteration of motor activity after three days of pre-treatment.

On the first day of reserpine pre-treatment small polyethylene cannulae were implanted in the thoracic aorta and jugular vein. Calcium metabolism was studied as described by Stoclet et al (1975). Five hours after the third reserpine administration, 15 μCi $^{45}CaCl_2$ was rapidly injected into the jugular vein. Twelve blood samples (0·1 ml each) were collected between 3 and 120 min after injection. Rats were then decapitated and the following tissues were rapidly removed: thoracic aorta (cleaned from adventitia), heart (ventricles), diaphragm, gastrocnemius and femur. Radioactivity was determined by liquid scintillation counting after complete digestion of serum (50 μl) and soft tissue samples in Soluene-100 (Packard). Bone radioactivity was measured after ashing (600 °C–6 h) and dissolution of ashes in 1 M HCl. Counts were corrected for quenching using the double channel method. Serum calcium concentrations were determined by atomic absorption photometry according to Girard & Rousselet (1967).

The disappearance of intravenously injected ^{45}Ca from blood has been represented using the power function plot. The best least squares fit of the logarithm

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