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.

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

CHRISTIANE HEITZ, JEAN-CLAUDE STOCLET*, *Laboratoire de Pharmacodynamie (E.R.A. 787, C.N.R.S.) Université Louis Pasteur, Faculté de Pharmacie, Strasbourg, France*

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

* Correspondence: B.P. 10, F 67048 Strasbourg Cedex, Université Louis Pasteur, Faculté de Pharmacie, Strasbourg, France.

Table 1. Effect of reserpine pre-treatment on calcium metabolism and on ^{45}Ca content (mg Ca $g^{-1} \times 10^3$) in various tissues of live rats.

	Serum calcium mg Ca $litre^{-1}$	λ	Ex. ^{45}Ca	Aorta	Heart	Diaphragm	Gastrocnemius	Femur
Control	116·2 ± 1·7 n = 10	− 0·76 ± 0·04 n = 10	0·16 ± 0·08 n = 9	2·78 ± 0·37 n = 10	1·11 ± 0·09 n = 10	1·60 ± 0·17 n = 10	1·11 ± 0·13 n = 10	20·00 ± 3·78 n = 10
Reserpine	110·5 ± 1·9 n = 9 NS	− 0·62 ± 0·02 n = 9 $P < 0·01$	0·18 ± 0·12 n = 9 NS	1·95 ± 0·23 n = 9 $P < 0·001$	0·86 ± 0·12 n = 8 $P < 0·001$	1·35 ± 0·21 n = 9 NS	1·01 ± 0·14 n = 9 NS	10·67 ± 1·54 n = 8 $P < 0·001$

Data are expressed as means ± s.e.m. of n experiments. Statistical comparisons were performed using Student's *t*-test (NS = non significant $P > 0·05$). λ represents the slope of the power function describing the decrease with time of serum specific activity. Ex. ^{45}Ca is the percentage of injected tracer found in the excreta at the end of the experiment. ^{45}Ca content was determined 120 min after injection.

of the specific activities against the logarithm of time was calculated as described by Stoclet et al (1975) to determine the average serum specific activity over 120 min (time integral of serum specific activity divided by time) and the slope λ of the curve describing the fall of serum specific activity beyond 30 min after tracer injection. In these conditions, λ represents the fall of specific activity for a prolonged period of time and is considered as an index of body calcium renewal (Marshall 1969). ^{45}Ca contained in tissues (mg Ca g^{-1}) was expressed as the ratio of radioactivity in tissues (d min^{-1}) to the average specific activity of serum calcium over 120 min (d min^{-1} mg Ca^{-1}).

To measure urinary and faecal calcium excretion, the animals were placed in individual metabolism cages, and urine and faeces were collected for 120 min after injection of ^{45}Ca. Radioactivity found in urine plus water used to rinse the cages and in ashed faeces (600 °C, 18 h) redissolved in 1 M HCl, was counted as indicated above. Total excreted radioactivity (Ex. ^{45}Ca) was expressed as a percentage of the injected radioactivity.

Data in Table 1 show that reserpine pre-treatment produced significant alterations of calcium metabolism. Serum calcium was not significantly modified, but λ was significantly reduced in treated rats. The slope λ represents the rate of disappearance of ^{45}Ca from blood after an initial period of equilibration of 30 min. The finding that the proportion E of injected tracer found in the excreta at the end of the experiment was very low and was not modified in reserpine-treated rats suggests that the reduction of λ corresponds to a reduction in body calcium turnover. Indeed there was a decrease in ^{45}Ca content in soft tissues and in bone of treated rats at 120 min after tracer injection. The effect was statistically significant in heart, aorta and femur, but not in diaphragm and gastrocnemius. It was specially marked in femur, where ^{45}Ca content was reduced by 50%.

The present results demonstrating an overall lowering by reserpine of calcium turnover in the aorta and heart in vivo are in agreement with previous in vitro observations of Hudgins & Harris (1970) and of Carrier & Jurevics (1973) showing that the efflux of calcium was decreased in aorta strips from reserpine-treated rabbits. In contrast, Hester & Carrier (1978) reported that reserpine pretreatment induced an increase in La^{3+}-resistant ^{45}Ca uptake in rabbit aorta strips. This latter result may seem in conflict with those mentioned above and the findings reported here. However the La^{3+}-resistant Ca pool represents only less than one third of total calcium content of the aorta (Godfraind 1976). In addition it undergoes a slower turnover than the La^{3+}-displaced one, which is more superficially located (Van Breemen et al 1972). Thus an overall lowering of calcium turnover in the aorta is not necessarily inconsistent with an increase in a slowly renewed pool which can be mobilized for contraction.

Depletion of catecholamines caused by reserpine may influence calcium turnover in tissues by two different mechanisms. The first mechanism is a direct influence on calcium influx and release in cells containing catecholaminergic receptors. This mechanism may explain the decrease of ^{45}Ca uptake caused by reserpine in heart and aorta, where noradrenaline increases calcium influx and induces contraction (Reuter et al 1973). It may also play a part in the effect of reserpine in femur, since stimulation of adrenergic receptors elicits increased calcium turnover in bone cells (Hsu & Cooper 1975).

The second mechanism may result from impairment of β-adrenergic stimulated parathormone secretion. This mechanism may cause the decrease in ^{45} Ca content of femur reported here after reserpine pre-treatment since parathyroid hormone increases calcium turnover in bone (Talmage & Elliott 1958). It may also play a part in the effect of reserpine on the aorta, since it was recently reported that parathormone alters calcium

storage and relaxes this smooth muscle (Schleiffer et al 1979).

Thus, the above two mechanisms may explain the effects of reserpine pretreatment reported here on heart, aorta and bone. Their respective participation requires further investigation. With respect to skeletal muscles we did not observe here any influence of reserpine. This result is consistent with the mechanisms action suggested above, since skeletal muscle fibres are not sympathetically innervated and since no influence of parathormone on calcium fluxes have been described in this tissue.

In conclusion, the present study demonstrates that reserpine pre-treatment alters calcium turnover in intact rats and that the changes are not restricted to cardiovascular tissues where they have been previously studied in vitro. Reserpine also decreases calcium renewal in bone.

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