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# Chronic treatment with electroconvulsive shock prevents the salbutamol-induced hypoactivity in rats

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Several lines of evidence (binding studies, reduced responsiveness of brain adenylate cyclase to noradrenergic stimulation) indicate that chronic treatment with electroconvulsive shock (ECS) induces down-regulation of central β-adrenoceptors. The effect of acute and chronic (10 days) treatment with ECS on salbutamol-induced suppression of exploratory activity in rats has been examined. This effect was prevented by chronic but not by acute treatment with ECS. Chronic treatment with ECS did not affect exploratory activity. The salbutamol-induced hypoactivity is mediated through central β-adrenoceptors (antagonistic effect of (−)-propranolol but not (+)-propranolol or practolol), so the results may be regarded as functional evidence at the behavioural level for the down-regulation of β-adrenoceptors produced by chronic treatment with ECS.

Chronic, but not acute, treatment with antidepressant drugs induces down-regulation of central β-adrenoceptors, as manifested by subsensitivity of the adrenoceptor-coupled adenylate cyclase system (Vetulani & Sulser 1975) and a decrease in the density of β-adrenoceptors (Banerjee et al 1977). Similar effects have also been reported after prolonged treatment with ECS (Vetulani & Sulser 1975: Bergstrom & Kellar 1979). Recently, we have found that long-term administration of several antidepressant drugs prevents the salbutamol-induced hypoactivity in rats, most probably as a behavioural consequence of the down-regulation of β-adrenoceptors (Przegaliński et al 1983). Therefore, it was of interest to study the effect of repeated treatment with ECS in this behavioural model. Looking for further evidence that the salbutamol-induced hypoactivity is mediated through central β-adrenoceptors, we have also studied the effect of acute treatment with (−)- and (+)-propranolol and practolol on the response to salbutamol.

*Methods*

Male Wistar rats (from licenced dealers), 250–270 g, were kept at room temperature, 20–21 °C, on a natural day–night cycle, housed in groups of 10–12, with free access to food and water. ECS (150 mA, 0·3 s) was administered acutely or repeatedly (once daily for 10 days) using ear electrodes. All shocked rats experienced generalized tonic-clonic seizures. Controls were handled in the same manner, except for the fact that no current was passed. Each group consisted of 10–12 rats. Salbutamol hydrochloride (Polfa) at a dose of 10 mg $kg^{-1}$ i.p. was injected 2 h after ECS (acute experiment) and 2 or 22 h after the last treatment with ECS (chronic experiment). In other experiments the same dose of salbutamol was administered to animals pretreated 1 h earlier with single doses of either (−)- or (+)-propranolol (ICI; 4 mg $kg^{-1}$ i.p.), or practolol (Polfa; 10 mg $kg^{-1}$ i.p.). Exploratory activity was investigated 2 h after salbutamol injection in the open field by a slight modification of the method of Janssen et al (1960), using an open arena without walls. A single animal was placed gently in the centre of the arena and allowed to explore freely. Ambulation (the number of sector crossings), rearing (the number of times the animal stood on its hind legs) and peeping (the number of times the animal peeped down from the edge of the arena) were recorded over 3 min by hand operated counters. Rearing and peeping reactions were pooled together because they are thought to represent the same kind of exploratory behaviour (Vetulani & Mogilnicka 1970). Statistical analyses were carried out using one-way analysis of variance, followed by individual comparisons with Duncan's test (Duncan 1955) where appropriate.

*Results*

As shown in Fig. 1, the exploratory activity of rats, treated acutely or repeatedly with ECS, did not differ significantly from that of controls. In the latter animals and in rats treated acutely with ECS, salbutamol produced a pronounced hypoactivity manifested by a 50–70% reduction in ambulation and rearing + peeping. On the other hand, in animals treated chronically with ECS, in most cases salbutamol did not reduce the exploratory activity. The only exception was a decrease in the number of rearing + peeping episodes 24 h after the last treatment with ECS.

Results of acute experiments with β-adrenoceptor blockers demonstrate (Fig. 2) that (−)-propranolol prevented the salbutamol-induced hypoactivity whereas (+)-propranolol and practolol were inactive (the lack of significant effect of salbutamol on rearing + peeping in animals pretreated with practolol may be masked by the sedative effect of the β-adrenoceptor blocker itself).

*Discussion*

Earlier, we (Przegaliński et al 1983) put forward arguments that the salbutamol-induced hypoactivity was mediated through central β-adrenoceptors. Further support for this concept comes from the present findings

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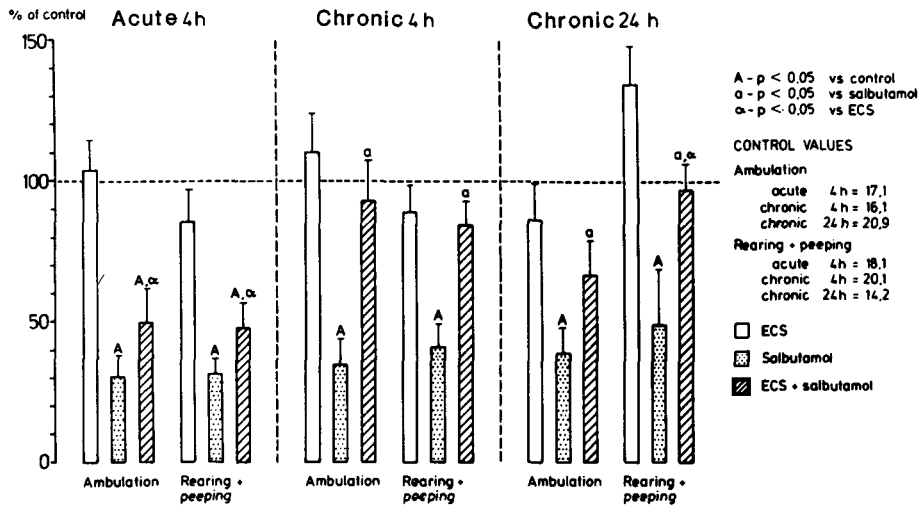


FIG. 1. The effect of acute and chronic treatment with ECS on the salbutamol-induced suppression of exploratory activity in rats. Each column shows the mean percentage of corresponding controls. Vertical bars represent s.e.m. of the means. For further details see text.

that this behavioural response to salbutamol is antagonized by (−)-propranolol (β-adrenoceptor antagonist) but not by (+)-propranolol (very weak antagonist of β-adrenoceptors; Howe & Shanks 1966) or practolol (β-adrenoceptor antagonist which does not penetrate into the brain; Scales & Cosgrove 1970).

In the light of the above findings the prevention of the salbutamol-induced hypoactivity by repeated treatment with ECS may be regarded as a behavioural consequence of the down-regulation of central β-adrenoceptors found after a similar treatment in biochemical studies (Vetulani & Sulser 1975; Bergstrom & Kellar 1979). The lack of effect of a single ECS on the brain adrenoceptor-coupled adenylate cyclase system (Vetulani & Sulser 1975) and the density of β-adrenoceptors (Bergstrom & Kellar 1979) on the one hand, and on the salbutamol-induced hypoactivity, on the other, also agrees well with this hypothesis.

Our present results, together with our earlier findings on antidepressant drugs (Przegaliński et al 1983), indicate a good time-course relationship between the pharmacological effect and therapeutic action of ECS and antidepressant drugs; hence, they support the idea (Sulser 1979) that the down-regulation of central β-adrenoceptors is involved in an antidepressant efficacy in clinic. They also indicate that the salbutamol-induced hypoactivity in rats may be used as a functional model for studying central β-adrenoceptors.

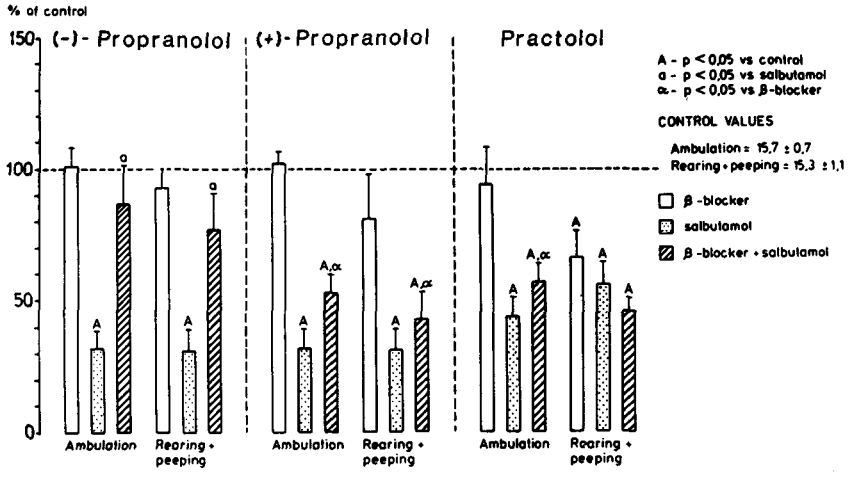


FIG. 2. The effect of acute treatment with (−)- and (+)-propranolol and practolol on the salbutamol-induced suppression of exploratory activity in rats. Each column shows the mean percentage of corresponding controls. Vertical bars represent s.e.m. of the means. For further details see text.

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# The effect of temperature on the α-adrenoceptor antagonist potency of indoramin and labetalol in the rat perfused mesenteric vascular bed

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The effect of reduction in temperature of perfusion from 37 to 27 °C and 20 °C on the ability of the adrenoceptor antagonists indoramin and labetalol to block pressor responses to noradrenaline in the perfused mesenteric vascular bed of the rat was examined. The results suggest that in the rat mesenteric bed, antagonist potency of both agents is increased at low temperatures.

Temperature is a factor that changes the adrenergic neuroeffector interaction, and vascular smooth muscle responses can be profoundly altered by local changes in temperature (Vanhoutte 1980). It has previously been reported (Clement 1980) that the ability of indoramin (a selective $\alpha_1$-adrenoceptor antagonist; Rhodes & Waterfall 1978) to increase blood flow in the cooled hands of acrocyanotic patients was less marked at low temperatures than at 37 °C. An investigation was therefore undertaken to examine the changes in α-adrenoceptor antagonist action of indoramin with temperature in an isolated vascular bed. A comparison was made with the mixed α and β-adrenoceptor antagonist labetalol, previously described by Brittain & Levy (1976).

*Materials and methods*

The perfused mesenteric vascular bed of the rat was prepared using a modification of the method described by McGregor (1965).

Male Sprague Dawley rats (180–220 g) were anaesthetized by intraperitoneal injection of 60 mg $kg^{-1}$ of pentobarbitone sodium (May & Baker). The abdomen was opened by midline incision, the ileum and colon exposed and the superior mesenteric artery identified and cannulated. The perfusion pump was in operation during the cannulation process. The perfused area was identified by blanching and included an area of the ileum and caecum. The caecal, ileo-colic, colic and pancreatico-duodenal branches of the artery were tied off and the perfused mesentery was severed close to the ileum obviating possible interference from the activity of intestinal smooth muscle.

The perfused mesenteric bed was placed in a water-jacketed bath and maintained at either 37, 27 or 20 °C as required. Perfusion was set at 2 ml $min^{-1}$ using a Watson Marlow flow inducer. Krebs-bicarbonate solution (mM): NaCl 118, KCl 4·8, $NaHCO_3$ 25·0, $MgSO_4$ 1·2, glucose 11·1, $CaCl_2$ 2·5, gassed with 5% $CO_2$ in $O_2$, and containing ascorbic acid ($10^{-4}$ M) and 0·1% Bovine serum albumin factor V (to prevent drug oxidation and reduce tissue oedema respectively) was used as perfusate. The concentration of solutions of noradrenaline (Koch-Light) (NA) were such that the bolus volume of NA injected was within the range 5–50 μl. Pressor responses to bolus injections of NA were recorded via Bell and Howell type 4/422 pressure transducers, connected to a Devices MX4 polygraph.

Indoramin (Wyeth) was added to the perfusion fluid at concentrations of either $10^{-7}$ M (at 37 and 27 °C) or $10^{-9}$ M (at 20 °C) and allowed to equilibrate in the tissue for 30 min.

In separate preparations, labetalol (Glaxo, Ware) was added to the perfusion fluid at concentrations of $10^{-6}$ M (at 37 °C) and $3 \times 10^{-8}$ M (at 27 and 20 °C) and equilibrated as before. Pressor responses to bolus injections of NA were again obtained in the presence of antagonist and dose-response curves to NA constructed before and after the addition of antagonist, from which antagonist $pA_2$ values were calculated using the method of Van Rossum (1963). Control tissues were also