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Repeated Treatment With Antidepressant Drugs Prevents Salbutamol-Induced Hypoactivity in Rats

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PRZEGALIŃSKI, E., L. BARAN, J. SIWANOWICZ AND K. BIGAJSKA. *Repeated treatment with antidepressant drugs prevents salbutamol-induced hypoactivity in rats.* PHARMACOL BIOCHEM BEHAV 21(5) 695–698, 1984.—We have found earlier that a number of antidepressant drugs, administered repeatedly, prevent the salbutamol-induced hypoactivity in rats. Our further experiments show that a similar effect is produced by repeated, but not acute, treatment with other antidepressants: clomipramine, mianserin and nialamide. Two non-antidepressant psychotropic drugs, haloperidol and diazepam, were inactive after repeated administration. These results seem to support our earlier hypothesis that prevention of the salbutamol-induced hypoactivity may be regarded as functional evidence at the behavioral level for the subsitivity of β-adrenoceptors.

Antidepressants Repeated treatment Salbutamol Hypoactivity Rat

WE have previously shown that repeated, but not acute, treatment with several antidepressant drugs: imipramine, desipramine, amitriptyline, fluvoxamine and citalopram [16], as well as with electroconvulsive shock [17], prevents the salbutamol-induced hypoactivity in rats. These results were interpreted as functional evidence at the behavioral level for the down-regulation of central β-adrenoceptors, reported by numerous authors on the basis of biochemical (subsensitivity of the adrenoceptor-coupled adenylate cyclase system and a decrease in the density of β-adrenoceptors) and electrophysiological (reduced responsiveness of cortical and cerebellar neurons to noradrenaline) studies [1, 2, 15, 20, 25, 27].

In this study we have investigated the effect of repeated treatment with other antidepressants: clomipramine (a monoamine uptake inhibitor), mianserin (an atypical antidepressant) and nialamide (a monoamine oxidase inhibitor) on the salbutamol-induced hypoactivity in rats. For comparison, the effect of two non-antidepressant psychotropic drugs, haloperidol and diazepam, was examined.

METHOD

The experiments were carried out on male Wistar rats, 240–270 g, bought from licensed dealers. The animals were kept at a room temperature of 20–21°C, on a natural day-night cycle, housed in groups of 10–12, with a free access to food and water throughout the experiment.

The following drugs were used: clomipramine hydrochloride (Ciba-Geigy), mianserin hydrochloride (Organon), nialamide (Sigma), haloperidol (Gedeon Richter), diazepam (Hoffmann-La Roche) and salbutamol sulphate (Polfa). Nialamide and diazepam were suspended in 1% Tween 80. Other drugs were dissolved in saline. The doses of the drugs (see below) refer to the respective salts.

Clomipramine (10 mg/kg PO), mianserin (10 mg/kg PO) and nialamide (40 mg/kg IP) were given in single doses (acute experiment) or twice a day, for 14 consecutive days (chronic experiment). Haloperidol (0.5 mg/kg IP) and diazepam (1 mg/kg IP) were administered only repeatedly (twice a day, 14 days). The controls received the respective vehicle. Each group consisted of 10–12 rats.

Salbutamol (10 mg/kg IP) was injected 2 hr after a single dose, as well as 2 and/or 22 hr after the last dose of the drugs. The exploratory activity was investigated 2 hr after salbutamol injection, i.e., at 4 and 4 or 24 hr after single or last dose of the drugs, respectively, in the open field, using a slightly modified method of Janssen *et al.* [6] in 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 for 3 min by hand-operated counters. The rearing and peeping reactions were pooled together, as they are thought to represent the same kind of exploratory behavior [24].

Statistical analyses were carried out using a one-way analysis of variance, followed by individual comparisons with the Duncan's test [4] where appropriate.

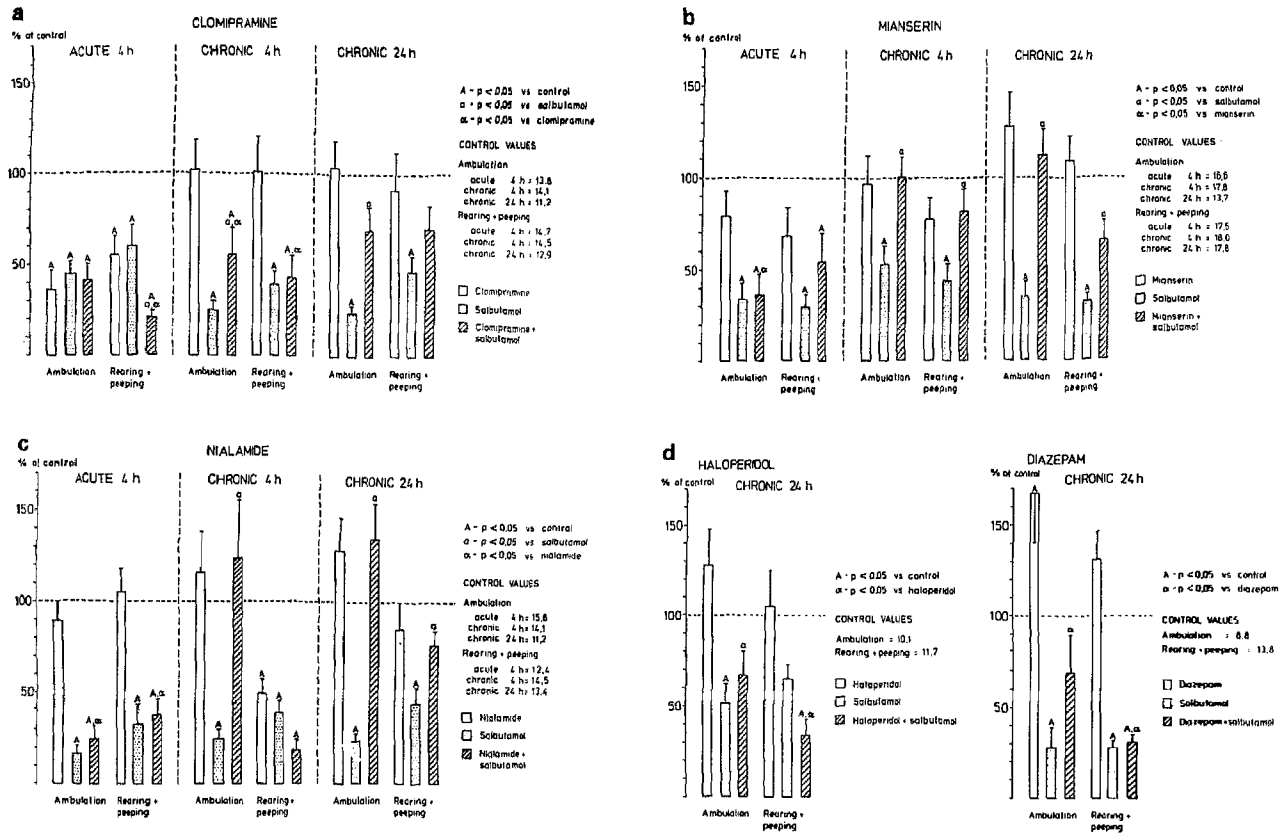

FIG. 1a–d. The effect of acute (single dose) and chronic (14 days, twice a day) treatment with clomipramine, 10 mg/kg PO (a); mianserin, 10 mg/kg PO (b); nialamide, 40 mg/kg IP (c); and chronic (14 days, twice a day) treatment with haloperidol, 0.5 mg/kg IP, and diazepam, 1 mg/kg IP (d) on the the salbutamol-induced suppression of the exploratory activity in rats. The exploratory activity (ambulation and rearing+peeping) was measured in the open field at 4 and/or 24 hr, respectively, after single or last dose of the drugs. Salbutamol (10 mg/kg IP) was injected 2 hr before the test. Respective control groups were treated with vehicle (acutely or repeatedly) and with the salbutamol solvent. Each column shows the mean percentage of corresponding controls. Vertical bars represent SE of the means.

RESULTS

Clomipramine administered acutely (Fig. 1a) significantly depressed the exploratory activity, which is reflected by a decrease in ambulation and rearing+peeping (by 65% and 45%, respectively). After repeated treatment with the drug (Fig. 1a), as well as after acute and repeated administration of mianserin (Fig. 1b) and nialamide (Fig. 1c), no significant changes in the exploratory activity were observed (the only exception being a reduction of rearing+peeping episodes at 4 hr after the last dose of nialamide).

In accordance with earlier data [12], salbutamol administered to the rats, pretreated acutely or repeatedly with the respective vehicle, reduced the exploratory activity, decreasing ambulation and rearing+peeping episodes by ca. 50% or more (Fig. 1a–d). Salbutamol also significantly reduced the exploratory activity in the rats pretreated acutely with antidepressant drugs (Fig. 1a–c), with two exceptions (lack of effect on ambulation after clomipramine—Fig. 1a, and on rearing+peeping after mianserin—Fig. 1b). On the other hand, in the animals pretreated repeatedly with antidepressants, salbutamol—in most cases—did not reduce the exploratory activity (Fig. 1a–c). While some exceptions were observed when the test was carried out 4 hr after the last dose of antidepressants (depression of exploratory activity after clomipramine—Fig. 1a), in no case salbutamol depressed the open field behavior 24 hr after the last administration of antidepressants.

Repeated treatment with haloperidol or diazepam did not prevent the salbutamol-induced hypoactivity examined 24 hr after their last administration. The effect of salbutamol was not studied 4 hr after acute treatment or 4 hr after the last dose following repeated treatment with haloperidol or diazepam, due to their potent sedative effect at those time intervals (results not shown).

DISCUSSION

Our results demonstrate that repeated treatment with antidepressant drugs such as clomipramine, mianserin and nialamide prevents the salbutamol-induced hypoactivity in rats. Although 4 hr after the last dose of clomipramine salbutamol still produced some hypoactivity, 24 hr after the last administration of all the drugs studied no effect of salbutamol on the exploratory activity was observed. The importance of own effect of antidepressants in this phenomenon can be excluded, since after a single dose those drugs did not generally affect the hypoactivity induced by salbutamol, though some exceptions were found (the lack of effect of salbutamol on rearing+peeping after mianserin and on ambulation after

clomipramine). However, at least in the latter case, a potent sedative effect of clomipramine could mask the salbutamol hypoactivity.

Some data indicate that the salbutamol-induced hypoactivity in rats is mediated through central β-adrenoceptors. In fact, this behavioral response to salbutamol can be produced after both peripheral and intracerebroventricular administration [5]. Moreover, the response was found to be antagonized by the β-adrenoceptor antagonists, d,l-propranolol [14] and l-propranolol [17], but not by d-propranolol—a very weak antagonist of β-adrenoceptors, or by practolol—a β-adrenoceptor antagonist which does not penetrate into the brain [17].

Therefore, prevention of the salbutamol-induced hypoactivity by a repeated treatment with clomipramine, mianserin and nialamide may be regarded as a behavioral consequence of the down-regulation of central β-adrenoceptors, found after a similar treatment in biochemical studies. In fact, it was reported that repeated administration of clomipramine, mianserin and nialamide produced subsensitivity of the adrenoceptor-coupled adenylate cyclase system [11–13, 26]. Moreover, clomipramine and nialamide were found to reduce the density of brain β-adrenoceptors [12,19]. As the latter effect was not demonstrated after repeated administration of mianserin [11,19], it may indicate that the results obtained in our behavioral model are better correlated with those found in the functional model of the sensitivity of the adrenoceptor-coupled adenylate cyclase system than with those demonstrated in β-adrenoceptor binding studies.

It is noteworthy that the prevention of the salbutamol-induced hypoactivity, demonstrated in the present study for clomipramine, mianserin and nialamide and reported earlier for other antidepressant drugs [16] and the electroconvulsive shock [17], seems to be a specific effect of the antidepressant treatment, since two non-antidepressant psychotropic drugs, i.e., diazepam (anxiolytic) and haloperidol (neuroleptic), when given repeatedly, are inactive in our behavioral model. It is of interest that both the drugs do not reduce the density of β-adrenoceptors after similar treatment [19].

On the other hand, since we used salbutamol—regarded as a β_2-agonist—in the present studies, interpretation of our results as reflection of the down-regulation of β-adrenoceptors may be questionable in the light of recent studies of Minneman *et al.* [10]. The latter authors demonstrated that the decrease in β-adrenoceptor binding in the cerebral cortex after chronic treatment with desipramine referred to β_1- but not to β_2-adrenoceptors, and that β_2-adrenoceptors were associated with blood vessels rather than with the neuronal tissue. However, at least three points should be raised in this place: (1) the β_2/β_1 selectivity of salbutamol is doubtful [7]; (2) there is no evidence that the results of Minneman *et al.* [10] can be referred to brain structures other than the cerebral cortex and to antidepressant drugs other than desipramine; (3) salbutamol is effective in the treatment of depression [8,21], a phenomenon which does not seem to be due only to the drug's effect on brain blood vessels.

Since the salbutamol-induced hypoactivity in rats is antagonized not only by the acute pretreatment with β-adrenoceptor antagonists but also by the α_2-adrenoceptor blocking agent yohimbine [20], and since behavioral, biochemical and electrophysiological studies indicate that repeated treatment with antidepressant drugs induces subsensitivity of α_2-adrenoceptors (for references see [9]), our results after repeated treatment with clomipramine, mianserin and nialamide can be interpreted as those reflecting subsensitivity of these receptors. However, the subsensitivity of α_2-adrenoceptors does not seem to be a common characteristic of all antidepressants. Clomipramine was found to produce no such effect in both electrophysiological [18] and biochemical [23] studies, while mianserin was supposed to induce even supersensitivity of α_2-adrenoceptors [3,22].

In conclusion, our earlier and present results indicate that repeated treatment with different antidepressant drugs prevents the salbutamol-induced hypoactivity, most probably in consequence of the down-regulation of central β-adrenoceptors. This effect seems to be specific and we suggest that this model might be used for studying potential antidepressant drugs.

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