DEPENDENCE OF EFFECTS OF THE TRIPEPTIDE MIF AND LITHIUM CHLORIDE ON DEGREE OF SUPERSENSITIVITY OF BRAIN DOPAMINE RECEPTORS

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It has frequently been shown that reducing access of dopamine (DA) to target receptors causes them to develop supersensitivity. A change in the receptor sensitivity of structures of the mesostriatal DA system lies at the basis of the side effects observed during neuroleptic therapy [2]. Prevention of the development of undesirable supersensitivity of brain DA receptors has been observed experimentally when administration of the C-terminal fragment of oxytocin (the tripeptide MIF) or of LiCl was combined with neuroleptics [4, 14]. In many cases, however, after the development of supersensitivity of DA receptors, administration of MIF and LiCl has no desensitizing effect [4, 8]. The mechanism of suppression of the development of supersensitivity of DA receptors by the peptide and lithium ions and the conditions under which this effect is manifested have been inadequately studied. The intensity of the behavioral manifestations of receptor supersensitivity is connected mainly with the degree of proliferation of DA-receptor subpopulations [7, 15]. Further analysis is accordingly required: to what extent can the desensitizing effect of MIF and LiCl vary depending on the degree of supersensitivity of these receptors.

The aim of this investigation was to study the reversing effect of MIF and LiCl in animals differing in their degree of behavioral supersensitivity of brain postsynaptic DA receptors, induced by weakening of DA transmission as a result of chemical destruction of presynaptic dopaminergic terminals.

EXPERIMENTAL METHOD

Experiments were carried out on noninbred male albino rats weighing initially 200-220 g. To induce supersensitivity, the nigrostriatal fibers of DA neurons in the compact zone of the substantia nigra were destroyed unilaterally (on the right) by the neurotoxin 6-hydroxydopamine (6-OHDA, from "Fluka Buchs"). Under ether anesthesia the animals were given 8 μg of the neurotoxin, dissolved in 4 μl of cold physiological saline containing 0.2% ascorbic acid, through a cannula at the rate of 1 μl/min, at a point corresponding to coordinates AP 4.0, L 1.0, H 8.7 mm on Fifkova's atlas. Supersensitivity of DA receptors was estimated 3, 5, 6, 7, and 8 weeks after the operation. Apomorphine- (APO-) induced rotations (turning of the animal through 360° to the side opposite to the destructive lesion were recorded every 4 min for 1 h. The number of rotations was counted in a 4-min interval and throughout the period of recording. Groups of animals with single- and double-peak rotation patterns were distinguished by the time course of rotational behavior when last tested. The groups thus distinguished were characterized by their sensitivity to inhibition of rotational behavior by haloperidol (1 mg/kg, intraperitoneally, 40 min before APO).

The action of a single dose (20 min before APO) and of subchronic administration of MIF (5 and 21 days) and of lithium chloride (21 days) on the character and intensity of inhibition of APO-induced rotations was studied on the groups of animals thus distinquished. MIF in a dose of 5 mg/kg was injected subcutaneously and LiCl in a dose of 5 μmoles/kg was injected intraperitoneally. In the case of subchronic administration of the substances, testing was carried out 24 h after the last injection. APO was dissolved in physiological saline containing 0.2% ascorbic acid and injected subcutaneously in a dose of 0.05 mg/kg. In each experimental and control series four or five animals of the selected groups were used. The control animals were given an equal volume of physiological saline. The results were subjected to statistical analysis (Wilcoxon—Mann—Whitney tests).

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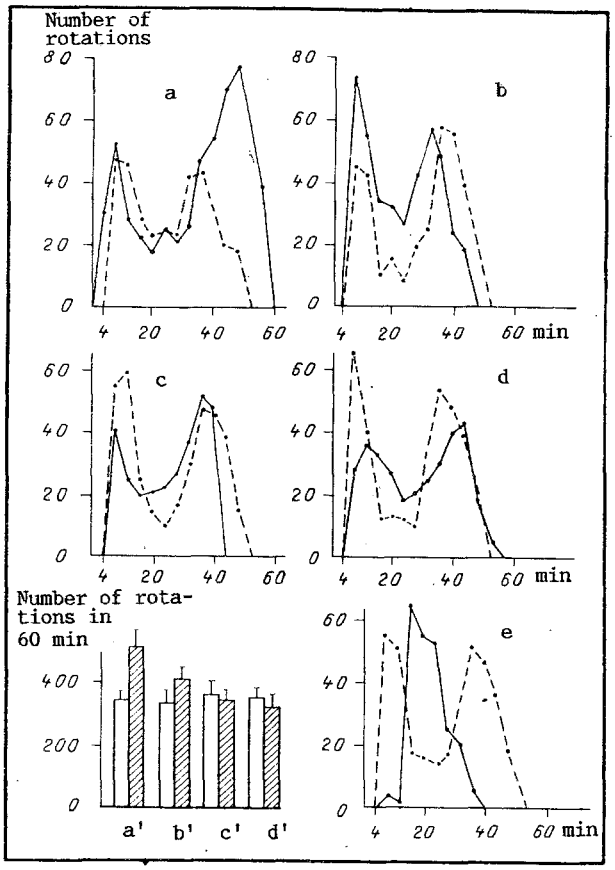

Fig. 1. Effect of MIF, LiCl, and haloperidol in rats with double-peak pattern of rotational behavior. Here and in Fig. 2: curves with broken lines and unshaded columns denote control (physiological saline + apomorphine); continuous curves and shaded columns denote test substances + apomorphine; a, a') single dose of MIF, b, b') MIF for 5 days, c, c') MIF for 21 days, d, d') LiCl for 21 days, e) single dose of haloperidol.

EXPERIMENTAL RESULTS

Contralateral rotations induced by APO, a direct agonist of DA receptors, are an indication of the development of supersensitivity of the denervated DA receptors. Steady rotational behavior began to appear in the 7th-8th week after injection of the neurotoxin. In 90% of rats the number of contralateral rotations during 1 h of recording was 350.7 ± 38.3. However, the time course of the rotational response differed among these animals. In 55% of rats a stable double-peak type of rotational behavior was observed (Fig. 1e). In the period from the 4th to the 12th minute and from the 32nd to the 40th minute the number of rotations was 51 ± 8.2; from the 12th to the 32nd minute their number fell by 2-2.5 times (19.2 ± 3.5). The time course of rotational behavior in the rats of group 2, which accounted for 35% of all animals undergoing the operation, differed significantly from that of group 1 (Fig. 2e). The rapid rise in the number of rotations during the first 4-8 min of testing (70.5 ± 5.2) was replaced by a gradual fall.

In rats with a double-peak pattern of rotation (group 1) exhaustion of DA of the ipsilateral striatum, induced by preliminary injection of the neurotoxin, was found to be 95% [13]. A high DA deficiency evokes a compensatory increase in binding of ^{3}H-spiroperidol, a D_2-receptor antagonist, by 26% [5], and of ^{3}H-SCH-23390, a D_1 receptor antagonist, by more than twice compared with the control [12]. A change in binding of ^{3}H-SCH-23390 was not observed in animals in which denervation was not accompanied by a high degree of DA exhaustion [12]. Haloperidol, a D_2-receptor antagonist, completely inhibited rotational behavior of rats of group 2 with a single-peak rotation pattern (Fig. 2e). Antagonism for number of rotations in the animals of group 1 was only 35%, but the character of the rotational response was transformed from double- to single-peak (Fig. 1e).

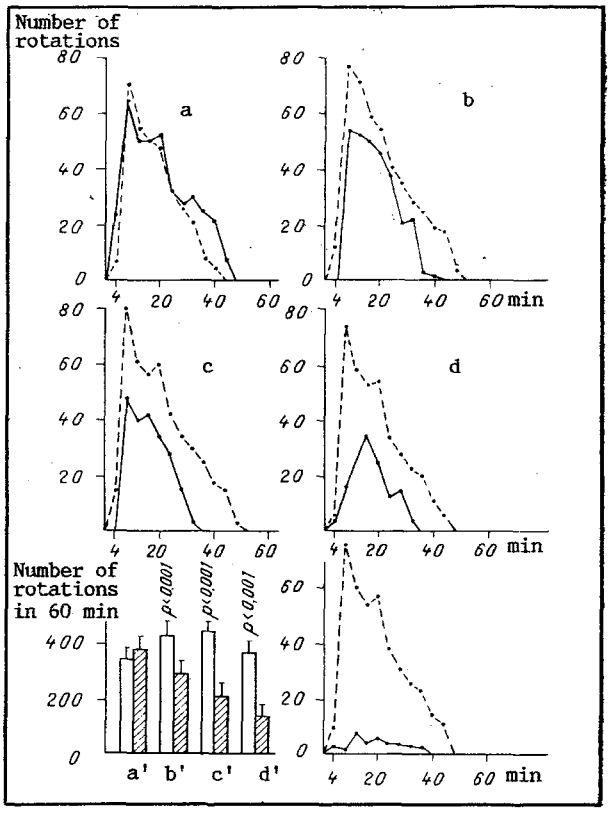

Fig. 2. Effect of MIF, LiCl, and haloperidol in rats with single-peak pattern of rotational behavior.

Similar data were obtained during inhibition of double-peak rotational behavior by selective D_2 antagonists (clebopride, spiroperidol) [1]. SCH-23390 did not transform rotational behavior into the single-peak form. The percentage of inhibition in this case was only 50%. Complete inhibition of APO-induced double-peak rotational behavior was possible only by combined administration of selective D_1- and D_2-antagonists or by the use of mixed antagonists of the cis-clopenthixol type [1]. This specificity of inhibition of rotations in these animals may be due to lowered affinity of binding sites for neuroleptics. In rats, during the development of supersensitivity after injection of the neurotoxin, a marked increase in binding sites for ^{3}H-haloperidol was shown to be accompanied by lowering of their affinity [7].

Administration of LiCl for 21 days did not change the total number of rotations in the animals of group 1, but reduced the peak values of rotations a little (Fig. 1d, d'). Subchronic adminstration of LiCl had no effect on APO-induced rotations in a previous study on animals whose tyroxine hydroxylase activity of the ipsilateral striatum was reduced by more than 90% 2 weeks after denervation by 6-OHDA [8]. In the present experiments significant (65%) inhibition of rotational behavior was observed in the animals of group 2 with a single-peak pattern (Fig. 2d, d'). Reduction of contralateral rotations by LiCl was not due to the effect of Li^+ on poetentiation of DA-mediation of the intact striatum. LiCl has been shown not to potentiate ipsilateral rotations induced by amphetamine, an indirect agonist of DA receptors [8]. The effect of LiCl on the postsynaptic component of DA mediation is therefore more likely. In experiments in vitro, LiCl was shown to inhibit striatal DA-stimulated adenylate cyclase [11].

MIF inhibited the manifestation of APO-induced rotations only in the animals of group 2 (Fig. 2, b, b', c, c'). After administration of the peptide for 5 days the number of APO-induced rotations fell by 35%, and after injections for 25 days, it fell by 54%. Conversely, in rats responding by a double-peak pattern of rotations, MIF caused no significant reduction in the number of rotations after administration of the peptide for either 5 or 21 days (Fig. 1b, b', c, c'). Unlike the rats of group 2, in the animals of group 1 the action of MIF was manifested only after a single injection. The duration of APO-induced behavior was increased in this case by 12 min and the total number of rotations increased by 45% (Fig. 1a, a'). MIF caused a rapid increase in the number of rotations in the first phase, and an almost twofold increase in their number in the second phase. MIF (a single dose) intensifies binding, through allosteric modulation, of ^{3}H-APO, but not of ^{3}H-spiroperidol, with the striatal membranes and inhibits activity of DA-sensitive adenylate cyclase [6].

On the whole, denervation leads to increased sensitivity of DA-receptors to the agonists. In animals with 90% exhaustion of endogenous EDA the number of binding sites of the DA-agonist ^{3}H-ADTH (which activates adenylate cyclase by a greater degree than APO) is increased by 85%, but subcomponents of binding of ^{3}H-ADTH sensitive and insensitive to guanine nucleotides, are increased by 134 and 74% respectively [9]. The high degree of supersensitivity of these animals to agonists (a fairly large increase in binding, coupled with the adenylate-cyclase component of ^{3}H-ADTH) determines the different trend of the modulating effect of MIF, namely an increase in APO-induced rotations. Since the hypothetical specific binding sites for MIF interact with the DA-receptor/adenylate cyclase complex [6], the direction and magnitude of the modulating effect of MIF depend on the degree of adaptive changes in the DA-receptors. With the lower degree of supersensitivity of DA-receptors in spontaneously hypertensive rats (the increase in ^{3}H-spiroperidol binding amounts to only 16%, with no change in the dissociation constant), the desensitizing effect of the cyclic analog of MIF is clearly manifested as early as on the 7th day of its administration [3].

Differences in the effects of LiCl and MIF on behavioral manifestations of supersensitivity of striatal postsynaptic DA-receptors in the animals of the two different groups are thus determined by the fact that their DA-receptors differ in their degree of supersensitivity. MIF and LiCl may not necessarily have a desensitizing effect during the development of the high degree of supersensitivity which is characteristic, for example, of persistent manifestations of the tardive dyskinesias [10]. However, their protective action against the development of DA-supersensitivity calls for close attention because of the problem of correction and prevention of side effects during long-term neuroleptic administration.

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