EFFECT OF REPEATED INJECTION OF HALOPERIDOL WITH APOMORPHINE ON DEVELOPMENT OF TOLERANCE TO CATALEPSY AND DOPAMINE RECEPTOR HYPERSENSITIVITY IN MICE

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UDC 612.014.467:615.357.452]-06:615.214.22]:08

KEY WORDS: dopamine receptors; tolerance; hypersensitivity.

Prolonged administration of neuroleptics into experimental animals depresses their behavioral effects, and after withdrawal of the drugs, behavioral hypersensitivity of the animals arises in response to administration of dopaminomimetic agents [1-3, 5, 12, 14]. It has been suggested that these changes are connected with the development of hypersensitivity of dopamine receptors to long-term blockade by neuroleptics. As binding experiments have shown, hypersensitivity is based on an increase in the number of functionally active receptors in the corpus striatum [1, 3, 10]. The importance of these adaptive changes in clinical and side effects of neuroleptics is not entirely clear. Hypersensitivity of dopamine receptors in the corpus striatum evidently lies at the basis of extrapyramidal disorders of hyperkinetic type arising in patients taking neuroleptics for long periods [9]. The possibility likewise cannot be ruled out that adaptive changes in the dopaminergic system of the corpus striatum may be linked with the development of resistance to neuroleptics, although this problem had not yet been discussed in the scientific literature. It has recently been reported that hypersensitivity of dopamine receptors is abolished by subsequent injection of dopaminomimetics L-dopa or bromocriptine [7, 10]. It is not yet clear how dopaminomimetics will affect the phenomena of tolerance and hypersensitivity if administered simultaneously with neuroleptics.

The aim of this investigation was to study tolerance and hypersensitivity of dopamine receptors during long-term simultaneous administration of haloperidol (HAL) and the dopaminomimetic apomorphine (APO) to mice. APO was chosen because this dopaminomimetic in small doses has an antipsychotic action [6].

EXPERIMENTAL METHOD

Experiments were carried out on male albino mice weighing initially 18-25 g and divided into groups (18 animals in each group). As a first step physiological saline was injected into the animals for 1 week, and they were placed daily in the experimental chambers where catalepsy was determined, in order to adapt them to the experimental procedure. The animals of one group then received injections of HAL in fixed doses of 0.1 and 5.0 mg/kg once a day for 20 days. Animals of the second group received HAL by the same scheme and in the same doses together with APO in doses of 0.1 and 1.0 mg/kg twice a day for 20 days. Control mice received physiological saline or APO in the same doses. Catalepsy was determined in the mice on the 1st, 7th, 14th, and 20th days of injection of the neuroleptics, 120 min after the injection, by the method in [8]. For this purpose the animals were placed with their forelimbs on a wire at a height of 4.5 cm and the duration of holding was measured in seconds. The animals were killed 72 h after the last injection of the substances, the brain was removed in the cold, and the corpus striatum isolated. Brains of three mice were pooled and binding of [^{3}H]spiroperidol (21 Ci/mmole, Amersham Corporation, England) was determined by the method in [10]. The standard incubation medium in a volume of 1 ml contained in Tris-EDTA buffer (pH 7.4): 10 μM pargyline, 0.5 mM [^{3}H]spiroperidol, and membrane suspension. After incubation for 30 min at 22°C the bound [^{3}H]spiroperidol was isolated by filtration on CF/B filers (Whatman, England) and radioactivity was determined on a liquid scintillation

Department of Pharmacology, Tartu University. (Presented by Academician of the Academy of Medical Sciences of the USSR A. V. Val'dman.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 98, No. 10, pp. 444-446, October, 1984. Original article submitted November 17, 1983.

 0007-4888/84/9810-1372$08.50

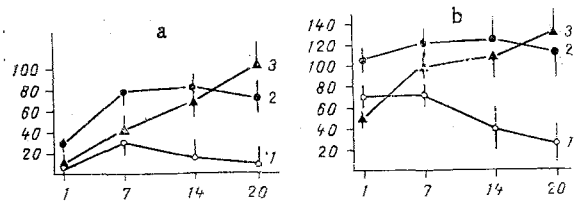

Fig. 1. Intensity of catalepsy in mice during repeated (for 20 days) injections of HAL and HAL + APO. Abscissa, days of injection ordinate, intensity of catalepsy (in sec). a: 1) HAL 0.1 mg/kg, 2) HAL 0.1 mg/kg + APO 0.1 mg/kg, 3) HAL 0.1 mg/kg + APO 1.0 mg/kg; b: 1) HAL 5.0 mg/kg, 2) HAL 5.0 mg/kg + APO 0.1 mg/kg, 3) HAL 5.0 mg/kg + APO 1.0 mg/kg.

TABLE 1. Specific Binding of [^{3}H]Spiroperidol (0.5) nM) with Suspension of Membranes from Mouse Striatum 72 h after Termination of Repeated (20 days) Injections of HAL or HAL + APO

Substance and dose (in mg/kg)	Binding of [^{3}H]spiroperidol	
	fmoles/mg protein	ratio to control (%)
Control (physiological saline)	175,2±12,6	—
HAL		
0,1	186,2±8,9	+6,2
5,0	246,6±8,6[a]	+40,8
HAL + APO		
0,1+0,1	188,9±8,9	+19,2
0,1+1,0	167,4±15,2	—4,5
5,0+0,1	211,6±8,8[ab]	+26,4
5,0+1,0	162,9±14,2[b]	—7,1
APO		
0,1	165,0±12,1	—6,9
1,0	154,1±12,2	—12,1

Legend. Mean results of three experiments and their standard errors are given. a) $P < 0.05$ relative to control, b) $P < 0.05$ relative to group receiving HAL.

counter (Beckman LS-6800, USA). Specific binding of [^{3}H]spiroperidol was determined as the difference between binding in the absence and in the presence of 1 μM unlabeled spiroperidol. Protein was determined by Lowry's method [11].

EXPERIMENTAL RESULTS

The time course of the changes in catalepsy in the mice during long-term administration of HAL or of HAL with APO is shown in Fig. 1. Tolerance to the cataleptogenic action of the neuroleptic began to be formed, not immediately, but after a certain period of time, during which the catalepsy either remained unchanged or actually intensified. The same phenomenon has been described by other workers also, and it depends on the frequency with which the determination of catalepsy was repeated and is connected with the formation of a conditioned reflex to the experimental procedure [13]. On the 14th and 20th days of administration, however, the catalepsy declined steadily, evidence of the formation of tolerance. APO in a dose of 0.1 mg/kg, injected once only, potentiated the cataleptogenic effect of HAL, but chronic administration prevented the development of tolerance. Potentiation of haloperidol catalepsy by small doses of APO was evidently associated with its presynaptic action. Many workers have shown that APO, in doses of 0.1 mg/kg or less, has a sedative action and inhibits dopamine metabolism through stimulation predominantly of presynaptic dopamine receptors [6] by a feedback mechanisms. The antipsychotic effect of APO also is determined, evidently, by its presynaptic action [6]. In a dose of 0.1 mg/kg, APO has a postsynaptic action also, and its ability to prevent the development of tolerance and hypersensitivity of dopamine receptors is connected with this effect. This conclusion is confirmed by the fact that injection of kainic acid, which selectively damages neuron bodies and dendrites and, consequently, postsynaptic receptors, into the corpus striatum prevents the formation of tolerance and hypersensitivity of the receptors arising during chronic administration of neuroleptics [15]. APO in a dose of 1.0 mg/kg, in a single injection, prevented the effect of HAL, but later, on the

7th-20th day, the catalepsy was actually intensified compared with the group of animals receiving the neuroleptic only (Fig. 1).

After discontinuation of the small dose (0.1 mg/kg) of HAL no increase in binding of [^{3}H]spiroperidol was observed, but after injection of HAL in a dose of 5 mg/kg a significant increase in binding was observed, indicating the development of hypersensitivity of the receptors. Parallel administration of APO in doses of 0.1 and 1.0 mg/kg prevented this effect (Table 1). Repeated administration of APO against the background of HAL thus prevented the development of tolerance to catalepsy and the development of receptor hypersensitivity. APO evidently gives rise to a unique kind of desensitization of dopamine receptors, as a result of which the behavioral effects of neuroleptics are potentiated. This hypothesis is supported by previous observations indicating that after termination of chronic administration of dopaminomimetics the behavioral effects of HAL are intensified.

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