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Apomorphine-Induced Stereotypic Cage Climbing in Mice as a Model for Studying Changes in Dopamine Receptor Sensitivity

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WILCOX, R. E., R. V. SMITH, J. A. ANDERSON AND W. H. RIFFEE. *Apomorphine-induced stereotypic cage climbing in mice as a model for studying changes in dopamine receptor sensitivity.* PHARMAC. BIOCHEM. BEHAV. **12**(1) 29–33, 1980.—We have previously confirmed in mice that apomorphine (APO) induces dopamine specific stereotypic cage climbing. Apparent changes in dopamine receptor sensitivity induced by chronic drug administration appear to be measurable by this technique. In the present experiments, murine stereotypic cage climbing was evaluated as a model system for assessing the dopamine receptor supersensitivity induced by chronic administration of the potent butyrophenone neuroleptic spiroperidol. Spiroperidol induced a significantly enhanced response induced by APO (about a 7-fold increase) manifest by 48 hr (but not 24 hr) following cessation of the last chronic injection. Time-response analyses demonstrated that the action of test doses of APO (1.0 or 4.5 mg/kg, IP) was significantly prolonged in the chronic-spiroperidol animals relative to controls. The supersensitivity in the spiroperidol-treated animals lasted more than three weeks for each dose of the neuroleptic and the APO dose-response curve was shifted to the left in spiroperidol-treated animals. Results are discussed in terms of the utility of the model for establishing dose-response, time-course, and duration of effect data within the same group of animals.

Neuroleptic Apomorphine Stereotypic activity Dopamine receptor sensitivity

DESTRUCTION of the nigrostriatal dopamine system by 6-hydroxydopamine [11,46], or temporary blockade of CNS dopamine receptors via chronic neuroleptic administration [5, 21, 22, 48], produces a characteristic pattern of enhanced behavioral responsiveness [14, 16, 27] to IP test doses of the dopamine agonist apomorphine [1,18]. Furthermore, both of these manipulations are associated with true alterations in the dopamine receptors themselves, with an increase in the maximum number of binding sites (B_{max}) but no change in the affinity (K_D) of binding [5, 11, 33].

Supersensitivity of dopamine receptors may be an important reason for the therapeutic effectiveness of L-dopa in Parkinson's disease [30], for the production of various dyskinesias in the course of L-dopa therapy [2, 4, 8, 32] and perhaps for the clinically relevant effects of the aporphines in Parkinsonism [15], Huntington's chorea [45], tardive dyskinesia [44], and schizophrenia [42].

An enhanced locomotor response to a test dose of apomorphine after either chronic apomorphine or dextroamphetamine was recently reported [3]. This encouraged us to attempt to extend these findings of an apparent supersensitivity of dopamine receptors after chronic apomorphine to the stereotypic cage climbing model [37, 38, 49] which is relatively specific for the dopaminergic agonist action of aporphines and related compounds. A significantly enhanced response to a 1.0 mg/kg test dose of apomorphine four, eight, and twelve days after cessation of the last chronic apomorphine injection was found using procedures which minimize experimenter bias and maximize accuracy of the data [51]. In the present experiments, we sought to characterize the utility of the cage climbing model as a means for assessing changes in dopamine receptor sensitivity induced by chronic drug administration. This report describes a preliminary evaluation of this model using the prototypical drug spiroperidol which is an antischizophrenic butyrophenone [9, 13, 19] with an extremely high affinity for dopamine receptors.

METHOD

Subjects

Experimentally naive CD-1 male albino mice (Charles River) weighing between 20 and 36 g at the time of testing were used in all investigations. Throughout the studies access to food and water was provided ad lib. Animals were maintained on a 12-hour light-dark cycle (lights on 6 AM to 6 PM) and all pharmacological testing was done between 10 AM and 5 PM. Between 10 and 20 mice were used in each group.

Drugs

Drugs used for the experiments were spiroperidol (Janssen Pharmaceuticals, New Brunswick, NJ) and R-

(−)-apomorphine hydrochloride hemihydrate (APO; MacFarland Smith, Ltd., Edinburgh, Scotland). Spiroperidol was prepared in a minimum amount of acid vehicle, (0.6% HCl; or tartaric acid, 1 mg tartaric/mg spiroperidol) and administered appropriately diluted to minimize injection trauma. APO was freshly prepared in distilled water without preservatives. Both drugs were administered intraperitoneally.

Experimental Design

Groups of mice (N=10) were administered spiroperidol (0.4, 2.0, or 4.0 mg/kg, IP) or isotonic saline once daily for 20 days and subsequently tested for cage climbing to APO as described below. In a second separate experiment, spiroperidol (8 mg/kg) was administered IP once.

Cage Climbing Behavior

A modification of the basic procedure of Protais [38] was employed throughout involving videotaping of behavior coupled with "blind" ratings [38,51]. Briefly, animals were given a saline preinjection to minimize nonspecific effects of the handling/injection routine [39] and placed individually into cylindrical cages, 12 cm dia., 14 cm high, with walls of vertical bars, 2 mm diameter, 1 cm apart, surmounted by fine wire mesh. Following a 60 min habituation period, animals were given a pre-APO rating of their behavior (see below) and administered a test dose of APO (either 4.5 or 1.0 mg/kg) and the behavior of the animals recorded on videotape (30 sec every 5 min) for the next hour. Videotaped behavior, scored via a 0–2 rating scale [38]: 0=four paws on cage floor; 1=two paws holding the vertical bars of the cage; 2=four paws holding the vertical bars of the cage, was later rated "blind" using procedures previously described [50].

Behavioral Testing and Analysis

Experimental groups each received one of three doses of spiroperidol (0.4, 2.0, 4.0 mg/kg) chronically with subsequent testing with one of two doses of APO (4.5 or 1.0 mg/kg). Two groups of mice, treated with 2.0 or 4.0 mg/kg spiroperidol and tested with 1.0 mg/kg APO, were selected for extended tests beginning 24 hr after the last chronic spiroperidol dose as follows: 1 day, 2, 3, 7, 15, 21, and 35 days. Statistical analyses were carried out in which scores of chronic spiroperidol treated mice were compared to the scores of chronic-saline animals (using parametric=*t*-test and nonparametric=Mann-Whitney U test procedures; c.f., [51,52].

RESULTS

Time-response data for control animals administered isotonic saline (one IP injection per day for 20 days) are presented in Fig. 1. Animals were tested for stereotypic cage climbing induced by 1.0 mg/kg APO, 4, 8, and 12 days after cessation of the last chronic saline injection. Stereotypy on the first test day (day 4) was less than activity on the subsequent days (analysis of variance and Neuman-Keuls tests $p<0.05$; [52,53]). Cage climbing on the second (day 8) and third (day 12) tests days was not significantly different from one another ($p>0.05$).

In Fig. 2 are shown time-response data for naive animals administered 1.0 or 4.5 mg/kg APO. With 1.0 mg/kg APO administration to naive mice, peak cage climbing occurs at 5 minutes with similar levels maintained through 20 minutes. The response to this dose of APO is not significantly different from the response to isotonic saline at any time throughout the 60 min period [38, 49]. Following administration of 4.5 mg/kg APO to naive animals, peak cage climbing occurs at 10–15 min with high levels of responding maintained until 40 min after injection of the apomorphine. Time response data for administration of 4.5 or 1.0 mg/kg APO to mice 48 hours after chronic spiroperidol (0.4 mg/kg IP, once daily for 20 days) are also indicated in Fig. 2. In mice tested with 4.5 mg/kg APO, the time of peak response is shifted to the right

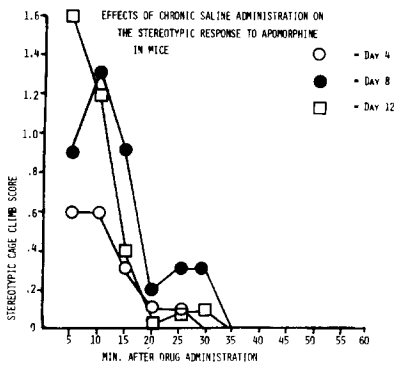

FIG. 1. Stereotypic cage climb activity after administration of chronic isotonic saline. Mice were injected once per day for 20 days with isotonic saline (0.1 ml/10 g body wt, IP) and subsequently tested for stereotypic cage climbing to 1.0 mg/kg apomorphine (see text). Indicated in the figure are mean cage climb scores (n=10) 4, 8, and 12 days following the last chronic saline injection.

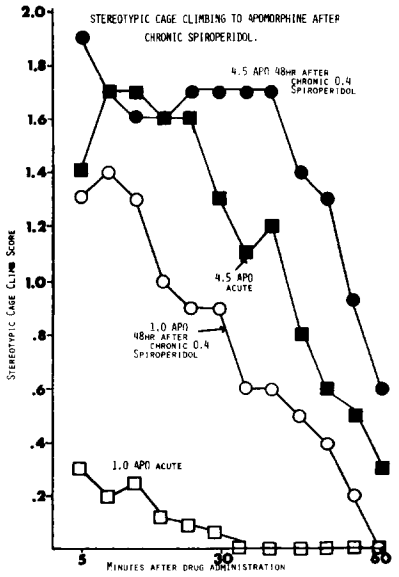

FIG. 2. Time-response analysis of stereotypic response to apomorphine (APO) in mice given acutely or after chronic administration of spiroperidol. Spiroperidol was administered once per day for 20 days (0.4 mg/kg IP). Indicated in the figure are mean cage climb scores to 1.0 mg/kg (n=32) or 4.5 mg/kg (n=36) APO given to naive mice or to mice 48 hr. following the last chronic spiroperidol injection (n=10; see text).

TABLE 1

CAGE CLIMBING TO APOMORPHINE AFTER CHRONIC SPIROPERIDOL

Test day*	Spiroperidol dose (mg/kg) 2	4
1	4.1 ± 1.3	3.0 ± 1.2
2	7.6 ± 1.6†	6.8 ± 1.7
3	6.8 ± 1.0‡	8.3 ± 1.3‡
7	5.8 ± 0.9†	9.9 ± 0.7‡
15	8.1 ± 1.7†	7.8 ± 1.4†
21	6.8 ± 1.0‡	7.7 ± 0.7‡
28	7.7 ± 0.9‡	10.0 ± 1.4‡
35	6.1 ± 1.6	5.4 ± 1.3

*Stereotypic cage climbing in mice to 1.0 mg/kg (IP) apomorphine was evaluated after chronic treatment with spiroperidol (one injection/day for 20 days). Scores represent mean ± SEM cumulative 60 min cage climb scores for n≥8 mice/group.

†$p<0.05$ chronic-spiroperidol animals vs. chronic-saline animals. Scores for chronic-saline animals are presented in Fig. 1. (t-test and Mann-Whitney U test).

‡$p<0.01$.

TABLE 2

EFFECT OF A SINGLE SPIROPERIDOL INJECTION ON CAGE CLIMBING TO APOMORPHINE

	Apomorphine dose (mg/kg) 1.0	2.0	4.0
Spiroperidol	0 ± 0	9.7 ± 1.6*	13.0 ± 0.9
Saline	1.1 ± 0.3	2.8 ± 0.7	11.1 ± 1.8

Spiroperidol (8 mg/kg) or saline (0.1 ml/10 g body wt) was administered IP to mice. Cage climbing to apomorphine was evaluated 72 hours later as described in Method. n=6 per group.

*$p<0.05$ spiroperidol vs. saline, Mann-Whitney U test.

in chronic spiroperidol-treated animals relative to controls. A greater total response is also observed in the experimental animals with a cumulative score of 16.3 vs. 13.8 in controls. Administration of spiroperidol results in a significant increase in the response to APO relative to that of controls (cumulative scores over 60 min, $p<0.05$).

In Table 1, data are shown for cumulative 60 min. cage climbing after administration of 1.0 mg/kg APO to animals given 2.0 or 4.0 mg/kg spiperone chronically. After chronic treatment with 2.0 mg/kg spiperone, supersensitivity is maximal at 3 weeks. Following 4.0 mg/kg chronic spiperone, the enhanced stereotypic response is still apparent with undiminished intensity at 4 weeks. Independent of the dose of spiperone administered in the present experiments, supersensitivity is manifest by at least 48 hours following the last chronic spiperone injection and continues unabated 28 days, or longer than the duration of the chronic neuroleptic treatments.

Table 2 presents dose response analyses for cage climbing in animals given APO to controls or 72 hr after a single injection of spiroperidol (8 mg/kg, IP). Significant increases at the 2 mg/kg test doses of APO were found in the spiroperidol treated mice ($p<0.05$, Mann-Whitney U test and t-test).

DISCUSSION

Behavioral measures of an apparent dopamine receptor supersensitivity defined via an enhanced behavioral response to dopamine agonists have been well documented [12,25]. Dopamine antagonist neuroleptics represent perhaps the most common means of inducing an increased sensitivity of postsynaptic receptors [23, 24, 47] although other agents such as narcotics [3, 7, 16, 26, 28, 40] appear able to produce similar changes (Wilcox *et al.*, in preparation).

Increased responsiveness to apomorphine in induction of stereotypic activity has been reported within one to two days after a single injection of haloperidol or chlorpromazine (rats: 9; mice: 10; 31). Generally, an injection (IP or SC) schedule of 3–6 weeks (range=1–7 weeks) with a drug free period of 1–2 weeks (range=2–21 days) has been employed to induced an enchance stereotypic response to apomorphine (reserpine, chlorpromazine, haloperidol: 43; haloperidol: 22; haloperidol, thioridazine, clozapine: 41). Under these conditions, the enhancement of the behavioral response was about 100–200% (range=0–460%). In the present experiments, 21 daily injections of spiroperidol induced a several fold increase in the behavioral response to 1.0 mg/kg APO. The increase in the response to 4.5 mg/kg APO was less dramatic possibly due to the intense cage climbing induced by this dose of APO in naive mice. The average cumulative cage climb score of 17.0 in chronic spiroperidol mice is similar to that induced by 15 mg/kg APO ($p>0.05$) in control mice (Wilcox, unpublished observations).

Recently, Martres [31] demonstrated that a single administration of the butyrophenone neuroleptic haloperidol can result in a state of hypersensitivity of presumably postsynaptic dopamine receptors as shown by four findings. (1) An increased cage climb response is observed in mice when the animals are placed in test cages identical to those used in the present study and given APO with no saline pretreatment and no habituation time. (2) The neuroleptic is found to be less able to antagonize APO-induced climbing behavior in mice tested as in No. 1. (3) Dopamine release is decreased compared with controls. (4) APO possesses a greater ability to facilitate dopamine release in haloperidol-injected mice.

Direct tests of changes in dopamine receptor function can be made via receptor binding assays following either selective lesions of brain dopamine systems using the neurotoxic drug 6-hydroxydopamine [29] or chronic neuroleptic administration [6]. The results of such studies correlate well with electro-physiological [7] and neuroanatomical [36] evidence of enhanced firing and cell depletion, respectively. Thus chronic administration of haloperidol to rats [7, 21, 36] increases striatal and mesolimbic dopamine binding of (^{3}H)-haloperidol or (^{3}H)-spiroperidol from 27–77% relative to controls [35]. We have confirmed in rats that chronic spiroperidol (0.4 mg/kg IP once daily for 35 days; animals sacrificed 7 days later) increases the maximum number of (^{3}H)-spiroperidol binding sites (34% increase in B_{max} with no change in the affinity of binding; Wilcox unpublished observations). Also, preliminary evidence suggests that spiperone treatment in mice enhances (^{3}H)-spiroperidol binding to striatal homogenates by 33% concomitant with enhanced behavioral sensitivity to APO (Wilcox, unpublished observations). These biochemical data, taken together with the behavioral and biochemical results of Martres *et al.*, [31] and the present behavioral test results suggest that the cage climb methodology utilized here provides a useful animal model for

assessing changes in dopamine receptor function after chronic drug treatment. The ease of testing large numbers of animals and of establishing within-animal time course data using the described methodology may have value as a screen for testing the effects of different dose regimens and treatment patterns for a wide variety of drugs with putative effects on dopamine receptors.

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