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The Effects of Some Atypical Neuroleptics on Apomorphine-Induced Behaviors as a Measure of Their Relative Potencies in Blocking Presynaptic Versus Postsynaptic Dopamine Receptors

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ROBERTSON, A. AND C. MACDONALD. *The effects of some atypical neuroleptics on apomorphine-induced behaviors as a measure of their relative potencies in blocking presynaptic versus postsynaptic dopamine receptors.* PHARMACOL BIOCHEM BEHAV 24(6) 1639–1643, 1986.—The effects of the atypical neuroleptics clozapine, thioridazine and sulpiride on behaviors induced by apomorphine were recorded, using a time-sampling observational paradigm. A low dose of apomorphine (0.1 mg/kg, SC) produced hypomotility. Of the neuroleptics tested, only sulpiride antagonized this hypomotility. Apomorphine in higher doses (0.2–1.0 mg/kg, SC) produced stereotyped behaviors (sniffing down and licking or gnawing). All three atypical neuroleptics antagonized stereotypy. The effects of sulpiride on apomorphine-induced hypomotility and stereotypy are consistent with the notion that this drug has strong presynaptic and weak postsynaptic blocking effects at dopamine receptors. The mechanisms of action of clozapine and thioridazine may be different from that of sulpiride. Perhaps the anticholinergic activities of these drugs mediate some of their behavioral effects. The effects of these atypical neuroleptics on apomorphine-induced stereotypy are opposite in direction to their effects on amphetamine-induced stereotypy, suggesting that these two behavioral patterns are not measures of the same neural process.

Atypical neuroleptics Clozapine Thioridazine Sulpiride Apomorphine Stereotyped behaviors Hypomotility Dopamine

STEREOTYPED behaviors induced by administration of apomorphine or amphetamine are generally assumed to be a reflection of the stimulation of dopaminergic neurons [2, 9, 12, 14, 23, 28, 36], and the relative abilities of neuroleptics to block these stereotypies has been widely used as an index of their abilities to block postsynaptic dopamine receptors [25,37]. Atypical neuroleptics have usually been observed to be much weaker than classical neuroleptics in suppressing stereotyped behaviors [4–6, 15, 19–20, 31], presumably indicative of weak postsynaptic antagonism. However we have recently observed, by using submaximal doses of amphetamine, that the atypical neuroleptics clozapine, thioridazine and sulpiride can all potentiate amphetamine-induced stereotypy [29,30]. These results are paradoxical if, in fact, a suppression of stereotypy is representative of antagonism at postsynaptic receptors.

As a first step toward resolving this paradox, we decided to study the effects of the same doses of neuroleptics, using the same method, on behaviors induced by the dopamine agonist apomorphine. There were two reasons for this. First, since we had shown that, in contrast to earlier reports [4–6, 15, 19–20, 31], these atypical neuroleptics have facilitatory effects on behaviors induced by amphetamine, it seemed reasonable to ask whether the same effect might not be observed, using the same type of method employing submaximal doses of the agonist (which permits facilitatory or suppressive effects to be measured), when apomorphine rather than amphetamine was administered. This seemed especially important since it has been reported within the same study, on at least two different occasions, that amphetamine and apomorphine-induced stereotypy are both antagonized by atypical neuroleptics [6,15]. Since our previous results demonstrated that this is not necessarily the case for amphetamine, it is legitimate to question whether the same might not be true for apomorphine. The possibility that atypical neuroleptics might actually enhance the stereotypy

produced by apomorphine, an effect thought to be mediated by postsynaptic dopamine agonist action [2,9], would necessitate a revision of the hypothesis that the behavioral effects of neuroleptics can be adequately accounted for by their effects on dopaminergic activity.

Second, the use of apomorphine provided an opportunity to measure the presynaptic activities of these neuroleptics, since low doses of apomorphine induce a hypomotility or immobility which is believed to be mediated by a presynaptic dopaminergic action [8]. An ability to block presynaptic dopamine receptors might explain the potentiating effects of atypical neuroleptics on amphetamine-induced stereotypy, as it might be expected to enhance the effects of amphetamine, which produces its behavioral effects by facilitating dopamine activity at presynaptic terminals [1]. In fact, such evidence already exists for sulpiride, which has been shown to block apomorphine-induced immobility [7, 13, 17, 22]. We wondered if we could replicate these reports, using the same doses and the same testing procedures that were effective in facilitating amphetamine-induced stereotypy, and, further, whether we could extend these findings to include clozapine and thioridazine.

METHOD

Subjects

Subjects were 54 male Long-Evans rats (Charles River Canada, Inc., St. Constant, Quebec), weighing 250–275 g at the start of the experiment. They were housed in groups of 3 per cage, on a 12:12 hr light:dark schedule, with food and water available ad lib. All testing was carried out during the light period, between 9:00 and 13:00.

Apparatus

Rats were placed in 4 Plexiglas activity boxes, 40×40×40 cm, where visual observations of their behaviors were carried out. Additionally, each box was equipped with 6 sets of photocell beams, 3 beams equally spaced on each wall. Interruptions of the photocell beams were automatically recorded. Each rat was assigned to the same box for the duration of the experiment.

Drugs

Sulpiride (dissolved in 1% lactic acid) was administered in doses of 5.0 and 20.0 mg/kg. Clozapine (in 1% lactic acid) and thioridazine (in sterile isotonic saline) were administered in doses of 5.0 and 10.0 mg/kg. All neuroleptics were injected SC 40 min before testing. Apomorphine (in sterile isotonic saline) was freshly made up before each test session, in doses of 0, 0.1, 0.2, 0.3, 0.5 and 1.0 mg/kg, and was administered SC to animals immediately, in order to minimize oxidative changes. All drugs were injected in a volume of 1.0 ml/kg, into the caudal region of the back.

Procedure

Rats were randomly divided into 7 groups (n=7–8 per group), according to the neuroleptic they received: 5.0 mg/kg and 20.0 mg/kg sulpiride, 5.0 mg/kg and 10.0 mg/kg thioridazine, 5.0 mg/kg and 10.0 mg/kg clozapine, and a vehicle control group. Only one vehicle control condition (saline) was included as our previous experiments [29–30] had shown the effects of lactic acid injections to be indistinguishable from the effects of saline injections under these same conditions. All subjects in each group received all 6 doses of apomorphine in consecutive drug tests.

TABLE 1

DESCRIPTION OF BEHAVIORS

Immobility: standing still or lying down; no detectable movement
Grooming: washing any part of body
Sniffing up: movement of snout in the air or at the wall; no forward locomotion; no snout contact with floor
Locomotion: movement of at least 3 paws in a forward direction; might be accompanied by sniffing up
Rearing: front paws raised in the air or against the wall; resting on hind quarters
Stereotypy: repetitive behaviors including:
1. Sniffing Down: sniffing at the floor; maintaining snout contact; no locomotion
2. Licking or Gnawing: scraping the floor or walls with tongue or teeth; no locomotion

For the first 3 days of the experiment, rats were placed in the activity boxes for 20 min habituation periods. Formal testing then began. For each 35 min test session, behavioral observations were taken during two 10 min intervals, from 0–10 min and 25–35 min. During these intervals, the behavior of each rat was recorded in shorthand form every 10 sec. Thus there was a total of 120 observations per rat for each 35 min test session. Any behavior which could be reliably described by the observer was included.

During the first test session, baseline observations of behaviors were recorded to ensure that the groups did not differ in any way. Drug testing then began. For each test, the rat received the appropriate dose of neuroleptic (or vehicle) combined with a dose of apomorphine, which was administered in ascending order: 0, 0.1, 0.2, 0.3, 0.5 and 1.0 mg/kg (in separate drug tests). There was a waiting period between drug tests of at least 3 days, during which time activity scores from the photocell beams were taken to ensure that there were not detectable alterations in baseline activity.

RESULTS

Data Analysis

A total of 6 reliably differentiable categories of behavior was recorded (see Table 1): (1) immobility, (2) grooming, (3) sniffing up, (4) locomotion, (5) rearing, and (6) stereotypy. Stereotyped behaviors were categorized according to Fog's ([11], p. 14) definition of stereotypy "... decreased variation in behavior, continuous repetition of behavior patterns or items . . ." and consisted of sniffing down and licking or gnawing.

The dependent variables for each subject were the total number of observations for each of the 6 behavioral categories over the 35 min test session. Observations were accumulated over the two observation periods (0–10 min and 25–35 min), as preliminary analyses demonstrated that drug effects were stable throughout the session. The data for each dependent variable were analyzed using two-way analyses of variance (Factor A=neuroleptic group; Factor B=dose of apomorphine) with repeated measures over the latter factor, followed by Dunnett's two-sided comparison between treatment and control groups [35]. Stereotyped behaviors (sniffing down and licking or gnawing) were analyzed both

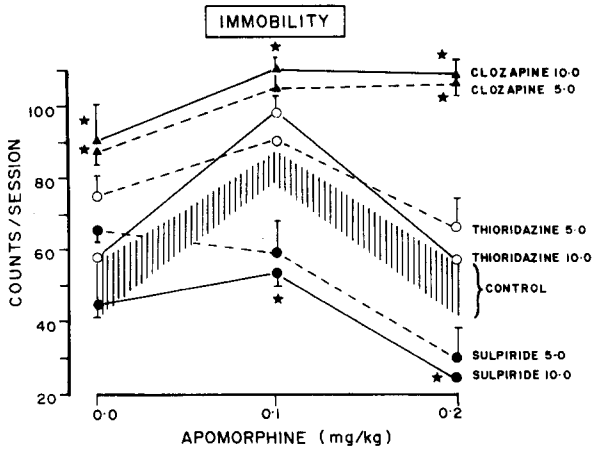

FIG. 1. Effects of neuroleptics on apomorphine-induced immobility. The vertical stripes represent the mean±S.E.M. of the control group. Vertical bars represent S.E.M.s. Asterisks indicate a significant difference between a neuroleptic group and the control group.

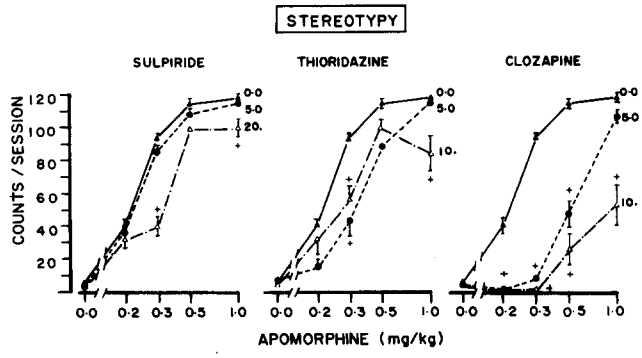

FIG. 2. Effects of neuroleptics on apomorphine-induced stereotypy. Doses of apomorphine are represented on a logarithmic scale. Vertical bars represent S.E.M.s. Crosses indicate a significant difference between a neuroleptic group and the control group.

separately and together. A difference was considered significant when the probability of a type I error was ≤ 0.01.

Effects of Neuroleptics on Apomorphine-Induced Immobility

The number of observations of immobility significantly increased from the 0.0 to the 0.1 mg/kg dose of apomorphine and returned to normal at the 0.2 mg/kg dose (Fig. 1), to drop sharply thereafter as the dose of apomorphine increased beyond 0.2 mg/kg. Only the 20.0 mg/kg dose of sulpiride decreased immobiblity induced by the 0.1 mg/kg dose of apomorphine. Thioridazine had no significant effects, while clozapine (5.0 and 10.0 mg/kg) increased apomorphine-induced immobility. Clozapine, however, also produced significant amounts of immobility when administered alone.

Effects of Neuroleptics on Apomorphine-Induced Stereotypy

Administration of the higher doses of apomorphine (0.2–1.0 mg/kg) produced dose-dependent increases in stereotyped behavior. At the same time, the incidence of all other behaviors was decreased. In control animals, stereotypy reached a maximum of 117.8±1.4 counts/session out of a possible 120 counts/session at the highest (1.0 mg/kg) dose of apomorphine tested.

All three atypical neuroleptics had dose-dependent suppressive effects on apomorphine-induced stereotypy (Fig. 2). The lower dose of sulpiride (5.0 mg/kg) had no effect. The higher dose (20.0 mg/kg) delayed the onset of stereotypy, as did both doses of thioridazine. When administered with the 10.0 mg/kg dose of thioridazine, the 1.0 mg/kg dose of apomorphine failed to produce maximal stereotypy. Clozapine was the most potent of the three atypical neuroleptics tested in decreasing apomorphine-induced stereotypy.

When stereotyped behaviors were considered separately, two distinct dose-response functions were observed. In control animals sniffing down formed an inverted U-shaped function, peaking at the 0.3 mg/kg dose of apomorphine, whereas licking and/or gnawing did not appear in significant amounts until the 0.5 mg/kg dose. It was found the lower

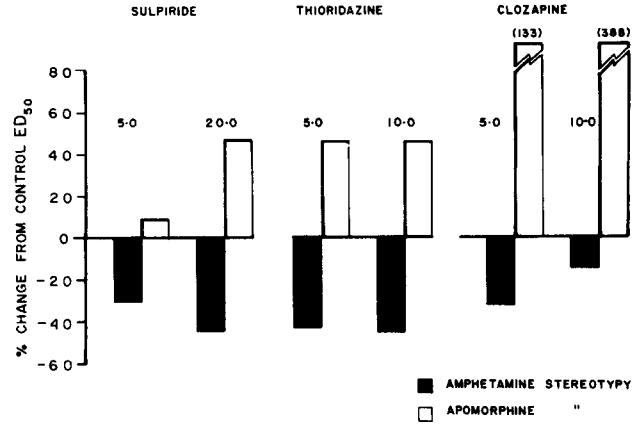

FIG. 3. ED_{50}s for amphetamine-induced (shaded bars) or apomorphine-induced (open bars) stereotypy following administration of the atypical neuroleptics, expressed as the % change from the respective control (non-neuroleptic) condition. ED_{50}s were obtained by interpolation (or, for 10.0 mg/kg clozapine + apomorphine, extrapolation) from the linearized log dose-response functions from Fig. 2 (for apomorphine) and from previous data ([29–30] for amphetamine).

doses of all three atypical neuroleptics mainly blocked sniffing down, while both sniffing down and licking/gnawing were decreased by the higher doses.

ED_{50}s for Apomorphine-Induced Stereotypy Following Neuroleptic Administration

For each neuroleptic group, the ED_{50} for apomorphine-induced stereotypy (defined as the dose of apomorphine required to produce 50% of the maximum stereotypy count, i.e., 60 counts/session) was determined by calculating the linear regression from the log dose-response functions shown in Fig. 2. These ED_{50}s are graphed in Fig. 3. For comparison, ED_{50}s for amphetamine-induced stereotypy are shown on the same graph, using data collected under identi-

cal conditions [29–30]. The ED_{50} for amphetamine-induced stereotypy was always decreased in the presence of the three atypical neuroleptics whereas the ED_{50} for apomorphine-induced stereotypy was always increased when the same neuroleptics were administered. Furthermore, 20.0 mg/kg dose of sulpiride and the 5.0 and 10.0 mg/kg doses of thioridazine were as potent in increasing amphetamine-induced stereotypy as they were in decreasing apomorphine-induced stereotypy (46–49% change from control ED_{50}s).

DISCUSSION

The data show that all three atypical neuroleptics suppressed apomorphine-induced stereotypy. Furthermore, the potencies of the highest dose of sulpiride and both doses of thioridazine in doing so were very comparable. However, at these same doses, sulpiride was the only one of the three drugs that blocked apomorphine-induced immobility. Thioridazine and clozapine had no such effects, although clozapine's effects were difficult to interpret since it produced significant amounts of immobility when administered alone (Fig. 1 at the 0 mg/kg dose of apomorphine).

From these data, it is possible to draw several conclusions. Insofar as apomorphine-induced stereotypy may be regarded as an effect mediated by postsynaptic dopaminergic receptor activation [9], the behavioral effects of these neuroleptics could be a reflection of their abilities to block these receptors. This conclusion would support a number of biochemical and behavioral data which indicate that thioridazine, clozapine and sulpiride, do, in these doses, block postsynaptic dopamine receptors [10, 13, 15, 17, 22, 24, 26]. Such observations do not, however, help to account for the ability of the same neuroleptics, in the same doses, to facilitate amphetamine-induced stereotypy [29–30]. Possibly, there are changes in the uptake, distribution or metabolism of amphetamine consequent to the administration of the atypical neuroleptics which cause increased brain levels of amphetamine, and therefore increased stereotypy. However this seems unlikely as we have previously reported that behaviors such as sniffing up, locomotion and rearing, which are increased by low doses of amphetamine, are not similarly facilitated [29–30]. It appears necessary, therefore, to find an alternative explanation for the effects of these same neuroleptics on amphetamine-induced stereotypy.

As apomorphine-induced immobility is believed to be an effect mediated by presynaptic dopaminergic receptor activation [8], the data suggest that only sulpiride, in doses which have significant postsynaptic effects, might also act presynaptically. This may explain sulpiride's divergent effects on apomorphine-induced stereotypy versus amphetamine-induced stereotypy. It is believed that amphetamine stimulates dopaminergic transmission mainly by facilitating impulse-dependent release whereas apomorphine acts primarily as a postsynaptic agonist [1,9]. Therefore sulpiride's action on amphetamine-induced stereotypy may reflect its affinity for presynaptic dopaminergic receptors, thus facilitating amphetamine's effects on presynaptic dopaminergic activity. Similarly, sulpiride's ability to act on these same presynaptic receptors may cause it to compete with low doses of apomorphine, thus decreasing apomorphine's effectiveness as a presynaptic agonist, and therefore inhibiting apomorphine-induced immobility. Because sulpiride also weakly competes with apomorphine at the postsynaptic receptor site, it would tend to decrease apomorphine's effectiveness as a postsynaptic receptor agonist. These suggestions are consistent with biochemical data which demonstrate that sulpiride has a stronger presynaptic than postsynaptic effect [16,34].

According to this analysis, thioridazine (and perhaps clozapine) has behavioral effects which reflect significant post-synaptic but not presynaptic dopaminergic blocking properties in the doses used in the present study. It is therefore difficult to account for its ability to enhance amphetamine-induced stereotypy in these same doses by a purely dopaminergic action. Possibly thioridazine's actions on non-dopaminergic neurons can account for some of its behavioral effects. For example, both thioridazine and clozapine have anticholinergic activity [21,33]. The possibility that such anticholinergic activity induces the increases in amphetamine-induced stereotypy would be consistent with observations made by others that scopolamine enhances amphetamine-induced stereotypy [3, 18, 27, 32] but not apomorphine-induced stereotypy [27,32].

It has been previously observed that the effects of neuroleptics on amphetamine-induced stereotypy are highly correlated with their effects on apomorphine-induced stereotypy. Worms *et al.* [37], for example, determined a correlation coefficient of +0.90 between the magnitude of the neuroleptic effects on the stereotypies produced by these two drugs, an observation which suggests that the effects are measures of the same process, which might best be described as antagonism of the behavioral syndrome resulting from dopaminergic stimulation. Although this would seem to be true for classical neuroleptics ([6,15], and personal observations), it is not the case, as Fig. 3 indicates, for the atypical neuroleptics clozapine, thioridazine and sulpiride. The observation of a dose-related suppression of apomorphine-induced stereotypy by the atypical neuroleptics at the same doses that *enhanced* amphetamine-induced stereotypy suggest that either the behavioral phenomenon of stereotypy or the action of neuroleptics on this phenomenon cannot be reduced to the activity of a unique dopaminergic process.

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