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Atypical Antipsychotic Drugs Block Selective Components of Amphetamine-Induced Stereotypy

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TSCHANZ, J. T. AND G. V. REBEC. *Atypical antipsychotic drugs block selective components of amphetamine-induced stereotypy*. PHARMACOL BIOCHEM BEHAV 31(3) 519–522, 1988.—Individual items of behavior produced by 1.0 or 5.0 mg/kg d-amphetamine were monitored in rats pretreated 15 minutes earlier with vehicle or with behaviorally relevant doses of haloperidol (0.1 or 0.25 mg/kg), clozapine (1.0 or 5.0 mg/kg), or thioridazine (1.0 or 5.0 mg/kg). Unlike haloperidol, the atypical antipsychotics failed to block all components of either the low- or high-dose response to amphetamine. These drugs, however, did block selective items of amphetamine-induced stereotyped behavior. Clozapine significantly attenuated the sniffing produced by 1.0 mg/kg d-amphetamine as well as the oral behavior (licking and/or biting) produced by 5.0 mg/kg d-amphetamine. Thioridazine, at a dose of 5.0 mg/kg, also reduced oral behavior and selectively blocked repetitive head bobbing. Taken together, these results suggest that although atypical antipsychotic drugs exert some common effects on the amphetamine behavioral response, these drugs do not influence all amphetamine-induced behaviors equally.

d-Amphetamine Atypical antipsychotics Haloperidol Stereotypy

THE drugs used to treat schizophrenia, the so-called antipsychotic drugs, can be described as either "classical" or "atypical" depending on their clinical profile. Although both types of drugs alleviate major thought disorders, the atypicals appear to have a broader therapeutic range in that they improve many of the negative and secondary symptoms of schizophrenia as well (10, 18, 19). The atypicals also have a lower potential than the classicals for eliciting extrapyramidal side effects (3, 11, 28, 33). This latter difference is reflected in animal tests of motor dysfunction in which the atypicals, unlike the classicals, either fail to produce catalepsy or elicit only a mild form of it (7,34).

Classical and atypical antipsychotic drugs also may differ in their ability to block the dose-dependent behaviors produced by amphetamine and other dopamine agonists in rats (13, 17, 27). There are reports, for example, that the locomotor activity produced by low doses of amphetamine is blocked by both classical and atypical antipsychotics, whereas only the classicals also reverse the focused, repetitive behavior (stereotypy) produced by higher doses. The apparent selectivity of the atypicals for drug-induced locomotion has been interpreted as evidence that these drugs, unlike the classicals, fail to block neostriatal dopamine receptors, which play a major role in stereotyped behavior (4,6). In fact, dopamine receptor blockade in the neostriatum often leads to catalepsy and other motor dysfunctions uniquely associated with the classical antipsychotic drugs (3,34). These and other reports (9) have led to behavioral screening tests for new antipsychotics in which a blockade of amphetamine-induced locomotion presumably measures therepeutic efficacy, whereas a blockade of focused stereotyped behavior indicates possible motor side effects (17).

This model assumes that the locomotion and stereotypy produced by amphetamine represent two entirely independent responses. In many respects, however, this clearly is not the case. Low doses of amphetamine, for example, not only increase locomotion, but also elicit repetitive sniffing, rearing, head bobbing, and other stereotyped behaviors, many of which also appear during the period of focused stereotypy produced by higher doses when bouts of licking and biting emerge and locomotor activity declines (23, 24, 30, 31). Thus, locomotion does not occur independently of all stereotyped behaviors, nor does stereotypy represent a single behavioral response (20,22). Automated measurements of locomotion fail to capture this behavioral complexity (8,22). Unless individual items of behavior are recorded, therefore, the action of the atypical antipsychotics in an amphetamine model may lead to erroneous or conflicting results. In fact, recent findings indicate that contrary to previous evidence the atypicals attenuate some amphetamine-induced stereotyped behaviors and actually enhance others (12, 25, 26).

In order to provide a detailed characterization of the atypical antipsychotics in the amphetamine model, we tested the

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ability of some of these drugs, administered at behaviorally and clinically relevant doses (5,14), to block individual behaviors produced by doses of amphetamine known to elicit different patterns of behavior. We also tested haloperidol, a well-known classical antipsychotic. Our results have important implications for the use of amphetamine in antipsychotic screening tests.

METHOD

Male, Sprague-Dawley rats, weighing between 300 and 400 g, were placed in separate, sound-attenuating behavioral chambers (32×32×40 cm) at least 48 hours prior to testing. Food and water were available on a continuous basis, and lighting was maintained according to a 12-hour, bright-light (8 a.m.–8 p.m.) and 12-hour, dim-light cycle. For several days, therefore, the chambers served as the animals' home cages. Accordingly, spontaneous behavioral activity during the bright-light period was virtually absent, even when the animals were handled briefly or injected with physiological saline and returned to the cage [see (22, 24, 31)]. Testing began at approximately 3 p.m. when each animal received a subcutaneous (SC) injection of one of three antipsychotic drugs administered at behaviorally and clinically relevant (5,14) doses (0.1 or 0.25 mg/kg haloperidol, 1.0 or 5.0 mg/kg clozapine, or 1.0 or 5.0 mg/kg thioridazine) or vehicle. Fifteen minutes later, every rat was challenged with a SC injection of either 1.0 or 5.0 mg/kg d-amphetamine sulfate (free base). Each animal was tested only once to avoid complications associated with multiple injections of these drugs. Five different animals were included in each pretreatment group for each dose of amphetamine.

A trained observer, who was unaware of the pretreatment conditions, rated individual components of the amphetamine response, including forward locomotion, rearing, sniffing, head bobbing, licking, and biting. Ratings were conducted for one-minute periods beginning 10 minutes after the injection of amphetamine and at successive 10-minute intervals thereafter until the behavioral response declined (60 and 120 minutes for the low and high dose of amphetamine, respectively). Each behavior was rated according to its duration (i.e., 1=discontinuous, 2=continuous) and intensity (0=not present, 1=mild, 2=moderate, 3=intense) for each observation period. The duration and intensity scores for each period were multiplied to yield a single value (0 through 6) as described elsewhere (23,24). Total scores for each behavior were obtained by summing individual scores across the entire drug response. Data were analyzed by a two-way analysis of variance and Tukey's HSD post hoc test.

RESULTS

In vehicle-pretreated controls, the predominant behaviors produced by 1.0 mg/kg d-amphetamine included locomotion, rearing, sniffing, and head bobbing. All these behaviors were apparent during the first observation period, and they continued throughout the drug response. These same behaviors never appeared concomitantly or were absent completely prior to amphetamine administration. Pretreatment with haloperidol (either 0.1 or 0.25 mg/kg) significantly reduced the total rating score for each behavioral response produced by amphetamine ($p<0.01$ in each case). In fact, amphetamine-induced locomotion, rearing, and head bobbing were blocked almost completely in these animals. Neither clozapine nor thioridazine mimicked these results. Pretreatment with clozapine (either 1.0 or 5.0 mg/kg) significantly

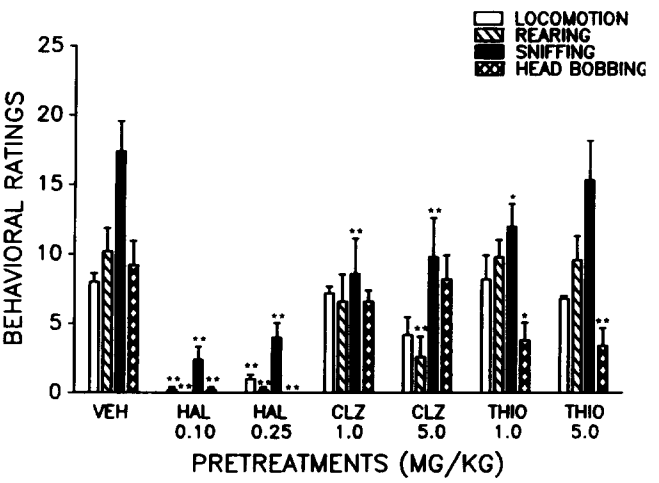

FIG. 1. Mean total scores for individual behaviors produced by 1.0 mg/kg d-amphetamine. All rats were pretreated 15 minutes earlier with vehicle (VEH) or with haloperidol (HAL), clozapine (CLZ), or thioridazine (THIO) at the doses indicated. Five different animals were included in each pretreatment group. The brackets indicate the standard error of the mean. (*$p<0.05$, **$p<0.01$, compared to VEH in each case.)

attenuated amphetamine-induced sniffing ($p<0.01$), but not locomotion or head bobbing. The high dose of clozapine also blocked rearing behavior ($p<0.01$). Thioridazine consistently blocked only head bobbing ($p<0.05$ at a dose of 1.0 mg/kg and $p<0.01$ at a dose of 5.0 mg/kg), although the low dose of this atypical antipsychotic also reduced amphetamine-induced sniffing ($p<0.05$). The effects of these three antipsychotic drugs on the behavioral response to a low dose of amphetamine are summarized in Fig. 1.

Administration of 5.0 mg/kg d-amphetamine produced in control animals a prolonged period of focused stereotypy during which locomotor activity declined or was absent. Rearing also was reduced, but appeared occasionally during bouts of focused stereotypy. Sniffing, head bobbing, and oral behavior (licking and/or biting) were the predominant responses. Figure 2 illustrates that although pretreatment with any of the antipsychotic drugs attenuated the response to amphetamine, each produced a unique pattern of effects. Haloperidol again produced the most complete blockade, virtually abolishing all components of the amphetamine response. Clozapine, on the other hand, selectively reduced oral behavior, both at low ($p<0.01$) and high ($p<0.01$) pretreatment doses. In contrast, thioridazine at either dose lowered the score for head bobbing ($p<0.01$ in each case), and at the high dose also blocked amphetamine-induced oral behavior ($p<0.01$). In addition, this dose of thioridazine enhanced the rearing response ($p<0.05$).

DISCUSSION

Atypical antipsychotic drugs, such as clozapine and thioridazine, are thought to be much more selective than haloperidol and other classical antipsychotics in their ability to block the behavioral response to amphetamine and related drugs (1, 4, 34). In fact, the atypicals, which have been reported to block the locomotor activity produced by dopamine agonists, generally are considered incapable of blocking drug-induced focused stereotyped behavior (13, 17, 27). Although our results confirm a more selective action of

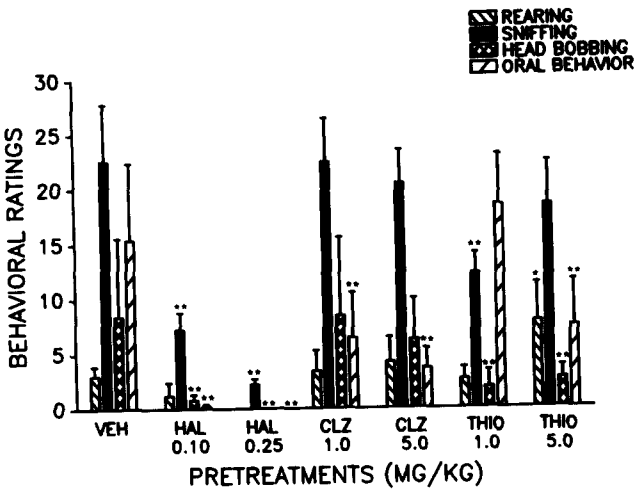

FIG. 2. Mean total scores for the predominant behaviors produced by 5.0 mg/kg d-amphetamine. All rats were pretreated as in Fig. 1. Five different animals were included in each pretreatment group. The brackets indicate the standard error of the mean. Symbols are as in Fig. 1.

the atypicals on the amphetamine behavioral response, these drugs appeared to exert less of an effect on locomotor activity than on many of the other stereotyped behaviors produced by amphetamine. Moreover, each drug blocked a unique combination of these behaviors.

An analysis of individual items of behavior revealed that compared to control rats injected with the low dose of amphetamine, clozapine-pretreated animals consistently showed a decrease in sniffing, whereas pretreatment with thioridazine attenuated sniffing and repetitive head bobbing. In rats injected with the high dose of amphetamine, which elicits these responses as well as licking and/or biting, clozapine significantly lowered only the score for oral behavior. Thioridazine, however, continued to suppress head bobbing and at the high dose also blocked amphetamine-induced licking and/or biting. Thus, although clozapine and thioridazine attenuate some of the same behaviors produced by amphetamine, these drugs do not influence all behaviors equally.

This finding also suggests that although the atypical antipsychotics easily can be distinguished from drugs like haloperidol, the atypicals do not comprise a homogeneous class of compounds. In fact, a growing body of biochemical evidence already indicates that these drugs exert different effects on monoaminergic neurons [see (21)]. To the extent that the behaviors produced by amphetamine are mediated by different neurochemical systems, as considerable evidence suggests (1, 16, 22), it seems likely that clozapine and thioridazine act in part via different mechanisms.

Neither of these drugs blocked amphetamine-induced locomotion. This finding contrasts with some evidence (13, 17, 27) but supports other data in which neither clozapine nor thioridazine significantly altered the locomotor response to dopamine agonists (2, 26, 29). These inconsistancies may result, in part, from the common practice of measuring motor activity by automated devices. Photocell beam counts, for example, can under- or overestimate forward locomotion depending on where the beams are placed in the cage and on how well they can discriminate locomotion from other bodily movements [see (8,22)]. Of course, other factors, including differences in the test dose of amphetamine or the antipsychotic drugs, also may be involved. Interestingly, although clozapine did not attenuate locomotion, the high dose of this drug did attenuate the rearing produced by 1.0 mg/kg d-amphetamine. Perhaps a higher dose of clozapine would attenuate the rearing produced by a higher dose of amphetamine. Surprisingly, however, thioridazine actually enhanced amphetamine-induced rearing, further emphasizing important differences between these atypical antipsychotics.

To the extent that certain amphetamine-induced behaviors cannot be expressed simultaneously (e.g., biting of the cage floor and rearing along the cage wall), a decrease in one behavior could lead to an increase in the other. Thus, thioridazine may enhance amphetamine-induced rearing not through any direct effect on the neuronal systems that control rearing but indirectly by reducing the oral behavior produced by amphetamine. Other reports [e.g., (25)] of a potentiation of certain amphetamine-induced behaviors by atypical antipsychotics also may involve a reduction in one of two competing responses. It is worth noting in this regard, however, that clozapine, which also attenuated the oral behavior produced by amphetamine, did not produce a corresponding increase in rearing, again pointing to a major difference between this antipsychotic drug and thioridazine in the amphetamine model.

The ability of classical antipsychotic drugs like haloperidol to abolish the behavioral response to amphetamine led to the widespread acceptance of this response as a model for certain forms of human psychosis (1, 16, 32). In order for this model to be used successfully in tests of antipsychotic efficacy, however, attention must focus on individual items of amphetamine-induced behavior (20, 22, 30). The unique effects of the atypical antipsychotics underscore this point. Although these drugs do not share the widespread blocking effects of haloperidol, they are capable of reducing certain items of focused stereotyped behavior, including licking and/or biting. Consistent with this finding, atypical antipsychotics have been shown to mimic haloperidol and to block the action of dopamine agonists in the neostriatum (21), which is known to play an important role in amphetamine-induced oral behavior (6,15). Atypical antipsychotics, therefore, cannot be dismissed as drugs that lack an effect on the focused stereotyped behaviors produced by amphetamine or on dopaminergic mechanisms in the neostriatum. These drugs should be treated, instead, as compounds that alter selective items of the amphetamine behavioral response. To the extent that a reduction in these behaviors serves as a model of antipsychotic efficacy, a further investigation of the neurochemical mechanisms underlying this process may shed new light on the mechanisms of action of antipsychotic drugs.

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