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Effects of Dopamine D_1 and D_2 Receptor Antagonists on Oral Activity in Rats

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LEVIN, E D , R E SEE AND D SOUTH *Effects of dopamine D_1 and D_2 receptor antagonists on oral activity in rats* PHARMACOL BIOCHEM BEHAV **34**(1) 43–48, 1989 —Two experiments were performed to investigate the actions of the selective D_1 blocker SCH 23390 and the selective D_2 blocker sulpiride, on oral movements in rats, these were quantified by a human observer scoring vacuous chewing movements (VCMs), jaw tremor and head movements, as well as a computer analysis system which measured the amplitude and slope of each movement In the first experiment it was found that both SCH 23390 and sulpiride decreased VCMs and head movements in a dose-dependent manner, with SCH 23390 more effectively decreasing head movements and sulpiride more effectively decreasing VCMs In a second experiment, the effectiveness of these two drugs in blocking the actions of selective D_1 (SKF 38393) and D_2 (LY 171555) agonists was studied The SKF 38393-induced increase in computer-scored movement was attenuated by both sulpiride and SCH 23390, whereas the LY 171555-induced decrease in VCMs was attenuated by sulpiride, while SCH 23390 exacerbated it These findings, together with our earlier results (12), suggest a simple relationship of D_1 receptors to oral movement, with increased activation resulting in increased oral movement and decreased activation resulting in decreased oral movement The relationship of D_2 receptors to oral movement shows a more complex pattern, with both stimulation and blockade decreasing oral movement One possibility may be the existence of more than one subpopulation of D_2 receptors mediating these effects

SCH 23390 Sulpiride SKF 38393 LY 171555 Oral movement Vacuous chewing movement D_1 D_2 Dopamine antagonists

LONG-TERM administration of antipsychotic drugs to schizophrenic patients can often result in tardive dyskinesia, a syndrome characterized by repetitive, involuntary abnormal movements in oral and facial areas Since all drugs which cause this syndrome are dopamine (DA) receptor antagonists, much of the research in this area has focused on the involvement of DA systems with oral movements Although the acute administration of DA antagonists such as chlorpromazine and fluphenazine decreases the rate of vacuous oral movements in rats (7), the specific dopaminergic action critical to their effect is not known since these drugs block both D_1 and D_2 DA receptors (9) The present study examined the effects of selective antagonists of these two subtypes of DA receptors in the control of vacuous chewing movements (VCMs) in rats

Rosengarten *et al* (19) found that the D_1 agonist, SKF 38393, increases VCMs This effect has been seen in other studies as well (16, 18, 24), especially in older animals We also replicated this effect and in addition found that the acute administration of a D_2 agonist had opposite effects on oral movement (12) The selective D_2 agonist, LY 171555, decreased the incidence of VCMs and jaw tremors, whereas the selective D_1 agonist, SKF 38393, increased both of these behaviors. The effects of the selective D_2 antagonist sulpiride on VCMs have also been examined in two laboratories, but the results are not in agreement Rosengarten *et al.* (19,20) found that sulpiride both increased VCMs and potentiated the effect of SKF 38393, implying that increasing D_1 receptor activity relative to D_2 activity increases VCMs On the other hand, Gunne *et al* (7) found that sulpiride decreased the incidence of VCMs However, these studies may not be directly comparable As addressed in the Discussion section, these discrepant findings may be the result of different testing paradigms We have found (14) that testing rats in a nonrestricted setting where they can easily engage in many other activities (as was done in the Rosengarten studies) can produce quite different results as compared to results obtained by testing rats in a restricted setting as was done in the Gunne study.

In the present study, we examined the effects of a broad range of doses of the selective D_1 blocker, SCH 23390 (2,8), and the selective D_2 blocker, sulpiride (9), on VCMs and head movements in rats The primary goal was to determine whether D_1 and D_2 antagonists had effects on oral movement opposite to D_1 and D_2 agonists In a second experiment we examined the effectiveness

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of these drugs in blocking the actions of specific D_1 and D_2 receptor agonists

METHOD

Subjects

The subjects were 41 female Sprague-Dawley rats (Simonsen, Gilroy, CA) with an initial weight of 200–250 g housed singly under a reversed light-dark cycle All behavioral testing took place during the dark portion of the cycle Before the onset of testing, all rats were habituated to being placed in plastic restraining tubes (5 7 cm diameter, 15 5 cm length) At one end of the tube was a 3 3 cm hole through which the rat's head protruded, and at the other end there was a plug to keep the rat from backing out Each animal was given at least five 6-min habituation sessions over a period of three weeks

Human Observer Scoring

During each 6-min testing session, the rat was placed in the testing tube which rested inside a sound-proof chamber illuminated only by a 6-W ultraviolet light bulb placed in front of and below the rat's mouth The rat was observed via a closed-circuit TV camera with a close-up lens The observer recorded each instance of VCMs, head movements and jaw tremor by pressing keys on a computer keyboard Statistical analysis was conducted on the total number and duration of VCMs and head movements during a session

Computerized Scoring

A computerized scoring system (6, 12, 13) was also used Small spots were painted on the upper and lower jaws of the rat, using an ultraviolet-sensitive dye A closed-circuit TV camera with a close-up lens and an ultraviolet filter was positioned 22 cm in front of the rat's mouth and the output from this camera was fed to a computer with a movement detection circuit The computer calculated the vertical distance (number of TV rasters) between the upper and the lower spots and stored these data, together with the human observer's reports, in computer memory 60 times per second Each raster of change represented 0 3 mm of movement The records of the measurements of the number of mouth openings were analyzed by detecting individual "movelets" (defined as individual openings or closings of the mouth as reflected by progressive increases or decreases in distance between the two spots) and then subdividing these into five different amplitude categories according to the number of rasters covered by the movelet (2, 3, 4–5, 6–9, ≥10) With this method we have found that the Amplitude 6–9 category best corresponds to VCMs When comparing the numbers of movelets to VCMs it is important to remember that each VCM is made up of two movelets (an opening and a closing) The smaller movelet categories between corresponded to observer scored bouts of tremor The slope of movelets in each of these categories was calculated by dividing the amplitude in rasters by the duration in 60ths of a second Thus, the slope provided a measurement of the speed at which the movements were made Such information may be important given that some of the drugs used in the present study are known to have sedative actions

Experiment 1

The effects of 3 doses of the D_1 antagonist, SCH 23390, and the D_2 antagonist, sulpiride, on spontaneous oral activity were examined The rats (tested once per week) were administered six different drug doses, given in a counterbalanced order to all rats, with control saline days given on the week between the third and fourth drug injections The three doses of SCH 23390 given were 0 01 mg/kg ("low"), 0 05 mg/kg ("middle") and 0 25 mg/kg ("high"), and the doses of sulpiride given were 4 mg/kg ("low"), 20 mg/kg ("middle") and 100 mg/kg ("high") Both drugs were mixed in saline with lactic acid and adjusted to a final pH of between 5 0 and 7 0 The high dose of 100 mg/kg sulpiride was given as a partial solution and suspension All of the other doses of sulpride and SCH 23390 were completely in solution All drug doses and saline were injected IP in a volume of 1 ml/kg 20 min before testing

Experiment 2

This experiment tested the effectiveness of these D_1 and D_2 antagonists in blocking the effects of D_1 and D_2 agonists One set of 12 rats was given the D_1 agonist, SKF 38393 (3 0 mg/kg), either alone or in combination with either SCH 23390 (0 25 mg/kg) or sulpiride (100 mg/kg) A second set of 12 rats were given the D_2 agonist, LY 171555 (0 1 mg/kg), either alone or in combination with either the D_1 or D_2 antagonist (at the same doses used with SKF 38393) The doses of the agonists were chosen because we have previously found them to be effective in increasing or decreasing oral movement in our previous study (12) The doses of the antagonists were the most effective doses from Experiment 1 of the current study The drugs were mixed in 0 9% saline and were administered (1 ml/kg) 20 minutes before testing in a counterbalanced order with three or four days between injections Tests run after saline injections at the beginning and end of the experiment served as control data

Statistics

All data were analyzed using repeated measures analyses of variance with drug dose as the repeated measure Individual analyses were conducted for each of the three observer-scored behaviors and each of the amplitude categories of computer-scored movelets When significant effects were detected pair-wise comparisons between saline and the drug doses were made using *t*-tests

RESULTS

Experiment 1

Observer-scored movement As shown in Fig 1, both SCH 23390 and sulpiride significantly decreased the frequency of both VCMs and head movements, $F(6,96) = 4\ 19$, $p < 0\ 005$ With VCMs, each of the doses of SCH 23390 and sulpiride caused significant decreases when compared to saline ($p < 0\ 05$) At the highest dose, sulpiride was significantly more effective than SCH 23390 With head movements, the main effect of drug treatment was also significant, $F(6,96) = 11\ 83$, $p < 0\ 0001$ The medium and high doses of SCH 23390 caused significant decreases compared with saline ($p < 0\ 01$), while only the highest dose of sulpiride caused a significant decrease ($p < 0\ 01$) The relative effectiveness of the two antagonists in decreasing head movements was the reverse of what was seen with VCMs At the medium and high doses SCH 23390 was more effective than sulpiride in decreasing head movements ($p < 0\ 01$) Drug treatment was not found to significantly affect tremor duration

Computer-scored movement. The high doses of both drugs were effective in decreasing the frequency of movelets (Fig 2) Although no effects were detected in the smallest two categories

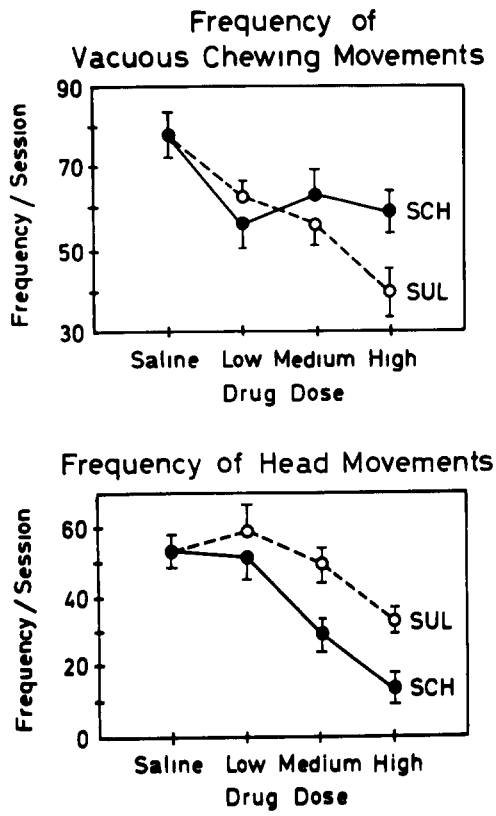

FIG 1 Experiment 1 Frequency of observer-scored movement during the 6-min session (mean ± SEM) SCH = SCH 23390, SUL = sulpiride, Low dose = 0 01 mg/kg SCH and 4 mg/kg SUL, Medium dose = 0 05 mg/kg SCH and 20 mg/kg SUL, High dose = 0 25 mg/kg SCH and 100 mg/kg SUL

(Amplitudes of 2 and 3), significant drug effects ($p<0$ 05) were seen in the middle and larger categories (Amplitudes of 4–5, 6–9 and ≥10). The effect was particularly well seen in the Amplitude 6–9 category which best corresponded to the VCMs scored by the

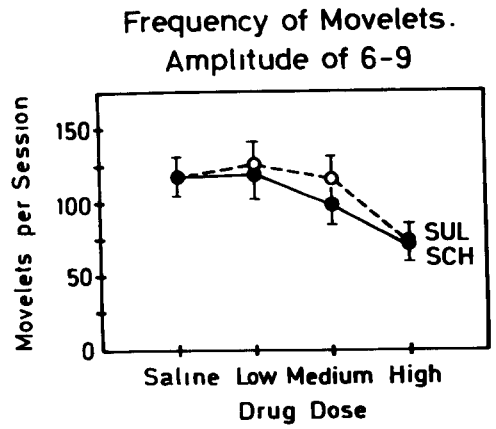

FIG 2 Experiment 1 Computer-scored "movelets" of Amplitude 6–9 during the 6-min session (mean ± SEM) SCH = SCH 23390, SUL = sulpiride, Low dose = 0 01 mg/kg SCH and 4 mg/kg SUL, Medium dose = 0 05 mg/kg SCH and 20 mg/kg SUL, High dose = 0 25 mg/kg SCH and 100 mg/kg SUL

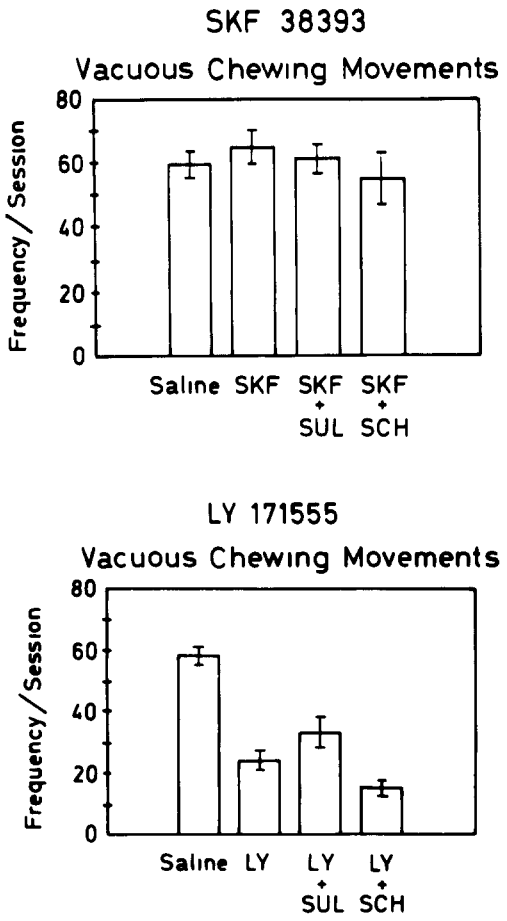

FIG 3 Experiment 2 Frequency of observer-scored vacuous chewing movement during the 6-min session (mean ± SEM) SKF = SKF 38393 (3 mg/kg), LY = LY 171555 (0 1 mg/kg), SCH = SCH 23390 (0 25 mg/kg), SUL = sulpiride (100 mg/kg)

human observer, $F(6,96) = 3.03$, $p<0$ 01 The high dose of SCH 23390 caused a significant decrease ($p<0$ 01) in all three of these categories, while the high dose of sulpiride caused a significant decrease ($p<0$ 05) in only the Amplitude 6–9 category

Both antagonists had effects in decreasing the slopes of movelets, indicating a sedative effect on oral movement Significant effects of drug treatment were seen in Amplitude categories 2 and 6–9 ($p<0.05$) With movelets of Amplitude 2, significantly lower slopes ($p<0$ 05) were seen with the medium and high doses of both drugs, while with movelets of Amplitudes 6–9, only the high dose of sulpiride significantly lowered slopes ($p<0$ 05)

Experiment 2

SKF 38393, observer-scored movement. SKF 38393 induced only a nonsignificant increase in VCMs in this experiment, in contrast to our previous finding of a more robust increase caused by this drug SKF 38393 was effective in attenuating the decreases in VCMs caused by either SCH 23390 or sulpiride (Fig 3) With head movements there was a significant drug effect, $F(3,33) = 3$ 24, $p<0.05$, characterized by a decline caused by the combined treatment of SKF 38393 and SCH 23390 ($p<0$ 001) No significant effects were seen on the duration of tremor

SKF 38393, computer-scored movement No effects were seen

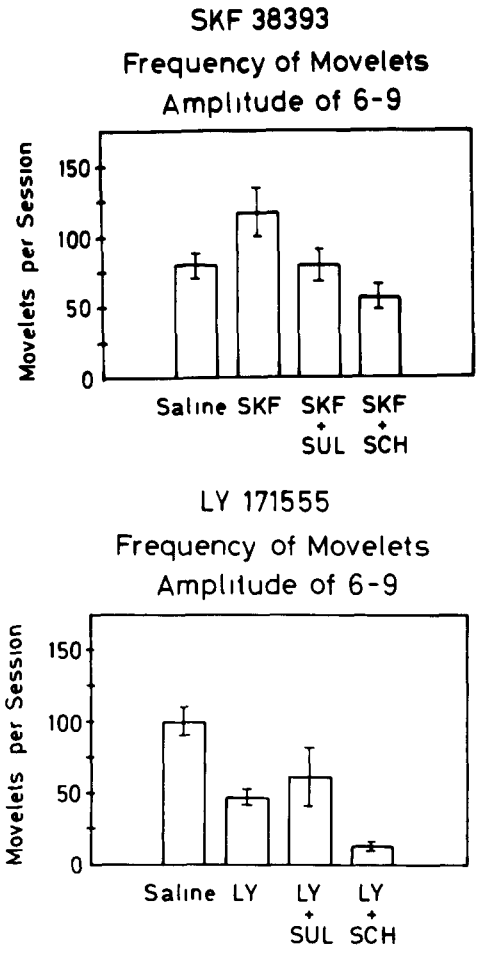

FIG 4 Experiment 2 Frequency of computer-scored "movelets" of Amplitude 6–9 during the 6-min session (mean ± SEM) SKF = SKF 38393 (3 mg/kg), LY = LY 171555 (0 1 mg/kg), SCH = SCH 23390 (0 25 mg/kg), SUL = sulpiride (100 mg/kg)

with the smallest category of movelets, but there were significant effects with all of the larger movelet categories ($p<0$ 01) In all cases, the effect was characterized by an increased number of movelets due to SKF 38393, which was reduced to control levels by sulpiride and reduced below control levels by SCH 23390 (Fig 4) SCH 23390 significantly reduced the SKF 38393-induced effect in all amplitude categories ($p<0$ 01), while the sulpiride-induced reduction was limited to marginally significant effects ($p<0$ 10) in the Amplitude 6–9 and ≥10 categories

Computer analysis also showed significant effects of drug treatment on the slope of movelets in the amplitude categories of 3 and 4–5 ($p<0$ 05) With both of these categories, SKF 38393 significantly increased slopes ($p<0$ 05), while both antagonists reversed this effect ($p<0$ 05)

LY 171555, observer-scored movement As shown in Fig 3, the D_2 agonist, LY 171555, was quite effective in decreasing the frequency of VCMs, $F(3,33) = 42$ 61, $p<0$ 0001 All conditions with LY 171555 treatment were significantly lower than saline ($p<0$ 0001) The D_2 antagonist, sulpiride, significantly attenuated the LY 171555-induced decrease ($p<0$ 05), while the D_1 antagonist, SCH 23390, significantly exacerbated it ($p<0$ 05) There was also a significant effect on head movement, $F(3,33) = 36$ 39, $p<0$ 0001. LY 171555 significantly decreased head movements relative to saline ($p<0$ 0001) The addition of either sulpiride or SCH 23390 to LY 171555 further decreased the frequency of head movements ($p<0$ 0001) There were no significant drug effects with observer-scored tremor duration because of the wide variability usually seen with this measure Typically some rats show quite a bit of tremor while others show none at all When LY 171555 was given either alone or in combination with an antagonist, none of the rats showed any tremor

LY 171555, computer-scored movement LY 171555 significantly decreased ($p<0$ 05) the number of movelets in all of the middle-sized categories (Amplitude 3, Amplitude 4–5 and Amplitude 6–9) (see Fig 4 for the effect on Amplitude 6–9) SCH 23390 served to further decrease the number of movelets ($p<0$ 05) except in the Amplitude 4–5 category Sulpiride significantly decreased the number of movelets in the Amplitude ≥10 category ($p<0$ 005) In the Amplitude 4–5 and 6–9 categories there were indications of a reversal of the effect of LY 171555, but these were not significant

Analysis of the data for slopes showed that there were only significant effects in the two largest amplitude categories ($p<0$ 05) In both of these categories the effect was due to SCH 23390 causing significantly lower slopes ($p<0$ 01)

DISCUSSION

In the present study, both the D_1 and D_2 antagonists decreased the rate of VCMs and head movements as measured by a human observer and "movelets" as measured by the computerized scoring technique Our previous study showed that the effects of D_1 and D_2 agonists on VCMs were opposite from each other (12) The D_1 agonist, SKF 38393, increased, while the D_2 agonist, LY 171555, decreased VCMs Our initial hypothesis was that each of the antagonists would act in an opposite way as the corresponding agonist The effect of the D_1 antagonist, SCH 23390, confirmed this hypothesis, but the D_2 antagonist, sulpiride, did not With D_1 receptors, decreased receptor activation by an antagonist lowered vacuous chewing activity, while increased receptor activation by an agonist raised it On the other hand, with D_2 receptors, either increased or decreased receptor activation lowered vacuous chewing activity Similar effects of sulpiride and LY 171555 were also seen in terms of decreasing the slope of movelets It is possible that the decreases in oral activity seen with the D_2 antagonist, sulpiride, were due to sedative effects, but given that significant decreases were seen at very low doses of 4 and 20 mg/kg which if anything produce increased activity (23), this was probably not the case

Previous studies have found discrepant results concerning the effect of sulpiride on vacuous chewing activity Rosengarten *et al* (20) found that sulpiride increased the incidence of VCMs of rats tested in an open cage On the other hand, Gunne *et al* (7) found, like the present study, that sulpiride decreased VCMs in rats tested in a restraining tube The present study is probably only directly comparable to the Gunne study in that both used a tube to restrain the rats during testing The opposite results in the Rosengarten study may be due to their paradigms of testing rats in an open-field setting We have previously found opposite effects of haloperidol on oral movement when rats were tested in an open cage vs a restricted tube (14) This difference may be due to effects of either or both of the testing paradigms On one hand, restraint in a tube may stress the rats, thus affecting oral movement (although all of the rats in our studies were thoroughly habituated to the tube before testing) On the other hand, in the open cage, opportunities for the rat to engage in other types of behaviors can affect the expression of oral activity (14) The differences in testing paradigms may also be the reason why we found that sulpiride attenuated the SKF 38393-induced increase in oral activity, while Rosengarten *et al* (20) found that sulpiride enhanced the effect of SKF 38393

Similar effects of D_1 and D_2 antagonists as seen in the present experiment have previously been seen in a variety of studies. Amalric *et al* (1) found that both D_1 and D_2 antagonists decreased the apomorphine-induced hyperactivity seen in animals with lesions of the dopamine projections to the nucleus accumbens Both SCH 23390 and sulpiride have been found to increase the firing rate of dopamine neurons in the substantia nigra (15) Several researchers have found that both SCH 23390 and D_2 antagonists cause catalepsy and block the stereotypies produced by apomorphine, amphetamine and the D_2 agonist, LY 171555 (3, 10, 17)

In Experiment 2, some of the effects of both agonists were blocked by the appropriate antagonist The D_1 agonist, SKF 38393, caused an increase in the number and slope of computer-scored movelets This was reversed by the D_1 antagonist, SCH 23390 Sulpiride, the D_2 antagonist, also had some effect in reversing the SKF 38393-induced increase in movelets, although it was not as effective as SCH 23390 The D_2 agonist, LY 171555, caused a decrease in the number of VCMs This decrease was significantly attenuated by sulpiride, even though when given by itself (as was done in Experiment 1) sulpiride decreased VCMs In contrast, the D_1 blocker, SCH 23390, significantly exacerbated the LY 171555-induced decrease in VCMs This may have been related to sedative effects caused by SCH 23390 With computer-scored movelets there were indications, albeit nonsignificant, that sulpiride attenuated LY 171555-induced decreases in the Amplitude categories of 4–5 and 6–9. As with VCMs, SCH 23390 significantly exacerbated the LY 171555-induced decreases. This attenuating effect of sulpiride seemed to be specific to oral movement, because with head movements both of the antagonists had additive effects with LY 171555

In the two experiments the baseline values of observer-scored VCMs were different. We have previously seen that different batches of rats sometimes differ in their baseline rates of oral movement. The two different scorers used for Experiments 1 and 2 were trained to score oral behavior in the same way by the same trainers, but it is possible that subtle differences in scoring criteria may have existed However, given that the computer-scored movement was also different in the same direction and to a similar degree, this does not seem to be the case It is more likely that the different batches of rats used in the two experiments had different baseline rates of oral movement Batch differences like this have also been seen in other types of spontaneous behavior such as locomotor activity This highlights why it is important to run baseline control measurements for each experiment and to only make direct statistical comparisons within experiments

In this study the effects of the D_1 drugs were relatively straightforward The agonist increased oral movement while the antagonist decreased it and the antagonist reversed the agonist-induced increase The data with the D_2 drugs were more complex Both the agonist and antagonist used in this study decreased VCMs The finding that sulpiride attenuated rather than exacerbated the effect of LY 171555 reinforces the idea that these two drugs act in opposite fashions on the same receptor population But the question remains as to why they have similar behavioral effects One possibility is that the state of activation of the D_2 receptor is not monotonically related to the frequency of VCMs Rather, the relationship may more resemble an inverted-U with the highest rates occurring in the middle of the range of activation Another possibility is that sulpiride and LY 171555 not only act on a common receptor population, but individually act on other receptors as well There is some evidence that substituted benzamide neuroleptics like sulpiride preferentially bind to a subpopulation of D_2 receptors (22) located presynaptically on cortical fibers innervating the striatum (5) These are distinguishable from D_2 receptors located on intrinsic striatal cells not only by their preferential binding of benzamides, but also because of their lower sensitivity to GTP (5) and requirement for sodium for receptor binding (11). Rubenstein *et al* (21), in examining the bimodal effects of sulpiride on locomotor activity, have suggested the possibility of two different types of D_2 receptors, one inhibitory and the other excitatory, localized on the same neuron Alternatively, they postulate localization of the same D_2 receptor on different postsynaptic neurons that mediate opposing functions The curious finding that LY 171555 and sulpiride, which have opposite effects on D_2 receptors, had similar behavioral effects may be due to their predominant activities being mediated through these different types of D_2 receptors Further receptor subclassification may help explain some of the complexities of D_1-D_2 relationships where with some behaviors and physiological functions these receptors act in concert and with others they act in opposition (4,25)

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