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The D2 Agonist Quinpirole Potentiates the Discriminative Stimulus Effects of the D1 Agonist SKF 38393

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WILLIAMS, J. E. G. AND W. L. WOOLVERTON. *The D2 agonist quinpirole potentiates the discriminative stimulus effects of the D1 agonist SKF 38393.* PHARMACOL BIOCHEM BEHAV **37**(2) 289–293, 1990.—Although there are two dopamine (DA) receptors (D1 and D2) in the brain, the functional role, particularly of D1 receptors, has remained unclear. Recent research has suggested that D1 and D2 receptors interact synergistically in the generation of certain D2 agonist-induced motor responses. On the other hand, an antagonistic interaction between the receptors has been reported for D1 agonist-induced perioral movements. The purpose of the present experiment was to characterize further the interaction between D1 and D2 receptors using a drug discrimination paradigm, a behavioral paradigm that is sensitive and selective for D1 and D2 agonist and antagonist activity. Rats (N = 8) were trained to discriminate the D1 agonist SKF 38393 (SKF; 10 mg/kg, IP, 30 minutes presession) from saline (1.0 ml/kg, IP, 30 minutes presession) in a 2-lever, food-reinforced drug discrimination paradigm. SKF (0.2–12.8 mg/kg) produced a dose-related increase in SKF-appropriate responding (maximum 87.5% at 12.8 mg/kg). The D2 agonist quinpirole (QUIN; 0.012–0.1 mg/kg, IP, 10 minutes presession) given alone did not substitute for SKF (maximum 37% SKF-appropriate responding at 0.05 mg/kg). QUIN (0.012 or 0.025 mg/kg) in combination with SKF significantly ($p<0.05$) shifted the SKF dose-response function to the left, suggesting that stimulation of D2 receptors can potentiate a behavioral effect mediated by D1 receptors. Furthermore, when taken together with previous findings that SKF failed to potentiate the discriminative stimulus effects of QUIN, the present results suggest that the nature of D1/D2 receptor interactions depends not only upon the behavior under investigation but also upon the receptor action that the behavior reflects.

Drug discrimination Dopamine D1 receptors D2 receptors Rats SKF 38393 Quinpirole Behavior

ALTHOUGH two distinct dopamine (DA) receptor subtypes (D1 and D2) have been characterized based upon their in vitro linkage to DA sensitive adenylate cyclase (10,20), the in vivo functional role, particularly of D1 receptors, remains unclear. A substantial amount of behavioral research is consistent with the hypothesis that D1 and D2 receptors interact synergistically in the generation of certain motor responses. D1 agonists have been shown to facilitate and D1 antagonists to block behavioral effects of D2 agonists such as the generation of stereotyped behavior and locomotor activity [see (3,21) for reviews]. Synergism between D1 and D2 receptors has also been evident in electrophysiological studies (24,25). On the other hand, we have reported that the D1 agonist SKF 38393 (SKF) failed to potentiate the discriminative stimulus (DS) effects of the D2 agonist quinpirole [QUIN; (28)]. These results raise the possibility that interactions between D1 and D2 receptors are not simply synergistic in the expression of D2-mediated behaviors.

Although relatively little is known, the available data suggest that there is also more than one type of functional interaction between DA receptors in the expression of D1-mediated behaviors. The finding that D1 agonists induce nonstereotyped perioral movements and that this effect can be reversed by the simultaneous administration of a D2 agonist (7,16) suggests an antagonistic interaction between DA receptors. More recently, Murray and Waddington (11) reported that a D2 antagonist can decrease grooming induced by D1 stimulation, suggesting a synergistic interaction for this behavioral response, while others have found that stimulation of D2 receptors is not necessary for the expression of D1-mediated behaviors (8,26). It should also be noted that D1-induced perioral movements can be enhanced by the coadministration of a D2 antagonist, an effect that suggests an antagonistic interaction between D1 and D2 receptors for this behavior (11,16).

Clearly, the interaction between D1 and D2 receptors is complex and may depend upon the nature of the behavioral effect that is being examined. The purpose of the present experiment was to characterize further the functional interaction between D1 and D2 receptors by examining the effect of administration of a D2 agonist on a D1-mediated behavioral effect. Accordingly, rats were trained in a two-lever, food-reinforced drug discrimination (DD) paradigm to discriminate the D1 agonist SKF from saline.

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Previous research has demonstrated this behavioral paradigm to be sensitive and selective for the action of D1 and D2 agonists and antagonists (5, 8, 9, 23, 30). After establishing the discrimination, a range of doses of the D2 agonist QUIN was tested alone and selected doses were tested in combination with SKF. The results suggest that stimulation of D2 receptors can potentiate this D1-mediated behavior.

METHOD

Animals and Apparatus

Eight male Sprague-Dawley rats (Holtzman Co., Madison, WI) were maintained at 280–300 g (80±5% of their initial free-feeding body weights) by restricting food intake. They were individually housed in stainless steel cages in a room maintained at 24°C and on a 12-hour light-dark cycle (7 a.m.–7 p.m. light). In addition to the 45 mg food pellets (P. J. Noyes Co., Lancaster, NH) delivered during the experimental sessions, diet was supplemented with Teklad 4% Mouse and Rat Diet (Winfield, IA) to maintain stable body weights. Water was continuously available except during experimental sessions.

Four identical operant chambers for rats (R. Gerbrands Co., Arlington, MA) were used. In each chamber, two response levers were mounted on one wall and a food receptacle was located between them. Each chamber was illuminated at the onset of experimental sessions by a single six-watt light located on the wall opposite the levers. Extraneous noise was diminished by enclosing each chamber in an insulated chest and by operating a ventilation fan mounted on the outside of each chest. An AIM-65 microcomputer (Dynatem Corp., Irvine, CA), connected to a custom-designed input/output interface (ERH Electronics, Delton, MI), located in an adjacent room, controlled external stimulus events and recorded lever presses.

Procedure

The rats were assigned randomly to one of the four experimental chambers. In two chambers, the right lever was designated the saline-appropriate lever and the left lever the drug-appropriate lever. In the other two chambers, the reverse assignments were made. Half of the rats were shaped initially by successive approximation to press the drug-appropriate lever after injections of 6.4 mg/kg of SKF 38393 and the remaining rats were shaped initially to press the saline-appropriate lever after saline (1.0 ml/kg) injections. Injections were given IP, 30 minutes before the session and the rats were returned to their home cage. Twenty minutes after the injection they were placed in the experimental chambers. Ten minutes later the house light was illuminated and food was available for every response on the injection-appropriate lever.

Ten-minute training sessions were conducted once a day, 5 days a week, following a double alternation sequence in which two sessions of drug pretreatments alternated with two sessions of saline pretreatments. Although this sequence was used in each rat, it was offset by a day on a random basis so that the type of session in effect for one rat on a given day was not predictive of the type of session for subsequent rats. In addition, the daily order in which sessions were conducted was nonsystematic. These manipulations controlled for the possibility of odor cues exerting discriminative control of behavior (6). During this training period, the response requirement on either lever was increased gradually so that under terminal conditions, every tenth response (fixed-ratio 10: FR 10) on the lever appropriate to the injection resulted in the delivery of a food pellet. In addition, the contingency that incorrect responses were counted and reset the response requirement on the injection-appropriate lever was added. The double alternation training sequence continued until a rat met the following two-part criterion for stimulus control over responding. First, in seven out of eight consecutive sessions, at least 80% of the responses before the delivery of the first food pellet had to occur on the injection-appropriate lever. Second, 90% of the responses that occurred throughout the 10-minute session had to be on the injection-appropriate lever.

Once a rat met the criteria for stimulus control, test sessions were conducted using a pretreatment sequence of drug, saline, test, drug, test, saline, drug, test, saline, test (4) as long as performance in the training sessions between tests remained at or above the criterion for stimulus control. If a rat's performance fell below criterion levels during the intervening training sessions, it was returned to the double alternation training sequence until discrimination again was at or above criterion levels. Test sessions were identical to training sessions except that food was available for responding on either lever. The SKF dose-response function was determined initially with SKF injections given 30 minutes presession. After the injection of SKF, the rat was returned to the home cage for 20 minutes and placed in the experimental chamber 10 minutes presession. Following this dose-response determination, the training dose of SKF was increased to 10 mg/kg to enhance the stability of performance in training sessions. Next, the QUIN dose-response function was determined with QUIN given 10 minutes presession and the rat placed immediately in the experimental chamber. To assess the effects of drug combinations, two injections were given before test sessions. The initial injection (SKF, 0.012–12.8, mg/kg or saline) was given 30 minutes presession and the rat was returned to the home cage. A second injection (QUIN, 0.012 or 0.025 mg/kg, or saline) was given 10 minutes presession and the rat was placed in the experimental chamber. Finally, the effects of SKF alone were redetermined. The effects of each dose or dose combination were determined twice in an unsystematic order, once preceded by a drug training session and once by a saline training session.

Data Analysis

The percentage of the total responses that occurred on the drug-appropriate lever and the rate of responding on both levers during test sessions were calculated for each rat and the results of both tests with a given combination were averaged. For each test condition, the mean and SEM were calculated for the group for both the percentage drug-appropriate responding and response rate. If a rat failed to receive a food pellet in any test session, the data for that session were not included in the calculation of drug-appropriate responding but were included in the calculation of response rate. If the mean percent drug-lever responding for the group was greater than or equal to 80, the test drug or combination was considered to have substituted for the training drug. For the interaction of SKF and QUIN, a two-way ANOVA for repeated measures was used to analyze each dependent variable. The QUIN+SKF dose-response function was compared to both the initial and the redetermined SKF dose-response function. Effects were considered significant for p values less than or equal to 0.05.

Drugs

SKF 38393 (7,8-dihydroxy-l-phenyl-2,3,4,5-tetrahydro-1H-2-benzazepine hydrochloride, Research Biochemicals, Inc., Natick, MA), and quinpirole (LY 171555; Eli Lilly and Co., Indianapolis, IN) were dissolved in 0.9% saline. Injections were generally administered in a volume of 1.0 ml/kg and the concentration was varied appropriately. However, because of solubility limitations,

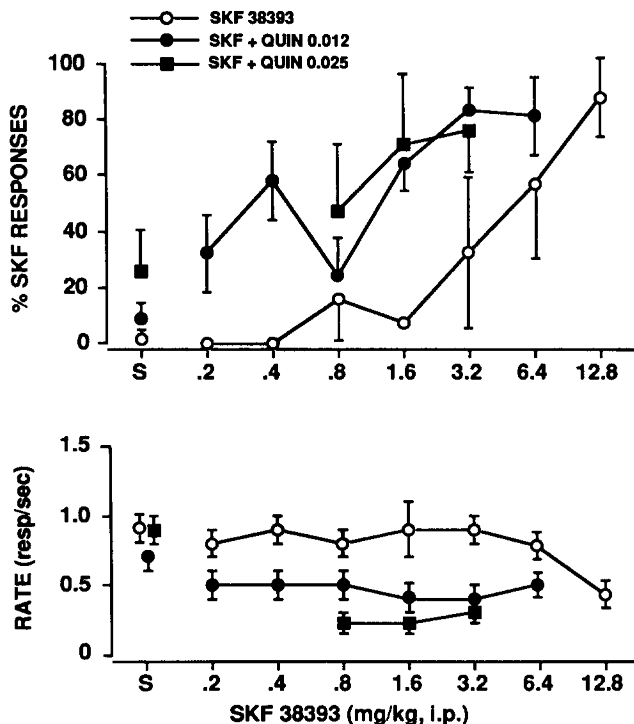

FIG. 1. Effects of SKF 38393 and quinpirole, alone and in combination, in rats trained to discriminate SKF 38393 (10.0 mg/kg, IP) from saline. Upper graph: percentage of responses during test sessions that occurred on the SKF-appropriate lever as a function of dose. Lower graph: response rate during test sessions as a function of dose. Each point represents the mean, and vertical lines are the S.E.M. (N=7 for each point). Open circles: SKF+saline pretreatment; Solid circles: SKF+0.012 mg/kg quinpirole; Solid squares: SKF+0.025 mg/kg quinpirole.

SKF was prepared in a maximum concentration of 5.0 mg/ml. For doses higher than 5.0 mg/kg, the injection volume was increased appropriately using the 5.0 mg/ml solution. All injections were given IP.

RESULTS

The median number of sessions required for the rats to meet the criteria for stimulus control was 66 (range: 40–144). SKF (0.2–12.8 mg/kg) engendered a dose-related increase in the percentage of responses that occurred on the drug lever in test sessions (Fig. 1, top). The highest dose tested, 12.8 mg/kg, occasioned 87.5% (±10% SEM) SKF-appropriate responding. At this dose five of seven rats emitted 100% SKF-appropriate responses, and the remaining two rats emitted 50% SKF-appropriate responses. Doses of SKF between 0.2 and 6.4 mg/kg had no effect on response rate while 12.8 mg/kg decreased rate (Fig. 1, bottom). The redetermined SKF dose-response function (data not shown) was not significantly different from the original for either %SKF responses, $F(1,6)=1.5$, n.s., or response rate, $F(1,6)=0.1$, n.s.

QUIN failed to substitute for SKF (points above S in Fig. 1). The highest dose of QUIN (0.05 mg/kg) tested resulted in a mean percent drug lever responding of 37 (±11.8%; data not shown). In five of the seven rats tested at this dose, less than 35% drug lever responding was observed. The remaining two rats emitted 63%, and 95% of their responses on the drug-appropriate lever. QUIN decreased response rate to 0.3 (±0.2 S.E.M.) resp/sec at 0.05 mg/kg.

The combination of 0.012 mg/kg QUIN and SKF shifted the dose-response function for %SKF responses to the left. The effect was statistically significant when compared to the initial dose-response function [Fig. 1, top panel; $F(1,6)=14.6$, $p<0.009$] and when compared to the redetermination of the dose-response function, $F(1,6)=99.0$, $p<0.0001$. In addition, there was a significant interaction between the main effects of 0.012 mg/kg QUIN and SKF for the initial SKF dose-response determination, $F(5,30)=6.1$, $p<0.001$, and the redetermination, $F(5,30)=12.9$, $p<0.0001$, indicating that the dose-response function for the combination of SKF+QUIN was not parallel to the SKF dose-response function. The 0.025 mg/kg dose of QUIN in combination with SKF also shifted with SKF dose-response function significantly to the left relative to the initial, $F(1,6)=17.1$, $p<0.006$, and redetermined, $F(1,6)=61.2$, $p<0.0001$, SKF dose-response function. This shift, however, did not exceed the shift seen with 0.012 mg/kg QUIN. For the combination of 0.012 mg/kg QUIN and SKF, response rate decreases appeared to be primarily determined by the effect of QUIN alone (Fig. 1, bottom panel). However, the combination of 0.025 mg/kg QUIN and SKF had greater effects on response rate than either drug alone.

DISCUSSION

The present experiment replicates previous findings that the D1 agonist SKF can function as a DS in rats and that the magnitude of the effect is directly related to drug dose (5, 8, 23). Similarly, the failure of QUIN to substitute for SKF in this behavioral preparation replicates previous findings that the DS effects of D1 and D2 agonists are qualitatively distinct and emphasizes the agonist selectivity of the preparation. As previous studies (8,23) have demonstrated the antagonist selectivity of this preparation, as well as a central site of action, it is likely that the effect of SKF in the present study was mediated by drug action at D1 receptors in the brain. Although QUIN lacked SKF-like DS effects, it significantly shifted the dose-response function for SKF to the left when given in combination with SKF. That is, a D2 agonist potentiated the behavioral effects of a D1 agonist. This interaction is similar to, although the converse of, previous findings that a D1 agonist can potentiate D2-mediated behavior (1, 2, 26). Thus, the present findings are consistent with and extend the notion that D1 and D2 receptors can interact in the expression of behavior mediated by DA.

The precise nature of the D1/D2 interaction is apparently more complex than was first believed. With regard to D2-mediated behaviors, a substantial amount of data is consistent with the hypothesis that D1 receptors play a permissive role in the expression of D2-mediated motor responses. Either administration of a D1 antagonist [e.g., (14,22)] or depletion of endogenous DA (2) can block motor effects of D2 agonists. Recently, the possibility has been raised that D1 and D2 receptors oppose each other in the expression of some D2-mediated behaviors (12). Some differences are apparent across preparations involving D1-mediated behaviors as well. It has been reported that a D2 agonist can reverse oral dyskinesia induced by a D1 agonist (15), suggesting that the two receptors oppose each other. More recently, Murray and Waddington (11) demonstrated that a D2 antagonist can block D1-mediated grooming, a finding that suggests that tonic D2 stimulation by endogenous DA plays a permissive role in the expression of this D1-mediated behavior. In contrast, White *et al.* (26) found that depletion of endogenous dopamine did not attenuate D1-induced grooming and suggested that tonic D2 stimulation did not play a permissive role in D1-mediated grooming. In the present study, a D2 agonist potentiated the behavioral effect of a D1 agonist, suggesting that exogenous D2 stimulation can enhance

a D1-mediated behavior. However, it is not clear that the permissive interaction postulated by other investigators and the potentiation demonstrated in the present study reflect the same underlying behavioral function of DA receptors. That is, synergism with endogenous receptor stimulation and potentiation by exogenous agonist administration are not necessarily part of the same process. In fact, previous studies utilizing drug discrimination suggest that stimulation of DA receptors with endogenous DA is not necessary for the expression of this behavioral effect of either type of DA agonist. In those studies, D2 antagonists did not block the DS effects of D1 agonists and vice versa (8, 23, 28). In short, antagonism, synergism and potentiation, as well as no interaction, have all been found to describe the interaction between DA receptors in behavioral studies.

The reasons for these differences between behavioral preparations is not clear. As we have noted previously (28), it is possible that the drug dose used is a critical variable in determining the type of functional interaction seen. Although doses of D1 agonists differed only slightly across preparations, higher doses of D2 agonists are generally used in studies of stereotyped behavior and locomotor activity [e.g., (2,22)] than in drug discrimination studies. The use of lower doses may enhance pharmacological selectivity or involve primarily higher affinity presynaptic D2 receptors rather than postsynaptic D2 receptors (19,27). Perhaps less DA is then available to compete with SKF for D1 receptors. A second possibility is that different behavioral paradigms measure DA activity at different sites in the CNS and that the interaction between DA receptors varies in different areas of the brain. For instance, it has been suggested that different areas of the striatum are involved in stereotyped behavior and perioral movements (17). Although the brain site(s) mediating the DS effects of these direct DA agonists remain to be established, the nucleus accumbens has been implicated in the DS effects of the indirect DA agonists (13,29). However, electrophysiology studies involving various brain regions have indicated a synergistic interaction between DA receptors in nucleus accumbens (25). On the other hand, neurons in the medial prefrontal cortex apparently do not demonstrate synergistic interactions between D1 and D2 receptors (18). A final possibility may relate to the conditioned/unconditioned distinction between behavioral preparations. Locomotor activity in response to agonist administration is an unconditioned response, whereas in a drug discrimination paradigm, an organism is trained to attend to some effect of receptor stimulation by an agonist. Endogenous DA may play a minimal role in the latter effect.

With regard to each of these accounts, however, it should be noted that the present results contrast with our previous findings that a D1 agonist failed to potentiate the DS effects of a D2 agonist (28). That is, different interactions were found within the same preparation even though the drug doses used were essentially identical and the same brain regions were undoubtedly involved. The nature of the interaction of D1 and D2 receptors may depend upon whether a D1 or a D2 agonist-induced behavior is being investigated. It is possible that the D1 and the D2 discriminations are based on drug action in different brain regions and that D1/D2 interactions differ in those brain regions. Nevertheless, what these as well as previous results emphasize is that the nature of the D1/D2 receptor interaction in the expression of DA-mediated behavior cannot be described simply as permissive or synergistic or antagonistic. The interaction may depend upon the behavior involved and whether DA receptor stimulation is endogenous or exogenous.

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