Pharmacology Biochemistry and Behavior, Vol. 63, No. 2, pp. 319–324, 1999

0091-3057/99/$–see front matter

PII S0091-3057(98)00266-4

Effects of Antidepressants in Rats Trained to Discriminate the Beta-2 Adrenergic Agonist Clenbuterol

MALATH M. MAKHAY AND JAMES M. O'DONNELL

Department of Pharmacology & Therapeutics, Louisiana State University Medical Center, Shreveport, LA 71130-3932

Received 28 August 1998; Revised 1 December 1998; Accepted 9 December 1998

MAKHAY, M. M. AND J. M. O'DONNELL. *Effects of antidepressants in rats trained to discriminate the beta-2 adrenergic agonist clenbuterol.* PHARMACOL BIOCHEM BEHAV **63**(2) 319–324, 1999.—The ability of indirectly acting agonists such as norepinephrine uptake inhibitors, serotonin reuptake inhibitors, and atypical antidepressants to substitute for clenbuterol, a beta-2 adrenergic agonist, was examined in rats trained to discriminate 0.03 mg/kg clenbuterol and saline using a fixed-ratio 10 (FR 10) schedule with water reinforcement. The beta-2 selective adrenergic agonist clenbuterol produced an orderly dose–response relationship, and its discriminative stimulus effects were antagonized by the beta-adrenergic antagonist propranolol. It was found that the effects of tricyclic antidepressants and selective norepinephrine uptake inhibitors did not generalize to the discriminative stimulus effects of clenbuterol, with the exception of high doses of protriptyline. Moreover, compounds from other drug classes, including fluoxetine and phenelzine, did not substitute for clenbuterol. Atypical antidepressants, such as trazodone, rolipram, and bupropion also did not engender drug-appropriate responding. Prenalterol and dobutamine, both purported to be beta-1 adrenergic receptor agonists, partially substituted for clenbuterol, but at relatively high doses. The present results show that the antidepressants tested do not share discriminative stimulus effects with clenbuterol, a beta-2 adrenergic agonist. © 1999 Elsevier Science Inc.

Clenbuterol Drug discrimination Antidepressants Rat Operant behavior Beta-adrenergic receptors

BETA-ADRENERGIC receptors have been implicated in the behavioral and neuropharmacological effects of antidepressant drugs. Repeated administration of antidepressants from different pharmacological classes has been shown to downregulate beta-adrenergic receptors (7,8,10,16). This suggests that stimulation of beta-adrenergic receptors, mediated indirectly via inhibition of reuptake or monoamine oxidase, in an effect shared by many antidepressant drugs. It also has been shown that directly acting beta-1 or beta-2 adrenergic agonists produce antidepressant-like effects in a number of behavioral tests (6,14,18,20,21). Consistent with these findings, it has been found that the behavioral effects of the tricyclic antidepressant desipramine are antagonized by the beta-adrenergic antagonist propranolol (6,20). For at least one behavioral effect of desipramine, the beta-2 adrenergic receptor subtype seems to be involved (12).

Even though beta-2 adrenergic agonists like clenbuterol produce antidepressant-like behavioral effects, it does not appear that stimulation of beta-2 adrenergic receptors is required for these effects. Repeated treatment with clenbuterol, which reduces the density and responsiveness of beta-2 adrenergic receptors in the brain (23,26), completely abolishes antidepressant-like behavioral effects of beta-2 adrenergic agonists. However, the antidepressant-like behavioral effects of the norepinephrine reuptake inhibitor desipramine, the monoamine oxidase inhibitor phenelzine, the serotonin reuptake inhibitor fluoxetine, and the beta-1 adrenergic agonists dobutamine and prenalterol are unaffected by clenbuterol-induced downregulation of beta-2 adrenergic receptors (20). This suggests that while stimulation of central beta-adrenergic receptors is sufficient to produce antidepressant-like behavioral effects, it is not required.

The use of drug discrimination offers an additional means for examining the involvement of beta-2 adrenergic receptors in the mediation of the behavioral effects of antidepressant drugs. Previously, it has been shown that clenbuterol, a cen-

Requests for reprints should be addressed to Malath M. Makhay, Department of Pharmacology & Therapeutics, Louisiana State University Medical Center, 1501 Kings Highway, Shreveport, LA 71130-3932.

trally active beta-2 adrenergic agonist (2,26), produces discriminative stimulus effects in rats (13,22). Pharmacological characterization of the clenbuterol cue shows it to be mediated via stimulation of central beta-2 adrenergic receptors (22). Thus, clenbuterol discrimination may provide an index of stimulation of these receptors in vivo. The present study examined whether the effects of antidepressant drugs from different pharmacological classes generalize to the discriminative stimulus effects of clenbuterol.

In the present study, a number of tricyclic antidepressants, a serotonin reuptake inhibitor, atypical antidepressants, and beta-1 adrenergic receptor agonists, were given in substitution for clenbuterol to determine if rats generalize to the clenbuterol stimulus cue. Also, the nonselective beta-adrenergic antagonist propranolol was administered with clenbuterol to determine if it would block clenbuterol's stimulus effects.

METHOD

Subjects

Twenty male Sprague–Dawley rats (Harlan, Indianapolis, IN), weighing 350 to 450 g, were used for the study. All animals were housed separately in polycarbonate cages in a room with constant temperature and humidity and illumination 12 h a day. The animals were given a minimum of six rodent chow pellets and 20 ml of water daily after experimental sessions. All training and testing sessions were conducted Monday through Saturday of every week.

Behavioral Apparatus

Twenty model E10-10 Coulbourn operant chambers (28 × 26 × 31 cm) were housed in light-proof, sound-attenuated, and fan-ventilated chambers. Each operant chamber was equipped with two levers, requiring a downward force equivalent to 15 g (0.15 N), that were mounted 3 cm from the side wall, 3 cm above a metal grid floor, and 5 cm from a centrally placed dipper that delivered 0.02 ml of water for 4 s. The experimental chambers were connected to a Micro PDP 11/73 computer using a LABLINC interface. A SKED-11 operating system was used to record behavior and control schedule contingencies (31).

Discrimination Training

After habituation to the operant chamber, the rats were trained to alternate daily between response levers on an FR 1 schedule of reinforcement during 20-min sessions. Once lever pressing was established, the reinforcement contingency was increased incrementally to an FR 10 schedule, while maintaining the lever alternation. Next, the rats were trained to discriminate between 0.03 mg/kg of clenbuterol and drug vehicle (0.9% saline solution). Injections were administered IP 30 min prior to the experimental session. Half of the rats were assigned randomly the left lever as "clenbuterol correct" and the right lever as "vehicle correct." Every tenth consecutive response on the injection-appropriate lever was reinforced on days when the rats were pretreated with clenbuterol, whereas every tenth response on the opposite lever was reinforced after vehicle injections. In each 2-week period there were 6 drug days and 6 vehicle days, with the constraint that there were not more than 2 consecutive drug or vehicle days. Discrimination sessions were continued until each rat reached the performance criterion of no more than two incorrect responses before 10 responses on the injection-appropriate lever on 9 of 10 consecutive sessions.

Test Sessions

Once drug discrimination was established and rats achieved the above-mentioned criteria, a series of generalization (substitution) and antagonism tests were conducted. Subsets of rats were administered doses of challenge drugs in an ascending order. If a test compound completely eliminated responding in a rat, higher doses were not tested. On test days, each rat was allowed 30 nonreinforced lever responses. The lever on which the rat first made 10 responses (the selected lever) and the prior number of responses, if any, on the other lever were recorded. The session ended and the rat was removed from the operant chamber. If a rat failed to demonstrate reliable discrimination (no more than two incorrect responses before 10 responses on the injection-appropriate lever and greater than 80% injection-appropriate responding in the session overall on three consecutive training sessions), testing with that animal was postponed and discrimination training continued until these performance criteria were achieved. Test drugs were given 30 min prior to the experimental session, except nisoxetine, which was administered 10 min prior to the session. Antagonists and training and testing drugs were administered simultaneously.

Drugs

Clenbuterol HCl, propranolol HCl, desipramine HCl, imipramine HCl, and phenelzine were purchased from Sigma Chemical (St. Louis, MO). Amitriptyline HCl, amoxapine, bupropion HCl, nisoxetine HCl, nortriptyline HCl, and trazodone HCl were purchased from Research Biochemicals, Inc. (Natick, MA). Protriptyline HCl was generously donated by Merck Pharmaceuticals (Rahway, NJ). Maprotiline was purchased from Tocris Cookson (St. Louis, MO). Fluoxetine HCl was generously donated by Eli Lilly (Indianapolis, IN). Dobutamine was purchased from Eli Lilly (Indianapolis, IN). Prenalterol HCl was donated by Hassle (Molndal, Sweden). All drugs were dissolved in 0.9% saline solution, except for the following: nisoxetine HCl, phenelzine, and fluoxetine were dissolved in deionized water; trazodone was dissolved in 100% dimethyl sulfoxide (DMSO); dobutamine was dissolved in 0.19 mg/ml sodium metabisulfite in deionized water; amoxapine was dissolved 0.8% NaCl and 0.2% ascorbic acid in water. Doses shown are those of the free bases. Drug and vehicle solutions were administered IP at a volume of 1.0 ml/kg body weight, except for trazodone (0.3 ml/kg).

Data Analysis

Drug discrimination results are expressed as the percentage of responses emitted on the drug-appropriate lever. Group averages are presented unless otherwise noted. Dose–effect functions were constructed by pooling measures of discriminative performance or latency for all subjects and plotting the resulting mean ± SEM as a function of dose. Rats that made fewer than five responses on either lever within 20 min were excluded from the analysis. To calculate ED_{50} values, the dose–response functions were subjected to nonlinear regression analysis (3,20). Drugs were considered to share discriminative stimulus effects with clenbuterol if the majority of subjects emitted ⩾80% clenbuterol-appropriate responding during the test session. Compounds engendering ⩾60–80% clenbuterol-appropriate responding were considered to give partial substitution. Rates are expressed as the latency (in seconds) between onset of the experimental session and completion of the fixed ratio.

RESULTS

Clenbuterol Discrimination

All rats achieved the clenbuterol-saline discrimination. A mean of 69 sessions was required to meet the discrimination criteria; the range was 52 to 120 sessions. However, it should be noted that the initial training dose was 0.10 mg/kg and was decreased to 0.03 mg/kg because of the very low response rate observed for some rats. On average, for the 20 rats across the first 10 sessions when the training criteria were met, 99 and 98% of the responses were injection appropriate with clenbuterol and saline, respectively. The mean response rate across the first 10 sessions when the criteria were met was 0.88 ± 0.07 responses per second. On those days when clenbuterol was administered acutely (i.e., clenbuterol training days), the mean response was 112% of saline control rates.

Clenbuterol produced dose-related increases in drug-appropriate responding and increases in latency to complete the fixed-ratio schedule. The ED_{50} dose for producing clenbuterol-appropriate responding was 0.016 mg/kg. A dose of 1.0 mg/kg propranolol reduced clenbuterol-appropriate responding to less than 25%.

Substitution Testing with Antidepressants

Figure 1A shows the results of dose–response testing with clenbuterol and substitution tests with a number of tricyclic antidepressants. Desipramine, nortriptyline, imipramine, and amitriptyline failed to substitute for clenbuterol and produced dose-related increases in latency (Fig. 1B). Protriptyline partially substituted for clenbuterol at the highest dose tested, 100 mg/kg, and increased latency. When propranolol was administered with protriptyline in rats that generalized to the clenbuterol stimulus cue, rats emitted saline-appropriate responding. Propranolol did not reduce latency when tested with high doses of protriptyline and actually eliminated responding (data not shown).

As shown in Fig. 2A, nisoxetine and fluoxetine failed to substitute for clenbuterol, engendering less than 60% drug-appropriate responding. Maprotiline produced mostly saline-appropriate responding; however, six animals tested at doses of 5.6 and three animals tested at 10 mg/kg gave partial generalization to the clenbuterol stimulus cue. When propranolol was administered to rats that generalized to the clenbuterol stimulus cue, rats emitted drug-appropriate responses (data not shown). All three drugs produced dose-related increases in latency as shown in Fig. 2B.

Figure 3A shows the results from testing typical antidepressants and an MAO inhibitor, phenelzine. All the compounds tested, trazodone, rolipram, bupropion, phenelzine, and amoxapine, failed to substituted for clenbuterol, and they produced dose-related increases in latency (Fig. 3B).

Finally, two beta-1 adrenergic agonists, dobutamine and prenalterol, were given in substitution for clenbuterol. Dobutamine and prenalterol produced 76 and 69% clenbuterol-appropriate responding, respectively (Fig. 4A). Both compounds also produced large dose-related increases in latency at the highest doses (Fig. 4B).

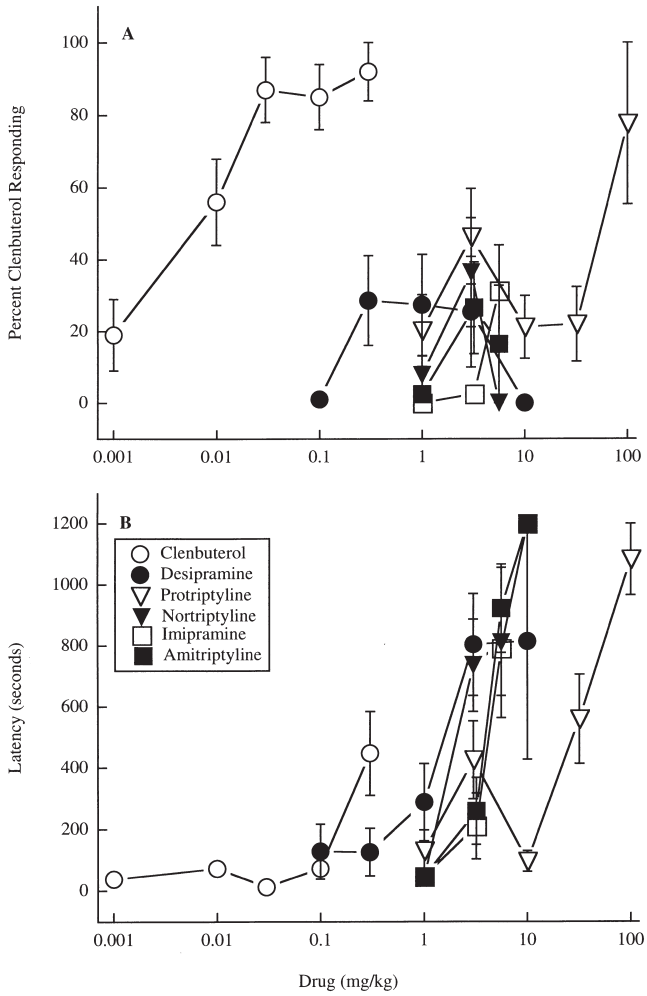

FIG. 1. (A) Discriminative stimulus generalization tests with tricyclic antidepressants. Lever selection is shown as a function of dose of drug. Data represent the percentage of responses made on the clenbuterol-appropriate lever as defined by completion of at least five responses. At the highest doses, the number of rats meeting this requirement were: desipramine, 4 of 17 (total number of rats tested); protriptyline, 5 of 15; nortriptyline, 2 of 8; imipramine, 7 of 12; and amitriptyline, 4 of 14. (B) Mean latency (in seconds) of the rats tested to complete the fixed-ratio 10 requirement. Although some rats did not complete the fixed-ratio (FR 10), the data are shown. When rats failed to complete the FR 10, a 1200-s latency was assumed (i.e., a complete 20-min session).

DISCUSSION

Antidepressant drugs from different pharmacological classes generally failed to substitute completely in rats trained to discriminate 0.03 mg/kg clenbuterol from saline. These included amitriptyline, amoxapine, desipramine, fluoxetine, imipramine, maprotiline, nisoxetine, nortriptyline, phenelzine, protriptyline, and trazodone. In addition, the type 4 phosphodiesterase (PDE4) inhibitor rolipram, which has been reported to have antidepressant activity (21,32,33), also did not substitute for clenbuterol. Bupropion, which is purported to have dopaminergic properties, did not engender drug-appropriate responding, which is consistent with a previous study that failed to demonstrate that it has any adrenergic activity (1). Overall, the present data suggest that stimulation of beta-2 adrenergic receptors is not an effect shared by drugs exhibiting antidepressant activity.

To determine if compounds that are purported to be selective for beta-1 adrenergic receptors share discriminative stim-

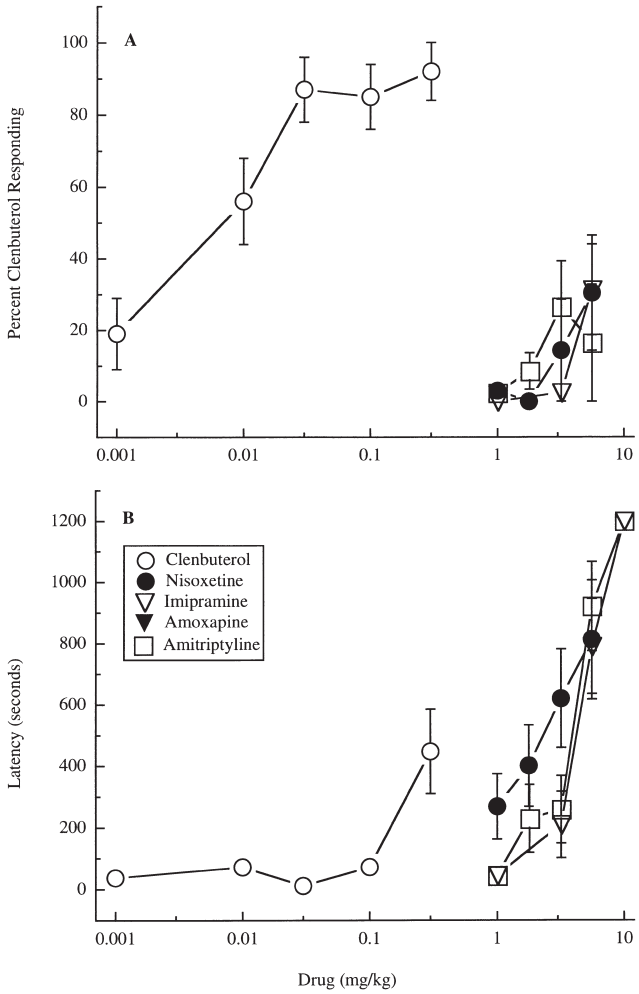

FIG. 2. (A) Discriminative stimulus generalization tests with NE uptake inhibitors. Lever selection is shown as a function of dose of drug. Data represent the percentage of responses made on the clenbuterol-appropriate lever as defined by completion of at least five responses. At the highest doses, the number of rats meeting this requirement were: maprotiline, 5 of 10 (total number of rats tested); nisoxetine, 11 of 15; and fluoxetine, 3 of 17. (B) Mean latency (in seconds) of the rats tested to complete the fixed-ratio 10 requirement. Although some rats did not complete the fixed-ratio (FR 10), the data are shown. When rats failed to complete the FR 10, a 1200-s latency was assumed (i.e., a complete 20-min session).

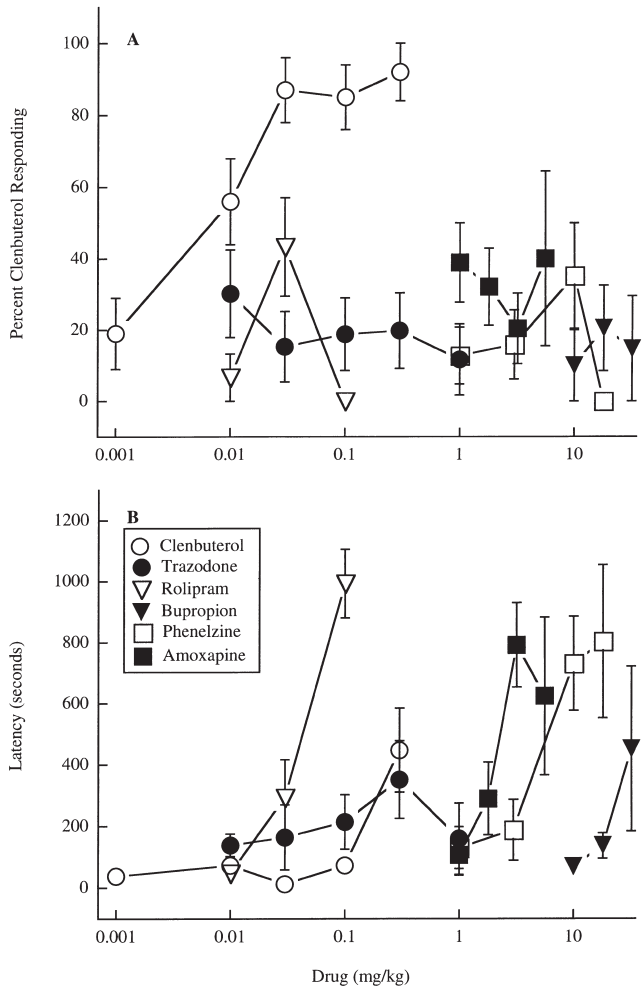

FIG. 3. (A) Discriminative stimulus generalization tests with the MAO inhibitor phenelzine, and the atypical antidepressants, trazodone, rolipram, bupropion, and amoxapine. Lever selection is shown as a function of dose of drug. Data represent the percentage of responses made on the clenbuterol-appropriate lever as defined by completion of at least five responses. At the highest doses, the number of rats meeting this requirement were: phenelzine, 6 of 17 (total number of rats tested); trazodone, 11 of 14; rolipram, 14 of 15; bupropion, 5 of 10; and amoxapine, 5 of 16. (B) Mean latency (in seconds) of the rats tested to complete the fixed-ratio 10 requirement. Although some rats did not complete the fixed-ratio (FR-10), the data are shown. When rats failed to complete the FR 10, a 1200 s latency was assumed (i.e., a complete 20-min session).

ulus properties with clenbuterol, dobutamine and prenalterol were tested. Following administration of prenalterol, at doses up to and including 100 mg/kg, rats never emitted more than 69% clenbuterol-appropriate responding, on average. Dobutamine gave 76% clenbuterol-appropriate responding, on average, when rats were administered doses up to and including 18 mg/kg. This is consistent with a previous study in which rats emitted, on average, less than 80% clenbuterol-appropriate responding when trained to discriminate 0.10 mg/kg clenbuterol from vehicle. At higher doses of these agonists, stimulation of beta-2 receptors is likely (13,22).

Previously, it has been shown that stimulation of beta-2 adrenergic receptors produces antidepressant-like behavioral effects. Clenbuterol and other beta-2 adrenergic agonists reduce locomotor activity, antagonize the effects of reserpine, reduce the time of immobility in a forced-swim test, and reduce response rate and increase reinforcement rate under a differential-reinforcement-of-low-rate schedule (5,6,9,18,20,21). These behavioral effects are similar to the behavioral profile of proven antidepressant drugs (4,30). While it appears that stimulation of beta-2 adrenergic receptors can produce antidepressant-like behavioral effects, it does not seem that stimulation of these receptors is essential. Downregulation of beta-2 adrenergic receptors, produced by repeated administration of clenbuterol, does not alter the ability of desipramine, phenelzine, or fluoxetine to produce antidepres-

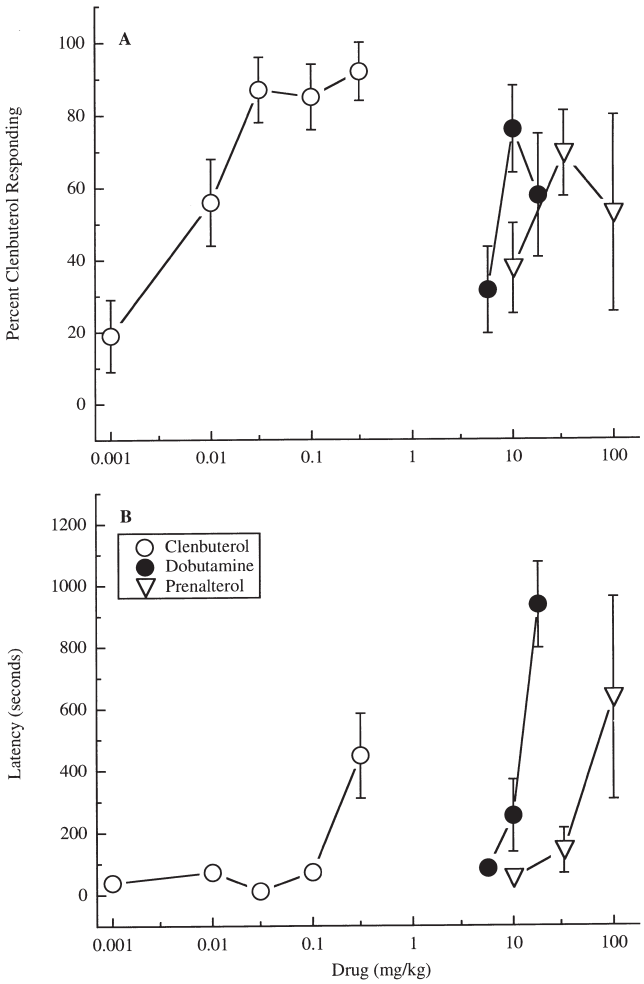

FIG. 4. (A) Discriminative stimulus generalization tests with beta-1 adrenergic receptor agonists. Lever selection is shown as a function of dose of drug. Data represent the percentage of responses made on the clenbuterol-appropriate lever as defined by completion of at least five responses. At the highest doses tested, the number of rats meeting this requirement were: dobutamine, 13 of 14 (total number of rats tested); and prenalterol, 4 of 16. (B) Mean latency (in seconds) of the rats tested to complete the fixed-ratio 10 requirement. Although some rats did not complete the fix-ratio (FR 10), the data are shown. When rats failed to complete the FR 10, a 1200-s latency was assumed (i.e., a complete 20-min session).

sant-like effects on DRL behavior (20). The present results are consistent with such a finding. They suggest that administration of antidepressant drugs, even those that inhibit the reuptake of norepinephrine, does not result in stimulation of central beta-2 adrenergic receptors in vivo.

This study evaluated the discriminative stimulus effects of clenbuterol, not the antidepressant-like effects. However, it appears that clenbuterol's discriminative stimulus effects and antidepressant-like effects are both mediated by beta-2 adrenergic receptors. Support for this conclusion lies in the fact that the beta-2 adrenergic antagonist ICI 118,551 blocks clenbuterol's effects under a differential-reinforcement-of-low-rate schedule (20), and clenbuterol's discriminative stimulus effects more potently than does the beta-1 adrenergic antagonist betaxolol (22).

The two antidepressants that substituted more fully than any other drug for clenbuterol were protriptyline and maprotiline, which engendered 80 and 75% drug-appropriate responding, respectively. In rats that generalized to the clenbuterol stimulus cue when administered protriptyline, propranolol was tested with protriptyline to determine if these effects are mediated by beta-adrenergic receptors. Complete blockade occurred, thus suggesting that protriptyline's stimulus effects are mediated by beta-adrenergic receptors. However, when propranolol was administered with maprotiline to rats that generalized to the clenbuterol stimulus cue, it completely failed to block its stimulus effects. This discrepancy might suggest that although protriptyline and maprotiline share discriminative stimulus effects with clenbuterol at certain doses, these two drugs do not share discriminative stimulus effects. Protriptyline's ability to share discriminative stimulus effects with clenbuterol might result from the fact that this drug is the least sedating of its class (11). Thus, its ability to substitute for clenbuterol may result more from its being able to be tested at very high doses than with a qualitative difference in its pharmacological effects relative to those of the other tricyclic antidepressants. Moreover, only five rats each were tested with protriptyline and maprotiline. The small sample size relative to the number of rats tested at lower doses might not afford a conclusive statement about these compounds' discriminative stimulus properties. Given norepinephrine's relatively low affinity for beta-2 adrenergic receptors (15,25), considerable inhibition of reuptake may be required before receptor stimulation similar to that produced by clenbuterol is achieved. The positive data obtained with protriptyline may help to explain a discrepancy between the present results and those of an earlier study (13). In the earlier study, it was found that desipramine partially substituted for clenbuterol; 77% drug-appropriate lever selection was observed at the maximally effective dose of desipramine. It is possible that differences in training and testing procedures may have made the sedative effects of desipramine less predominant in the earlier study. Thus, like protriptyline in the present study, desipramine may have produced significant drug-appropriate responding before large, response rate-decreasing effects were observed.

It is unlikely that the inability of the antidepressant drugs to substitute for clenbuterol results from their inability to produce discriminative stimulus effects. Previously, it has been shown that rats and pigeons can be trained to discriminate the tricyclic antidepressant imipramine from saline (28,34). In addition, the PDE4 inhibitor rolipram has been shown to produce discriminative stimulus effects in rats [(27,29); Makhay and O'Donnell, unpublished results]; tricyclic antidepressants were found not to substitute for the discriminative stimulus effects of rolipram.

Pharmacological characterization of the discriminative stimulus effects of clenbuterol indicates that the drug cue is mediated by central beta-2 adrenergic receptors (22). The failure of antidepressant drugs to substitute in challenge tests strongly indicates that these drugs do not cause appreciable stimulation of beta-2 adrenergic receptors in vivo.

Thus, it appears that while stimulation of beta-2 adrenergic receptors may produce antidepressant-like behavioral effects (5,6,9,18,19,21), stimulation of these receptors is not required. It is possible that the ability of beta-2 adrenergic agonists to produce antidepressant-like behavioral effects is due to their indirect stimulation of beta-1 adrenergic receptors caused by increased norepinephrine release due to stimulation of facilitatory, presynaptic beta-2 adrenergic receptors (17,24).

REFERENCES

1. Blitzer, R. D.; Becker, R. E.: Characterization of the bupropion cue in the rat: Lack of evidence for a dopaminergic mechanism. Psychopharmacology (Berlin) 85:173–177; 1985.
2. Conway, P. G.; Tejani-Butt, S.; Brunswick, D. J.: Interaction of beta adrenergic agonists and antagonists with beta adrenergic receptors *in vivo*. J. Pharmacol. Exp. Ther. 241:755–762; 1987.
3. Draper, N. R.; Smith, H.: Applied regression analysis. New York: Wiley; 1966.
4. Enna, S.; Malick, J. B.; Richelson, E.: Antidepressants: Neurochemical, behavioral, and clinical perspectives. New York: Raven Press; 1981.
5. Finnegan, K. T.; Terwilliger, M. M.; Berger, P. A.; Hollister, L. E.; Csernansky, J. G.: A comparison of the neurochemical and behavioral effects of clenbuterol and desipramine. Eur. J. Pharmacol. 134:131–136; 1987.
6. Frances, H.; Simon, P.: Reserpine-induced hypothermia: Participation of beta-1 and beta-2 adrenergic receptors. Pharmacol. Biochem. Behav. 27:21–24; 1987.
7. Frazer, A.; Conway, P. G.: Pharmacologic mechanisms of actions of antidepressants. Psychiatr. Clin. North Am. 7:575–586; 1984.
8. Frazer, A.; Ordway, G.; O'Donnell, J. M.; Vos, P.; Wolfe, B.: Effect of repeated administration of clenbuterol on the regulation of beta adrenoreceptors in the central nervous system of the rat. In: Antidepressants and receptor function (Ciba Found. Symp. 123). New York: Wiley Press; 1986:170–190.
9. Geyer, M. A.; Frampton, S. F.: Peripheral mediation of effects of clenbuterol on locomotor and investigatory behavior in rats. Pharmacol. Biochem. Behav. 30:417–420; 1988.
10. Heydorn, W. E.; Frazer, A.; Weiss, B.: Electrical stimulation of sympathetic nerves increases the concentration of cyclic AMP in rat pineal gland. Proc. Natl. Acad. Sci. USA 78:7176–7179; 1981.
11. Huang, Y.: Inhibitory effect of noradrenaline uptake inhibitors on contractions of rat aortic smooth muscle. Br. J. Pharmacol. 117:533–539; 1996.
12. Matsumoto, K.; Ojima, K.; Ohta, H.; Watanabe, H.: Beta-2 but not beta-1 adrenoceptors are involved in desipramine enhancement of aggressive behavior in long-term isolated mice. Pharmacol. Biochem. Behav. 49:13–18; 1994.
13. McElroy, J. E.; O'Donnell, J. M.: Discriminative stimulus properties of clenbuterol: Evidence for beta adrenergic involvement. J. Pharmacol. Exp. Ther. 245:155–163; 1988.
14. McElroy, J. E.; Stimmel, J. J.; O'Donnell, J. M.: Effects of centrally acting beta adrenergic agonists on discrete trial conditioned avoidance behavior in rats. Psychopharmacology (Berlin) 97:108–114; 1989.
15. Minneman, K. P.; Hegstrand, L. R.; Molinoff, P. B.: The pharmacological specificity of beta-1 and beta-2 adrenergic receptors in rat heart and lung in vitro. Mol. Pharmacol. 16:21–33; 1979.
16. Mobley, P. L.; Sulser, F.: Down-regulation of the central noradrenergic receptor system by antidepressant therapies: Biochemical and clinical aspects. In: Enna, S. J.; et al., eds. Antidepressants: Neurochemical, behavioral, and clinical perspectives. New York: Raven Press; 1981:31–51.
17. Murugaiah, K. D.; O'Donnell, J. M.: Presynaptic beta-2 adrenergic receptors regulate the release of norepinephrine from cerebral cortical slices. Life Sci. 57:327–332; 1995.
18. O'Donnell, J. M.: Effects of clenbuterol and prenalterol on performance during differential reinforcement of low response rate. J. Pharmacol. Exp. Ther. 241:68–75; 1987.
19. O'Donnell, J. M.: Behavioral consequences of activation of beta adrenergic receptors by clenbuterol: Evidence for mediation by the central nervous system. Brain Res. Bull. 21:491–497; 1988.
20. O'Donnell, J. M.: Behavioral effects of beta adrenergic agonists and antidepressants after down-regulation of beta-2 adrenergic receptors. J. Pharmacol. Exp. Ther. 254:147–157; 1990.
21. O'Donnell, J. M.: Effects of clenbuterol and other beta adrenergic agonists on locomotor activity. Res. Commun. Chem. Pathol. Pharmacol. 82:375–379; 1993.
22. O'Donnell, J. M.: Pharmacological characterization of the discriminative stimulus effects of clenbuterol in rats. Pharmacol. Biochem. Behav. 58:813–818; 1997.
23. O'Donnell, J. M.; Frazer, A.: Effects of clenbuterol and antidepressant drugs on beta adrenergic receptor/N-protein coupling in the cerebral cortex of the rat. J. Pharmacol. Exp. Ther. 234:30–36; 1985.
24. O'Donnell, J. M.; Frith, S.; Wilkins, J.: Involvement of beta-1 and beta-2 adrenergic receptors in antidepressant-like effects of centrally administered isoproterenol. J. Pharmacol. Exp. Ther. 247:379–389; 1994.
25. O'Donnell, J. M.; Wolfe, B. B.; Frazer, A.: Agonist interactions with beta adrenergic receptors in rat brain. J. Pharmacol. Exp. Ther. 228:640–647; 1984.
26. Ordway, G. A.; O'Donnell, J. M.; Frazer, A.: Effects of clenbuterol on central beta1- and beta2-adrenergic receptors in the rat. J. Pharmacol. Exp. Ther. 241:187–195; 1987.
27. Ortmann, R.; Meisburger, J. G.: Rolipram forms a potent discriminative stimulus in drug discrimination experiments in rats. Psychopharm. 89:273–277; 1986.
28. Schechter, M. D.: Discriminative stimulus control with imipramine: Transfer to other anti-depressants. Pharmacol. Biochem. Behav. 19:751–754; 1983.
29. Schneider, H. H.; Yamaguchi, M.; Andrews, J. S.; Stephens, D. N.: Discriminative stimulus properties of the stereoisomers of the phosphodiesterase inhibitor rolipram. Pharmacol. Biochem. Behav. 50:211–217; 1995.
30. Seiden, L. S.; Marek, G. J.; O'Donnell, J. M.; Li, A.; Dunn, R.; Jolly, D.: The role of noradrenergic and serotonergic systems in the screening of antidepressant drugs. In: Sandler, M., ed. Progress in catecholamine research: Clinical aspects. New York: A. R. Liss; 1988:337–342.
31. Snapper, A. G.; Kadden, R. M.; Inglis, G. B.: State notation of behavioral procedures. Behav. Res. Methods Instrum. 14:329–343; 1982.
32. Wachtel, H.: Potential antidepressant activity of rolipram and other selective cyclic adenosine 3′,5′ monophosphate phosphodiesterase inhibitors. Neuropharmacology 22:267–272; 1983.
33. Wachtel, H.: Defective second-messenger function in the etiology of endogenous depression: Novel therapeutic approaches. In: Briley, M.; Fillion, G., eds. Concepts of depression. London: MacMillan Press; 1988:277–293.
34. Zhang, L.; Barrett, J. E.: Imipramine as a discriminative stimulus. J. Pharmacol. Exp. Ther. 259:1088-1093; 1991.