Effects of Antidepressants in Rats Trained to Discriminate Centrally Administered Isoproterenol

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ABSTRACT
Previous work has shown that the discriminative stimulus effects of centrally administered isoproterenol are mediated primarily via β₁-adrenergic receptors. In the present study, this model was used to investigate the ability of antidepressant drugs displaying various pharmacological profiles to stimulate β₁-adrenergic receptors in vivo; this was assessed by determining whether they substituted for the discriminative stimulus effects of isoproterenol. Rats were trained to discriminate centrally administered isoproterenol (10 μg i.c.v.) from artificial cerebral spinal fluid using a water-reinforced, two-lever operant task (fixed ratio 10 schedule). After acquisition of the discrimination, drugs were tested for substitution (i.p.). The tricyclic antidepressants protriptyline and desipramine, the norepinephrine uptake inhibitor nisoxetine, the monoamine oxidase antidepressants protriptyline and desipramine, the norepinephrine, the major endogenous-adrenergic transmitter in the brain, has a greater affinity for β₁-adrenergic receptors than β₂-adrenergic receptors (Minneman et al., 1979; O’Donnell et al., 1984). Furthermore, although down-regulation of β₂-adrenergic receptors via repeated administration of clonidine, a β₂-adrenergic agonist, reduces the behavioral effects of β₂-selective-adrenergic agonists; antidepressants as well as β₁-adrenergic agonists remain fully effective (O’Donnell, 1990). The results of drug discrimination studies also are more consistent with a role for the β₁ subtype in the mediation of the effects of antidepressant drugs. It was found that antidepressant drugs, as a class, do not substitute for the discriminative stimulus effects of clonidine, β₂-adrenergic agonist. In contrast, desipramine does substitute in rats trained to discriminate centrally administered (i.e., i.c.v.) isoproterenol. Through the use of subtype-selective-adrenergic agonists and antagonists, it has been shown that the discriminative stimulus effects of i.c.v. isoproterenol are mediated by β₁-adrenergic receptors (Crissman et al., 2001), even though this agonist exhibits similar affinity for and

Substantial research has implicated β-adrenergic receptors in the mechanism of action of antidepressant drugs. Stimulation of either β₁- or β₂-adrenergic receptors is sufficient to produce antidepressant-like effects on behavior in animal models such as learned helplessness, the forced-swim test, and differential-reinforcement-of-low-rate (DRL) behavior (Martin et al., 1986; Finnegan et al., 1987; Frances and Simon, 1987; O’Donnell, 1987, 1990, 1993). In addition, repeated treatment with antidepressants from distinct pharmacological classes results in the down-regulation of central β-adrenergic receptors (Mobley and Sulser, 1981; Frazer and Conway, 1984; Ordway et al., 1991); the reduction in the density of β₁-adrenergic receptors is much greater than that of β₂-adrenergic receptors (Ordway et al., 1991). This suggests a greater involvement of the β₁ subtype in the mediation of the effects of antidepressant drugs that act on noradrenergic systems.

Norepinephrine, the major endogenous-adrenergic transmitter, has a greater affinity for β₁-adrenergic receptors than β₂-adrenergic receptors (Minneman et al., 1979; O’Donnell et al., 1984). Furthermore, although down-regulation of β₂-adrenergic receptors via repeated administration of clonidine, a β₂-adrenergic agonist, reduces the behavioral effects of β₂-selective-adrenergic agonists; antidepressants as well as β₁-adrenergic agonists remain fully effective (O’Donnell, 1990). The results of drug discrimination studies also are more consistent with a role for the β₁ subtype in the mediation of the effects of antidepressant drugs. It was found that antidepressant drugs, as a class, do not substitute for the discriminative stimulus effects of clonidine, β₂-adrenergic agonist. In contrast, desipramine does substitute in rats trained to discriminate centrally administered (i.e., i.c.v.) isoproterenol. Through the use of subtype-selective-adrenergic agonists and antagonists, it has been shown that the discriminative stimulus effects of i.c.v. isoproterenol are mediated by β₁-adrenergic receptors (Crissman et al., 2001), even though this agonist exhibits similar affinity for and

ABBREVIATIONS: DRL, differential-reinforcement-of-low-rate; aCSF, artificial cerebral spinal fluid; L-NNA, Nω-nitro-L-arginine; L-AT, N-acetyl-L-tryptophan 3,5-bis benzyl ester; FR, fixed ratio.
Antidepressants and Isoproterenol Discrimination

Efficacy at β1- and β2-adrenergic receptors (O’Donnell et al., 1984). β1-Adrenergic receptor mediation also has been observed for the effects of i.c.v. isoproterenol on DRL behavior (O’Donnell et al., 1994). The ability of desipramine to substitute for the discriminative stimulus effects of i.c.v. isoproterenol suggests that its administration does result in the stimulation of central β1-adrenergic receptors in vivo (Crisman et al., 2001). These data suggest that antidepressants that interact with noradrenergic neurons produce their effects, in part, via the β1-adrenergic receptor. The present study examined whether antidepressants from different pharmacological classes generalize to the discriminative stimulus effects of centrally administered isoproterenol.

Rats were trained to discriminate i.c.v. administration of 10 μg of isoproterenol from artificial cerebral spinal fluid (aCSF). Once the acquisition criterion was achieved, substitution tests were carried out with antidepressant drugs and related compounds. Drugs tested were the tricyclic antidepressants desipramine and protriptyline, the monoamine oxidase inhibitor phenelzine, the norepinephrine uptake inhibitor nisoxetine, the serotonin uptake inhibitor fluoxetine, the monoamine oxidase inhibitor, and L-NNA, a nitric-oxide synthase inhibitor, and N-acetyl-L-tryptophan 3,5-bis benzyl ester (L-AT), a neurokinin-1 receptor antagonist. Those drugs that generalized to isoproterenol’s cue were tested after pretreatment with the β1-adrenergic antagonist betaxolol to verify mediation of the discriminative stimulus effects by β1-adrenergic receptors.

Materials and Methods

Subjects. Male Sprague-Dawley rats, weighing 250 to 350 g at the beginning of the experiment (n = 4–8/dose determination), were housed individually in polycarbonate cages containing wood shavings in a room that was kept at a constant temperature (22°C) and on a 12-h on/12-h off light cycle (light on at 6:00 AM). Rats had free access to food, except during the experimental sessions. Access to water was limited to 25 ml after daily test sessions. All experiments were carried out according to the National Institutes of Health Guide for the Care and Use of Laboratory Animals (revised 1996).

Apparatus. Ten experimental chambers (model E10-10; Coulbourn Instruments, Allentown, PA) were each equipped with a house light, two levers, which required a downward force equivalent to 15 g (0.15 N) to constitute a response, and a centrally located water dipper, which delivered a 0.02-ml water reinforcer when schedule requirements were met. A MED Associates (St. Albans, VT) operating system was used to record responses and control schedule contingencies.

Discrimination Training. Rats were trained to alternate daily between the response levers under a fixed-ratio 1 schedule of reinforcement (FR1) during daily 20-min sessions. The reinforcement contingency was increased incrementally to an FR10 schedule, i.e., every 10th response was reinforced. Once unbiased lever pressing under this schedule was established, each rat was implanted with a cannula into the right lateral ventricle (see below) for i.c.v. administration of the training drug (10 μg of isoproterenol dissolved in 10 μl of aCSF) or the aCSF vehicle. These solutions were administered using a syringe pump; the 28-gauge infusion cannula was left in place for an additional minute after administration of the drug or vehicle. After i.c.v. injection, the rats received 0.3 ml of saline i.p.

This was done to minimize the possibility that the i.p. administration of test drugs would alter stimulus cues in any subsequent tests that involved this route of administration. Rats were trained to discriminate 10 μg of isoproterenol from 10 μl of aCSF. For each rat, one lever was designated the vehicle lever and the other designated the drug lever. The rats were trained 6 days a week, receiving isoproterenol or vehicle according to a predetermined schedule. The animals did not receive the same treatment more than 3 days in a row. A performance criterion of 90% treatment-appropriate responding for 10 consecutive days, with no more than three incorrect responses before 10 responses were made on the treatment-appropriate lever, was used to indicate successful discrimination training.

Cannula Implantation. Rats were anesthetized (120 mg/kg ketamine and 6 mg/kg xylazine) and placed in a stereotaxic frame. A 22-gauge guide cannula (Plastics One, Roanoke, VA) was implanted in each rat’s right lateral ventricle (~0.8 mm relative to bregma, 1.5 mm relative to the midline structure, ~3.6 mm relative to dura) and cemented to the skull. The rats were allowed to recover at least 1 week, after which behavioral testing was resumed. Cannula placement was verified by dye infusion in three rats before surgeries were performed on trained animals.

Test Sessions. Once the training criterion was met, a series of generalization and antagonism tests were carried out. Test sessions were conducted only after 3 days of accurate discrimination of vehicle and drug. During a test session, responses were recorded until completion of an FR10 on one lever or a period of 20 min expired; no reinforcement was delivered. Immediately after completion of the FR10, the rat was removed from the experimental chamber and returned to its home cage. Those antidepressants that substituted for isoproterenol’s discriminative stimulus were retested in the presence of 1 mg/kg betaxolol. This dose of betaxolol was shown to completely antagonize the discriminative stimulus effects of isoproterenol (Crisman et al., 2001).

Data Analysis. Drug discrimination results are expressed as the mean percentage of animals’ responses on the isoproterenol-appropriate lever. The effects of drugs were considered to generalize to the discriminative stimulus effects of isoproterenol when their administration resulted in greater than 80% isoproterenol-appropriate responding. For the calculation of ED50 values for the generalization tests, dose-response curves were subjected to nonlinear regression analysis (Draper and Smith, 1966; O’Donnell, 1990). t tests were used to assess the statistical significance of the antagonistic effects of betaxolol; statistical significance was assumed when p < 0.05.

Drugs. Mirtazapine (Organon NV, Oss, The Netherlands), venlafaxine (Wyeth-Ayerst, Princeton, NJ), fluoxetine, nisoxetine, protriptyline, buspirone, trazodone, N-nitro-L-arginine, phenelzine, bupropion, N-acetyl-L-tryptophan 3,5-bis benzyl ester, isoproterenol, desipramine, and betaxolol (Sigma-Aldrich, St. Louis, MO) were used. All drugs are hydrochloride salts, except isoproterenol, which is a bitartrate salt, phenelzine, which is a sulfate salt, and L-NNA and L-AT, which are free bases. Isoproterenol was administered i.c.v.; all other drugs were administered i.p. Isoproterenol and aCSF were administered 10 min before the start of the session. The other drugs (i.e., those used in substitution tests) were administered 20 min before the start of the test session, except for the β1-adrenergic antagonist betaxolol, which was administered 25 min before testing.

Results

Establishment of Discrimination Baseline. The rats used in this study met the training criterion after an average of 28 ± 3 sessions. Once the training criterion was reached, drug appropriate responding was maintained during daily maintenance training sessions.

Discriminative Stimulus Effects of Antidepressants with Noradrenergic Activity. Figure 1 shows the results of substitution tests obtained during sessions when seven different compounds with noradrenergic activity were tested for their ability to substitute for the 10-μg i.c.v. training dose.
of isoproterenol. Protriptyline, desipramine, nisoxetine, phenelzine, mirtazapine, venlafaxine, and bupropion engendered dose-related increases in the percentage of isoproterenol-appropriate responding. At the highest dose tested for each drug, greater than 90% isoproterenol-appropriate responding was observed. Based on ED$_{50}$ values (Table 1) the rank-order potency of these drugs for producing isoproterenol-appropriate responding was bupropion $>$ protriptyline $>$ phenelzine $>$ venlafaxine $>$ desipramine $>$ mirtazapine $>$ nisoxetine. At the dose ranges tested, none of these drugs produced large increases in the latency to complete the FR10 requirement.

Pretreatment with the $\beta_1$-selective-adrenergic antagonist betaxolol antagonized the ability of the drugs with noradrenergic activity to produce isoproterenol-appropriate responding (Fig. 2). All of the drugs tested for substitution in the presence of betaxolol produced less than 13% isoproterenol-appropriate responding. In contrast, at the doses tested, each of the drugs produced at least 90% isoproterenol-appropriate responding in the absence of betaxolol pretreatment.

**Discriminative Stimulus Effects of Antidepressants with Serotonergic Activity.** Figure 3 shows generalization results and latencies when ranges of doses for three different antidepressants with serotonergic activity were tested for generalization to isoproterenol's discriminative stimulus effects. The selective serotonin uptake inhibitor fluoxetine failed to substitute for isoproterenol at doses ranging from 0.01 to 3 mg/kg. When administered 10 mg/kg fluoxetine, only one of six rats completed the fixed ratio requirement; this rat responded on the isoproterenol lever. The weak norepinephrine-serotonin uptake inhibitor trazodone produced 47% isoproterenol-appropriate responding at a dose of 3 mg/kg. When administered 10 mg/kg trazodone, all four rats failed to complete the fixed ratio requirement. Buspirone, a partial agonist at 5-hydroxytryptamine$_{1A}$ receptors, resulted in only 62 and 35% substitution at the 1- and 3-mg/kg doses, respectively.

**TABLE 1**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Generalization to Isoproterenol Discrimination$^a$</th>
<th>Antagonism of 6-Hydroxydopamine$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupropion</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Protriptyline</td>
<td>0.01</td>
<td>0.12</td>
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<tr>
<td>Phenelzine</td>
<td>0.03</td>
<td></td>
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<tr>
<td>Venlafaxine</td>
<td>0.07</td>
<td>0.25</td>
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<tr>
<td>Desipramine</td>
<td>0.32</td>
<td>0.50</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>0.44</td>
<td>0.19</td>
</tr>
<tr>
<td>Nisoxetine</td>
<td>1.69</td>
<td>0.90</td>
</tr>
</tbody>
</table>

$^a$ ED$_{50}$ values for generalization to the discriminative stimulus effects of i.c.v. isoproterenol in rats, as calculated by nonlinear regression analysis (Draper and Smith, 1966; O'Donnell, 1990).

$^b$ ED$_{50}$ values for inhibition of 6-hydroxydopamine-induced depletion of heart norepinephrine in mice (Fuller, 1981).
Discriminative Stimulus Effects of Two Novel, Putative Antidepressants. Administration of 1 to 10 mg/kg L-AT, a neurokinin-1 receptor antagonist, and 0.3 to 10 mg/kg L-NNA, a nitric-oxide synthase inhibitor, did not result in isoproterenol-like discriminative stimulus effects (Fig. 4). At 10 mg/kg, the neurokinin-1 receptor antagonist resulted in 25% isoproterenol-appropriate responding. L-NNA produced, at most, 40% drug-appropriate responding; at the highest dose tested, 10 mg/kg, it caused a large increase in the latency to complete the fixed ratio schedule (Fig. 4).

Fig. 3. Effects of fluoxetine (n = 8), buspirone (n = 5), and trazodone (n = 4–6) in rats trained to discriminate 10 μg of isoproterenol from aCSF. Abscissa: dose, log scale; ordinates: mean (± S.E.M.) percentage of responses on the isoproterenol-appropriate lever (top) and mean (± S.E.M.) latency (in seconds) to complete the fixed ratio 10 requirement (bottom). When rats failed to complete the FR10, a 1200-s latency was assumed. Animals were tested 20 min after drug administration.

Fig. 4. Effects of L-AT (n = 4) and L-NNA (n = 5) in rats trained to discriminate 10 μg of isoproterenol from aCSF. Abscissa: dose, log scale; ordinates: mean (± S.E.M.) percentage of responses on the isoproterenol-appropriate lever (top) and mean (± S.E.M.) latency (in seconds) to complete the fixed ratio 10 requirement (bottom). When rats failed to complete the FR10, a 1200-s latency was assumed. Animals were tested 20 min after drug administration.

The present data provide functional evidence that administration of antidepressants with noradrenergic activity, at behaviorally relevant doses, results in activation of central β1-adrenergic receptors. Previous pharmacological characterization of the discriminative stimulus effects of isoproterenol revealed mediation by this subtype of the receptor (Crissman et al., 2001), even though isoproterenol exhibits comparable affinity for β1- and β2-adrenergic receptors (Minneman et al., 1979). Similarly, the antidepressant-like effect of centrally administered isoproterenol on DRL behavior is mediated by β1-adrenergic receptors (O’Donnell et al., 1994).

Discussion

Antidepressant drugs that enhance noradrenergic activity substituted in rats trained to discriminate centrally administered isoproterenol from aCSF. This included desipramine, protriptyline, phenelzine, mirtazapine, venlafaxine, and buspirone; the norepinephrine uptake inhibitor nisoxetine also substituted. The ability of these drugs to produce isoproterenol-like discriminative stimulus effects was antagonized by betaxolol, indicating that the effects were mediated by β1-adrenergic receptors. Previous pharmacological characterization of the discriminative stimulus effects of isoproterenol revealed mediation by this subtype of the receptor (Crissman et al., 2001), even though isoproterenol exhibits comparable affinity for β1- and β2-adrenergic receptors (Minneman et al., 1979). Similarly, the antidepressant-like effect of centrally administered isoproterenol on DRL behavior is mediated by β1-adrenergic receptors (O’Donnell et al., 1994).

The present data provide functional evidence that administration of antidepressants with noradrenergic activity, at behaviorally relevant doses, results in activation of central β1-adrenergic receptors in vivo. In contrast, previous results indicate that these drugs do not stimulate β2-adrenergic receptors in vivo. This is evidenced by the inability of desipramine, as well as other antidepressants and norepinephrine uptake inhibitors, to substitute in rats trained to discriminate the β2-adrenergic agonist clenbuterol from saline (Makhay and O’Donnell, 1999). Related neurochemical data also suggest that inhibition of norepinephrine uptake results in the stimulation of central β1-, but not β2-, adrenergic receptors. Repeated or continuous administration of such drugs reduces the density of β1-adrenergic receptors, but generally
spares β2-adrenergic receptors (Ondrey et al., 1988). This
does not reflect an intrinsic inability of the β2-subtype to
undergo desensitization because repeated treatment with the
β2-adrenergic agonist clenbuterol causes rapid and extensive
down-regulation of β2-adrenergic receptors (Frances et al.,

There seems to be a relationship between the potency with
which the norepinephrine uptake inhibitors substitute for iso-
proterenol and the potency with which they inhibit norepineph-
rine uptake in vivo. Fuller (1981) assessed the actions of such
drugs in vivo by determining their potency for antagonizing the
ability of 6-hydroxydopamine to produce norepinephrine deple-
tions in the mouse heart. The potency orders for the three
norepinephrine uptake inhibitors that were tested in that study
and the present study are the same: protriptyline > desipra-
mine > nisoxetine (Table 1); however, exact comparisons can-
not be made due to the species differences. Protriptyline is
13-fold more potent in the drug discrimination assay. This is not
surprising because in comparison of the behaviorally relevant
doses of these antidepressants in other tests (O’Donnell and
Seiden, 1982, 1984; Finnegan et al., 1987), the i.c.v. isopro-
terol drug discrimination model seems to be particularly sensi-
tive.

The ability of bupropion to substitute for isoproterenol,
together with the antagonism of this effect by betaxolol,
indicates that this drug activates central β1-adrenergic re-
cipients; however, the manner by which it does so is unclear.
Bupropion has been reported to inhibit norepinephrine up-
take and down-regulate β-adrenergic receptors (Gandolfi et
al., 1983; Alhaider and Mustafa, 1988; Ascher et al., 1995); how-
however, there are a number of contradictory reports (Bryant
et al., 1983; Ferris and Beaman, 1983; Suranyi-Cadotte et
al., 1995). In rats trained to discriminate the norepinephrine
uptake inhibitor reboxetine from vehicle, doses of 2.5 and 10
mg/kg bupropion did not substitute (Dekeyne et al., 2001). In
contrast, other norepinephrine uptake inhibitors did substitu-
t for reboxetine. This study did not examine the involve-
ment of β-adrenergic receptors in the mediation of the dis-
criminative stimulus effects of reboxetine. Overall, these
data suggest that bupropion may indirectly stimulate central
β1-adrenergic receptors by a mechanism that may not in-
volve inhibition of norepinephrine uptake.

The drugs with primarily serotonergic actions that were
tested, fluoxetine, buspirone, and trazodone, did not, in gen-
eral, substitute for isoproterenol. At 10 mg/kg, fluoxetine
administration resulted in isoproterenol-appropriate re-
sponding in one of six rats tested; the other rats failed to
complete the fixed ratio requirement. Although fluoxetine is
known to lose its serotonergic selectivity at higher doses
(Perry and Fuller, 1997), and thus might be expected to
substitute, the response rate-decreasing effects of these doses
likely precluded any such observation. The failure of the
serotonergic antidepressant drugs to indirectly stimulate β1-
adrenergic receptors in vivo is consistent with findings sug-
gest ing that activation of noradrenergic and serotonergic ac-
tivity represents parallel mechanisms (Miller et al., 1992).

Although the processes of uptake inhibition and receptor
down-regulation are common mechanisms for antidepress-
ants acting via the noradrenergic system to produce their
effects, research has shown that antidepressant-like effects
can result from modification of certain intracellular events,
independent of postsynaptic receptor stimulation; the puta-
tive antidepressants L-NNa and L-AT are thought to act via
such a process. Repeated treatment with L-NNa has been
shown to down-regulate cortical β-adrenergic receptors to an
extent comparable with that seen after repeated treatment
with imipramine (Karolewicz et al., 1999). In addition, L-
NNa produces an antidepressant-like effect in mice, reduc-
ting the time of immobility in the forced-swim test (Harkin
et al., 1999). The failure of L-NNa, at behaviorally relevant
doses, to substitute for a β1-mediated cue suggests that the
antidepressant-like effects of this drug most likely do not
involve enhancement of noradrenergic activity and stimula-
tion of central β1-adrenergic receptors.

Neurokinin biosynthesis in particular brain regions is
down-regulated after repeated administration of clinically
effective antidepressants, raising the speculation that alter-
ations in neurokinin synthesis may contribute to the efficacy
of antidepressant drugs (Barden et al., 1983; Brodin et al.,
1994; Shirayama et al., 1996). Furthermore, neurokinin-1
receptor antagonists are active in animal models sensitive to
antidepressants (Kramer et al., 1998; Papp et al., 2000). In
the present study, behaviorally relevant doses of the neuro-
kinin-1 receptor antagonist L-AT failed to generalize to the
isoproterenol cue, suggesting that, although this drug pro-
duces antidepressant-like effects, it does not do so by directly
or indirectly increasing the stimulation of central β1-
adrenergic receptors.

The noradrenergic and serotonergic systems seem to act in
a parallel manner in mediating antidepressant efficacy (Mill-
er et al., 1992). Although sufficient evidence suggests sepa-
rate targets of antidepressant activity that ultimately may
lead to a common effect, e.g., the modulation of β1-adrenergic
receptors or associated signaling molecules (Mason et al.,
1993; Papp et al., 1994; Matsumoto et al., 1995; Ye et al.,
1997, 2000; Nelson, 1999; Takahashi et al., 1999), their direct
mechanisms of action differ. The present results are consis-
tent with such an interpretation. Although drugs that inter-
act with noradrenergic neurons substituted for the discrimi-
native stimulus effects of isoproterenol, drugs that interact
with serotonergic neurons did not. Furthermore, although
antagonism of nitric-oxide synthase and neurokinin-1 recep-
tors is sufficient to produce antidepressant-like effects, stim-
ulation of the β1-adrenergic receptor does not result from admin-
istration of drugs that act via these mechanisms. Thus,
although stimulation of central β1-adrenergic receptors is
sufficient to produce antidepressant-like effects on behavior
(O’Donnell et al., 1994), it does not seem that stimulation of
these receptors is an effect shared by antidepressants from
all pharmacological classes.

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