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ORIGINAL INVESTIGATION

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Abstract Bupropion is a novel, non-tricyclic antidepressant with a primary pharmacological action of monoamine uptake inhibition. The drug resembles a psychostimulant in terms of its neurochemical and behavioural profiles in vivo, but it does not reliably produce stimulant-like effects in humans at clinically prescribed doses. Bupropion binds with modest selectivity to the dopamine transporter, but its behavioural effects have often been attributed to its inhibition of norepinephrine uptake. This experiment examines monoaminergic involvement in the discriminative stimulus effects of bupropion. Rats were trained to press one lever when injected IP with bupropion (17.0 mg/kg), and another lever when injected with saline. In substitution tests, dose-response curves were obtained for several monoamine uptake inhibitors. Nine of ten dopamine uptake blockers fully substituted for bupropion; the exception, indatraline (LU 19-005), partially substituted (71% bupropion-appropriate responding). Serotonin and norepinephrine uptake blockers (zimelidine and nisoxetine, respectively) produced negligible or limited substitution, and the anti-muscarinic dopamine uptake blocker benztropine produced limited partial substitution. A series of dopamine D_1-like and D_2-like receptor agonists were also tested: only the D_2-like agonist RU 24213 fully substituted; three other D_2-like agonists and four D_1-like agonists partially substituted (50% < drug responding < 80%). Antagonism of the discriminative effects of bupropion was obtained with a D_1- and a D_2-like dopamine antagonist. The results demonstrate strong similarities with those obtained using other dopamine uptake inhibitors as training drugs, and support the view that the behavioural effects of bupropion are primarily mediated by dopaminergic mechanisms.

Key words Bupropion · Cocaine · Dopamine transporter · Uptake inhibition · Antidepressants · Drug abuse · Drug discrimination · D_1 receptors · D_2 receptors

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Introduction

Bupropion (*dl*-2-*tert*-butylamino-3′-chloropropiophenone hydrochloride; Wellbutrin, Burroughs-Wellcome; Baltzly and Mehta 1968) is a novel antidepressant which is structurally and pharmacologically distinct from other classes of antidepressants: the tricyclics, the selective serotonin reuptake inhibitors, and the monoamine oxidase inhibitors (Soroko et al. 1977; Ferris et al. 1981). Early reports of its therapeutic efficacy (e.g. Fabre and McLendon 1978; Fann et al. 1978) have recently been supplemented by evidence that bupropion is at least as effective in the treatment of depression as the tricyclics (e.g. Workman and Short 1993; Sachs et al. 1994) and other antidepressants (Preskorn 1994). In terms of its neuropharmacological activity, bupropion is more potent than the tricyclics in blocking dopamine uptake, but is much less potent than tricyclics at blocking serotonin and norepinephrine uptake in vitro (Ferris et al. 1981). Bupropion does not stimulate dopamine release (Heal et al. 1992), nor does it enhance dopamine turnover (Nielsen et al. 1986). Its in vivo profile is consistent with these results in suggesting that its primary pharmacological action is inhibition of dopamine uptake: for example, it prevents dopamine depletion by either 6-hydroxydopamine (Canning et al. 1979) or alpha-methyl-*m*-tyrosine (Cooper et al. 1980). Thus bupropion possesses many

pharmacological characteristics in common with those psychomotor stimulants, such as cocaine, whose primary mechanism of action is thought to be blockade of dopamine uptake.

Behavioural studies have further emphasized the resemblance: in rodents, bupropion stimulates locomotor activity (e.g. Nielsen et al. 1986), suppresses eating (Zarrindast and Hosseini-Nia 1988), and increases rates of operant behaviour under several different schedules of reinforcement (McKearney 1982; Seiden et al. 1985). Studies of the discriminative stimulus effects of bupropion also reveal similarities between bupropion and psychomotor stimulants. Rats trained to discriminate bupropion from saline typically demonstrate poor substitution of tricyclics for the bupropion stimulus (Jones et al. 1980), but drug-lever selection often exceeds 80% for psychomotor stimulants which inhibit dopamine uptake or promote dopamine release, such as cocaine, *d*-amphetamine or methylphenidate (Jones et al. 1980; Blitzer and Becker 1985). Correspondingly, the discriminative stimulus effects of bupropion substitute for those of various psychomotor stimulants. For example, bupropion fully substitutes for cocaine in rats (Lamb and Griffiths 1990; Broadbent et al. 1991; Baker et al. 1993) and monkeys (Kleven et al. 1990), as well as for the selective dopamine uptake inhibitor GBR 12909 in monkeys (Melia and Spealman 1991), and for *d*-amphetamine in rats (Heal et al. 1992). If these similarities between bupropion and certain stimulants reflect enhanced dopamine transmission, it might be expected that bupropion, like many stimulants, would have reinforcing properties. Indeed, studies have documented that primates trained to self-administer cocaine would readily self-administer bupropion (Woods et al. 1983; Lamb and Griffiths 1990). Further, Ortmann (1985) showed that bupropion can produce a conditioned place preference in rats.

Despite these findings, recent electrophysiological and behavioural evidence has been presented suggesting that doses of bupropion which are behaviourally active in antidepressant tests produce their effects via norepinephrine rather than dopamine (Cooper et al. 1994). Furthermore, there are other results which are inconsistent with dopaminergic involvement in the drug's behavioural effects. For example, the drug's stimulant effects occur at doses which are not associated with inhibition of prolactin release in rats (Stern et al. 1979). Also, certain stimulants with limited dopaminergic activity, such as caffeine, can substitute for the discriminative stimulus effects of bupropion (Jones et al. 1980; Blitzer and Becker 1985), and some compounds which elevate dopaminergic transmission, such as L-dopa and bromocriptine, fail to substitute for bupropion (Blitzer and Becker 1985). The antidepressant viloxazine substitutes for bupropion at doses which *inhibit* locomotor activity, and viloxazine does not substitute for the psychomotor stimulant *d*-amphetamine (Jones et al. 1980). Finally, the drug discrimination procedure has indicated that the stimulus effects of bupropion may not be antagonized by neuroleptics (Blitzer and Becker 1985), a result which is difficult to assimilate with a role for dopamine in bupropion's stimulus effects.

In humans, bupropion fails to decrease plasma prolactin levels at acute therapeutic doses, perhaps suggesting that dopamine transmission may not be critical to its effects; however, at these doses the drug also fails to elevate growth hormone levels, unlike many specific inhibitors of norepinephrine and serotonin uptake (Laakmann et al. 1982; Whiteman et al. 1982). Other studies in humans have suggested that bupropion might differ in several ways from psychomotor stimulants. For example, unlike *d*-amphetamine, clinically prescribed doses of bupropion in healthy volunteers produce negligible effects on electroencephalogram measures, pupillary dilation, auditory vigilance or attentional processes (Hamilton et al. 1983). Most people, including experienced stimulant abusers, find therapaeutic doses of bupropion difficult to distinguish from inactive placebo (Peck et al. 1979; Miller and Griffith 1983). However, high doses have been reported to produce prominent subjective effects, including perceptual disturbances, hallucinations and vivid dreams (Becker and Dufresne 1982). We are not aware of any reports in the literature describing bupropion abuse in the patient population, or of any illicit street use of the drug, but it should be noted that the chemically related anorectic drug diethylpropion has been associated with abuse (Clein and Benady 1962; Cox et al. 1983).

In the present study, we used the drug discrimination technique to characterize more fully the role of monoamine uptake in the stimulus effects of bupropion. To date, only non-selective releasers or uptake inhibitors have been tested for substitution. Thus we first tested for substitution of uptake inhibitors having various selectivities for the different monoamine transporters. Then, given the evidence supporting a primary role for dopamine in these effects, we examined whether D_1-like or D_2-like postsynaptic dopamine receptors were preferentially involved in bupropion's discriminative stimulus effects, first by testing for substitution of dopamine receptor subtype agonists, and secondly, by testing whether dopamine receptor subtype antagonists attenuate these effects.

Materials and methods

Subjects

Male Sprague-Dawley rats (Charles Rivers, Wilmington, Mass., USA) weighing 295–390 g served as subjects. Rats were individually housed with free access to water under a 12-h light/dark cycle (lights on 0700 hours). Testing was between 1430 and 1630 hours. Rats were fed 15 g standard lab chow 30 min after testing.

Apparatus

Six two-lever operant-conditioning chambers (BRS/LVE, model RTC-022) housed within light- and sound-attenuating boxes, supplied with white noise throughout testing. Ambient illumination was by a lamp in the top center of the front panel. Levers were 17 cm apart, with a pair of red lamps above the left lever and a pair of white lamps above the right. Each lever press with a force of 0.4 N applied over 1 mm produced an audible click and was recorded as a response. Reinforced responses dispensed one 45 mg pellet (BioServe) into the centrally located food tray.

Procedure

Rats were first trained to press both levers under a fixed-ratio 1 (FR 1) schedule of food reinforcement, i.e. each response produced a food pellet. Responding on each lever was trained separately in random order, with the active lever on a given test session indicated by illumination of the lamps directly above it. The fixed-ratio value was increased from 1 to 20 (each 20th response produced food) over several training sessions. Rats were then trained to discriminate intraperitoneal (IP) injection of bupropion (17 mg/kg) from IP injection of saline, with lamps above both levers illuminated. After injection of bupropion, responses on only one lever were reinforced; after injection of saline, responses on the other lever were reinforced. The assignment of bupropion- and saline-appropriate levers was counterbalanced across rats. Rats were placed inside the test chambers immediately after injection, and there was a 5-min timeout period during which all lamps were off and responding was not reinforced. Then, all lamps were illuminated and only responses on the appropriate lever were reinforced: the FR value was reset to 20 if the rat pressed the inappropriate lever within a sequence. Sessions ended after 20 food presentations or 15 min, whichever occurred first. Each food presentation was followed by a 20-s timeout period during which all lamps were off, and responding had no scheduled consequences. Drug- and saline-training sessions were ordered in an ABBA sequence, with test sessions interposed between repetitions of a given type. Testing began for individual rats after meeting criterion performance over six consecutive training sessions. The criteria were: for drug training, at least 85% drug-appropriate responding overall and during the first FR of the session; for saline training, at most 15% drug-appropriate responding overall and during the first FR.

For testing, different doses of bupropion or other compounds were given before sessions with conditions and schedule requirements identical to training, except that 20 consecutive responses on either lever were reinforced. In addition to bupropion, a series of indirect dopamine agonists was tested, along with a selective serotonin uptake inhibitor (zimelidine), a selective norepinephrine uptake inhibitor (nisoxetine), and a series of dopamine receptor subtype agonists: D_1-like agonists (SKF 82958, SKF 38393, SKF 75670 and SKF 77434) and D_2-like agonists [pergolide, RU 24213, (−)-NPA and quinpirole]. For the antagonist tests, the D_1-like antagonist SCH 23390 or the D_2-like antagonist spiperone were injected (IP) 25 min before a given dose of bupropion. A test session was run for a given rat if it attained criterion performance on both of the immediately preceding saline- and drug-training sessions.

Drugs

The drugs tested were: bupropion HCl (Burroughs-Wellcome, Research Triangle Park, N.C., USA); (−)-cocaine HCl (National Institute on Drug Abuse, Rockville, Md., USA); GBR 12909 [1-[2-[*bis*(4-fluorophenyl)methoxy]ethyl]-4-[3-phenylpropyl]piperazine diHCl], GBR 12935 [1-[2-(diphenylmethoxy)ethyl]-4-[3-phenylpropyl]piperazine diHCl], nomifensine maleate, zimelidine diHCl, (±)SKF 82958 [(±)-6-chloro-7,8-dihydroxy-3-allyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine HBr], (±)SKF 38393 [(±)-1-phenyl-2,3,4,5-tetrahydro-(1H)-3-benzazepine-7,8-diol HCl], (±)SKF 77434 [(±)-7,8-dihydroxy-3-allyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine-7,8-diol HCl], (−)-NPA [R(-)-propylnor-apomorphine HCl], R(+)SCH 23390 [R(+)-7-chloro-8-hydroxy-3-methyl-1phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine HCl], (−)-quinpirole HCl, spiperone HCl (all Research Biochemicals Inc., Wayland, Mass., USA); WIN 35,428 [2β-carbomethoxy-3-ß-(4-fluorophenyl)-tropane 1,5-naphthalenedisulfonate; Sterling Winthrop, Rensselaer, N.Y., USA; Clarke et al. 1973]; LU 19-005 [(±)-2-(1,4-benzodioxan-2-yl)-2-imidazoline HCl; Hyttel and Larsen 1985], LU 17-133 [(−)-*cis*-1-[3-(3,4-dichlorophenyl)indan-1-yl]-4-methyl-piperazine; Bøgesø 1983; both Lundbeck A/S, Sweden]; EXP-561 [1-amino-4-phenyl-bicyclo[2,2,2]octane; DuPont Merck, Wilmington, Del., USA; Wong et al. 1977]; BTCP [*N*-[1-(2-benzo(b) thiophenyl)-cyclohexyl]piperadine; J. M. Kamenka, INSERM U249; Vignon et al. 1988]; mazindol (Sandoz Pharmaceuticals, Hanover, N.J., USA); benztropine mesylate (Aldrich Chemical Co., Milwaukee, Wisc., USA); nisoxetine HCl, pergolide mesylate (both Eli Lilly and Co., Indianapolis, Ind., USA); RU 24213 [*N*-*n*-propyl-*N*-phenylethyl-*p*-(3-hydroxy-phenyl)-ethylamine; Roussel-Uclaf, Paris, France; Euvard et al. 1979]; and SKF 75670 [3-methyl-7,8-dihydroxy-3-allyl-1-phenyl-2,3,4,5-tetrahydro-1 H-3-benzazepine HBr; Smith Kline Beecham, Philadelphia Pa., USA]. All drugs were dissolved in sterile water, with the exceptions of cocaine, bupropion, WIN 35,428 and benztropine, which were dissolved in 0.9% saline. Mazindol was first diluted in lactic acid and then adjusted to neutral pH. All drugs were injected immediately before placing the rats in the test chamber (i.e. 5 min before the schedule started), with the exceptions of the following: nisoxetine (35 min before placing the rats in the test chamber, 40 min before the session); zimelidine, LU 19–005, LU 17–133, SCH 23390 and spiperone (30 min before the session); benztropine, EXP 561 (15 min before the session). All drugs were administered IP at 1 ml/kg body weight.

Data analysis

On-line experimental control and data collection were by PDP11/73 minicomputer operating SKED software (State Systems Inc.). The response rate and the percentage of responses on the bupropion-trained lever (exclusive of behaviour during the timeout periods) were derived for individual rats. Means were calculated for each measure at each drug dose tested. Any rat failing to emit at least 20 responses was not included in the calculation of mean drug-appropriate responding at that dose. If more than three of six rats tested at a given dose failed the response rate requirement, no mean value was calculated for percentage of drug-appropriate responding at that dose. At least 20% drug-appropriate responding was adopted as a conservative criterion at which to assume a significant difference from saline; 80% or higher drug-appropriate responding was taken as similar to the training dose. ED50 values and their 95% confidence limits were calculated using standard ANOVA and linear regression techniques (Snedecor and Cochran 1967).

Results

The mean number of training sessions required for acquisition of the discrimination was 52.1 (SE = 10.1) sessions. Bupropion maintained reliable discriminative control throughout the study (drug-appropriate responding > 93%), and the dose-effect function for bupropion was stable over time. ED_{50} values for bupropion from four separate determinations, spanning more than a year, are presented in Table 1. All values are similar:

there were no significant differences in the potency of the drug between these replications (see Table 1).

Cocaine, the cocaine analog WIN 35,428, and the specific dopamine uptake inhibitors GBR 12909 and GBR 12935, each fully substituted for bupropion (Fig. 1). In addition, all of the drugs reduced response rates with an order of potency that was similar to that obtained for discriminative stimulus substitution (Fig. 1). Six other drugs which inhibit monoamine uptake were tested for substitution of their discriminative stimulus effects for those of bupropion (Fig. 2). The atypical antidepressants nomifensine and mazindol, and the putative antidepressant LU 17-133, all fully substituted for bupropion. Similarly, the phencyclidine-derived dopamine uptake inhibitor BTCP, and the non-specific monoaminergic uptake inhibitor EXP 561, also fully substituted. LU 19-005 was the only uptake inhibitor not to substitute fully: maximum bupropion-appropriate responding was 71% at 5.6 mg/kg. Again, all of the drugs suppressed response rates in a dose-dependent manner.

The ED_{50} values for substitution for the discriminative stimulus effects of bupropion are shown in Table 2. WIN 35,428 was the most potent compound, and was approximately 40 times more potent on a molar basis than GBR 12909, which had the lowest in vivo potency. The other compounds had potencies which were generally distributed uniformly within these two extremes.

Since bupropion also inhibits the uptake of norepinephrine and serotonin to some extent, specific uptake inhibitors of each monoamine were tested (Fig. 3). Neither the norepinephrine uptake inhibitor, nisoxetine (maximum bupropion-appropriate responding 22.5% at 17 mg/kg), nor the serotonin uptake inhibitor zimelidine (maximum bupropion-appropriate responding 2.7% at 17 mg/kg), fully substituted for the discriminative stimulus effects of bupropion. Both drugs reduced response rates dose-dependently, thus precluding the testing of higher doses and demonstrating that tests for bupropion-like discriminative stimulus effects were conducted across the range of behaviourally active doses. The muscarinic antagonist benztropine, a drug which also inhibits dopamine uptake, substituted partially and dose-dependently (maximum bupropion-appropriate responding 41.3% at 10 mg/kg), and also reduced response rates (Fig. 3).

The relative contributions of dopamine receptor subtypes to the mediation of bupropion's discriminative stimulus effects were assessed by testing for substitutions of D_1-like and D_2-like agonists. None of the D_1-like agonists SKF 82958, SKF 38393, SKF 77434 and SKF 75670 fully substituted for the stimulus effects of bupropion (Fig. 4). The maximal efficacy in substitution for bupropion was obtained with SKF 82958, which marginally failed to yield full substitution (maximum bupropion-appropriate responding: 79%). The other D_1-like agonists produced partial substitution, with maximal effects ranging from 52% (SKF 75670) to 67% (SKF 38393). For both bupropion-like discriminative stimulus effects and response rate effects, SKF 82958 and SKF 77434 were equipotent, followed by SKF 75670, with SKF 38393 least potent.

The effects of the D_2-like agonists quinpirole, pergolide, RU 24213 and (−)-NPA are shown in Fig. 5. Of these drugs, only RU 24213 produced full substitution (maximum bupropion-appropriate responding: 87%). The maximal efficacy of the other D_2-like agonists ranged from 57% (quinpirole) to 69% (pergolide). The order of potency was similar for both discriminative stimulus effects and response rate effects, with (−)-NPA most potent followed by quinpirole, pergolide, and RU 24213.

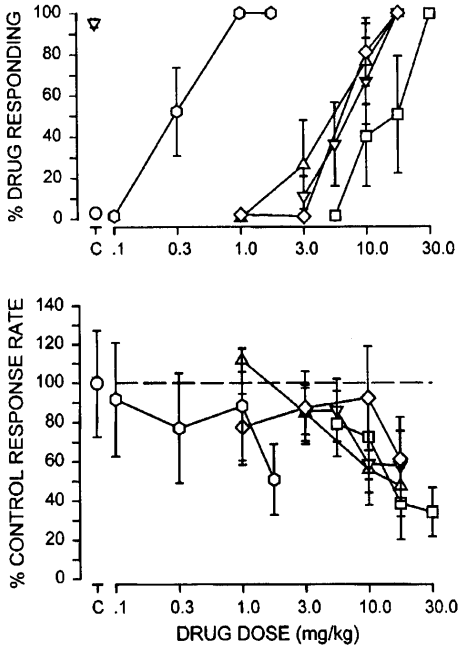

Fig. 1 *Top panel* Effects of monoamine uptake inhibitors bupropion, cocaine, GBR 12909, GBR 12935 and WIN 35,428 on the percentages of responses on the bupropion-correlated lever in rats. Each point represents performance in a minimum of three rats out of at least six rats tested at each dose, except for WIN 35,428 ($n = 5$ at all points). *Lower panel* Effects of the same compounds on rates of responding expressed as a percentage of saline control response rates. Each point represents all subjects tested (at least six rats) at each dose, except for WIN 35,428 ($n = 5$). *Vertical bars* on all points represent ± 1 SEM; at points for which no bars are apparent the point encompasses the error. Δ Cocaine, ∇ bupropion, □ GBR 12909, ◇ GBR 12935, ○ WIN 35, 428, ○ saline

Table 1 ED_{50} values for bupropion on four replications

Drug	ED_{50} value (mg/kg)	95% CL
Bupropion – 1st determination	6.77	5.01–9.16
Bupropion – 2nd determination	6.42	5.43–7.58
Bupropion – 3rd determination	7.28	5.61–9.46
Bupropion – 4th determination	7.12	5.83–8.71

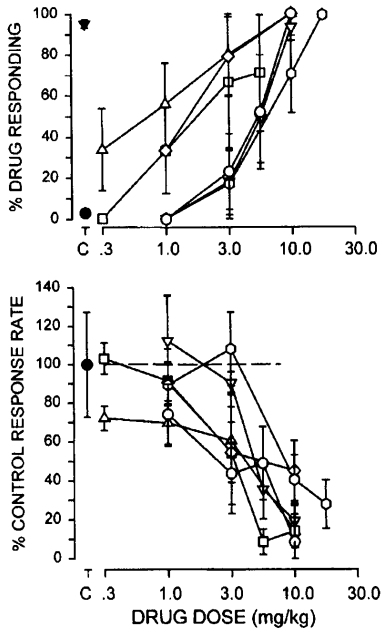

Fig. 2 *Top panel* Effects of the monoamine uptake inhibitors mazindol, nomifensine, BTCP, LU 19-005, LU 17-133 and EXP 561 on the percentages of responses on the bupropion-correlated lever in rats. Each point represents performance in a minimum of three rats out of at least six rats tested at each dose. *Lower panel* Effects of the same compounds on rates of responding expressed as a percentage of saline control response rates. Each point represents all subjects tested (at least six rats) at each dose. *Vertical bars* on all points represent ± 1 SEM; at points for which no bars are apparent the point encompasses the errors. ● Saline, ▼ bupropion, Δ mazindol, ∇ BTCP, □ LU 19-005, ◇ nomifensine, ○ LU 17-133, ○ EXP 561

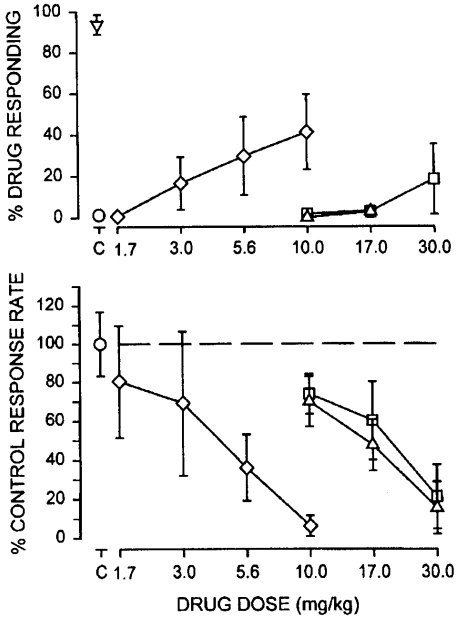

Fig. 3 Effects of the norepinephrine uptake inhibitor nisoxetine, the serotonin uptake inhibitor zimelidine and the anticholinergic agent benztropine on the percentages of responses on the bupropion-correlated lever in rats (*top panel*). Effects of the same compounds on rates of responding expressed as a percentage of saline response rates are shown in the *lower panel*. Data are included using the criteria as indicated in Figs. 1 and 2. *Vertical bars* on all points represent ± 1 SEM; at points for which no bars are apparent the point encompasses the error. ○ Saline, ∇ bupropion, □ nisoxetine, Δ zimelidine, ◇ benztropine

Table 2 Binding affinities at the dopamine transporter and substitution potencies for bupropion

Drug	ED_{50} (μmols/kg)	Ki (nM)[a]
WIN 35, 428	0.58	7
Mazindol	2.46	16
Nomifensine	4.35	12
LU 19-005	6.05	8
LU 17-133	11.68	25
Cocaine	13.44	32
GBR 12935	13.52	13
BTCP	13.93	10
EXP 561	21.64	84
Bupropion	24.53	118
GBR 12909	25.42	12

[a]Derived from displacement of [^{3}H]WIN 35,428; values from Izenwasser et al. (1994)

The effects of the D_1-like antagonist, SCH 23390, and the D_2-like antagonist, spiperone, in combination with the training dose of bupropion are presented in Fig. 6. Both compounds reduced drug-appropriate responding at the higher doses. In addition, both antagonists reduced response rates dose-dependently when administered alone (filled symbols). Further, the decreases in drug-appropriate responding produced by the training dose of bupropion were obtained only at doses of either antagonist that markedly disrupted rates of responding. SCH 23390 was marginally more potent than spiperone in antagonizing the discriminative stimulus effects of bupropion (Table 3).

Pretreatment with the D_1 antagonist produced a dose-dependent shift to the right in the bupropion dose-effect curve, with 0.03 mg/kg essentially inactive (Fig. 7, compare filled circles to open squares). The ED_{50} value in the presence of SCH 23390 was nearly identical to that obtained in its absence (Table 3). At the higher dose of SCH 23390, response rates were substantially decreased, though an antagonism of the discriminative effects of bupropion was evident with a shift to the right in its dose-effect curve (Fig. 7, compare filled circles to open triangles). The significant antagonism of bupropion is indicated by the lack of overlap in the respective 95% confidence limits for the bupropion ED_{50} values when administered alone and when administered with the 0.1 mg/kg dose of SCH 23390.

Pretreatment with the D_2 antagonist also produced a dose-dependent shift to the right in the bupropion dose-effect curve with 0.1 mg/kg essentially inactive

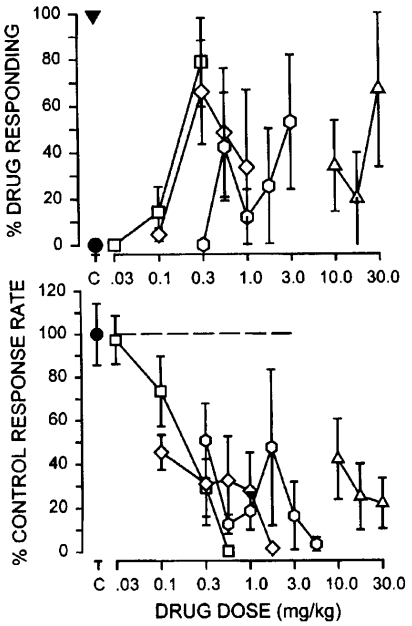

Fig. 4 Effects of the D_1-like agonists SKF 82958, SKF 77434, SKF 75670 and SKF 38393 on the percentages of responses on the bupropion-correlated lever in rats (*top panel*). Effects of the same compounds on rates of responding expressed as a percentage of saline response rates are shown in the *lower panel*. Data are included using the criteria as indicated in Figs. 1 and 2. *Vertical bars* on all points represent ± 1 SEM; at points for which no bars are apparent the point encompasses the error. ▼ Bupropion, ● saline, □ SKF 82958, Δ SKF 38393, ◇ SKF 77434, ○ SKF 75670

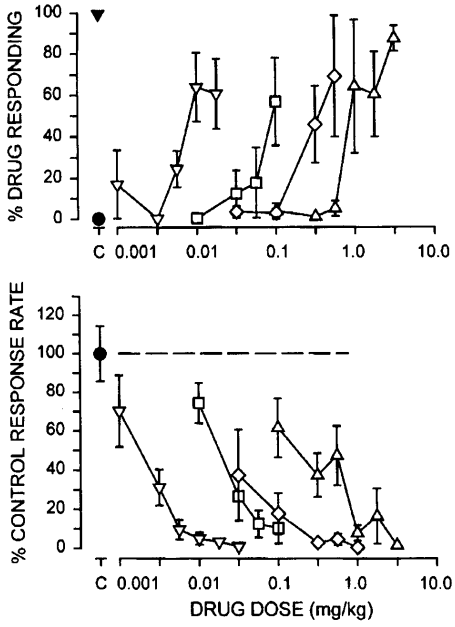

Fig. 5 Effects of the D_2-like agonists (−)-NPA, quinpirole, pergolide and RU 24213 on the percentages of responses on the bupropion-correlated lever in rats (*top panel*). Effects of the same compounds on rates of responding expressed as a percentage of saline response rates are shown in the *lower panel*. Data are included using the criteria as indicated in Figs. 1 and 2. *Vertical bars* on all points represent ± 1 SEM; at points for which no bars are apparent the point encompasses the error. ▼ Bupropion, ● saline, □ quinpirole, Δ RU 24213, ∇ (−)-NPA, ◇ pergolide

(Fig. 8, compare filled circles to open triangles; Table 3, ED_{50} values with overlapping 95% confidence limits). At the higher dose, an antagonism of the discriminative effects of bupropion was evident as an approximate two-fold shift to the right in its dose-effect curve (Fig. 8, compare filled circles to open diamonds; Table 3).

Table 3 ED_{50} values for interactions of bupropion with dopamine antagonists

Drug	ED_{50} value (μmol/kg)	95% CL
SCH 23390 + bupropion 17 mg/kg	0.34	0.12–0.86
Spiperone + bupropion 17 mg/kg	1.06	0.30–3.75
Bupropion alone	26.36	20.31–34.25
Bupropion + 0.03 SCH 23390	26.54	17.78–39.68
Bupropion + 0.1 SCH 23390*	73.93	49.96–110.27
Bupropion + 0.1 spiperone	24.76	22.52–27.19
Bupropion + 0.3 spiperone*	46.56	42.54–51.15

*Significantly different from bupropion alone based on the lack of overlap of 95% confidence limits

Discussion

Discriminative control of performance by bupropion was maintained at a high level throughout the study, in accordance with Jones et al. (1980), who trained various doses of bupropion and concluded that doses above 10 mg/kg were necessary to maintain reliable responding. In that study, a training dose of 20 mg/kg permitted testing over 18 months without difficulty. The only other study examining the discriminative stimulus effects of bupropion used a training dose of 40 mg/kg (Blitzer and Becker 1985).

Of the drugs tested here, only nomifensine and cocaine have previously been shown to substitute for bupropion (Jones et al. 1980; Blitzer and Becker 1985). There are several reports of bupropion cross-generalizing to the discriminative stimulus effects of cocaine in various species: rats (Lamb and Griffith 1990; Broadbent et al. 1991; Baker et al. 1993), rhesus monkeys (Kleven et al. 1990), and pigeons (Johanson and Barrett 1993). Given such cross-generalization, it might be expected that cocaine and its structural analog, WIN 35,428, would fully substitute for bupropion. Similarly, bupropion has been shown to substitute fully for the selective dopamine uptake inhibitor GBR 12909 (Melia and Spealman 1991). Accordingly, in the present study GBR 12909 and its structural and functional analog,

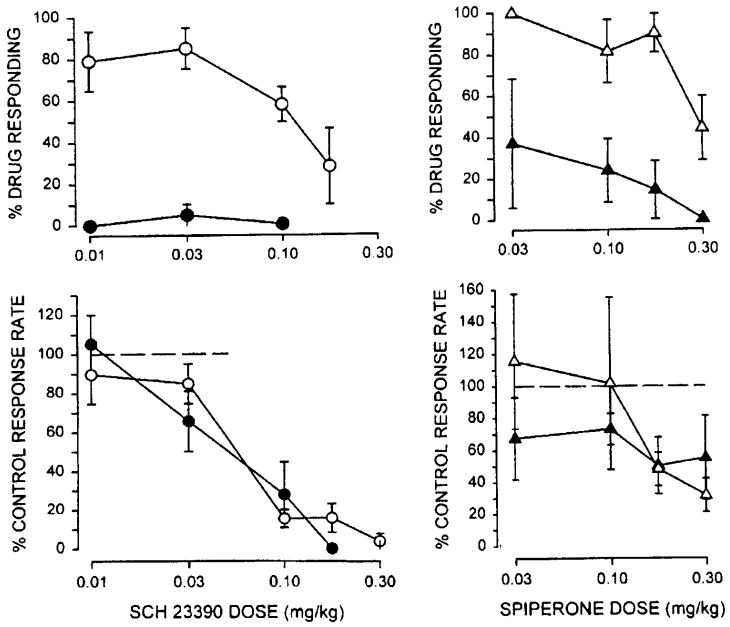

Fig. 6 Effects of the dopamine antagonists, SCH 23390 and spiperone, alone and in combination with the training dose of bupropion. *Filled symbols* Effects of SCH 23390 (*left panel*) and spiperone (*right panel*) on the percentage of responses on the bupropion-correlated lever (*top panels*). Each point for SCH 23390 represents performance in a minimum of six subjects out of at least six to 11 subjects tested at each dose. Each point for spiperone represents performance in a minimum of three subjects out of at least five to six subjects tested at each dose. Effects of the same compounds on rates of responding expressed as a percentage of saline response rates are shown in the *lower panels*. Effects of the antagonists in combination with the training dose (17 mg/kg) of bupropion are represented by the *open symbols*. Each point represents all subjects tested at each dose. *Vertical bars* on all points represent ±1 SEM; at points for which no bars are apparent the point encompasses the error. ● SCH 23390, ○ SCH 23390 + bupropion 17.0, ▲ spiperone, △ spiperone + bupropion 17.0

GBR 12935 (Berger et al. 1985; Andersen 1987), fully substituted for bupropion.

Indeed, with the single exception of LU 19-005, all of the monoamine uptake inhibitors tested that are effective in inhibiting the uptake of dopamine fully substituted for bupropion. Bupropion discriminative effects were produced by these drugs, regardless of their relative selectivities among the transporters. For example, similar to GBR 12909 and GBR 12935, BTCP binds with high affinity to the dopamine transporter and is a potent inhibitor of dopamine uptake, with high selectivity for inhibition of dopamine uptake relative to the other monoamines (Vignon et al. 1988). In contrast, nomifensine (Heikkila and Manzino 1984; Andersen 1987, 1989), EXP 561(albeit with less potency, Wong et al. 1977), and to a lesser extent mazindol (Heikkila and Manzino 1984; Andersen 1989) are relatively selective in inhibiting the uptake of norepinephrine. LU 17-133, which has approximately equal

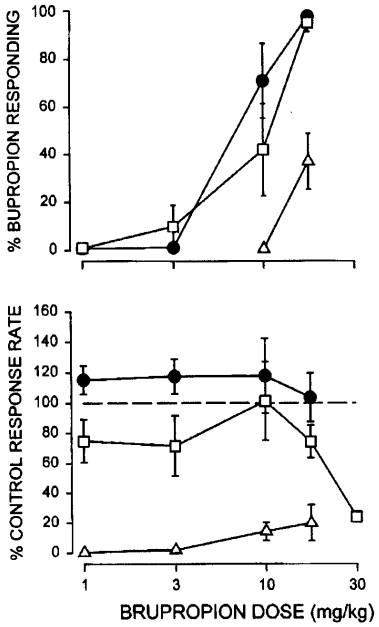

Fig. 7 Antagonism of the dose-effects of bupropion by the D_1-like antagonist SCH 23390 in rats trained to discriminate bupropion from saline injections. *Upper panel* Percentages of responses on the bupropion-correlated lever; *lower panel* rates of responding expressed as a percentage of saline response rates. Data are included using the criteria as in Figs. 1 and 2. *Vertical bars* on all points represent ± 1 SEM; at points for which no bars are apparent the point encompasses the error. ● Bupropion, □ +0.03 SCH 23390, Δ +0.1 SCH 23390

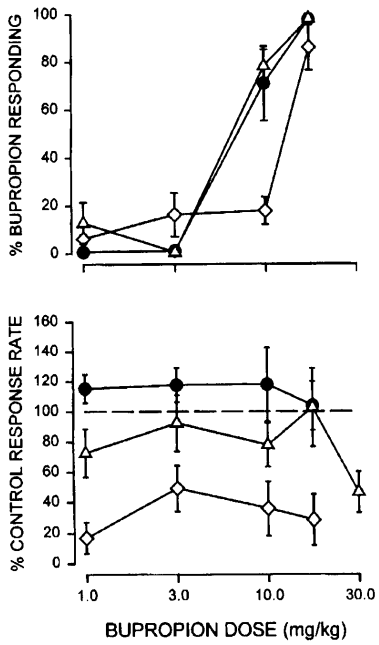

Fig. 8 Antagonism of the dose-effects of bupropion by the D_2-like antagonist spiperone in rats trained to discriminate bupropion from saline injections. *Upper panel* Percentages of responses on the bupropion-correlated lever; *lower panel* rates of responding expressed as a percentage of saline response rates. Data are included using the criteria as in Figs. 1 and 2. *Vertical bars* on all points represent ± 1 SEM; at points for which no bars are apparent the point encompasses the error. ● Bupropion, Δ +0.1 spiperone, ◇ +0.3 spiperone

potency for inhibition of dopamine and norepinephrine uptake and relatively lower potency for inhibition of serotonin uptake (Hyttel et al. 1988), also fully substituted for bupropion. The one uptake inhibitor that did not fully substitute, LU 19-005, inhibits uptake of dopamine, serotonin and norepinephrine with relatively similar, high potencies (Hyttel and Larsen 1985). In contrast to the present findings with bupropion, LU 19-005 has been shown to substitute fully for the *d*-amphetamine discriminative stimulus (Hyttel et al. 1988). Although the injection-test interval and route of administration differed between studies (30 min IP here, versus 75 min SC in the earlier study), these factors might be expected to affect potency rather than efficacy. However, LU 19-005 has an unusually long duration of action, with effects detectable over 2 days after administration (e.g. Rosenzweig-Lipson et al. 1992); perhaps more importantly, of all the compounds tested here, it is unique in having a high affinity for the serotonin transporter.

LU 17-133, a structurally related indan derivative of LU 19-005, has an in vitro profile more similar to that of mazindol or nomifensine. Like those drugs, it fully substituted for bupropion in the present study. However, in a previous study it did not substitute for a *d*-amphetamine discriminative stimulus (Hyttel et al. 1988). Again, differences between the studies in terms of route of administration and injection-test interval (2 h in the study by Hyttel et al.) might have played a role.

To assess further the relationship between pharmacological activity at the dopamine uptake site and substitution for the discriminative stimulus effects of bupropion, a correlation was calculated for the relationship between the substitution potencies of the uptake inhibitors and their affinities for binding to the dopamine transporter (binding data from Izenwasser et al. 1994). Table 2 presents binding affinities (K_i values in nM) at the dopamine transporter determined by displacement of [^{3}H]WIN 35,428, and substitution potencies (ED_{50} μmol/kg) for each test compound from the present study. For several of these compounds, the binding could be modelled significantly better for two sites than for one site (Izenwasser et al. 1994). For these drugs the K_i value for the high-affinity site is given in the table. The correlation between measures was $R = 0.57$ ($P = 0.065$). However, GBR 12909, and to a lesser extent GBR 12935, were much less potent in vivo than would be expected based on their affinities for the dopamine transporter. This finding is consistent with a number of previous findings which show that these analogs do not readily penetrate the CNS (e.g. Bonnet and Costentin 1986; Bergman et al. 1989; Kelley and Lang 1989; Spealman et al. 1989; Howell and Byrd 1991; Melia and Spealman 1991; Pögün et al. 1991). Eliminating both GBR 12909 and GBR 12935 from the regression analysis yielded a stronger correlation: $R = 0.72$, $P = 0.028$). The finding that these compounds substitute with less potency than would be predicted from their binding profiles may be explained by the short pretreatment times adopted for these drugs in the present study. A longer pretreatment time would have allowed these compounds to achieve higher concentrations at their sites of activity and therefore would likely have allowed the overall correlation to approximate more closely that found without their inclusion.

A relationship between the binding affinity of drugs at the dopamine uptake site and their effects on behaviour has been identified in other species and behavioural assays. Thus Spealman et al. (1989) reported a high correlation between drug potencies for displacing [^{3}H]cocaine in primate striatum with their potencies in producing stimulant behavioural effects. Bergman et al. (1989) reported a weaker relationship between the same in vitro measure and the potencies of the drugs for maintaining self-administration behaviour. Ritz et al. (1987) showed that the correlation among potencies in maintaining self-administration and affinity for the dopamine transporter was high, and greater than that for behavioural potency and affinity for either the norepinephrine or the serotonin transporter. The locomotor stimulant effects of cocaine analogs have been shown to correlate with their in vivo displacement of

[^{3}H]WIN 35,428 (Cline et al. 1992), but dopamine uptake inhibitors structurally dissimilar from cocaine may not follow this trend (Vaugeois et al. 1993; Izenwasser et al. 1994). The present study extends previous findings to the discrimination of bupropion using a structurally diverse set of compounds, and suggests that the discriminative effects of bupropion are mediated by indirect dopaminergic agonist actions.

Compounds that selectively inhibit the uptake of serotonin or norepinephrine (zimelidine and nisoxetine, respectively) did not substitute for bupropion, a finding consistent with the literature on the discriminative stimulus effects of other dopamine uptake inhibitors, such as cocaine (e.g. Colpaert et al. 1979; McKenna and Ho 1980; Broadbent et al. 1991; Cunningham and Callahan 1991; but see Terry et al. 1994) and GBR 12909 (Melia and Spealman 1991). On the other hand, benztropine is a potent dopamine uptake inhibitor (e.g. Coyle and Snyder 1969) which substituted only partially. Ambivalent results have been presented regarding substitution of benztropine for cocaine; the present results are in accord with those, e.g. Colpaert et al. (1979), who report partial substitution, and imply that the drug's actions at non-dopaminergic sites mitigate against full substitution. Antimuscarinic effects of benztropine are not likely those that limit its full substitution because these actions have been shown previously to potentiate the effects psychomotor stimulant drugs such as cocaine (e.g. Wilson and Schuster 1975).

Partial substitution was also found for most of the D_1-like and D_2-like direct agonists tested, with only the D_2-like agonist RU 24213 fully substituting (albeit that the D_1-like agonist SKF 82958 produced near-complete substitution). Similar results have been reported for cocaine-trained rats (e.g. Barrett and Appel 1989; Callahan et al. 1991; Witkin et al. 1991), and GBR 12909-trained monkeys (Melia and Spealman 1991). In most of these studies, D_1-like agonists substituted for dopamine uptake inhibitors with efficacies similar to, or less than, those of D_2-like agonists, although recently it has been suggested that substitution by D_1-like agonists in cocaine-trained rats may be preferentially favoured at low training doses of cocaine (Terry et al. 1994).

With the exception of quinpirole, relative potencies of the D_2-like agonists [(−)-NPA > quinpirole > pergolide > RU 24213] are in accordance with their affinities for the D_2 receptor [(−)-NPA > pergolide > RU 24213 > quinpirole; Arnt and Hyttel 1988; Andersen and Jansen 1990]. For the D_1-like agonists, SKF 75670 was less potent behaviourally than might be expected from the affinities of these drugs for the D_1 receptor (behaviourally: SKF 82958 > SKF 77434 > SKF 75670 > SKF 38393; binding: SKF 82958 > SKF 75670 > SKF 77434 > SKF 38393; Arnt and Hyttel 1988; Andersen and Jansen 1990). Quinpirole's unexpected behavioural potency may reflect its high affinity for the D_3 receptor subtype (e.g. Sokoloff et al. 1990), but this cannot be confirmed until the binding characteristics of all compounds at the various dopamine receptor subtypes are available. It is not clear why RU 24213 should be the most efficacious agonist in substitution tests. Although RU 24213 is unusual in having kappa antagonist properties (Fortin et al. 1991), a characteristic associated with dopamine release (e.g. Werling et al. 1988; Devine et al. 1993), the drug has not previously exhibited full substitution for the dopamine uptake inhibitor cocaine (Witkin et al. 1991). It may be more parsimonious to attribute full substitution here to a wider separation between discriminative stimulus and rate suppressant effects.

In one of the original characterizations of the discriminative stimulus effects of bupropion (Blitzer and Becker 1985), it was concluded that there was little evidence to support a role for dopamine in the drug's discriminative stimulus effects. This conclusion was based on the findings of limited substitution by L-dopa and bromocriptine, and the failure of neuroleptics to block the bupropion discriminative stimulus. It should be noted that some similar results have been reported concerning the discriminative stimulus effects of the dopamine uptake blocker cocaine: namely, limited substitution of bromocriptine (e.g. Broadbent et al. 1991), and ineffective antagonism by neuroleptics (e.g. Colpaert et al. 1976; Witkin et al. 1991). The present results show that D_2-like agonists other than bromocriptine can fully substitute for bupropion. The discrepancy between studies might arise because the substitution of bromocriptine for dopamine uptake inhibitors is critically dependent upon kinetic factors (cf. Callahan and Cunningham 1993). The involvement of D_2-like receptors is further supported by the antagonism tests reported here: these clearly indicate that both D_1-like and D_2-like receptors are involved in bupropion's discriminative stimulus effects. It is unclear why a previous attempt to block these effects using neuroleptics was unsuccessful (Blitzer and Becker 1985); though the high training dose of bupropion (40 mg/kg) might have been responsible. As can be seen in Figs. 7 and 8, the antagonists potentiated the effects of bupropion on response rates. At a higher bupropion dose, an even greater effect on response rates would be expected and would probably obscure the antagonism.

As regards the finding that either a D_1-like or a D_2-like antagonist was effective at blocking bupropion's stimulus effects, analogous results have been reported for receptor subtype antagonists in combination with other dopamine uptake inhibitors, such as cocaine (e.g. Spealman et al. 1991) and GBR 12909 (e.g. Melia and Spealman 1991). Other behavioural effects of bupropion, e.g. sniffing, have also been shown susceptible to reversal by either a D_1-like or a D_2-like antagonist (Zarrindast et al. 1996).

Recent data challenging the role of dopamine in the behavioural effects of bupropion have been presented

by Cooper et al. (1994). These authors reported that the behavioural and electrophysiological effects of bupropion are more likely to be mediated by norepinephrine than by dopamine. The IC50 dose of bupropion for inhibition of neural firing in the locus coeruleus (13 mg/kg) was of a similar magnitude to the doses which produce behavioural effects in antidepressant models, whereas a four-fold higher dose was necessary to inhibit the firing of dopamine neurons and to produce stimulation of behaviour. However, the fact that electrophysiological effects of bupropion were recorded in an area populated by noradrenergic neurons does not imply that the drug's effects are necessarily mediated by noradrenergic rather than dopaminergic mechanisms of action. Moreover, the minimally effective doses in the locus coeruleus and A10 regions appeared to be similar, with dose-effect curves for the two regions differing primarily in maximal effect and slope. Finally, because the training dose used in the present study was not dissimilar from doses which are behaviourally active in antidepressant tests, it would certainly be premature to discount dopaminergic mediation of the behavioural effects observed in antidepressant assays.

Thus the present results, namely, the correlation between substitution potencies of monoamine uptake inhibitors with their binding affinities for the dopamine uptake site, the limited substitutions of serotonin and norepinephrine uptake inhibitors, the (at least) partial substitution of diverse direct agonists, and the attenuation of the stimulus effects by dopamine D_1- and D_2-like antagonists, all strongly argue for dopaminergic mediation of bupropion's discriminative stimulus effects. Interestingly, these dopaminergic effects were obtained at a training dose which is not associated with inhibition of prolactin secretion (Stern et al. 1979), suggesting a dissociation between dopaminergic involvement in the hormonal and stimulus effects of bupropion. In other respects, the drug discrimination procedure has emphasized the similarities between bupropion and psychomotor stimulant drugs, and suggests that differentiating between dopamine uptake inhibitors using such a procedure may be difficult.

Finally, because bupropion appears to have low abuse liability and competes for sites through which cocaine exerts its activity, it may be deserving of further consideration as a therapeutic agent for psychostimulant addiction. Open clinical studies using bupropion (Avants et al. 1993; Margolin et al. 1995; Montoya et al. 1996) as a treatment for cocaine abusers have provided some documentation of potential that might be established in more rigorous clinical evaluation.

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