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Nicotine and bupropion share a similar discriminative stimulus effect

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Abstract

Bupropion is a weakly potent central nervous system (CNS) stimulant that is marketed both as an antidepressant and as an anti-smoking aid. The mechanism(s) by which it produces its effects is not well understood. In the present study, the effect of bupropion was examined in rats trained to discriminate the stimulus effect of 0.60 mg/kg of (−)-nicotine from saline in a two-lever drug discrimination task. In tests of stimulus generalization (substitution), the nicotine (ED_{50} = 0.17 mg/kg) stimulus completely generalized to bupropion (ED_{50} = 5.50 mg/kg). In addition, interaction studies were conducted that evaluated the effect of 3.0 mg/kg of bupropion, a dose that when given alone produced saline-appropriate responding, in combination with various doses of nicotine. This application resulted in an enhancement of the potency of nicotine (ED_{50} = 0.05 mg/kg), as indicated by a leftward shift of the nicotine dose–effect function. In tests of stimulus antagonism, various doses of bupropion were administered prior to the training dose of nicotine and were found to be ineffective as antagonists of the nicotine stimulus. In contrast, the nicotinic acetylcholine receptor (nicotine receptor) antagonist mecamylamine (AD_{50} = 0.40 mg/kg) completely blocked the stimulus effect of nicotine. Mecamylamine did not attenuate the stimulus generalization of bupropion. The results demonstrated that bupropion can produce a nicotine-like response in nicotine-trained animals, but it does so via a mechanism of action that is unlike that of nicotine. It is speculated that bupropion may be somewhat effective as an anti-smoking treatment in people who are motivated to quit smoking because low doses of bupropion produce a nicotine-like effect(s) that serve as a suitable substitute for nicotine.

Keywords: Mecamylamine; Stimulant; Smoking; Depression

1. Introduction

Nicotine is the principal constituent of tobacco (*Nicotiana tabacum*) and appears to be responsible for the maintenance of tobacco consumption by smokers. Typically, nicotine is absorbed in small amounts from inhaled smoke and quickly distributed throughout the body, where it exerts potent effects on both the peripheral and central nervous systems. In fact, the mechanism responsible for the continuation of smoking behavior appears to involve the interaction of nicotine at central nicotinic acetylcholine receptors and eventual increases in dopamine activity in the nucleus accumbens, an area of the brain thought to be important to drugs of abuse (e.g., Corrigall et al., 1994; Di Chiara and Imperato, 1988).

Tobacco smoking is a major health concern and many people have stopped smoking or attempted to quit smoking. Most smokers find it difficult to quit and, as might be expected, various products have been marketed as aids for smoking cessation. These include nicotine-replacement therapies in combination with counseling/behavioral modification programs. This approach provides the user with nicotine through gum, patches, nasal spray, or oral inhaler. The strategy is to replace the nicotine that is no longer being absorbed through inhaled smoke and to gradually diminish the body's urge for nicotine (for review, see Raw et al., 1998). Psychological counseling is considered to be an essential feature of the therapy. These delivery systems are thought to be equally effective, with about 20% of those that received therapy not smoking at 1 year and up to 10% remaining non-smokers if treatment is continued (e.g., Britton and Jarvis, 2000; Raw et al., 1998).

Recently, bupropion, a weakly potent central nervous system (CNS) stimulant that is marketed as an antidepressant agent, was approved to be marketed as an aid to smoking cessation. Clinical studies have shown that the administration of bupropion, in combination with counseling, produces comparable efficacy to nicotine replacement therapies at the 1-year benchmark for smoking cessation

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(Britton and Jarvis, 2000; Harrison, 2001; Hurt et al., 1997; Jorenby at al., 1999). However, the mechanism by which it facilitates smoking cessation is not well understood. Early studies of bupropion for its antidepressant indication suggested that it functioned as a weak dopamine and/or norepinephrine agonist through inhibition of catecholamine reuptake (e.g., Butz et al., 1982; Dufresne et al., 1984, 1985; Ferris et al., 1982). More recent studies have indicated that bupropion blocked the effect of nicotine in a number of behavioral assays in mice (Fryer and Lukas, 1999; Slemmer et al., 2000). The fact that bupropion appears to be the first non-nicotine compound shown to be somewhat effective in smoking cessation has led to renewed interest in its actions.

A particularly useful procedure for examining the central effects of chemical agents is drug discrimination. In this assay, for example, human or non-human animals can be trained to perform a response (e.g., right-side lever-press) after a particular dose of nicotine has been administered and to complete a different response (left-side lever-press) after saline vehicle has been delivered. The nicotine or non-drug treatment is used to inform the animal to make the appropriate response in order to gain a reinforcer. In order to establish the discrimination, nicotine must be given repeatedly to subjects—a requirement that makes the paradigm somewhat analogous to the human smoker (for review, see Rosecrans, 1989). Once acquired, stimulus generalization (substitution) and antagonism tests can be performed to determine if a test compound can mimic or block the effect of the training drug. Such tests have indicated that nicotine exerts its stimulus effect, at least in part, through an interaction at nicotine receptors; in particular, at a subtype of nicotine receptors termed $\alpha4\beta2$ receptors (e.g., Stolerman et al., 1997). This conclusion is based on the fact that the stimulus effect of nicotine is blocked by mecamylamine, a nonselective receptor antagonist of nicotine receptors antagonist, and dihydro-β-erythrodine, a nicotine receptor antagonist that shows high affinity for the $\alpha4\beta2$ subunit (e.g., Hirschhorn and Rosecrans, 1974; Kumar et al., 1987; Rose et al., 1989; Shoaib et al., 2000). Although nicotine has been the subject of numerous discrimination studies, bupropion has received limited attention as a training drug (Blitzer and Becker, 1985; Jones et al., 1980; Terry and Katz, 1997). In these latter studies, bupropion stimulus generalization occurred to several CNS stimulants and catecholamine uptake inhibitors. The compounds included (+)-amphetamine, caffeine, cocaine, methylphenidate, mazindol, nomifensine, and GBR 12909 (1-(2-(bis-(4-fluorophenyl)methoxy)ethyl)-4-(3-phenylpropyl)piperazine). On the other hand, dopamine receptor antagonists have been shown to have no effect (Blitzer and Becker, 1985) or block (Terry and Katz, 1997) the stimulus effect of bupropion; inconsistent data that hinder the establishment of a definitive bupropion–catecholamine interaction. To date, a detailed evaluation of the stimulus properties of nicotine and bupropion has not been reported. A review of the drug discrimination literature revealed an abstract by Cohen et al. (1999) that indicated partial generalization (63–75%) of bupropion in rats trained to discriminate nicotine from saline. Unfortunately, a full report of the study's methodology and results has not yet appeared in the literature. Thus, the present investigation was undertaken to establish a more detailed description and comparison of the stimulus activities of these two agents. Specifically, animals were trained to discriminate the stimulus effect of 0.60 mg/kg of nicotine from saline vehicle. Once achieved, tests of stimulus generalization were conducted with bupropion. In addition, a number of interaction studies were performed that evaluated the effect of various doses of bupropion in combination with various doses of nicotine. In a final series of comparative tests, the nicotine receptor antagonist mecamylamine was evaluated in combination with nicotine and bupropion.

2. Materials and methods

2.1. Animals

The animals were eight male Sprague–Dawley rats (Charles River Laboratories) weighing 300–350 g at the beginning of the study. The animals were housed individually and, prior to the start of the study, their body weights were reduced to approximately 80% of their free-feeding weight. During the entire course of the study, the animals' body weights were maintained at this reduced level by partial food restriction; in their home cages, the animals were allowed drinking water ad lib. This study was approved by the Institutional Animal Care and Use Committee (IACUC) of Virginia Commonwealth University.

2.2. Drug discrimination

2.2.1. Training

The rats were trained (15-min training session) to discriminate subcutaneous injections (15-min presession injection interval) of 0.60 mg/kg of (−)-nicotine from vehicle (sterile 0.9% of saline) under a variable-interval 15-s schedule of reward (i.e., sweetened milk). Daily training sessions were conducted with (−)-nicotine or saline; on every fifth day, learning was assessed during an initial 2.5 min nonreinforced (extinction) session followed by a 12.5-min training session. For four of the animals, the left lever was designated the nicotine-appropriate lever, whereas the situation was reversed for the remaining animals. Data collected during the extinction session included responses per minute (i.e., response rate) and number of responses on the nicotine-appropriate lever (expressed as a percent of total responses). Animals were not used in the stimulus generalization studies (see below), until they made greater than 80% of their responses on the nicotine-appropriate lever after administration of (−)-nicotine, and less than 20% of their responses on the same nicotine-appropriate lever after administration of saline, for 3 consecutive weeks.

2.2.2. Stimulus generalization and antagonism

Tests of stimulus generalization were conducted to determine if the (−)-nicotine stimulus would generalize to bupropion. Tests of stimulus antagonism were performed to determine if bupropion would antagonize the nicotine stimulus and mecamylamine would antagonize the nicotine stimulus and the stimulus generalization of bupropion. In addition, the effects of a fixed dose of bupropion (3.0 mg/kg) were examined in combination with various doses of (−)-nicotine. During these phases of the study, maintenance of the (−)-nicotine/saline discrimination was ensured by continuation of the training sessions on a daily basis (except on a generalization or antagonism test day; see below). On 1 of the 2 days before a generalization or antagonism test, half of the animals would receive (−)-nicotine and half would receive saline; after a 2.5-min extinction session, training was continued for 12.5 min. Animals not meeting the original criteria (i.e., $\geq 80\%$ of total responses on the drug-appropriate lever after administration of training drug, and $\leq 20\%$ of total responses on the same lever after administration of saline) during the extinction session were excluded from the next generalization or antagonism test session. During the investigations of stimulus generalization and antagonism, test sessions were interposed among the training sessions. The animals were allowed 2.5 min to respond under nonreinforcement conditions; the animals were then removed from the operant chambers and returned to their home cages. An odd number of training sessions (usually five) separated any two generalization or antagonism test sessions. Tests of stimulus generalization examined the effects of various doses of bupropion, administered in a random order using a 15-min presession injection interval. An antagonist (i.e., mecamylamine) or 3.0 mg/kg of bupropion was administered using a 30-min presession injection interval to those animals making criteria and, 15 min prior to testing, (−)-nicotine was administered. Doses of the test drug or combination of drugs were administered in a random order. If a particular dose of a challenge drug resulted in disruption of behavior (i.e., no responding), only lower doses would be evaluated in subsequent weeks. Stimulus generalization was said to have occurred when the animals, after a given dose of challenge drug or combination of drugs, made $\geq 80\%$ of their responses (group mean) on the (−)-nicotine-appropriate lever. Stimulus antagonism was said to have occurred when the animals made $\leq 20\%$ of their responses on the (−)-nicotine-appropriate lever. Animals making fewer than five total responses during the 2.5-min extinction session were considered as being disrupted. Where stimulus generalization or antagonism occurred, ED_{50} or AD_{50} values respectively were calculated by the method of Finney (1952). The ED_{50} and AD_{50} doses are doses at which the animals would be expected to make 50% of their responses on the nicotine-appropriate lever.

2.2.3. Drugs

(−)-Nicotine bitartrate, bupropion HCl, and mecamylamine HCl were obtained from Sigma-Aldrich (St. Louis, MO). Solutions of all drugs were made fresh daily in 0.9% sterile saline, and all agents were administered via subcutaneous injection in a 1.0 ml/kg injection volume. Doses of (−)-nicotine refer to the weight of the base and doses of bupropion and mecamylamine refer to the weight of the salt.

3. Results

Eight rats were trained to discriminate 0.60 mg/kg of (−)-nicotine from saline vehicle. Once trained, the animals made $\geq 95\%$ of their responses on the (−)-nicotine-appropriate lever when administered training drug, and $\leq 10\%$ of their responses on the same lever following administration of saline. Response rates (mean responses/min) were not noticeably different after nicotine (11.9 ± 3.1 responses/min) training dose and saline (13.7 ± 2.6 responses/min) treatments. Administration of doses of (−)-nicotine lower than the training dose resulted in the animals making fewer responses on the (−)-nicotine-appropriate lever (Fig. 1); the calculated ED_{50} dose for (−)-nicotine is 0.17 mg/kg (95% CL = 0.08–0.29 mg/kg). Response rates were not very different after doses of nicotine (11.9–13.1 responses/min) and saline (13.7 response/min).

The (−)-nicotine stimulus generalized to bupropion (ED_{50} = 5.50 mg/kg; 95% CL = 2.33–12.98 mg/kg) in a dose-related manner (Fig. 1). Complete stimulus generalization occurred at 21.0 mg/kg of bupropion. The animals' response rates following the administration of doses of

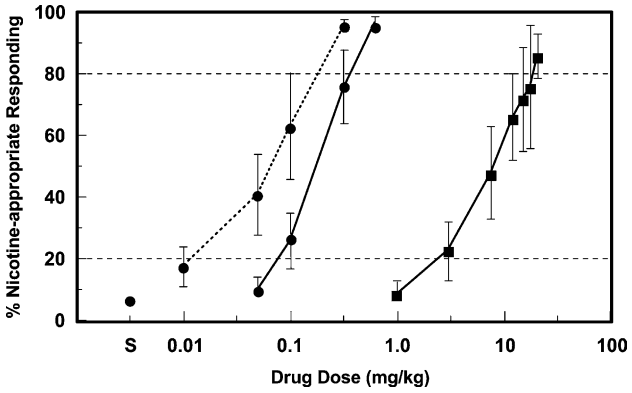

Fig. 1. Results of stimulus generalization studies with bupropion (solid squares), (−)-nicotine (solid line, solid circles), and 3.0 mg/kg of bupropion in combination with (−)-nicotine (broken line, solid circle) in rats trained to discriminate 0.60 mg/kg of (−)-nicotine from saline vehicle. *Ordinate*: Mean (n = 5–8 rats at each point) percent (± S.E.M.) of responses made on the nicotine-designated lever after the subcutaneous administration of 0.60 mg/kg of nicotine and 1.0 ml/kg of 0.9% saline (S). Data were collected during 2.5-min extinction periods. *Abscissa*: Drug doses plotted on a logarithmic scale.

Table 1
Results of stimulus antagonism studies using animals trained to discriminate 0.60 mg/kg of (−)-nicotine from saline vehicle

Treatment	Dose	N[a]	% Drug-appropriate responding (± S.E.M.)[b]	Response rate (responses/min ± S.E.M.)[b]
Bupropion + nicotine (0.60 mg/kg)	0.10	4/4	97% (2)	10.8 (2.9)
	1.0	4/4	91% (3)	12.8 (2.7)
	3.0	4/4	99% (1)	17.2 (5.6)
	5.0	2/5	–[c]	
Mecamylamine + nicotine (0.60 mg/kg)	0.10	3/3	85% (8)	20.1 (3.0)
	0.25	4/4	55% (17)	11.0 (2.2)
	0.50	8/8	30% (8)	17.0 (2.8)
	0.75	6/7	30% (9)	8.5 (2.1)
	1.0	7/7	33% (10)	6.0 (1.7)
	3.0	8/8	16% (6)	7.4 (2.3)
	AD_{50} = 0.4 (0.2–1.0) mg/kg			
Mecamylamine + bupropion (21.0 mg/kg)	0.10	6/6	84% (7)	11.7 (2.2)
	0.50	8/8	82% (5)	10.5 (1.7)
	1.0	6/6	93% (3)	13.1 (2.2)
	1.25	4/6	95% (3)	10.7 (2.8)
	1.5	3/6	94% (1)	12.0 (3.5)
	2.0	0/6	–[c]	

[a] N = number of animals responding/number administered drug.
[b] Data obtained during 2.5-min extinction session.
[c] Disruption of behavior; fewer than half of the animals made five responses during the extinction session following administration of the drug dose combination.

bupropion (8.4–15.9 responses/min) were not appreciably different from response rates that occurred following administration of nicotine or saline. Tests of stimulus antagonism were conducted by administration of doses of bupropion in combination with the training dose of (−)-nicotine. Doses of 0.10, 1.0, and 3.0 mg/kg of bupropion failed to antagonize the (−)-nicotine stimulus; 5.0 mg/kg of bupropion plus 0.60 mg/kg of (−)-nicotine produced disruption of behavior (Table 1). In contrast, mecamylamine antagonized the (−)-nicotine stimulus (AD_{50} = 0.40 mg/kg; 95% CL = 0.20–1.0 mg/kg); however, doses producing antagonism resulted in depressed response rates (Table 1). Mecamylamine, at doses from 0.10 to 1.5 mg/kg, failed to antagonize the nicotine-like response produced by 21.0 mg/kg of bupropion; administration of a higher dose (2.0 mg/kg) of mecamylamine in combination with bupropion resulted in disruption of behavior. Lastly, doses of (−)-nicotine were examined in the presence of a fixed dose of bupropion (3.0 mg/kg, which by itself produced 23% (−)-nicotine-appropriate responding). Stimulus generalization occurred in a dose-related manner (Fig. 1), and an ED_{50} dose for (−)-nicotine was calculated for the combination (ED_{50} = 0.05 mg/kg; 95% CL = 0.02–0.14 mg/kg).

4. Discussion

The results indicate that (−)-nicotine and bupropion share a discriminative stimulus effect. This is based on the dose-dependent substitution of bupropion in rats trained to discriminate the stimulus effect of 0.60 mg/kg of (−)-nicotine from saline vehicle (Fig. 1). A comparison of ED_{50} values revealed that nicotine (ED_{50} = 0.17 mg/kg) is over 30 times more potent than bupropion (ED_{50} = 5.50 mg/kg). This result appears to be in apparent conflict with a previous finding that indicated only partial (i.e., 63–75% nicotine-appropriate responding) substitution of bupropion in (−)-nicotine (0.40 mg/kg training dose)-trained rats (Cohen et al., 1999). Unfortunately, a further comparison of the two results is precluded at this time because the latter result has been reported only in abstract form. In addition, the extent of cross generalization that occurs between nicotine and bupropion cannot be stated at this time because studies that have used bupropion as training drug have not evaluated the effect of nicotine. This issue should be examined in future studies.

The present antagonism results confirmed the finding from many other laboratories that the stimulus effect of nicotine is blocked by mecamylamine and re-emphasize the conclusion that this effect is mediated, at least in part, via neuronal nicotinic receptors (e.g., Hirschhorn and Rosecrans, 1974; Kumar et al., 1987; Rose et al., 1989; Rosecrans, 1989; Shoaib et al., 2000; Stolerman et al., 1977). This mechanism, however, is not directly involved in the stimulus effect of bupropion because mecamylamine was unable to attenuate the nicotine-like response generated by bupropion (Table 1). Therefore, it can be concluded that the stimulus effect shared by nicotine and bupropion in nicotine-trained animals is generated via different mechanisms of action.

The mechanism(s) by which bupropion exerts its effect(s) is unclear. Its actions to increase catecholamine activity are probably important (e.g., Butz et al.,1982; Ferris et al., 1982; Terry and Katz, 1997; Vassout et al., 1993; but see Blitzer and Becker, 1985) and more recent evidence indicates it can block a number of behavioral effects induced by nicotine (Fryer and Lukas, 1999; Slemmer et al., 2000). The present results, however, are not consistent with the conclusion that bupropion functions as a nicotine antagonist. Specifically, various doses of bupropion were examined in combination with nicotine and found to have little influence on the high level of nicotine-appropriate responding produced by the 0.60 mg/kg training dose of nicotine (Table 1). The discrepancy between these studies might be accounted for by a number of experimental variables. These factors include differences in species (mice versus rats), species metabolism of bupropion (e.g., Sanchez and Hyttel, 1999; Schroeder, 1983; Suckow et al., 1986; Welch et al., 1987), doses of nicotine employed, and duration of nicotine administration (i.e., acute versus chronic).

The present results may have a number of implications for the use of bupropion in research investigations and smoking cessation. For example, the data would support the idea that bupropion may aid some people who are motivated to end their smoking behavior because its nicotine-like effect(s) could serve as a nicotine substitute for the smoker. This

replacement effect, however, would probably not be identical to that of nicotine because bupropion produces its effect through a mechanism that is different from that of nicotine. A subtle difference between the stimulus properties of the two agents could be exploited in a number of ways. One approach would be to train human and/or animal subjects in a three-choice discrimination task. The protocol would involve subjects trained to distinguish the effect of nicotine versus bupropion versus placebo (or saline). Such a study (or studies) could provide important information about the extent to which the subjective effect(s) of nicotine and bupropion overlap.

Another issue that should be investigated concerns the probable importance of the dose of bupropion being studied. In the present study, the administration of 3.0 mg/kg of bupropion in combination with various doses of nicotine enhanced the potency of nicotine (Fig. 1). The leftward shift of the nicotine dose–effect curve resulted in a three-fold increase in the potency of nicotine (i.e., ED_{50} shift from 0.17 to 0.05 mg/kg). These data are of particular interest because when this dose of bupropion was given alone it produced saline-appropriate responding (Fig. 1). This indicates that a relatively low dose of bupropion can modulate the effect of nicotine even though it did not produce, by itself, a marked nicotine-like effect. Thus, more research effort should be directed toward the effect(s) produced by relatively low doses of bupropion. Such data might provide a more complete understanding of the pharmacology of bupropion, especially since its clinical effects appear to be related to dose. Specifically, the antidepressant dose range of bupropion is considered to be 300–750 mg and it is within this dose range where concerns have been raised about the occurrence of seizures and the possibility of drug-induced psychotic symptoms, the latter a noted risk when prescribing CNS stimulants (e.g., Dufrensne et al., 1984, 1985; Golden et al., 1985). On the other hand, the anti-smoking doses of bupropion are stated to be 150 and 300 mg; doses above 300 mg are not recommended and, in fact, are strongly discouraged (GlaxoWellcome, 2001). It has been shown in a number of studies that doses up to 300–400 mg of bupropion do not exert marked CNS stimulant effects in humans. For example, Miller and Griffith (1983) reported that the effects of bupropion up to 400 mg produced little resemblance to (+)-amphetamine. They speculated that because bupropion is such a weakly potent CNS stimulant they were possibly examining only the "lower portion" of the dose–response curve for bupropion and, therefore, if the dose was continually elevated, an amphetamine-like effect(s) would occur. In a more recent study, however, Rush at al. (1998) examined these lower doses of bupropion in human subjects trained to discriminate the effect of 20 mg of (+)-amphetamine from placebo. The administration of 50 to 400 mg of bupropion in substitution tests produced low to moderate levels of (+)-amphetamine-like responding that was accompanied by subject-rated drug effects such as "alert/energetic", "elated", and "vigorous" that somewhat overlapped with those of (+)-amphetamine. Might these effects form the basis of the usefulness of bupropion in smoking cessation? If so, to what degree do they compare to the antidepressant effects of bupropion and are they produced by the same mechanism(s)? Clearly, more research will be needed to determine the extent to which the dose of bupropion is a critical factor in understanding its mechanism(s) of action and how its effects relate to smoking behavior and depression. This issue might also be evaluated in a three-choice discrimination task. Perhaps subjects could be trained to distinguish the effect of a relatively high dose of bupropion versus low dose of bupropion versus saline. Tests could then be conducted to determine potential differences in subjective effects and mechanisms of action.

In summary, the results of the present study indicate that nicotine and bupropion share a similar stimulus effect that is produced through different mechanisms of action. In addition, it was shown that bupropion was not a nicotine antagonist but potentiated the stimulus effect of nicotine. From these data, it was speculated that bupropion may help some people refrain from smoking because it produces an effect(s) that serves as a suitable substitute for nicotine in the individual who is motivated to quit smoking.

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