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Effects of Acute and Chronic Bupropion on Locomotor Activity and Dopaminergic Neurons[1]

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NIELSEN, J A , N J SHANNON, L BERO AND K E MOORE *Effects of acute and chronic bupropion on locomotor activity and dopaminergic neurons* PHARMACOL BIOCHEM BEHAV 24(4) 795–799, 1986 —Acute administration of bupropion (10 or 30 mg/kg) to rats increased locomotor activity in a dose-related manner The highest dose increased the dopamine (DA) concentration while both doses reduced the concentration of dihydroxyphenylacetic acid (DOPAC) in the striatum The enhancement of locomotor activity and the decrease of striatal DOPAC concentrations were increased with chronic administration (up to 40 days) of bupropion The rate of DA synthesis in the striatum was increased by the acute administration of d-amphetamine but was not altered by acute or chronic administration of bupropion

Bupropion Locomotor activity Chronic administration Dopamine DOPAC Striatum Rats

BUPROPION has antidepressant effects in man [6, 7, 18, 25, 37] It has a chemical structure that is quite different from that of the tricyclic antidepressants, and unlike these latter compounds (e.g., imipramine, amitriptyline), bupropion causes locomotor stimulation in rodents [4,31]. The neurochemical actions resulting from the *in vitro* or acute *in vivo* administration of bupropion also differ from those of the tricyclic antidepressants. While the latter compounds inhibit synaptosomal uptake of norepinephrine (NE) and 5-hydroxytryptamine (5HT) but have minimal effects on dopamine (DA) uptake, bupropion is more effective in inhibiting DA than NE or 5HT uptake [9] These and other data have led to the suggestion that DA neuronal systems are important for the central actions of this drug [4].

Bupropion is similar to other antidepressants in that it requires 5–21 days of treatment before attaining clinical efficacy [18]. Little is known about the behavioral and neurochemical effects of chronic bupropion treatment in animals, but unlike tricyclic antidepressants chronic administration of bupropion failed to desensitize α- and β-adrenergic, imipramine, $5HT_2$ or DA receptors, and also failed to alter the activity of NE-stimulated adenylate cyclase in brain [8] On the other hand, there are reports that acute bupropion increases affinity of dopamine receptors in striatum [1] and that chronic bupropion down-regulates β-adrenergic receptors and inhibits norepinephrine-stimulated adenylate cyclase in frontal cortex [11]

The purpose of the present experiments was to investigate the effects of chronic bupropion treatment on locomotor activity and on some neurochemical characteristics of DA neurons which terminate in the striatum of rats

METHOD

Male Sprague-Dawley rats (Spartan Farms, Haslett, MI and Zivic-Miller Laboratories, Allison Park, PA) were housed in a temperature- (22°C) and light- (lights on between 0600 hr and 1800 hr) controlled room with food and tap water provided ad lib

Locomotor activity of individual rats was determined using Woodard Actophotometers which consist of a circular runway with 6 photocells equally spaced along the outer walls and a central light source. Activity cages were shielded from background noise by a sound-attenuating cabinet Rats were accommodated to the apparatus for 60 min before being injected with drug or vehicle and returned to the actophotometer for 120 min The number of photocell interruptions was recorded every ten minutes

Concentrations of DA and dihydroxyphenylacetic acid (DOPAC) in the striatum were determined by radioenzyma-

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TABLE 1
EFFECTS OF ACUTE ADMINISTRATION OF BUPROPION ON DOPAMINE AND DOPAC CONCENTRATIONS IN THE STRIATUM

	Dopamine	DOPAC
Saline	81 5 ± 10 2	12 1 ± 1 1
Bupropion (10 mg/kg)	99 4 ± 10 6	8 6 ± 0 7*
Bupropion (30 mg/kg)	106 8 ± 12 5*	8 5 ± 0 9*

Rats were injected SC with saline or bupropion 60 min prior to decapitation Values (ng/mg protein) represent means ± 1 S E (N=8)
*Significantly different from saline control ($p<0$ 05)

TABLE 2
EFFECTS OF ACUTE AND CHRONIC ADMINISTRATION OF BUPROPION ON DOPAMINE AND DOPAC CONCENTRATIONS IN THE STRIATUM

		Dopamine		DOPAC	
Pretreat Time (days)		13	40	13	40
Pretreatment	Treatment				
Saline	Saline	85 3 ± 7 1	88 6 ± 12 1	11 3 ± 0 8	14 8 ± 1 6
Saline	Bupropion (10)	93 8 ± 10 4	100 0 ± 8 9	8 0 ± 0 6†	10 2 ± 0 9*
Saline	Bupropion (30)	112 3 ± 11 1*	112 9 ± 9 8*	7 6 ± 0 9*	8 9 ± 1 6*
Bupropion (10)	Bupropion (10)	106 4 ± 14 3	111 4 ± 6 9	5 1 ± 0 5†	7 1 ± 0 6†
Bupropion (30)	Bupropion (30)	111 7 ± 7 9	123 6 ± 14 1	4 4 ± 0 6†	4 9 ± 0 5†

Rats were injected SC twice daily with saline or bupropion (numbers in parentheses represent mg/kg) for 13 or 40 days (Pretreatment) On the day of the experiment (day 14 and 41, respectively) rats were injected with saline or bupropion (Treatment) 40 min prior to decapitation Values (ng/mg protein) represent means ± 1 S E (N=6–8)
*Significantly different from values in the saline-saline group ($p<0$ 05)
†Significantly different from values in appropriate saline-bupropion groups ($p<0$ 05)

tic assay (Table 1 [34]) or by high performance liquid chromatography with electrochemical detection (Table 2 [20]) The *in vivo* rate of DA synthesis in the striatum was estimated by measuring the accumulation of dihydroxyphenylalanine (DOPA) 30 min after the administration of an inhibitor of aromatic-L-amino-acid decarboxylase (3-hydroxybenzylhydrazine, NSD 1015, Sigma, St Louis, MO), for details of the method see [5] Protein contents of homogenates of striatum were determined as described by Lowry *et al* [16] Bupropion hydrochloride, obtained from Burroughs Wellcome Co., Research Triangle Park, NC, and d-amphetamine sulfate were dissolved in saline and injected subcutaneously in a volume of 1 ml/kg Doses are reported as the respective salts of these drugs

Treatment effects were determined using a one-way analysis of variance followed by the Student-Newman-Keuls test [30]

TABLE 3
THE RATE OF DOPAMINE SYNTHESIS IN THE STRIATUM FOLLOWING ACUTE ADMINISTRATION OF BUPROPION OR d-AMPHETAMINE

Treatment	DOPA Accumulation
Saline	15 3 ± 2 0
d-Amphetamine	28 2 ± 1 8*
Bupropion	11 5 ± 1 3

Groups of rats were injected SC with either bupropion (10 mg/kg), d-amphetamine (1 mg/kg) or saline vehicle 40 min before death Each rat was also injected with NSD 1015 (100 mg/kg, IP) 30 min prior to death Values (mean ± 1 S E , N=6–7) represent the rate of DOPA accumulation (ng DOPA/mg protein/30 min)
*Significantly different ($p<0$ 05) from saline-treated controls

RESULTS

Locomotor Activity

The effects of bupropion on locomotor activity in rats are summarized in Fig 1 After being placed into the actophotometer cages, naive animals exhibit a brief period of activity but after about 30 min they accommodate to the cage and the level of activity falls If left undisturbed the animals then remain fairly inactive in the actophotometers for several hours In the experiments depicted in Fig 1, the animals were removed from the actophotometers at 60 min, injected with saline or bupropion, and then immediately returned

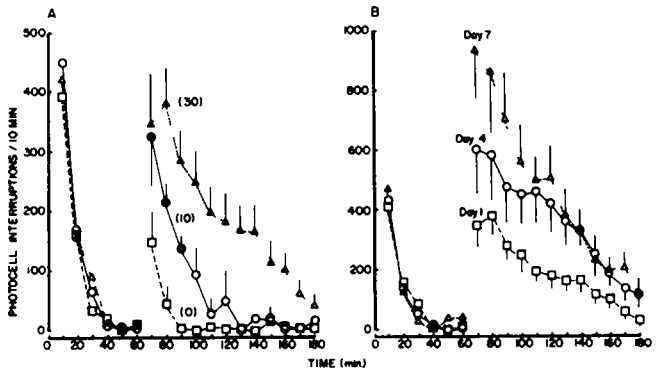

FIG 1 Effects of acute and chronic administration of bupropion on locomotor activity in rats Rats were placed individually into actophotometer cages for a 60-min acclimation period during which time photocell interruptions were recorded at 10-min intervals The animals were then injected subcutaneously with bupropion or saline-vehicle, returned to the actophotometers and photocell interruptions were recorded at 10-min intervals (A) Locomotor activity after acute administration of saline (□), 10 (○) or 30 (△) mg/kg of bupropion (B) Locomotor activity after the first (day 1, □), seventh (day 4, ○) or thirteenth (day 7, △) injection of bupropion (30 mg/kg every 12 hr) Symbols represent the means and vertical lines 1 S E calculated from 6–7 rats per group, where not shown, the S E is less than the radius of the symbol There were no significant differences in the activity of the different groups of rats during the acclimation period, for clarity S E s are not indicated during this period In panel A, solid symbols represent values from bupropion-treated rats that are significantly different ($p<0$ 05) from saline-treated controls

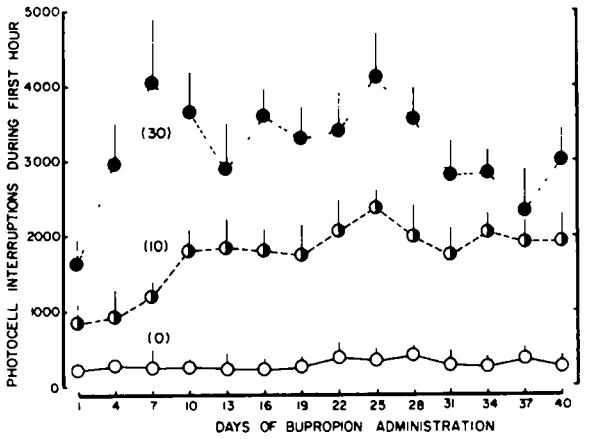

FIG 2 Locomotor activity of rats treated chronically with bupropion Saline vehicle (○), 10 (◑) or 30 (●) mg/kg bupropion were injected subcutaneously every 12 hr for 40 days. Locomotor activity was recorded every 3 days for 60 min before and 120 min after the morning injection (see legend to Fig 1 for details) Symbols represent the means and vertical lines 1 S E of total photocell interruptions during the 60 min period immediately following the injections (N=6–7)

Following the injection of saline the rats exhibited a brief period of activity If injected with 10 or 30 mg/kg of bupropion (Fig 1A) they exhibited a dose-related increase in activity After the highest dose the hyperactivity was maintained for approximately 1 5 hours

The effects of repeated injections of bupropion on motor activity are summarized in Fig 1B. The activity of rats receiving subcutaneous injections of bupropion twice a day increased progressively during the first week That is, during the first hour after 7 injections (first injection of day 4) and after 13 injections (first injection on day 7) locomotor activity was significantly greater than that seen after the first injection Chronic administration of bupropion, however, did not alter activity during the daily accommodation periods (i e , 11 hours after the previous injection of bupropion) The locomotor response to bupropion did not continue to increase progressively after the first week, but remained fairly constant during the next 4 weeks (Fig 2)

Biochemical Dynamics of DA in the Striatum

The effects of an acute injection of bupropion on the concentrations of DA and DOPAC in the rat striatum are summarized in Table 1 After both 10 and 30 mg/kg of bupropion the DOPAC concentration in the striatum was significantly reduced while at the higher dose the concentration of DA was increased. The same pattern was seen after chronic administration of bupropion (see summary of results in Table 2) As might be expected, a single injection of 10 or 30 mg/kg

TABLE 4

THE RATE OF DOPAMINE SYNTHESIS IN THE STRIATUM FOLLOWING ACUTE AND CHRONIC ADMINISTRATION OF BUPROPION

Pretreatment	Treatment	DOPA Accumulation
Saline	Saline	11 5 ± 0.8
Saline	Bupropion (10)	8 1 ± 0 8
Saline	Bupropion (30)	10 1 ± 0 8
Bupropion (10)	Bupropion (10)	7 9 ± 0 8
Bupropion (30)	Bupropion (30)	10 3 ± 0 9

Rats were injected SC twice daily with saline or bupropion (numbers in parentheses represent mg/kg) for 40 days (Pretreatment) On day 41, rats were injected (Treatment) with saline or bupropion 40 min prior to sacrifice Each rat also was injected with NSD 1015 (100 mg/kg, IP) 30 min prior to sacrifice Values (mean ± 1 S E , N=6–7) represent the rate of DOPA accumulation (ng DOPA/mg protein/30 min) None of the treatments significantly altered the rate of DOPA accumulation in striatum

bupropion following 13 or 40 days of twice daily injections of saline produced effects similar to those depicted in Table 1, a slight increase in the concentration of DA after the highest dose and a significant decrease in the concentration of DOPAC after both doses. In animals that were injected chronically with bupropion, these biochemical effects were maintained, indeed, there was a greater decline of DOPAC in the striatum of those animals that received chronic bupropion treatments There was no difference between the responses of animals pretreated with bupropion for 13 or 40 days

The acute administration of bupropion did not alter the

rate of DA synthesis (DOPA accumulation following the administration of a decarboxylase inhibitor) in the striatum, whereas administration of d-amphetamine induced a marked acceleration of DA synthesis (Table 3). Furthermore, chronic administration of bupropion failed to alter the rate of DOPA accumulation in the striatum (Table 4)

DISCUSSION

The acute administration of bupropion (10–30 mg/kg) increased locomotor activity in rats, the magnitude and time course of the stimulation were dose-related. Cooper *et al.* [4] reported that while high doses of bupropion (25–100 mg/kg) increase the activity of rats in an open-field test, a lower dose (12.5 mg/kg) was without effect The inability of these investigators to observe a stimulant effect at the lower dose was probably due to the fact that they averaged activity over a 90 min period and, as shown in the present study, the stimulatory effect of 10 mg/kg bupropion lasted for only 30 min Thus, at doses of 10 mg/kg and above, bupropion resembles psychomotor stimulants in increasing motor activity In this regard, the mechanism of action of bupropion may be more similar to that of methylphenidate than to that of d-amphetamine because reserpine has been shown to block the locomotor stimulatory effects of methylphenidate and bupropion but not those of d-amphetamine Furthermore, α-methyl-p-tyrosine has been shown to block the stimulatory effects of d-amphetamine, but not those of methylphenidate or bupropion [26].

The response to bupropion also resembled that of psychomotor stimulants in other behavioral paradigms. In a two-lever operant task, rats trained to discriminate bupropion from saline generalized the bupropion cues to a variety of psychomotor stimulants including d-amphetamine and methylphenidate [2,14] It should be noted, however, that the bupropion cue was also mimicked by viloxazine, an antidepressant which reduces locomotor activity [2,14], and that humans who formerly abused psychomotor stimulants reported no similarities between bupropion and d-amphetamine [13] In another behavioral task designed to differentiate antidepressants from other classes of psychoactive compounds, bupropion in some respects resembled the psychomotor stimulants That is, in a differential-reinforcement-of-low-rate (DRL) 72-second schedule of reinforcement, a high dose of bupropion (60 mg/kg, IP) increased response rate but did not significantly alter reinforcement rate [28] This pattern of response is unlike that produced by other antidepressants which decreased response rate and increased reinforcement rate [21, 22, 28, 29] It does resemble the pattern obtained with the psychomotor stimulants d-amphetamine and methylphenidate under a DRL 17 5-second schedule [24], however, other drugs which are not psychomotor stimulants (e g , chlordiazepoxide) elicited the same response pattern [21,22]

The ability of bupropion to increase locomotor activity did not diminish with repeated injections, that is, tolerance did not develop Rather, the stimulatory effect was enhanced These results are similar to those reported for d-amphetamine tolerance does not develop to the central stimulant actions of amphetamine in rats [32,33] and augmentation of these effects with repeated administration has been observed [17, 27, 36]

Psychomotor stimulants exert a variety of effects on mesotelencephalic DA neurons Some stimulants, such as methylphenidate and amfonelic acid, are without effect or slightly increase the concentration of DOPAC in the striatum while other stimulants, typified by amphetamine, reduce striatal DOPAC concentrations [3, 10, 12] There is one report that a high dose of bupropion (30 mg/kg) increased striatal DOPAC concentrations in rats [35] but in the present study both acute or chronic administration of bupropion reduced the concentration of DOPAC in the striatum, and in this respect it resembled d-amphetamine On the other hand, whereas amphetamine increased the rate of DA synthesis (DOPA accumulation) in the striatum [19,23] acute and chronic administration of bupropion were without effect With respect to the lack of effect on DOPA accumulation in the striatum, bupropion resembles amfonelic acid [15] Thus, although selective destruction of DA neurons with 6-hydroxydopamine blocks the locomotor stimulant actions of both amphetamine and bupropion [4] the results of the present study indicate that the two drugs have different effects on DA synthetic processes in the terminals of nigrostriatal neurons

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