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Bupropion hydrochloride ((±) α-t-butylamino-3-chloropropiophenone HCl): a novel antidepressant agent

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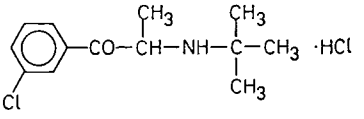
Tricyclic compounds such as amitriptyline and related substances are considered to be clinically effective antidepressant agents (Kuhn, 1958; Hollister, 1972) with a mode of action dependent on the inhibition of the neuronal reuptake of one or more biogenic amine transmitters in the central nervous system (Glowinski & Axelrod, 1964). The tricyclics have not proved to be ideal agents in treating depression due to their slow onset of action, cholinolytic side effects, interactions with pressor amines and monoamine oxidase inhibitors and also due to a tendency to elicit cardiac arrhythmias or standstill (Jefferson, 1975). Monoamine oxidase inhibitors are likewise considered to be effective antidepressant agents (American Psychiatric Association, 1974) which act by inhibiting intraneuronal monoamine oxidase in the central nervous system (cns). However, the currently available inhibitors also inhibit monoamine oxidase in the liver and the ingestion of phenethylamine-type pressor substances in the diet, normally an event made innocuous with the effective destruction of the amines by liver monoamine oxidase, may lead to hypertensive crisis (Marley & Blackwell, 1970).

We therefore sought an agent that would be active in antidepressant screening models, but differ chemically and pharmacologically from the tricyclics, and not be sympathomimetic, cholinolytic nor an inhibitor of monoamine oxidase. Bupropion (Wellbatrin) which was synthesized by one of the authors (N.B.M.) (Baltzly & Mehta, 1968; Mehta, 1974, 1975) meets these criteria and has the following structure:



The pharmacological properties of bupropion have to date been reported only in abstract form (Soroko, Mehta & others, 1970) as has its clinical effectiveness as an antidepressant in an open study by Fann, Schroeder & others (1974) and in a double-blind, placebo-controlled study by Fabre, McLendon &

* Correspondence.

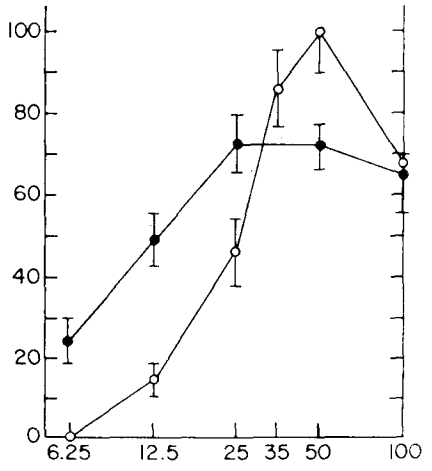


FIG. 1. The prevention of tetrabenazine sedation by intraperitoneal pretreatment with bupropion and the effect of bupropion on locomotor activity in mice. (●) Prevention of the loss of exploratory motor activity which follows the administration of tetrabenazine (35 mg kg^{-1}, i.p.). Each point represents the mean of data from at least 36 mice. Symptoms were scored at 1 h after bupropion administration and 30 min after tetrabenazine administration on a modification of the arbitrary scale defined by Vernier, Hanson & Stone (1962). Tetrabenazine at 30 min after 35 mg kg^{-1} (i.p.) caused 90 to 100% of mice to remain motionless when placed in a new environment. 100% effectiveness of a compound represents total negation of tetrabenazine effects. (○) % increase in spontaneous motor activity as measured in a photocell activity cage. Each point represents the mean of data from at least 10 mice. Results are reported as % change from control values obtained in a saline-treated group of mice. Bars give s.e. of the mean. Ordinate: % effect. Abscissa: bupropion (mg kg^{-1}, i.p.).

Mallette (1977). A description of the pharmacology of the drug follows.

Actions on cns. Bupropion in doses from 6·25 – 25 mg kg^{-1} (i.p.) produced a dose-dependent prevention of tetrabenazine-induced sedation in mice (Fig. 1). It also prevented tetrabenazine-induced blepharospasm and fall in rectal temperature, and it corrected the 'hunched' posture characteristic of tetrabenazine action. The compound was approximately half as potent by the oral route as by the intraperitoneal route. The duration of action following 25 mg kg^{-1} (i.p.) was approximately 3 h. An equieffective dose of amitriptyline (5 mg kg^{-1}) in mice had a similar duration of action. Bupropion, like tricyclic agents, but unlike the stimulants (+)-amphetamine and methylphenidate, was essentially inactive when given after the tetrabenazine sedation was established. In addition, both bupropion (12·5 – 50 mg kg^{-1}, i.p.) and amitriptyline (5–10 mg kg^{-1}, i.p.) markedly antagonized the 6° drop in rectal temperature seen at 17 h after reserpine (5 mg kg^{-1}, i.p.).

Bupropion, after a semiquantiative visual scoring of motor activity under blind conditions, was not classified as a locomotor stimulant in mice in doses up to 25 mg kg^{-1} (i.p.). Although a coordinated increase in locomotor activity was detectable at 12·5 and 25 mg kg^{-1} (i.p.) with photocell activity measuring units, the activity at these doses and at doses as high as 100 mg kg^{-1} (i.p.) was not associated with stereotyped gnawing, licking and cornering activity as was observed with (+)-amphetamine. The curve for increase in locomotor activity was to the right of the antitetrabenazine curve (Fig. 1) suggesting that the locomotor stimulant action was not the cause of the antitetrabenazine effect.

For comparison, Fig. 2 presents the antitetrabenazine and motor activity dose-response relations for amitriptyline in mice and Fig. 3 gives similar data for (+)-amphetamine HCl and methylphenidate HCl. (+)-Amphetamine and methylphenidate were much more potent motor stimulants than bupropion or amitriptyline in mice and the curves for increase in locomotor activity with both of these agents were slightly to the left of the curves for antitetrabenazine action indicating that the motor stimulant action was the basis for the antitetrabenazine effect (Fig. 3).

In other comparative studies, bupropion at 25–50 mg kg^{-1} (i.p.), antagonized for approximately 30 min the intense motor activity produced by (+)-amphet-

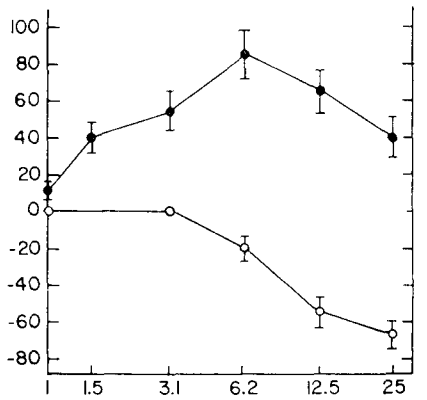


FIG. 2. The prevention of tetrabenazine sedation by intraperitoneal pretreatment with amitriptyline and the effect of amitriptyline on locomotor activity in mice. (●) Prevention of the loss of exploratory motor activity which follows the administration of tetrabenazine (35 mg kg^{-1}, i.p.). Each point represents the mean of data from at least 24 mice. (○) % increase in spontaneous motor activity as measured in a photocell activity cage. Each point represents the mean of data from at least 6 mice. Details are the same as in Fig. 1. Bars give s.e. of the mean. Ordinate: % effect. Abscissa: amitriptyline (mg kg^{-1}, i.p.).

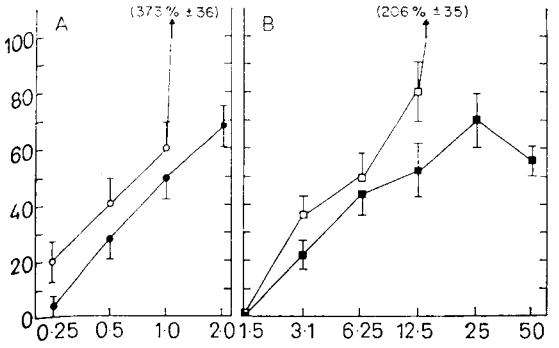


FIG. 3. The prevention of tetrabenazine sedation by intraperitoneal pretreatment with A—(+)-amphetamine and B—methylphenidate and the effect of these agents on locomotor activity in mice. Prevention by (+)-amphetamine (●) and methylphenidate (■) of the loss of exploratory motor activity which follows the administration of tetrabenazine (35 mg kg^{-1}, i.p.). Each point represents the mean of data from at least 18 mice. Percent increase in spontaneous motor activity induced by (+)-amphetamine (○) and methylphenidate (□) as measured in a photocell activity cage. Each point represents the mean of data from at least 6 mice. Details are the same as in Fig. 1. Bars give s.e. of the mean. Ordinate: % effect. Abscissa: mg kg^{-1}, i.p.

amine (2 mg kg^{-1}, i.p.) in mice. Amitriptyline, at 6·25–12·5 mg kg^{-1} (i.p.) on the other hand, enhanced (+)-amphetamine motor stimulation. Bupropion, at 25 mg kg^{-1} (i.p.), also reduced the mortality caused by (+)-amphetamine (20 mg kg^{-1}, i.p.) in aggregated mice. Amitriptyline, in doses producing significant antitetrabenazine action (5 mg kg^{-1}, i.p.), had no or slight effect on the mortality caused by (+)-amphetamine (20 mg kg^{-1}, i.p).

In rats, bupropion, at doses of 6·25–100 mg kg^{-1} (i.p.), did not prevent the sedation produced by tetrabenazine. In this it was similar to amitriptyline which also is ineffective in preventing tetrabenazine sedation in rats (Shore, 1966). (+)-Amphetamine in rats at 0·25–2 mg kg^{-1} (i.p.) caused approximately 40 to 250% increase in locomotor activity which was associated with stereotyped gnawing, licking and cornering behaviour. These stereotypes were not observed in the rat with doses of bupropion producing 40 to 250% increase in motor activity (25–50 mg kg^{-1}, i.p.), but were on some occasions observed with doses exceeding 50 mg kg^{-1} (i.p.).

Biochemical studies. The biochemical profile for the interactions of bupropion with biogenic amines and MAO further distinguishes it from other antidepressant compounds. Bupropion did not inhibit monoamine oxidase in the brain, liver or heart of rats at one hour following injection of 6–100 mg kg^{-1} (i.p.). Bupropion was without effect on brain MAO in *in vitro* experiments over the range 10^{-7}–10^{-4} M. At doses of 12·5–100 mg kg^{-1} (i.p.) it was without effects on whole brain noradrenaline and 5-HT concentrations at 1 to 6 h after administration. In rat hypothalamic synaptosomes, bupropion was found to be approximately 60-fold less potent as an inhibitor of noradrenaline uptake than were amitriptyline and imipramine (Table 1). But it was 6-fold more potent as an inhibitor of dopamine uptake in striatal synaptosomes than was imipramine and 20-fold more potent than amitriptyline largely due to the low affinity of the tricyclic compounds for the striatal uptake system. Bupropion had little effect on 5-HT uptake in concentrations as high as 10^{-5} M.

Cardiovascular actions. Studies to delineate cardiovascular activity were carried out. The mean blood pressure of 5 anaesthetized cats was unaffected by the intravenous bolus administration of bupropion (5, 10, 20 mg kg^{-1}). Three dogs were given 5 and 10 mg kg^{-1} doses, and 3 dogs were given two 20 mg

Table 1. *Comparison of the potency of bupropion to imipramine and amitriptyline as inhibitors of biogenic amine uptake into synaptosomal preparations of various rat brain areas.*

	IC50 Values (mean ± s.e.)		
	Hypothalamus		Striatum
Drug	Noradrenaline (M)	5-HT (M)	Dopamine (M)
Imipramine	0·95 ± 0·3 × 10^{-7} (3)	3·1 ± 0·8 × 10^{-7} (3)	1·9 ± 0·2 × 10^{-5} (3)
Amitriptyline	0·97 ± 0·1 × 10^{-7} (4)	3·5 ± 0·5 × 10^{-7} (4)	6·5 ± 1·0 × 10^{-5} (4)
Bupropion	6·5 ± 0·6 × 10^{-6} (11)	20 ± 3%* (5)	3·4 ± 0·4 × 10^{-6} (10)

*Percent inhibition of uptake at 10^{-5} M compound.

Drugs were incubated in presence of the tissue for 5 min at 37° before the addition of 2 × 10^{-7} M [1-^{3}H]-noradrenaline, 2 × 10^{-7} M [^{3}H]dopamine or 2 × 10^{-7} M ^{3}H-5-HT. Incubation was continued for an additional 5 min at 37° in an atmosphere of 5% CO_2 in oxygen. A minimum of 3 and in most cases 5 different concentrations of the drug producing from 30–70% inhibition of uptake of the biogenic amines were used to determine the IC50 values. The results were plotted on semilogarithmic paper and the line determined by connecting the points on the graph. Data are expressed as mean of IC50 values ± the standard error. The numbers in parentheseis are the number of individual IC50 values obtained.

kg^{-1} doses of bupropion as intravenous boluses. At 5 mg kg^{-1} the drug was without significant effect. After 10 and 20 mg kg^{-1}, transient falls in arterial pressure of 20–50 mm Hg occurred. Cardiac output was decreased moderately as was peripheral resistance. Recovery occurred within 10 min. The pressor response to intravenous noradrenaline was moderately potentiated and the responses to tyramine and amphetamine (i.v.) were not influenced. The depressor responses to peripheral vagal stimulation and to intravenous acetylcholine were unaffected. At 5 and 10 mg kg^{-1} (i.p.) the drug did not change the duration of PR and QRS of the lead II electrocardiogram indicating that neither impulse formation nor conduction in the heart were influenced. A lack of obvious change in QT interval indicated that refractory period and repolarization were not changed. It seems clear that large intravenous doses were without deleterious actions on the systemic circulation of the cat and dog. Bupropion at 4×10^{-5} M had no direct effect on the contractile response of the electrically-driven isolated guinea-pig left hemi-atrium but produced a 4-fold increase in sensitivity to noradrenaline.

Autonomic effects. Bupropion was without direct agonist activity in guinea-pig isolated ileum, rabbit aorta and rabbit atria at concentrations of 10^{-7}–10^{-4} M. It had little or no effect at 10^{-7}–10^{-5} M on several concentration-response curves: (1) isoprenaline in rabbit atria, (2) noradrenaline in rabbit aorta, (3) histamine and acetylcholine in guinea-pig ileum. At 10^{-4} M, bupropion caused a 6-fold shift of the acetylcholine curve to the right. Similar shifts were produced by much lower concentrations of amitriptyline and atropine. Relative cholinolytic potencies for a 6-fold shift were 1, 4000 and 300 000 for bupropion, amitriptyline and atropine, respectively.

Additional studies aimed at investigating cholinolytic actions in the rat *in vivo* revealed that bupropion, in doses from 6·25–100 mg kg^{-1} (i.p.) was ineffective in blocking the chromodacryorrhea ('bloody tears') induced by methacholine (10 mg kg^{-1}, i.p.) (Winbury, Schmalgemeier & Hambourger, 1949), nor did it antagonize the tremors or the lachrymation and salivation induced by oxotremorine (0·5 mg kg^{-1}, s.c.). Atropine blocked the effects of methacholine and oxotremorine at 0·5–1 mg kg^{-1} (i.p.) as did amitriptyline at 12 mg kg^{-1} (i.p.).

Acute toxicity. Acute toxicity estimations were based on 10 animals/dose level and a one week observation time. The LD50 values in mice were 230 ± 9 mg kg^{-1} (i.p.) and 575 ± 26 mg kg^{-1} (oral). At doses above 50 mg kg^{-1} (i.p.) and 100 mg kg^{-1} (oral) signs of cns stimulation occurred. Intensity gradually increased with increasing dose. At 200 mg kg^{-1} (i.p.) and 500 mg kg^{-1} (oral) uncoordinated hops, Straub tail, analgesia, ataxia, prostation and loss of righting reflex occurred. In rats the LD50 values were 210 ± 9 mg kg^{-1} (i.p.) and 600 ± 54 mg kg^{-1} (oral). At doses of 100 mg kg^{-1} (i.p.) and 300–400 mg kg^{-1} (oral) and higher, tremors and spasms were observed.

Thus, bupropion, a compound chemically dissimilar from tricyclic antidepressants, has some cns activities in animals which resemble the tricyclics and others which do not. It is not cholinolytic or sympathomimetic, is only a relatively poor inhibitor of the uptake of noradrenaline and 5-HT, does not block MAO, and has exhibited indications of efficacy in the treatment of depression in man (Fann & others, 1974; Fabre & others, 1977).

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