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Effect of bupropion on dopamine and 5-hydroxytryptamine-mediated behaviour in mice

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When bupropion (12·5–50 mg kg^{-1}) was administered 30 min before methamphetamine it significantly antagonized methamphetamine-induced stereotyped behaviour in mice, but when given 5 min after methamphetamine it significantly potentiated the behaviour. When it was administered to mice pretreated with 100 mg kg^{-1} pargyline, intense locomotor stimulation and stereotyped behaviour was observed whereas when clomipramine was administered similarly the animals showed locomotor stimulation, head twitches and abduction and extension of hind limbs. Unlike clomipramine, bupropion failed to potentiate the 5-hydroxytryptamine-mediated behaviour seen after 5-hydroxytryptophan, 100 mg kg^{-1}, i.v. These observations are in agreement with reports that bupropion is more potent as an inhibitor of dopamine uptake than as an inhibitor of 5-hydroxytryptamine uptake in-vitro.

Bupropion hydrochloride ((±)-α-t-butylamino-3-chloropropiophenone-HCl) is an antidepressant that differs structurally as well as biochemically from other antidepressants. It is neither an inhibitor of monoamine oxidase nor does it cause release of catecholamines from synaptosomes in-vitro (Soroko et al 1977). When compared with tricyclics, it is a weak inhibitor of noradrenaline and 5-hydroxytryptamine uptake into nerve endings. On the other hand, bupropion is more potent than either imipramine or amitryptyline as an inhibitor of dopamine uptake into synaptosomal preparations of rat striatum (Ferris et al 1981). Stern et al (1979) implicated dopamine in the actions of bupropion in-vivo, reporting that bupropion decreases prolactin levels in both rat and man. Further, it is reported to be capable of producing selective inhibition of dopamine uptake in brain in-vivo (Canning et al 1979). The inhibitory effect on dopamine uptake has also been correlated with certain behavioural effects of bupropion like locomotor stimulation and stereotyped sniffing (Cooper et al 1980). However, no behavioural studies have been carried out on the effects of bupropion on the 5-HT mediated behaviour. Therefore following experiments were planned.

Methods

Male albino mice (20–30 g) with free access to a standard diet: and tap water were used once only. They were individually housed in Perspex cages with one of the vertical faces netted with 1 cm^2 wire mesh, 2 mm in diameter, 30 min before drug treatment for adaptation to their environment. All observations were made in a noiseless diffusely illuminated room between 10 and 16 h.

Stereotyped behaviour was assessed over a 30 s period at 10 min intervals according to the scoring system of Ozawa & Miyauchi (1977).

The behavioural effects of bupropion and clomipramine administration 5 h after pargyline (100 mg kg^{-1}) were also observed. The animals were particularly observed for stereotyped behaviour. The number of animals showing a minimum of one head twitch in the 2 min observation period was noted. The 5-hydroxytryptophan (5-HTP, 100 mg kg^{-1}) induced behavioural effects were assessed according to Hyttel & Fjalland (1972). 5 min after injection of 5 HTP, each mouse was observed every 15 min for head twitches, excitation, tremors and abduction and extension of hind limbs. One point was alloted for each sign present so that the maximum score for any animal was 4 points.

Bupropion HCl (Burroughs Wellcome, USA), clomipramineHCl (Ciba-Geigy, Basle, Switzerland), pargyline HCl (Abbot Lab., USA) were dissolved in distilled water. 5-HTP (Sigma, USA) was dissolved in 0·9% NaCl. Methylamphetamine hydrochloride (M.A.; Burroughs Wellcome) ampoules were used. The solutions were always prepared fresh and their strength

Table 1. Behavioural observations in mice receiving bupropion or clomipramine 5 h after pargyline (100 mg kg^{-1} i.p.)

Drug	Dose mg kg^{-1} i.p.	Behavioural observations (a)	(b)	(c)	(d)
Saline	—	—	—	—	—
Bupropion	12·5	++	0·8 ± 0·18	—	—
Bupropion	25	++	2·1 ± 0·23	—	—
Bupropion	50	+++	3·9 ± 0·1	2	4
Clomipramine	5	+	—	2	3
Clomipramine	10	++	—	4	6
Clomipramine	20	+++	0·7 ± 0·21	9	10

(a) Excitation: signs of excitation include locomotor stimulation, salivation, piloerction, exophthalmos, Straub tail and tremors. +, ++, +++ indicate degree.

(b) Stereotyped behaviour score: mean ± s.e.m. (n = 10) of the maximum intensity observed.

(c) Head twitches: no. of animals of 10 showing a minimum of one head twitch in 2 min observation period.

(d) Abduction and extension of hind limbs: no. of animals showing the behaviour (n = 10).

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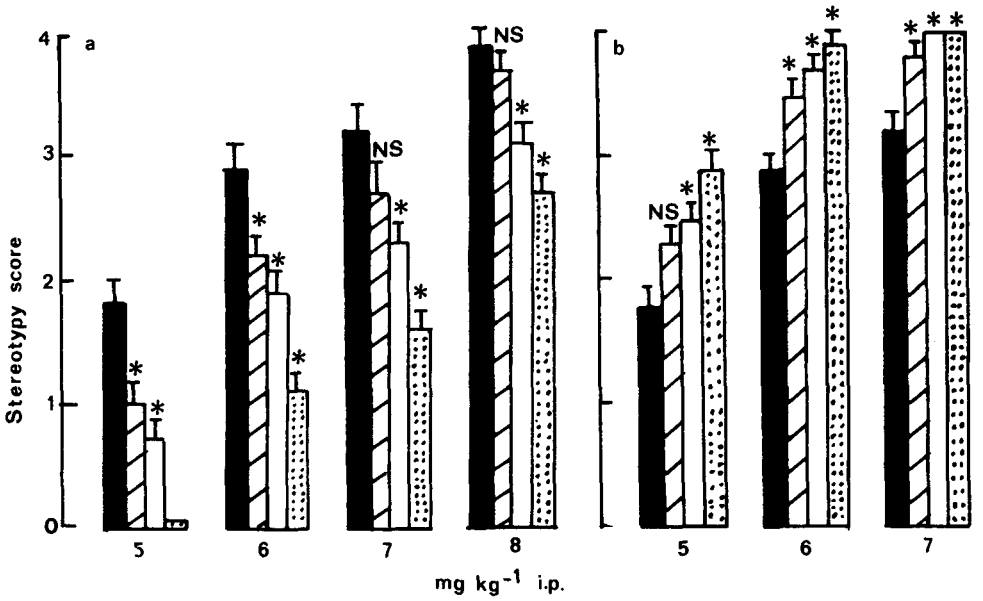

FIG. 1. Effects of bupropion 12·5 (hatched columns) 25 (open columns) and 50 (stippled columns) mg kg^{-1} i.p. on methamphetamine (5, 6, 7 and 8 mg kg^{-1} i.p.) induced stereotyped behaviour (closed columns). Bupropion was injected either 30 min before (a) or 5 min after (b) methamphetamine. Vertical bars show s.e.m. (n = 10) *$P < 0·05$ vs methamphetamine controls. N.S: $P > 0·05$ (Mann-Whitney U test).

was so adjusted that the requisite dose of a drug was injected in a constant volume of 10 ml kg^{-1}. Drugs were given intraperitoneally (i.p.) except 5-HTP which was injected into the tail vein. The results were statistically analysed by Mann-Whitney U tests for non-parametric data.

Results

Mice receiving bupropion 12·5 mg kg^{-1} showed no obvious behavioural changes whereas those receiving 25 and 50 mg kg^{-1} appeared to be stimulated and also exhibited periods of stereotypic sniffing. Methamphetamine (5–8 mg kg^{-1}) produced a dose-dependent degree of stereotyped behaviour in mice. 30 min pretreatment with bupropion (12·5, 25 and 50 mg kg^{-1}) significantly antagonized this, whereas the same doses given 5 min after methamphetamine significantly potentiated the behaviour (Fig. 1a, b, respectively).

Mice receiving pargyline, 100 mg kg^{-1}, did not show significant behavioural changes. When either bupropion (12·5–50 mg kg^{-1}) or clomipramine (10, 20 mg kg^{-1}) was given to these animals, they appeared to be excited and showed piloerection, salivation, increased locomotor activity, exophthalmos and tremors. In addition, the animals receiving bupropion showed a dose-dependent degree of stereotyped behaviour whereas mice receiving clomipramine characteristically demonstrated head twitches and abduction and extension of hind limbs which was absent in mice on the 12·5 and 25 mg kg^{-1} doses of bupropion. Only 2 of 10 animals on 50 mg kg^{-1} bupropion demonstrated head twitches and 4 out of 10 demonstrated abduction and extension (Table 1).

Bupropion, 50 mg kg^{-1}, potentiated the 5HTP, 100 mg kg^{-1}, induced syndrome, other doses had no effect. Clomipramine, 5–20 mg kg^{-1}, significantly potentiated the syndrome (Table 2).

Discussion

The observation of a mild degree of stereotyped behaviour with 25 and 50 mg kg^{-1} of bupropion is in agreement with that of Cooper et al (1980). Soroko et al (1977) have observed that bupropion in these doses antagonized the intense motor stimulation produced by (+)-amphetamine. Bupropion at 25 mg kg^{-1} also

Table 2. Effect of bupropion or clomipramine (30 min pretreatment) on 5 HTP (100 mg kg^{-1} i.v.) induced behaviour. The behavioural score is mean ± s.e.m. (n = 10). * indicates statistical significance ($P < 0·05$) when compared with 0·9% NaCl-pretreatment controls using Mann-Whitney U test.

Pretreatment drug	Dose mg kg^{-1}	Behavioural score	% Mortality
Saline	—	1·1 ± 0·18	0
Bupropion	12·5	1·3 ± 0·27	0
Bupropion	25	1·7 ± 0·27	10
Bupropion	50	2·2 ± 0·15*	30
Clomipramine	5	2·6 ± 0·18*	10
Clomipramine	10	4·0*	40
Clomipramine	20	4·0*	80

reduced the mortality caused by (+)-amphetamine (20 mg kg^{-1}) in aggregated mice (Maxwell et al 1981). Our observation that 30 min pretreatment with bupropion significantly antagonized induced methamphetamine-stereotyped behaviour is in agreement with those observations. Amphetamine is reported to release catecholamines from the brain tissue after being transported into the synaptosomes by the cocaine sensitive neuronal uptake mechanisms (Azzaro et al 1974). Bupropion is reported to be a selective dopamine uptake blocker. Thus prior treatment with it might be reponsible for preventing the access of amphetamine to dopamine-containing synaptosomes. The blockade of neuronal uptake of dopamine released by methanphetamine might explain the potentiation of methamphetamine's effects when bupropion is administered 5 min after it.

Monoamine oxidase inhibitor pretreatment is reported to increase all the monoamine concentrations in the central nervous system (Baldessarini 1980). In the pargyline-pretreated animals, clomipramine elicited head-twitches and abduction and extension of hind limbs, behaviour reported to be mediated by central actions of 5-hydroxytryptamine (Corne et al 1963), while bupropion produced intense locomotor stimulation and stereotypic movements but no head-twitches. The weak inhibitory action of bupropion on the 5-HT uptake as opposed to the more selective 5-HT uptake inhibition by clomipramine (Baldessarini 1980) may explain these differing behavioural observations in the two groups.

As expected, clomipramine also potentiated 5-HTP induced behaviour. Bupropion failed to potentiate the 5-HT-mediated behaviour, except at 50 mg kg^{-1}. These behavioural observations confirm the biochemical in-vitro reports that bupropion is a more potent uptake blocker of dopamine than that of 5-HT.

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Contractile effect of 1-*O*-hexadecyl-2-*O*-acetyl-*sn*-glycero-3-phosphocholine on strips of isolated rat intestine

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The contractile effects of AGEPC were examined on various regions of rat isolated intestine. The duodenum, jejunum and ileum showed only the tonic component of contraction to AGEPC at the low dose ($<10^{-9}$ M) but at the high dose (10^{-7} M) biphasic contractions were induced, consisting of a phasic followed by a tonic component. In the colon, however, the AGEPC-induced maximum contraction was comparable in magnitude to that produced by acetylcholine; also the contraction profile was different from that elicited from the other regions of the intestine. Low doses of AGEPC caused a slow, sustained contraction and at high doses phasic and tonic components were not dissociated.

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The unique phospholipid, 1-*O*-alkyl-2-*O*-acetyl-*sn*-glycero-3-phosphocholine (AGEPC) was first identified as a potent platelet-activating factor (Demopoulos et al 1979; Benveniste et al 1979). Subsequent studies showed that it had stimulatory effects on a variety of other cells besides blood platelets. Two research groups (Findlay et al 1981; Stimler et al 1981) have reported independently that AGEPC contracts strips of isolated guinea-pig ileum; the contraction which is slow and resistant to washing is followed by a desensitization of the muscle to further doses of AGEPC. To clarify whether AGEPC has similar effects on intestinal