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Psychopharmacological investigation of the monoamine oxidase inhibitory activity of molindone, a dihydroindolone neuroleptic

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24 h pretreatment with molindone enhanced the behavioural effects of L-dopa and 5-HTP, precursors of biogenic amines (catecholamines and 5-HT respectively) preferentially deaminated by MAO-A, confirming that a metabolite of molindone inhibits MAO-A. 24 h pretreatment with molindone enhanced the behavioural effects of tryptamine and antagonized reserpine-induced ptosis, and in molindone-pretreated rats L-tryptophan induced behavioural effects, probably because of the MAO-A inhibitory activity exerted by a metabolite of molindone. Since 24 h pretreatment with molindone, unlike 30 min pretreatment with clomipramine, failed to antagonize fenfluramine and *p*-chloramphetamine-induced behavioural syndromes, it suggests that molindone and/or its metabolites most probably do not exert 5-HT neuronal uptake blocking activity and the potentiation of 5-HTP-induced behavioural syndrome is due to a metabolite's MAO-A inhibitory activity. As 2 h pretreatment with molindone induced catalepsy and antagonized apomorphine-induced climbing behaviour in mice and stereotypy in rats, while 24 h pretreatment failed to induce catalepsy and to antagonize apomorphine-induced behaviour, it appears that, at 24 h, the tissue levels of molindone are inadequate to block postsynaptic striatal and mesolimbic DA receptors and that, though a metabolite of molindone is biologically active so far as inhibition of MAO-A is concerned, the metabolites are devoid of neuroleptic activity. Further, since 2 h pretreatment with molindone failed to enhance the behavioural effects of L-dopa, it suggests that at 2 h the degree of MAO-A inhibition induced by molindone and/or the metabolite is not sufficient to counteract the neuroleptic activity of the parent compound.

Molindone, a dihydroindolone neuroleptic used for the treatment of schizophrenia (Ayd 1974), induces catalepsy and antagonizes amphetamine and apomorphine-induced stereotypes (Rubin et al 1967; Nandal et al 1980) by blocking postsynaptic striatal dopamine (DA) receptors (Bunney et al 1975). Recently Meller & Friedman (1982), on the basis of biochemical studies, have reported that molindone in-vivo, at doses of 10 and 40 mg kg^{-1} i.p., produces a long-lasting (>72 h) irreversible inhibition of monoamine oxidase (MAO)-type A enzyme. Further, in their study, as molindone itself was found to be a very weak in-vitro inhibitor of MAO-A, Meller & Friedman (1982) postulated that in-vivo a metabolite of molindone might be responsible for producing the long-lasting, irreversible inhibition of MAO-A. In the present study we have investigated whether 24 h pretreatment with molindone, as reported for other MAO inhibitors (Chen 1964), augments the behavioural responses induced by L-dopa, 5-hydroxytryptophan (5-HTP), L-tryptophan and tryptamine, and antagonizes those of reserpine. We have also studied the effect of 24 h pretreatment with molindone on fenfluramine and *p*-chloramphetamine (PCA)-induced behavioural syndromes and on apomorphine-induced stereotypy and cage-climbing behaviour. Further, the effect of 2 h pretreatment with molindone on L-dopa-induced behavioural syndrome and on apomorphine-induced behaviours was also investigated.

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MATERIALS AND METHODS

Animals

Male albino mice (20–30 g) and rats (120–180 g), with free access to a standard diet and tap water were used once only. For behavioural observations animals were placed individually in open-topped transparent plastic cages (27 × 20 × 15 cm for mice, 30 × 20 × 20 cm for rats) immediately after drug administration. For observation of apomorphine-induced cage-climbing behaviour, mice were individually housed in Perspex cages, 27 × 20 × 15 cm with one of the vertical faces netted with 1 cm^2 wire mesh, 2 mm in diameter, 30 min before apomorphine treatment for adaptation to their new environment. For observation of apomorphine stereotypy, rats were placed

in individual cages made of wire netting, measuring 30 × 20 × 20 cm, 30 min before apomorphine treatment for adaptation to their new environment. Observations were made by an experienced observer who was unaware of the animal's treatment. All observations were made between 10 and 17 h at 27–30 °C in a noiseless, diffusely illuminated room.

Drugs, solutions and treatment schedules

Molindone HCl (Endo), (±)-fenfluramine HCl (Walter Bushnell), (±)-*p*-chloramphetamine HCl (Sigma), clomipramine HCl (CIBA-GEIGY) were dissolved in distilled water, and apomorphine HCl (Sigma) was dissolved in distilled water with 0·2 mg ml^{-1} ascorbic acid. L-Tryptophan (Sigma), DL-5-hydroxytryptophan (Sigma) and tryptamine HCl (Sigma) were dissolved in 0·9% NaCl (saline). Reserpine (CIBA-GEIGY) injection solution was diluted with distilled water. L-Dopa (Sigma) was dissolved in a minimum of 0·5 M HCl, neutralized to pH 5 with $NaHCO_3$ and then diluted with distilled water. All drugs were injected intraperitoneally, except 5-HTP and tryptamine which were injected intravenously through the tail vein and apomorphine which was administered subcutaneously. In mice the volume of drug injection was 10 ml kg^{-1}, in rats it was 2 ml kg^{-1} except for L-tryptophan which was injected in a volume of 5 ml kg^{-1}. Doses refer to the forms mentioned. For each dose 10 animals were used. Molindone was injected 24 h before 5-HTP, L-tryptophan, tryptamine, reserpine, fenfluramine and PCA and 24 or 2 h before L-dopa and apomorphine. Control groups received the requisite volume of vehicle i.p. at the stated time intervals before receiving the specified drugs. Clomipramine was injected 30 min before fenfluramine and PCA. Control groups received the requisite volume of vehicle i.p. 30 min before fenfluramine and PCA.

Behavioural studies

L-Dopa-induced behavioural syndrome in mice

Following injection of L-dopa the animals were observed for 1 h and note was made of the number of animals that responded with piloerection, salivation, exophthalmos, Straub tail, increased motor activity, and rapid running and jumping movements, each feature being assigned an arbitrary score value of one (maximal score for a group of 10 animals = 60).

5-HTP-induced behavioural syndrome in mice

The method followed was similar to that of Southgate et al (1971). Following injection of 5-HTP the animals were observed for 30 min for the presence of head twitches, fore limb movements, tremors, hind limb abduction, and backward locomotion, each feature being assigned a score value of one (maximal score for a group of 10 animals = 50).

Tryptamine-induced behavioural syndrome in mice

The method followed was similar to that of Jalfre et al (1982). Immediately after the tryptamine injection the animals were observed for 30 min for the presence of head twitches, tremors, pedalling movements of the front paws, exophthalmos, and hind limb abduction, each feature being assigned a score value of one (maximal score for a group of 10 animals = 50).

L-Tryptophan, fenfluramine and PCA-induced behavioural syndromes in rats

Following injection of L-tryptophan, fenfluramine and PCA, the animals were observed for 90 min and note was made of the number of animals that responded with wet dog shakes, lateral head weaving, hind limb abduction, Straub tail, tremors, and reciprocal forepaw treading (Trulson & Jacobs 1976; Bedard & Pycock 1977; Marsden & Curzon 1978), each feature being assigned a score value of one (maximal score for a group of 10 animals = 60).

Reserpine-induced ptosis in rats

Animals were observed for ptosis 1 h after reserpine injection. Ptosis in each eye was scored on a 0–4 scale by the method of Lapin (1967) as follows: absence of ptosis = 0 point, less than half closed = 1 point, half closed = 2 points, more than half closed = 3 points, complete ptosis = 4 points. The mean of the score of both eyes of each rat was determined and taken to compute the mean value of the group.

Apomorphine-induced cage-climbing behaviour in mice.

The method of Costall et al (1978) was followed. The animals were tested for climbing behaviour following apomorphine (0·5–1·5 mg kg^{-1} s.c.), taking the percent of time spent climbing during the 30 min after the first climb as the 'climbing index'. The maximum time (min) spent in a single climb throughout the duration of the apomorphine effect was also determined.

Apomorphine-induced stereotyped behaviour (SB) in rats

The intensity of apomorphine-induced SB was assessed over 30 s at 10 min intervals throughout its duration, using the scoring system of Costall &

Naylor (1974) where periodic sniffing = score 1, continuous sniffing = 2, periodic biting, gnawing or licking = 3 and continuous biting, gnawing or licking = 4. The maximum intensity of SB scored by each rat in the group was taken to compute the mean value of the group.

Catalepsy testing in mice and rats

Two and 24 h after molindone treatment the animals were tested for catalepsy by placing both front limbs of the animal on a 4 cm high wooden block (mice) or over an 8 cm high horizontal bar (rat) and measuring the time that the animal maintained this posture. The animals were considered cataleptic if they maintained this imposed posture for more than 10 s.

Statistics

The results were evaluated statistically by the Mann-Whitney U-Test for non-parametric data. Effects of molindone pretreatment on apomorphine-induced cage-climbing behaviour were analysed by the two-tailed Student's *t*-test.

RESULTS

Animals, when observed 2 h after molindone (2·5–20 mg kg^{-1}) treatment, appeared sedated, exhibited ptosis and gave a positive response when tested for catalepsy. However, the animals when observed 24 h after molindone (2·5–20 mg kg^{-1}) treatment, did not exhibit ptosis or any obvious behavioural syndrome and gave a negative response when tested for catalepsy.

Effect of 2 or 24 h pretreatment with molindone on apomorphine-induced cage-climbing behaviour in mice

Apomorphine (0·5–1·5 mg kg^{-1} s.c.)-induced dose-dependent climbing behaviour: Apomorphine, 0·5, 0·75 and 1 mg kg^{-1} induced a threshold to submaximal response respectively, thus these doses were used for subsequent interaction studies. 2 h pretreatment with molindone (2·5–10 mg kg^{-1}) significantly ($P < 0·01$ or less) antagonized apomorphine-induced climbing behaviour (Table 1). However, 24 h pretreatment with molindone (10, 20 mg kg^{-1}) did not significantly ($P > 0·05$) influence apomorphine-induced climbing behaviour (Table 2).

Effect of 2 or 24 h pretreatment with molindone on apomorphine-induced SB in rats

Apomorphine (0·5–3 mg kg^{-1} s.c.)-induced dose-dependent SB in rats: Apomorphine, 0·5, 1·0 and 2·0 mg kg^{-1} induced a threshold to submaximal response respectively, thus these doses were used for subsequent interaction studies. 2 h pretreatment with molindone (2·5–10 mg kg^{-1}) significantly ($P < 0·01$ or less) antagonized apomorphine-induced SB (Table 3). However, 24 h pretreatment with molindone (10, 20 mg kg^{-1}) did not significantly ($P > 0·05$) influence apomorphine-induced SB.

Table 1. Effect of 2 h pretreatment with molindone on apomorphine-induced climbing behaviour in mice. Molindone was injected i.p. whilst apomorphine (1 mg kg^{-1}) was administered s.c. Both the climbing index and the maximum time are expressed as the mean ± s.e.m. (n = 10). Animals with dose designated 0 received vehicle before apomorphine.

Drug	Dose mg kg^{-1}	Climbing index (%)	Max. time (min)
Molindone	0·0	72·9 ± 2·7	12·2 ± 0·6
	2·5	40·4 ± 3·2*	6·2 ± 0·4*
	5·0	8·2 ± 3·4*	1·3 ± 0·2*
	10·0	0·0	0·0

* Differs from vehicle-treated, $P < 0·01$ or less (Student's *t*-test).

Effect of 2 or 24 h pretreatment with molindone on L-dopa-induced behavioural syndrome in mice

In vehicle pretreated mice L-dopa (100 mg kg^{-1}) induced piloerection alone in all animals tested. At 150 mg kg^{-1}, in addition to piloerection, it induced slight salivation in 70–80% of the animals. Two h pretreatment with molindone (5, 10, 20 mg kg^{-1}) did not significantly ($P > 0·05$) affect the intensity of L-dopa-induced behavioural syndrome. However,

Table 2. Effect of 24 h pretreatment with molindone on apomorphine-induced climbing behaviour in mice. Molindone was injected i.p. whilst apomorphine was administered s.c. Both the climbing index and the maximum time are expressed as the mean ± s.e.m. (n = 10).

Drug	Dose mg kg^{-1}	Climbing index (%)	Max. time (min)
Apomorphine	0·5	22·8 ± 3·4	2·6 ± 1·1
Molindone +	10		
apomorphine	0·5	21·6 ± 3·7	2·2 ± 0·9
Molindone +	20		
apomorphine	0·5	23·2 ± 2·9	2·7 ± 1·2
Apomorphine	0·75	45·9 ± 3·3	6·7 ± 0·6
Molindone +	10		
apomorphine	0·75	47·4 ± 3·6	7·1 ± 0·4
Molindone +	20		
apomorphine	0·75	46·8 ± 3·1	6·9 ± 0·7
Apomorphine	1·0	70·6 ± 3·2	10·7 ± 0·5
Molindone +	10		
apomorphine	1·0	72·2 ± 3·8	11·2 ± 0·8
Molindone +	20		
apomorphine	1·0	71·5 ± 3·6	10·9 ± 0·7

Table 3. Effect of 2 h pretreatment with molindone on apomorphine-induced stereotyped behaviour (SB) in rats. Molindone was injected i.p. whilst apomorphine (2 mg kg^{-1}) was administered s.c. Each value represents the mean ± s.e.m. (n = 10). Animals with dose designated 0 received vehicle before apomorphine.

Drug	Dose mg kg^{-1}	Maximum intensity of SB (scored)
Molindone	0·0	3·2 ± 0·13
	2·5	2·3 ± 0·15*
	5·0	1·1 ± 0·10*
	10·0	0·0

* Differs from vehicle-treated, $P < 0·01$ (Mann-Whitney U-Test).

24 h pretreatment with molindone (10, 20 mg kg^{-1}) significantly ($P < 0·001$) increased the intensity of behavioural syndrome induced by L-dopa (Table 4).

Effect of 24 h pretreatment with molindone on 5-HTP and tryptamine-induced behavioural syndromes in mice

5-HTP at 45 and 90 mg kg^{-1} induced head twitches in 20 and 100% of the vehicle-pretreated animals, respectively (Table 4). Tryptamine (5 mg kg^{-1}) did not induce any behavioural effect while at 10 mg kg^{-1} it induced head twitches in 80% of the control animals (Table 4). 24 h pretreatment with molindone (10, 20 mg kg^{-1}) significantly ($P < 0·001$) increased the intensity of behavioural syndromes induced by 5-HTP and tryptamine (Table 4).

Effect of 24 h pretreatment with molindone on L-tryptophan-induced behavioural syndrome and on reserpine-induced ptosis in rats

L-Tryptophan (25, 50 mg kg^{-1}) did not induce any behavioural effects in vehicle-pretreated animals (Table 5). However, in molindone (10, 20 mg kg^{-1})-pretreated animals it significantly ($P < 0·001$) induced behavioural effects (Table 5). Further, 24 h pretreatment with molindone (10, 20 mg kg^{-1}) significantly ($P < 0·001$) antagonized reserpine (2·5 mg kg^{-1})-induced ptosis in rats (Table 5).

Effect of 24 h pretreatment with molindone on fenfluramine and PCA-induced behavioural syndromes in rats

24 h Pretreatment with molindone (10, 20 mg kg^{-1}) significantly ($P < 0·01$ or less) increased the behavioural effects of fenfluramine (5, 10 mg kg^{-1}) and PCA (2·5, 5 mg kg^{-1}) (Table 6). In contrast, 30 min pretreatment with clomipramine (5 mg kg^{-1}) significantly ($P < 0·01$ or less) decreased the behavioural effects of fenfluramine (5, 10 mg kg^{-1}) and PCA (2·5, 5 mg kg^{-1}) (Table 6), while pretreatment with 10 mg kg^{-1} clomipramine abolished the behavioural effects of fenfluramine (5 mg kg^{-1}) and PCA (2·5 mg kg^{-1}) and significantly ($P < 0·001$) decreased the behavioural effects of fenfluramine (10 mg kg^{-1}) and PCA (5 mg kg^{-1}) (Table 6).

Table 5. Effects of 24 h pretreatment with molindone on L-tryptophan-induced behavioural syndrome and reserpine-induced ptosis in rats. Each value represents the mean ± s.e.m. (n = 10).

Pretreatment (mg kg^{-1} i.p.)	Intensity of behavioural score after L-tryptophan 25 mg kg^{-1} i.p.	50 mg kg^{-1} i.p.	Ptosis score after reserpine 2·5 mg kg^{-1} i.p.
Vehicle	0·0 ± 0·00	0·0 ± 0·00	3·4 ± 0·16
Molindone (5)	0·3 ± 0·15	0·5 ± 0·16	3·0 ± 0·00
Molindone (10)	1·2 ± 0·13*	2·4 ± 0·18*	1·9 ± 0·10*
Molindone (20)	2·9 ± 0·21*	4·2 ± 0·22*	0·7 ± 0·15*

* Differs from vehicle-treated, $P < 0·001$ (Mann-Whitney U-Test).

DISCUSSION

MAO-A preferentially deaminates endogenous amines such as 5-HT and noradrenaline (Johnston 1968) and although DA was originally thought to be a common substrate for MAO-A and MAO-B (Yang & Neff 1974), recent studies have shown that in-vivo DA is also deaminated almost entirely by MAO-A in the rat brain (Waldmeier et al 1976). Thus our observation that 24 h pretreatment with molindone, in the same range of doses as used by Meller & Friedman (1982), enhanced the behavioural effects of L-dopa and 5-HTP, precursors of biogenic amines

Table 4. Effects of 24 h pretreatment with molindone on L-dopa, 5-HTP and tryptamine-induced behavioural syndromes in mice. Each value represents the mean ± s.e.m. (n = 10).

Pretreatment (mg kg^{-1} i.p.)	Intensity of behavioural score after L-Dopa (mg kg^{-1} i.p.) 100	150	5-HTP (mg kg^{-1} i.v.) 45	90	Tryptamine (mg kg^{-1} i.v.) 5	10
Vehicle	1·0 ± 0·00	1·7 ± 0·15	0·2 ± 0·13	1·0 ± 0·00	0·0 ± 0·00	0·8 ± 0·13
Molindone (5)	1·4 ± 0·16	2·2 ± 0·13	0·6 ± 0·16	1·5 ± 0·16	0·3 ± 0·15	1·2 ± 0·13
Molindone (10)	4·2 ± 0·13*	4·9 ± 0·10*	2·3 ± 0·15*	3·4 ± 0·16*	1·2 ± 0·13*	2·2 ± 0·13*
Molindone (20)	4·7 ± 0·15*	5·3 ± 0·15*	3·1 ± 0·10*	4·2 ± 0·13*	2·6 ± 0·16*	3·7 ± 0·15*

* Differs from vehicle-treated, $P < 0·001$ (Mann-Whitney U-Test).

Table 6. Effects of pretreatment with molindone or clomipramine on fenfluramine and *p*-chloramphetamine (PCA)-induced behavioural syndromes in rats. Molindone or clomipramine was given i.p. 24 h or 30 min, respectively, before fenfluramine and PCA. Each value represents the mean ± s.e.m. (n = 10).

Pretreatment (mg kg^{-1} i.p.)	Intensity of behavioural score after fenfluramine		Intensity of behavioural score after PCA	
	5 mg kg^{-1} i.p.	10 mg kg^{-1} i.p.	2·5 mg kg^{-1} i.p.	5 mg kg^{-1} i.p.
Vehicle	1·4 ± 0·16	3·3 ± 0·18	1·7 ± 0·15	3·5 ± 0·19
Molindone (5)	1·8 ± 0·13	3·7 ± 0·21	2·1 ± 0·10	3·9 ± 0·24
Molindone (10)	2·6 ± 0·18*	4·5 ± 0·22*	2·9 ± 0·16*	4·7 ± 0·21*
Molindone (20)	3·5 ± 0·23*	5·4 ± 0·28*	3·8 ± 0·21*	5·6 ± 0·25*
Vehicle	1·6 ± 0·16	3·5 ± 0·16	1·9 ± 0·10	3·7 ± 0·22
Clomipramine (5)	0·4 ± 0·16*	2·2 ± 0·13*	0·7 ± 0·15*	2·4 ± 0·16*
Clomipramine (10)	0·0	0·6 ± 0·16*	0·0	0·8 ± 0·13*

* Differs from vehicle-treated, $P < 0·01$ or less (Mann-Whitney U-Test).

(catecholamines and 5-HT respectively) preferentially deaminated by MAO-A, confirms the biochemical report of Meller & Friedman (1982) that a metabolite of molindone produces a long-lasting irreversible inhibition of MAO-A. Our contention that a metabolite of molindone exerts MAO-A inhibitory activity is further supported by our finding that 24 h pretreatment with molindone, as reported for other MAO-A inhibitors (Neff & Fuentes 1976), effectively antagonized reserpine-induced ptosis in rats. Our other observations, that L-tryptophan induced behavioural effects in molindone pretreated rats, and 24 h pretreatment with molindone enhanced the behavioural effects of tryptamine, a common substrate for both MAO-A and MAO-B (Yang & Neff 1974), also indicate that a metabolite of molindone exerts MAO inhibitory activity.

The 5-HTP-induced behavioural syndrome is potentiated by MAO inhibitors (Chen 1964) and also by 5-HT uptake blockers like clomipramine (Hyttel & Fjalland 1972). Since 24 h pretreatment with molindone enhanced the 5-HTP-induced behavioural syndrome it is possible that molindone and/or one of its metabolites may also be exerting 5-HT uptake blocking activity. However, this possibility appears improbable because of our observation that 24 h pretreatment with molindone, unlike clomipramine, failed to antagonize fenfluramine and PCA-induced behavioural syndromes which occur as a result of fenfluramine and PCA being taken up into the 5-HT neurons and releasing 5-HT (Buus Lassen 1974; Trulson & Jacobs 1976). Clomipramine and other 5-HT uptake blockers antagonize the behavioural effects of PCA and fenfluramine by blocking their entry into the 5-HT neurons and preventing the subsequent release of 5-HT (Buus Lassen 1974; Fuller 1980; Joshi et al 1983), while MAO inhibitors enhance fenfluramine-induced behavioural effects (Southgate et al 1971). Thus the enhancement of PCA and fenfluramine-induced behavioural syndrome by 24 h pretreatment with molindone can be readily explained on the basis of the MAO-A inhibitory activity exerted by a metabolite of molindone. Further, MAO-A inhibitors like clorgyline, unlike MAO-B inhibitors, have been found to be useful for the treatment of certain depressive illnesses (Murphy et al 1979; Mendis et al 1981). Recently Small et al (1981) found molindone to be useful in the treatment of refractory depression, an observation which concurs with the biochemical report of Meller & Friedman (1982) and our present study indicating that a metabolite of molindone exerts MAO-A inhibitory activity.

Our intention of studying whether 24 h pretreatment with molindone induces catalepsy and antagonizes apomorphine-induced behaviour was to determine whether the metabolites, like the parent compound, exert neuroleptic activity. Since 2 h pretreatment with molindone did induce catalepsy and antagonized apomorphine-induced behaviour while 24 h pretreatment with molindone failed to induce catalepsy and to antagonize apomorphine-induced behaviour, it indicates: (i) that after 24 h the tissue levels of molindone present in the body after metabolism and excretion are inadequate to block postsynaptic striatal and mesolimbic DA receptors, and (ii) that, though a metabolite of molindone is biologically active as far as inhibition of MAO-A is concerned, the metabolites of molindone do not exert neuroleptic activity.

The mediation of autonomic and behavioural effects by L-dopa is attributed to its enzymatic conversion to DA and noradrenaline which then act on central and peripheral receptors (Butcher & Engel 1969; Carlsson 1969; Pazo et al 1982). Since 2 h pretreatment with molindone failed to increase the intensity of behavioural syndrome induced by L-dopa it suggests that after 2 h the degree of

MAO-A inhibition induced by molindone and/or its metabolites is not sufficient to counteract the neuroleptic activity of the parent compound.

In conclusion, we suggest that a metabolite of molindone exerts MAO-A inhibitory activity and unlike the parent compound does not exhibit neuroleptic activity.

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