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Alterations of Serotonin Neurotransmission and Inhibition of Mouse Killing Behavior: II. Effects of Selective and Reversible Monoamine Oxidase Inhibitors of Type A

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ISEL, F., L. CIESIELSKI, S. GOBAILLE, V. MOLINA AND P. MANDEL. *Alterations of serotonin neurotransmission and inhibition of mouse killing behavior: II. Effects of selective and reversible monoamine oxidase inhibitors of type A.* PHARMACOL BIOCHEM BEHAV **29**(1) 97–104, 1988.—Three groups of rats were tested for mouse killing behavior after IP injection of selective and reversible type A monoamine oxidase inhibitors. The rats were either spontaneous killers, or non-killers which acquired killing behavior following para-chlorophenylalanine treatment or electrolytical destruction of dorsal and median raphe nuclei. Moclobemide (para-chloro-N-(2-morpholinoethyl)-benzamide), cimoxatone (3-(4-(3-cyanophenyl-methoxy)phenyl)-5-(methoxy-methyl)-2-oxazolidinone, MD 780515), toloxatone (5-(hydroxymethyl)-3-(3-methylphenyl)-2-oxazolidinone) and amiflamine ((+)-4-dimethylamino-2, alpha-dimethylphenethyl amine, FLA 336 (+)) were used as selective and reversible monoamine oxidase inhibitors of type A. Cimoxatone, toloxatone and amiflamine inhibited mouse killing behavior of spontaneous killer rats without apparent sedation, whereas moclobemide was not efficient at doses which did not decrease locomotor activity. A similar inhibition of mouse killing behavior was obtained in spontaneous and serotonin depleted killer rats. The results are discussed in relation to the behavioral expression of serotoninergic supersensitivity in the three groups of killer rats described earlier using serotonin agonist and uptake inhibitors.

Inhibitors of monoamine oxidase Mouse killing behavior Serotonin Para-chlorophenylalanine Raphe lesions Supersensitivity

MOUSE killing behavior (MKB) by rats is widely used to evaluate experimental aggression [19, 25, 26, 40, 45, 46]. The decrease in serotonin (5-HT) neurotransmission has been implicated in some forms of aggressive behavior (for review see [31,43]). Impairment of serotonin turn-over rate was found in the raphe area and forebrain of spontaneous killer rats [25,41].

Serotonin depleting treatments following electrolytic destruction of the dorsal and median raphe nucleus [12, 23, 28, 44] or para-chlorophenylalanine (PCPA) treatment [13,28], a known inhibitior of tryptophan hydroxylase [20], have been shown to induce MKB in non-killer rats [13, 34, 42, 44] and to potentiate aggressiveness in isolated spontaneous killer rats (K rats) [15,47]. Tryptophan-free diet, which decreases 5-HT and its metabolite 5-hydroxyindole acetic acid (5-HIAA), was also shown to induce MKB in non-killer rats and to facilitate killing in K rats [14, 18, 46].

On the other hand an inhibition of MKB was shown in experiments in which central 5-HT mechanisms were activated by administration of 5-HT precursors [13,42], of 5-HT agonists [9,27] or of 5-HT uptake inhibitors [22,27]. In the brain, 5-HT is metabolized predominantly by type A monoamine oxidase (MAO A), rather than by type B monoamine oxidase (MAO B) (for review see [38]). An inhibition of MKB has been already observed using MAO inhibitors; however the drugs used in these studies were either irreversible or non-specific MAO A inhibitors [16, 32, 36].

After administration of 5-HT agonists or uptake inhibitors, the inhibition of MKB was more potent in killer rats obtained by either PCPA treatment or midbrain raphe lesions than in spontaneous killer rats; an expression of serotoninergic supersensitivity in muricidal behavior of serotonin depleted rats has been suggested [28]. When central 5-HT terminals were specifically destroyed by intraventricular injection of 5,7-dihydroxytryptamine, serotoninergic supersensitivity has been reported in rats using the behavioral syndrome induced by a 5-HT precursor: L-5-hydroxytryptophan (5-HTP) [30,39], or an agonist:

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5-methoxy-N,N-dimethyltryptamine [29, 30, 39]. An enhanced sensitivity to 5-HTP has also been described after 5-HT depleting treatment with PCPA [10]. Serotoninergic supersensitivity is also supported by binding studies; a decrease in the apparent Kd for (3H) 5-HT binding, without changes in the maximum number of binding sites, was found in the forebrains of dorsal and median raphe lesioned rats [6] and an increase in specific (3H) 5-HT binding, without changes in the apparent Kd, appeared after PCPA treatment [6,33].

Many compounds have been shown to be selective MAO A or MAO B inhibitors (for review see [11]). Moclobemide [8], cimoxatone [5,17], toloxatone [5] and amiflamine [2] are reversible and specific inhibitors of MAO A. Since 5-HT neurotransmission is involved in MKB, we investigated the effect of these reversible and specific MAO A inhibitors on MKB in K rats and in non-killer rats which became killers after PCPA treatment or midbrain raphe destruction. The present study is addressed to determine whether a behavioral expression of 5-HT supersensitivity could be demonstrated for MAO A inhibitors, as it has already been shown for 5-HT agonists and uptake inhibitors [28].

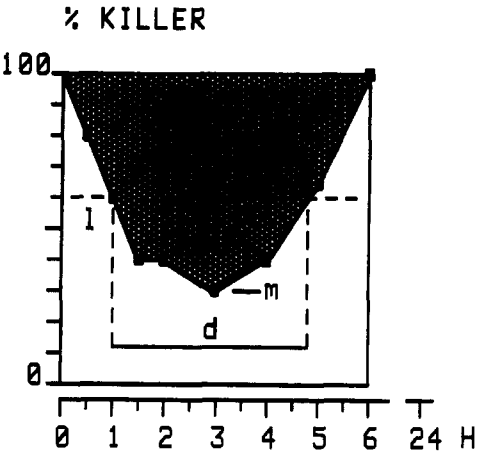

FIG. 1. Parameters of mouse killing behavior. m: maximum of MKB inhibition (%) after drug administration. l: latency time to reach 40% of inhibition of MKB. d: duration of inhibition in at least 40% of muricidal rats tested. Efficacy (%) is the ratio of the filled area to the total area (areas were determined by weighing or by numerical integration).

METHOD

Animals

Male adult 3-month-old Wistar rats from our colony weighing 250–350 g were used. They were housed individually in plastic opaque cages (21×40×15 cm) with food and water ad lib and they were maintained in a 12-hr light-dark cycle (light on 7:00 a.m.).

Drugs

Toloxatone and cimoxatone were generous gifts from the Centre de Recherche Delalande, Rueil-Malmaison, France; moclobemide was synthesized at the Laboratory of Organic Chemistry, Sanofi Recherches, Montpellier, France; amiflamine was provided by Astra Läkmedel AB, Södertälje, Sweden; PCPA (d,l-p-chlorophenylalanine methyl ester, HCl) was purchased from Sigma Chemical Co., St. Louis, MO.

Procedure

The procedure used was the same as that previously reported for the study of agonists and uptake inhibitors of serotonin [28].

In brief, the experimental conditions were as follows. Rats were tested for muricidal activity after one month of social isolation. The rats which did not kill a mouse introduced in their cages in 24 hr period were classified as non-killer rats (NK rats) and were submitted either to PCPA treatment or electrolytical destruction of the dorsal and median raphe nuclei. Rats which killed the mouse consistently in less than 5 min on five consecutive days were classified as spontaneous killer rats (K rats).

One group of NK rats received 150 mg/kg of PCPA for two consecutive days. Those rats which became killers were confirmed for mouse killing behavior (MKB), and classified as PCPA killer rats (PCPA K). They were used for experiments 10 days after the last PCPA injection.

Another group of NK rats was anesthetized with 40 mg/kg (IP) sodium pentobarbital and electrolytical destruction of the dorsal and median raphe nuclei was carried out as described earlier [44]. After a recovery period of 3 weeks the rats were tested for MKB; those rats which became killers were classified as raphectomized killer rats (Ra K) and used for experiments one month after surgery.

Rats of each group were tested for spontaneous locomotor activity by means of an actograph apparatus, at the same time as MKB experiments were performed and in the same 12 hr light-dark cycle. Tests began at 10:00 a.m. and the motility was then measured during the following 60 min intervals as the "horizontal activity," that is the total number of infrared photobeams broken during 3 hr.

The three groups of killer rats received drugs by intraperitoneal injection (IP) in a randomized order. A dose response curve was established in control K rats. The rats were statistically compared to their respective control groups.

In order to allow a statistical analysis of a possible difference, the PCPA K and Ra K rats were compared to the K rats at the same dose producing about 50% of MKB inhibition. After drug injections, animals were tested for MKB every 30 min spanning 6 hr, and at 24 hr. Toloxatone and amiflamine were dissolved in saline whereas moclobemide and cimoxatone were dissolved in 1% of Tween 80 and injected in a volume of 2 ml/kg. The respective control groups received equivalent volumes of saline or Tween 80.

Histology

At the end of the experiments, one group of 8 Ra K rats was sacrificed and their brains were removed, fixed in 10% formalin and embedded in paraffin. The extent of the lesion damage for each rat was assessed by microscopic examination of cresyl violet stained sections.

Parameters of Inhibition of MKB

Muricidal inhibition was measured by the following parameters (Fig. 1):

(a) Percentage of killer rats which no longer kill at different times after drug administration.

(b) Latency of inhibition of MKB (Latency). time necessary for MKB to decrease from 100% to 60% in the tested rats as determined from the experimental kinetic curve. Two standard groups of 10 rats, one of which exhibiting 100% MKB, the second exhibiting 60% of MKB, are significantly

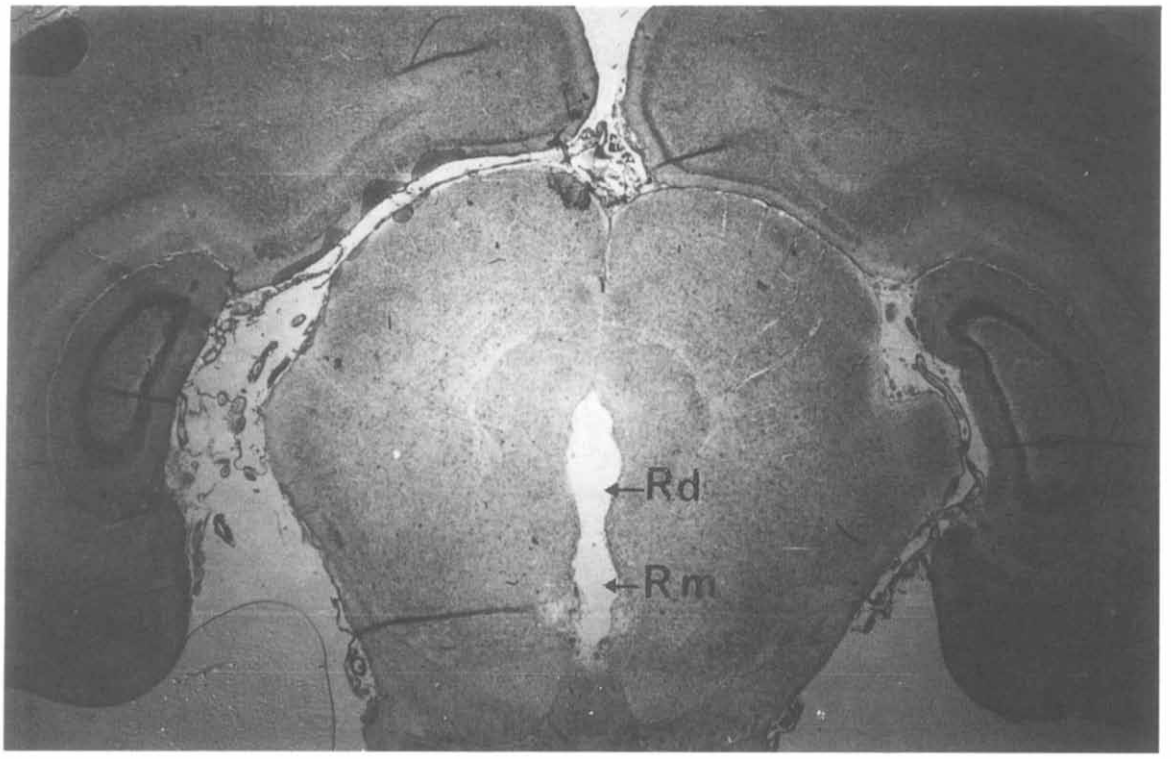

FIG. 2. Histological control of electrolytical lesions of raphe. Rd: raphe dorsalis, Rm: raphe medialis.

different at the 0.05 level according to the Fisher exact probability test.

(c) Maximal percentage of MKB (Maximum) after drug injection.

(d) Efficacy: The efficacy was determined as the ratio of the area of the inhibition surface (surface above the kinetic curve for MKB) to the total area determined in the same interval 0–6 hr (Fig. 1).

(e) Duration of MKB inhibition in at least 40% of rats tested.

Statistics

(a) Mean values for locomotor activity were compared for the significance of their differences by the Fisher-Student's *t*-test.

(b) The significance of MKB inhibition was determined by the Fisher exact probability test. The inhibition of MKB was significant at the 0.05 level if at least 4 rats were inhibited in a treated group of 10 rats when all rats from a control group of 10 rats presented MKB.

(c) Efficacies are analogous to the ratio of observed population to expected population; so, inter-group comparison of efficacies in PCPA K and Ra K rats with respect to drug treated K rats at the same dose had been analysed by the Chi^2 test.

(d) Latency and duration were determined by interpolation on the kinetic curve of MKB at the 40% level of inhibition. Although they were good indicators of the kinetic of MKB inhibition and have been presented in the tables, they could not be statistically analysed.

RESULTS

We have earlier reported that 10% of naive rats bred in our laboratory became K rats after 1 month of social isolation. It has also been observed that with PCPA treatment and with midbrain raphe lesions, respectively, 40% PCPA K rats and 50% Ra K rats were obtained [28]. There was no significant difference of body weight in PCPA K rats compared to PCPA-treated non-killer rats and in Ra K rats compared to midbrain raphe lesioned non-killer rats, although the body weight of lesioned rats was slightly lower than that of non-lesioned control rats.

Fifty days after midbrain raphe lesions and 10 days after PCPA treatment a depletion of 5-HT and 5-HIAA in all brain structures studied was observed [28]. The histological study showed that the lesions were localized in both raphe dorsal and median nuclei (Fig. 2).

Effect of MAO A Inhibitors on MKB of K Rats

Even at a dose significantly decreasing locomotor activity, moclobemide did not reduce MKB (Table 1). At the lowest dose injected, locomotor acitivty was normal after 2 hr of drug administration. At this time MKB was not inhibited.

The dose-dependent inhibition of MKB was observed with cimoxatone, toloxatone and amiflamine (Tables 2–4), without affecting locomotor activity, except for the highest dose of cimoxatone. For cimoxatone and toloxatone the maximal MKB inhibition was observed between sixty and ninety min after drug injection and the inhibition of MKB was no longer significant after 4 hr or later (Tables 2–3). For amiflamine, the maximal MKB inhibition occurred only after 2–3 hr and the inhibition of MKB was no longer significant after 6 hr (Table 4, Fig. 3). The drug injections had no apparent secondary effects and the general pattern of behavior of the rats did not seem to alter.

TABLE 1

EFFECTS OF MOCLOBEMIDE ON MKB AND LOCOMOTOR ACTIVITY

Rats	Dose μmol/kg (IP)	N	Maximum %	Latency Min	Duration Min	Efficacy %	Locomotor Activity Counts Per 60 Min 0–1 hr	1–2hr	2–3 hr
K Rats	0	10	0	—	—	0	253 ± 80	151 ± 53	77 ± 21
	18.6	10	20	—	—	7	73 ± 28‡	39 ± 15‡	103 ± 31
	37.2	10	30	—	—	12	40 ± 11‡	21 ± 10‡	41 ± 13†
PCPA K	0	10	0	—	—	0	261 ± 58	147 ± 28	100 ± 30
	18.6	10	30	—	—	10	92 ± 29‡	52 ± 19‡	96 ± 33
RA K	0	10	0	—	—	0	251 ± 62	130 ± 27	92 ± 29
	18.6	10	40*	30	0	6	88 ± 35‡	67 ± 22†	105 ± 38

Parameters of MKB are determined as described in the Method section from an experiment with N rats; latency and duration are given when the inhibition of MKB is significant.

Locomotor activity: N=6.

Mean ± standard deviation.

Intra-group comparison with respect to vehicle treated rats of the same group: *$p<0.05$; †$p<0.005$; ‡$p<0.0005$.

Inter-group comparison with respect to drug treated K rats at the same dose: There is no significant difference.

TABLE 2

EFFECTS OF CIMOXATONE ON MKB AND LOCOMOTOR ACTIVITY

Rats	Dose μmol/kg (IP)	N	Maximum %	Latency Min	Duration Min	Efficacy %	Locomotor Activity Counts Per 60 Min 0–1 hr	1–2hr	2–3 hr
K Rats	0	10	0	—	—	0	225 ± 67	115 ± 28	73 ± 19
	5.9	20	50*	40	65	18.5	185 ± 52	138 ± 33	90 ± 25
	8.9	10	70†	17	100	25.8	173 ± 47	141 ± 32	88 ± 23
	11.8	11	91‡	14	258	57.9	160 ± 39*	114 ± 27	76 ± 20
PCPA K	0	20	0	—	—	0	302 ± 69	180 ± 31	112 ± 29
	5.9	23	48‡	63	81	29.0	281 ± 65	195 ± 33	97 ± 31
RA K	0	20	0	—	—	0	256 ± 75	130 ± 37	98 ± 30
	5.9	21	57‡	48	114	29.8	212 ± 57	122 ± 35	91 ± 26

For legend see Table 1.

TABLE 3

EFFECTS OF TOLOXATONE ON MKB AND LOCOMOTOR ACTIVITY

Rats	Dose μmol/kg (IP)	N	Maximum %	Latency Min	Duration Min	Efficacy %	Locomotor Activity Counts Per 60 Min 0–1 hr	1–2hr	2–3 hr
K Rats	0	10	0	—	—	0	222 ± 61	153 ± 31	117 ± 31
	24.2	10	60*	45	65	18.8	230 ± 60	161 ± 45	135 ± 28
	48.3	19	63†	42	125	31.1	205 ± 52	142 ± 38	148 ± 41
	72.5	11	82‡	54	140	32.2	210 ± 68	138 ± 47	165 ± 69
PCPA K	0	10	0	—	—	0	288 ± 70	175 ± 50	139 ± 34
	48.3	14	50*	75	72	21.7	251 ± 68	162 ± 41	125 ± 29
RA K	0	10	0	—	—	0	237 ± 54	143 ± 42	125 ± 32
	48.3	12	58†	41	103	25.0	243 ± 59	157 ± 38	160 ± 44

For legend see Table 1.

TABLE 4

EFFECTS OF AMIFLAMINE ON MKB AND LOCOMOTOR ACTIVITY

Rats	Dose μmol/kg (IP)	N	Maximum %	Latency Min	Duration Min	Efficacy %	Locomotor Activity Counts Per 60 Min 0–1 hr	1–2hr	2–3 hr
K Rats	0	10	0	—	—	0	232 ± 57	120 ± 21	128 ± 15
	1.5	12	50*	54	138	32.0	200 ± 40	137 ± 18	120 ± 22
	3.0	12	67†	24	312	57.0	209 ± 50	105 ± 20	135 ± 17
	6.0	11	91‡	21	362	73.8	248 ± 62	140 ± 28	148 ± 36
PCPA K	0	10	0	—	—	0	292 ± 53	159 ± 29	125 ± 18
	1.5	14	50*	52	140	31.0	276 ± 48	138 ± 33	111 ± 21
RA K	0	10	0	—	—	0	261 ± 63	144 ± 25	99 ± 24
	1.5	13	46*	95	75	24.4	270 ± 58	140 ± 30	105 ± 29

For legend see Table 1.

Effect of MAO A Inhibitors on MKB of PCPA K and Ra K Rats and Comparison With Spontaneous K Rats

As it was observed with K rats, MKB was also blocked in PCPA K, as well as in Ra K rats, when cimoxatone, toloxatone and amiflamine were administered. The kinetic profile of MKB inhibition as well as the time of maximal inhibition were similar in both PCPA K and Ra K rats compared to the control K rats (Fig. 3). These drugs, tested at the efficacious doses, did not decrease the locomotor activity and rats showed no apparent secondary effects.

When injected in PCPA K and in Ra K rats, moclobemide produced only a rather slight decrease of MKB at the dose used. However, as it was mentioned in K rats, at this dose moclobemide lowered locomotor activity.

The action of cimoxatone, toloxatone and amiflamine have been compared in PCPA K and Ra K rats to the action of these drugs in K rats. In order to allow a statistical analysis of the significance of a difference from the group of K rats, the dose of drug chosen was that producing about 50% of MKB inhibition in K rats. For these three efficient MAO A inhibitors studied, the maximal percentage of MKB inhibition was seen at the same time in K rats, as well as in PCPA K and in Ra K rats (Fig. 3).

The effects on MKB, of these three MAO A inhibitors (cimoxatone, toloxatone and amiflamine) tested at the dose inducing about 50% of MKB inhibition in K rats, do not differ statistically in the 3 groups of killer rats (Tables 2–4). Neither the maximum, nor the efficacy were significantly different. Likewise, either latency or duation of MKB inhibition did not differ in the three groups of killer rats.

DISCUSSION

Noradrenaline (NA) and 5-HT are selective substrates for MAO A and the increase in the brain levels of these amines by the MAO A inhibitors is well established [2, 3, 37, 38, 48]. One may wonder whether MKB inhibition by MAO A inhibitors involves a noradrenergic mechanism, since alpha 1-adrenergic blockers inhibit MKB [35]. However, there is sufficient convincing evidence showing that MKB inhibition of K rats does not operate via noradrenergic routes. For example: (a) the destruction of the locus coeruleus, which contains NA-producing neurones, did not affect MKB of K rats [21], (b) there is no evidence concerning an effect of NA increase on muricidal behavior in K rats, and (c) NA level and turn-over rates in K rats compared to non-killer rats were found similar [24,44] or higher [32]. These data suggest that an increase of NA by MAO A inhibitors would not induce MKB inhibition.

Studies on 5-HT level and turn-over rates have led to some controversial results. A reduction of 5-HT turn-over in the pons-medulla area, that contains the raphe region, was observed in killer rats compared to non-killer rats [25], but no difference in 5-HT level and turn-over rates appeared in whole brain [32] or amygdala [24]. A lower 5-HT turn-over rate has also been reported in killer rats as opposed to "friendly" rats; however the lowest turn-over was found in "indifferent" ones [41]. On the other hand MKB was blocked by drugs that activate 5-HT neurotransmission: 5-HT precursors, agonists or uptake inhibitors [9, 13, 27, 42]. All these data suggest that the antimuricidal effect of MAO A inhibitors may be invoked via potentiation of serotoninergic neurotransmission.

The dose-effect relationship on the inhibition of MKB was observed after treatment of K rats with the reversible inhibitors of MAO A, cimoxatone, toloxatone and amiflamine. Except for the highest dose of cimoxatone, no reduction of locomotor activity was observed. Locomotor activity was slightly reduced during the first hour after cimoxatone injection, but had returned to control values at the time when maximal MKB inhibition was obtained. It was reported that amiflamine produced a decrease in locomotion, rearing and activity [1]. This activity occurred only during the initial 30 min of drug injection and at a dose higher than used in this report (7.3 μmol/kg IP). Thus, it may be concluded that the observed inhibition of MKB is not due to sedation of the rats.

Moclobemide did not decrease the MKB, in our experimental conditions, although locomotor activity was affected. It is noteworthy that moclobemide has been shown to be a potent reversible and specific inhibitor of MAO A activity *in vivo*, with ED 50 for MAO A inhibition being 10 μmol/kg per os [8]. However, this value is rather lower than might be expected from the *in vitro* experiments and it has been suggested that moclobemide may act as a pro-drug and may be converted in the body into some active principle, which in turn is responsible for the observed *in vivo* effect [8]. At the present moment it is not understood why moclobemide is not

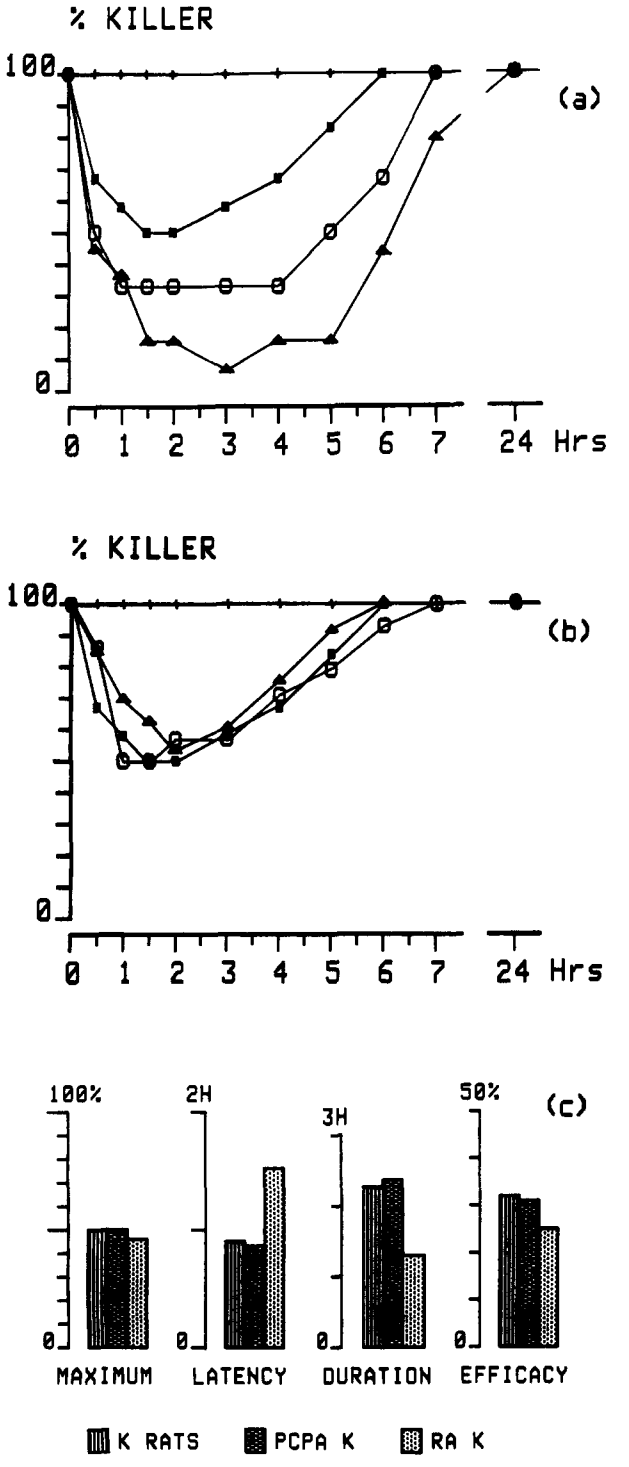

FIG. 3. Kinetic of inhibition of MKB after drug administration in K rats, PCPA K and Ra K rats. (a) Dose-response of amiflamine in K rats + control. ■ amiflamine 1.5 μmol/kg. ○ amiflamine 3.0 μmol/kg, ▲ amiflamine 6.0 μmol/kg. (b) Amiflamine 1.5 μmol/kg in K rats, PCPA K and Ra K rats. ■ K rats, ○ PCPA K rats, ▲ Ra K rats. (c) Parameters of MKB (maximum, latency, duration, efficacy) in K rats and in rats in which serotoninergic neurotransmission has been altered (PCPA K and Ra K rats), after administration of amiflamine at the dose of 1.5 μmol/kg. Statistical analyses were performed on maximum and efficacy of PCPA K and Ra K rats as compared to K rats: there is no significant difference.

able to effect MKB in K rats; a metabolic transformation might be involved in this phenomenon.

Amiflamine inhibited MKB of K rats more efficiently than cimoxatone and toloxatone. For instance, amiflamine produced similar effects as cimoxatone at a 4-fold lower dose. Concerning the MAO A inhibition, *in vivo*, these two drugs have almost identical efficiency [2,8], while *in vitro* cimoxatone showed a one hundred-fold lower Ki as compared to amiflamine [2,5]. This may be explained by the fact that amiflamine is selectively taken up into serotoninergic nerve terminals by the neuronal uptake mechanisms [4]; thus, amiflamine is increased at the intraneuronal level which may be responsible for its more efficient action.

Toloxatone was found to be less potent in inhibiting MKB of K rats, as compared to cimoxatone and amiflamine. A much higher dosage was necessary to produce a comparable effect. These observations are in agreement with the effects on MAO A inhibition *in vitro* and *in vivo*; for instance the IC 50 of the MAO A inhibition by toloxatone was about 5 times higher than by amiflamine [2,5].

In previous work, we have shown that 5-HT agonists (5-methoxy-N-N-dimethyl-tryptamine and 8-hydroxy-2-(di-n-propyl-amino) tetralin) and inhibitors of 5-HT uptake (fluoxetine and citalopram) produced a higher inhibition of MKB in PCPA K and in Ra K rats as compared to K rats [28]. This suggests a behavioral expression of serotonin supersensitivity, in PCPA-treated and raphectomized rats [28]. Such a supersensitivity has also been reported in other behavioral models after destruction of central 5-HT nerve terminals or treatment with PCPA [10, 29, 30, 39]. Binding studies on 5-HT receptors reported by others do favour our viewpoint. The increase in the maximum number of specific binding sites without any alteration of the Kd is a strong evidence supporting supersensitivity of 5-HT receptors [6,33]. Supersensitivity of 5-HT receptors may easily explain the enhanced response on MKB, in PCPA K and Ra K rats, of 5-HT agonists, as well as of uptake inhibitors [28]. Indeed, once 5-HT uptake is impaired by uptake inhibitors, there exists the possibility of a prolonged effect of this molecule in the synaptic cleft.

In view of the observed inhibition of MKB in K rats by MAO A inhibitors involving activation of 5-HT neurotransmission and of supersensitivity of serotoninergic receptors in PCPA-treated and in midbrain raphe lesioned rats, it may be argued that a higher inhibition of MKB by MAO A inhibitors is expected in PCPA K and Ra K rats. However, the inhibition of MKB, either in PCPA K or in Ra K rats, by the inhibitors of MAO A used is similar to that in K rats. One possible explanation of this effect may be that the increased sensitivity of the postsynaptic serotoninergic receptors is accompanied by concomitant decline of 5-HT release in PCPA K and Ra K rats. Indeed, it was shown that the residual 5-HT in neurones, partially depleted by PCPA or 5,7-dihydroxytryptamine treatment has little availability for release and therefore, is not as accessible to 5-HT receptors [7,33].

In spite of the 5-HT receptor supersensitivity, MAO A inhibitors do not produce a stronger MKB inhibition in PCPA K and Ra K rats. This might be explained by the mainly intracellular effect of the MAO A inhibitors on 5-HT which would not necessarily be released, as compared to the agonists or uptake inhibitors which produce a stronger effect on the directly accessible supersensitive receptors. It would be very interesting to confirm, in other behavioral models, the difference in response to MAO A inhibitors compared to 5-HT agonists or uptake inhibitors, in 5-HT depleted rats by

PCPA treatment or midbrain raphe lesions.

In conclusion, the activation by MAO A inhibitors, of serotonin neurotransmission, like other serotonin mimetics (agonists and uptake inhibitors) strongly decreased the muricidal activity in the three groups of killer rats (spontaneous K, PCPA K and Ra K rats). It is noticeable that MAO A inhibitors do not display higher efficiency on MKB in PCPA K and Ra K rats, as it was observed using agonists and uptake inhibitors. The data presented in this paper provide additional information concerning the relative efficiency of the different serotonin mimetic drugs. Finally, MKB does seem an interesting and reliable model for evaluating the efficiency of new drugs working via serotonin mechanisms.

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