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Alterations of Serotonin Neurotransmission and Inhibition of Mouse-Killing Behavior: III Effects of Minaprine, CM 30366 and SR 95191

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ISEL, F. AND P. MANDEL. *Alterations of serotonin neurotransmission and inhibition of mouse-killing behavior: III Effects of minaprine, CM 30366 and SR 95191.* PHARMACOL BIOCHEM BEHAV **33**(3) 655–662, 1989.—Three closely related aminopyridazine derivatives: minaprine [3-(2-morpholino-ethylamino)-4-methyl-6-phenyl pyridazine, dihydrochloride], CM 30366 [3-(2-morpholino-ethylamino)-4-methyl-6-(4-hydroxyphenyl) pyridazine, hydrobromide] and SR 95191 [3-(2-morpholino-ethylamino)-4-cyano-6-phenyl pyridazine] were examined for their inhibitory effects on mouse-killing behavior (MKB). Three groups of killer rats were used: spontaneous killer rats (K rats) and nonkillers which became killers following para-chlorophenylalanine (PCPA) treatment or electrolytical destruction of the dorsal and median raphe nuclei. When given intraperitoneally (IP), the three drugs inhibited MKB of K rats without sedation. When given orally, minaprine showed no antimuricidal effect in K rats. After chronic IP administration of minaprine, MKB inhibition in K rats decreased after 25 days of treatment, probably because serotonin receptors became subsensitive. Minaprine and SR 95191, a derivative of minaprine, are inhibitors of type A monoamine oxidase (MAO), whereas CM 30366, a metabolite of minaprine, has no effect on MAO activity. SR 95191 displayed a similar MKB inhibition in the three groups of killer rats, and in this respect, it behaved like other type A MAO inhibitors. Minaprine and CM 30366 were less efficient in their antimuricidal effect in PCPA-treated and raphe-lesioned killer rats as compared with spontaneous killer rats. Moreover, the time courses of MKB inhibition and MAO A inhibition by minaprine did not correlate. The effects of minaprine on MKB seemed not related in a simple way to an alteration of serotonin level through MAO A inhibition, and rise the question of an alternative mechanism of antimuricidal action, until now unknown.

Minaprine CM 30366 SR 95191 Monoamine oxidase inhibitors Mouse-killing behavior Serotonin Raphe lesions Para-chlorophenylalanine Supersensitivity

THE involvement of central serotoninergic mechanisms in mouse-killing behavior (MKB) is well documented (28, 33, 38, 40, 42). Decrease of serotonin (5-HT) following social isolation (28,37), electrolytic destruction of the dorsal and median raphe nuclei (13, 27, 30, 41), para-chlorophenylalanine (PCPA) treatment (14,30), or a tryptophan-free diet (15, 23, 43), induced muricidal behavior. Procedures which activate 5-HT neurotransmission, such as administration of 5-HT precursors (14,39), 5-HT agonists (9,29), 5-HT uptake inhibitors (26,29), or monoamine oxidase inhibitors (17, 18, 34, 35), have been shown to inhibit MKB.

Monoamine oxidase (MAO) is known to exist in two forms. The form mainly responsible for the deamination of 5-HT is selectively inhibited by clorgyline and is referred as MAO A (19). The second form, named as MAO B, selectively deaminates benzylamine and phenethylamine and is inhibited by l-deprenyl (25). In the past few years, the interest in MAO inhibitors (MAOI) as potential therapeutic drugs has been revived due to the development of new MAOI which act reversibly, are short-acting and show high selectivity for one or another MAO type (46). Moclobemide (7), cimoxatone (20), toloxatone (36) and amiflamine (3) are such type A MAOIs.

In a previous work we studied the action of these MAOIs on MKB in three groups of killer rats obtained either by psychosocial isolation (spontaneous killer rats: K rats), by PCPA administration (PCPA K), or by electrolytical midbrain raphe destruction (Ra K) (18). The effects of these type A MAOIs were compared to other serotonin-mimetic drugs (5-HT agonists and uptake inhibitors) (30). Cimoxatone, toloxatone and amiflamine displayed a similar efficiency on MKB inhibition in the three groups of killer rats, whereas 5-HT agonists and uptake inhibitors showed a stronger MKB inhibition in PCPA K and Ra K rats compared to control K rats. An expression of serotoninergic supersensitivity in MKB was shown with 5-HT agonists and uptake inhibitors, but not with type A MAOIs (18,30). Thus, MKB appears to be an additional interesting model for evaluating new drugs with serotoninergic effects in these three types of killer rats.

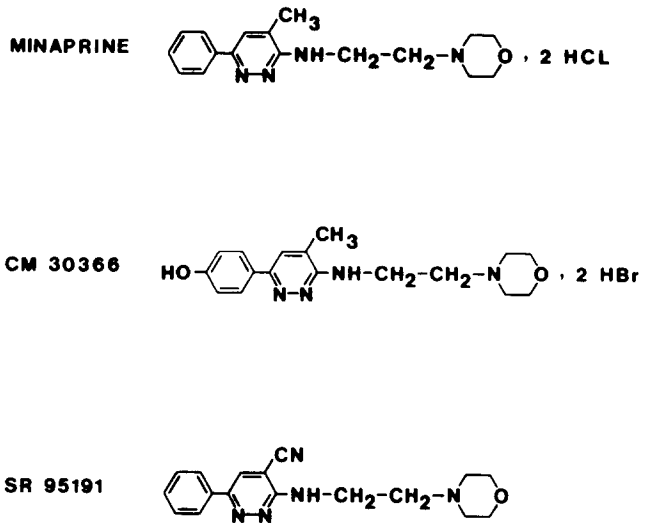

FIG. 1. Chemical structures of minaprine, CM 30366 and SR 95191.

In this study we have investigated the action of three structurally closely related aminopyridazine derivatives, minaprine, CM 30366 and SR 95191 (Fig. 1) on MKB in the three groups of killer rats mentioned above. Minaprine and SR 95191 have been shown to inhibit MAO of type A (21, 22, 45). CM 30366, the main metabolite of minaprine (8), has no effect on MAO activity in vitro or ex vivo, but has been reported to be an atypical dopaminomimetic drug (44). In this report the action of these three drugs on MKB are discussed with relevance to their respective MAO inhibitory activity. MKB has also been investigated after chronic administration of the antidepressant minaprine, considering that the therapeutic effect of antidepressants becomes apparent only after long lasting (about two weeks) treatment.

METHOD

Animals

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

Drugs and Chemicals

Minaprine and SR 95191 were supplied by Sanofi Recherche (Montpellier, France). CM 30366 was kindly provided by C. G. Wermuth (Faculté de Pharmacie, Strasbourg, France). D,l-p-chlorophenylalanine methyl ester, HCl (PCPA) was purchased from Sigma Chemical Co. (St. Louis, MO). All drugs were dissolved in saline and administered in a volume of 2 ml/kg. Minaprine was given either intraperitoneally (IP) or orally (PO). For the chronic treatment, minaprine was administered IP at a dose of 10 mg/kg twice daily for 25 days between 9–10 a.m. and 5–6 p.m. CM 30366 and SR 95191 were injected IP. Doses were indicated in the legend to figures. The respective control groups were treated in parallel and received equivalent volumes of saline. The muricidal tests were started between 9–10 a.m.

Mouse-Killing Behavior (MKB)

The procedure used to test MKB was the same as that previously reported (18, 24, 30).

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 a 24-hr period were classified as nonkiller rats (NK rats) and were submitted either to PCPA treatment or to electrolytical

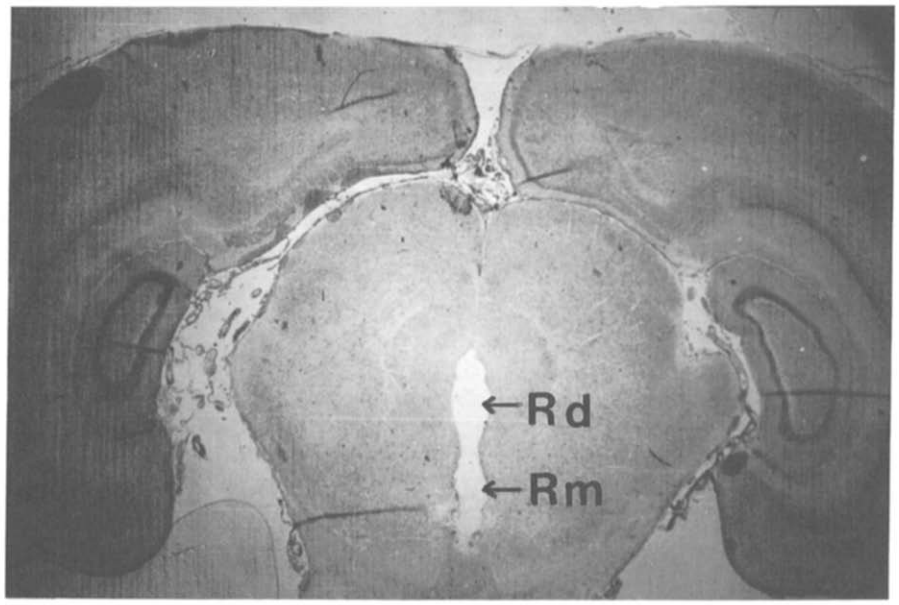

FIG. 2. Histological control of electrolytical lesions of the raphe nuclei. Rd: raphe dorsalis; Rm: raphe medialis.

TABLE 1

EFFECTS OF ACUTE (IP AND PO) AND CHRONIC (IP) MINAPRINE ON MKB IN K RATS

			Maximum Latency	Duration	Efficacy		Locomotor Activity Counts per 2 hr	
Treatment	Dose mg/kg	N	%	min	min	%	4–6 hr	6–8 hr
(IP)	0	20	0	—	—	0	158 ± 48	151 ± 52
	3	10	20	—	—	4.0	168 ± 54	167 ± 31
	5	10	50*	120	180	28.0	150 ± 46	122 ± 34
	10	24	92†	77	>390	55.0	162 ± 50	139 ± 56
(PO)	0	10	0	—	—	0	143 ± 50	135 ± 33
	10	10	10§	—	—	2.0§	153 ± 42	143 ± 52
	50	10	30	—	—	9.0	154 ± 47	125 ± 44
(IP)								
control	0	10	0	—	—	0	164 ± 52	119 ± 22
acute	10	14	93†	156	>320	50.7	156 ± 53	127 ± 30
chronic 15 days	10	14	79†	163	>320	44.3	151 ± 43	138 ± 37
chronic 25 days	10	14	71*	267	>210	32.1‡	141 ± 51	124 ± 29

Parameters of MKB were 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 activities are given at the time of maximal MKB inhibition. N = 6. Mean ± standard deviation.

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

Intergroup comparison with respect to acute-treated K rats at 10 mg/kg IP: ‡$p<0.005$; §$p<0.0005$.

Significant differences in efficacies are only shown for intergroup comparisons.

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).

PCPA killer rats (PCPA K) were obtained after injection of 150 mg/kg (IP) of PCPA for two consecutive days to NK rats and raphe-lesioned killer rats (Ra K) were obtained after anaesthesia of NK rats with 40 mg/kg (IP) sodium pentobarbital and electrolytical destruction of the dorsal and median raphe nuclei (41). We have reported that 40% and 50% of NK rats became killers after PCPA treatment and midbrain raphe lesions respectively (30). PCPA K were used 10 days after the last PCPA injection and Ra K one month after surgery.

The three groups of killer rats were statistically compared with each other or within a group; comparisons were made between

TABLE 2

EFFECTS OF MINAPRINE ON MKB IN K RATS, PCPA K AND Ra K RATS

			Maximum Latency	Duration	Efficacy		Locomotor Activity Counts per 2 hr	
Rats	Dose mg/kg (IP)	N	%	min	min	%	4–6 hr	6–8 hr
K Rats	0	20	0	—	—	0	158 ± 48	151 ± 52
	10	24	92‡	77	>390	55.0	162 ± 50	139 ± 56
PCPA K	0	10	0	—	—	0	147 ± 55	132 ± 40
	10	10	60*§	320	130	30.0#	159 ± 47	137 ± 33
Ra K	0	10	0	—	—	0	160 ± 51	149 ± 49
	10	9	33¶	—	—	17.8#	154 ± 54	150 ± 41

Parameters of MKB were 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 activities are given at the time of maximal MKB inhibition. N = 6. Mean ± standard deviation.

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

Intergroup comparison with respect to drug-treated K rats at the same dose: §$p<0.05$; ¶$p<0.005$; #$p<0.0005$.

Significant differences in efficacies are only shown for intergroup comparisons.

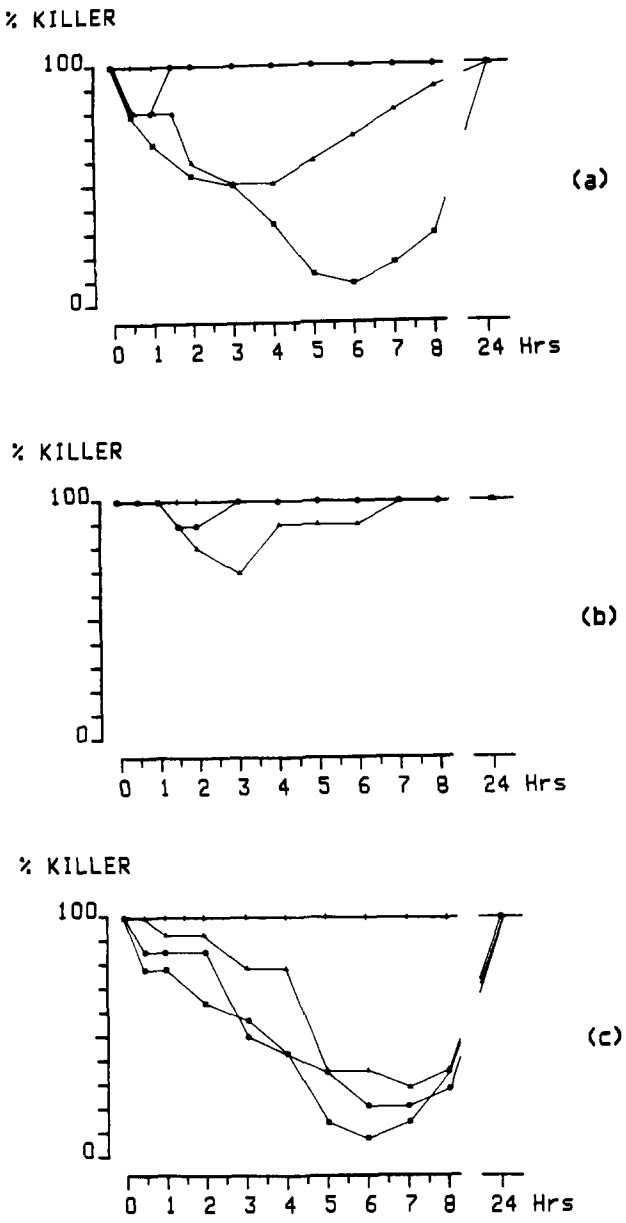

FIG. 3. Kinetic of inhibition of MKB after minaprine administration in K rats. (a) Dose-response of minaprine IP. +: Control; ●: minaprine, 3 mg/kg; ▲: minaprine, 5 mg/kg; ■: minaprine, 10 mg/kg. (b) Dose-response of minaprine PO. +: control; ●: minaprine, 10 mg/kg; ▲: minaprine, 50 mg/kg. (c) Chronic treatment with minaprine 10 mg/kg IP. +: control; ■: acute; ●: chronic treatment, 15 days twice daily; ▲: chronic treatment, 25 days twice daily.

drug and control conditions. After drug administration, animals were tested for MKB every 30 min or one hour spanning 8 hr, and at 24 hr.

Rats of each group were tested for spontaneous locomotor activity as an indication of the sedative effect of the drugs by means of an actograph apparatus (18,30). Each rat was placed in a Plexiglas box (100 × 20 cm) with 7 pairs of infrared photocells 2 cm above the solid floor. Locomotor activities were measured by the total number of infrared photobeams broken during 1-hr or 2-hr

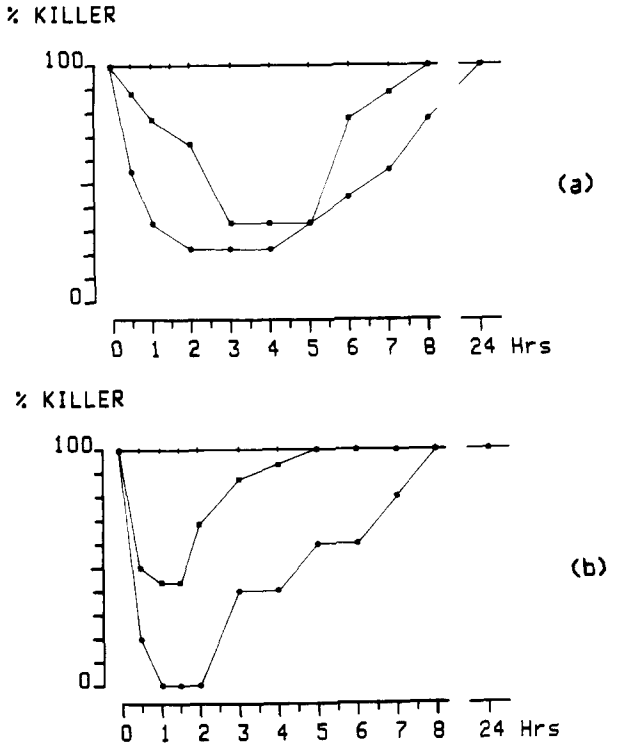

FIG. 4. Kinetic of inhibition of MKB after CM 30366 and SR 95191 administration in K rats. (a) Dose-response of CM 30366 IP. +: Control; ■: CM 30366, 30 mg/kg; ●: CM 30366, 50 mg/kg. (b) Dose-response of SR 95191 IP. +: control; ■ SR 95191, 5 mg/kg; ●: SR 95191, 10 mg/kg.

intervals, at the same time as MKB experiments were performed and in the same 12-hr light-dark cycle.

The extent of raphe lesions in Ra K was histologically assessed by microscopic examination of cresyl violet-stained sections at the end of the experiments.

Muricidal inhibition was measured by the following parameters:

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

b) Latency of inhibition of MKB in at least 40% of the tested rats as determined from the experimental kinetic curve.

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

d) Efficacy determined as the ratio of the number of nonkilled mice to the total number of mice introduced in the cages of the killer rats during the time interval 0 to 8 hr after drug or vehicle administration.

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

Statistics

Mean values for locomotor activity were compared for the significance of their differences by the Fisher-Student's *t*-test. The significance of MKB inhibition was determined by the Fisher exact probability test. Intergroup comparisons 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 (2×2) test.

RESULTS

Effect of Minaprine on MKB of K Rats

A dose-dependent inhibition of MKB appeared without appar-

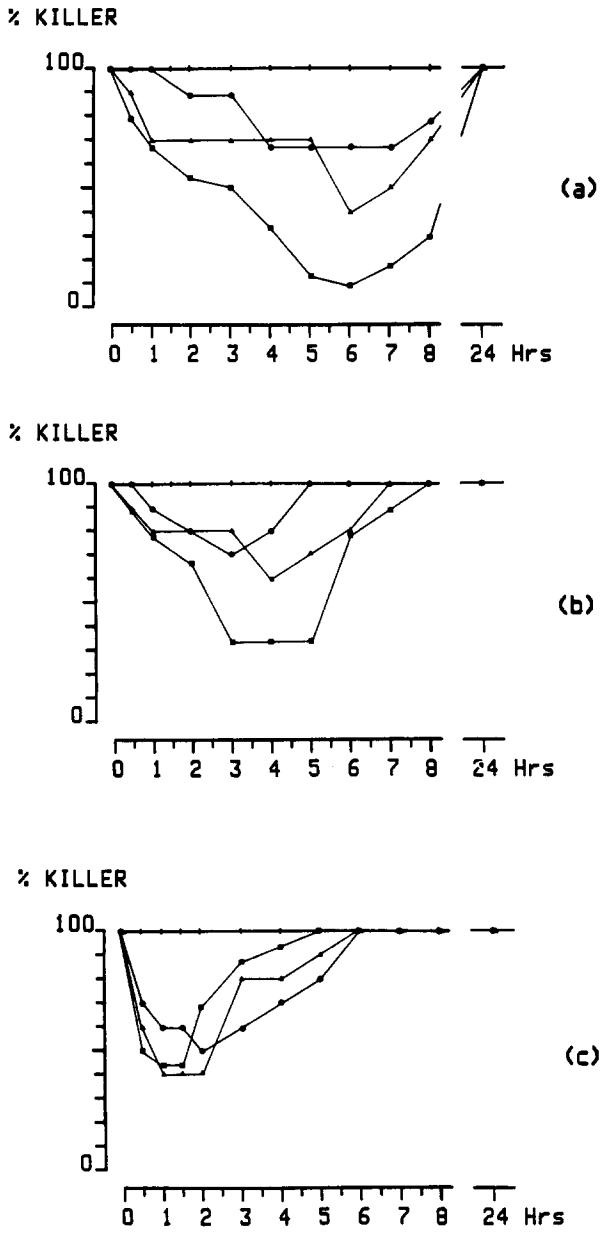

FIG. 5. Kinetic of inhibition of MKB after drug administration in K rats, PCPA K and Ra K rats. (a) Minaprine, 10 mg/kg IP. ■: K rats; ▲: PCPA K rats.; ●: Ra K rats. (b) CM 30366, 30 mg/kg IP. ■: K rats; ▲: PCPA K rats; ●: Ra K rats. (c) SR 95191, 5 mg/kg IP. ■: K rats; ▲: PCPA K rats; ●: Ra K rats.

ent sedation when K rats were treated IP with minaprine (Fig. 3a and Table 1). A significant decrease of MKB was already observed at a dose of 5 mg/kg of minaprine, while the dose producing 50% of type A MAO inhibition (ED_{50}) was of 12.8 mg/kg (21). The maximal MKB inhibition occurred respectively 3–4 hr after 5 mg/kg of minaprine IP and 5–6 hr after 10 mg/kg. MKB was still inhibited 8 hr after injection of 10 mg/kg of minaprine, but returned to control values 24 hr after drug injection.

When administered orally, no significant inhibition of MKB was observed up to 50 mg/kg of minaprine (Fig. 3b and Table 1); the ED_{50} for type A MAO inhibition was of 95 mg/kg (21).

Finally, the effect of minaprine (10 mg/kg IP) on MKB of K rats was examined after repeated IP administration during 25 days twice daily. As shown in Fig. 3c and Table 1, no significant differences were recorded after the acute and the chronic treatment for 15 days. However, after 25 days of treatment, the latency time of MKB increased, and the efficacy was significantly reduced ($p<0.005$; Table 1).

At the different doses administered, no significant reduction of locomotor activity was observed with minaprine in rats of each group (Table 1).

Effect of CM 30366 on MKB of K Rats

CM 30366 (30 and 50 mg/kg IP) blocked MKB in a dose-dependent manner without apparent sedation effects (Fig. 4a and Table 3). The maximum of MKB inhibition was observed at about 3–4 hr after drug administration and decreased thereafter. CM 30366 had no inhibitory effect on MAO A or MAO B activity at doses up to 50 mg/kg IP (P. Worms, personal communication). For the highest dose used, MKB was still slightly inhibited 8 hr after CM 30366 administration.

Effect of SR 95191 on MKB of K Rats

A dose-dependent inhibition was observed with SR 95191 (5 and 10 mg/kg IP) without apparent sedation effects (Fig. 4b and Table 4). The maximum of MKB inhibition was reached between 1 and 2 hr after drug injection. The ED_{50} value for type A MAO inhibition was of 7.5 mg/kg IP (22). SR 95191 inhibited MKB at similar doses as minaprine. MKB inhibition occurred earlier and was sustained for a slightly shorter period of time. For the highest dose used, MKB had returned to 100% 8 hr after SR 95191 injection.

Effects of Minaprine, CM 30366 and SR 95191 on MKB of PCPA K and Ra K Rats

When PCPA K rats were treated with minaprine 10 mg/kg IP, MKB was significantly inhibited. The maximal percentage of MKB inhibition was observed after the same period of time, as compared to the control K rats. However, the maximum of MKB inhibition and the efficacy were significantly reduced as compared to the action of the same dose on MKB of K rats. Latency was increased while the duration of MKB inhibition was decreased (Fig. 5a and Table 2).

Fifty days after midbrain raphe lesions, the histological study showed that the lesions were localized in both dorsal and median raphe nuclei (Fig. 2). We have earlier shown that, according to our stereotaxic coordinates, a clear decrease of 5-HT and its metabolite, 5-hydroxyindole acetic acid (5-HIAA), occurred in all brain structures studied of the midbrain raphe-lesioned rats (30). This indicated that the lesions were localized in both raphe nuclei, since these structures are innervated by 5-HT pathways originating from both dorsal and median raphe nuclei. Minaprine at the dose of 10 mg/kg IP had no significant effects on MKB of Ra K rats; the maximum and the efficacy of the inhibition were statistically different from that of K rats (Table 2).

CM 30366 at 30 mg/kg IP reduced slightly, but significantly MKB of PCPA K rats with a lower maximum and efficacy of MKB inhibition as compared to K rats. The maximal inhibition was reached at the same period of time as in K rats. Here again, CM 30366 had no significant effect on MKB of Ra K rats (Fig. 5b and Table 3).

TABLE 3

EFFECTS OF CM 30366 ON MKB IN K RATS, PCPA K AND Ra K RATS

			Maximum	Latency	Duration	Efficacy	Locomotor Activity	
	Dose mg/kg						Counts per 2 hr	
Rats	(IP)	N	%	min	min	%	2–4 hr	4–6 hr
K Rats	0	10	0	—	—	0	210 ± 63	135 ± 40
	30	9	67†	132	204	30.0	196 ± 65	142 ± 46
	50	9	78†	27	405	53.3	224 ± 72	139 ± 47
PCPA K	0	10	0	—	—	0	226 ± 80	146 ± 48
	30	10	40*	240	0	16.0§	214 ± 75	154 ± 51
Ra K	0	10	0	—	—	0	244 ± 78	155 ± 54
	30	10	30	—	—	8.0#	231 ± 69	152 ± 51

For legend see Table 2.

In contrast, the effects of SR 95191 on MKB in the three groups of killer rats (K rats, PCPA K and Ra K rats) did not differ (Fig. 5c and Table 4). Neither the maximum, nor the efficacy were different. The kinetic profile of MKB inhibition and the time of maximal inhibition were similar in the three groups of killer rats.

At the doses administered, no significant reduction of locomotor activity was observed with the three compounds studied in PCPA K and Ra K rats (Tables 2, 3, 4).

DISCUSSION

The effects of minaprine on brain monoamines and related metabolites were similar to that of other type A MAOIs (6,21). Minaprine was shown, ex vivo, to be a specific and short-acting type A MAOI of moderate potency, although this drug displayed in vitro a rather weak MAO inhibition (21). The involvement of (an) active metabolite(s) in its mechanism of action has been suggested (21). Given IP, minaprine was found to inhibit MKB of K rats. Unexpectedly inhibition of MKB seemed not to correlate with the time course of the ex vivo MAO A inhibition (21). Minaprine, at 10 mg/kg IP, induced a maximal MKB inhibition about 6 hr after injection, when type A MAO activity had returned to control values (21). When given orally, minaprine had no effect on MKB in K rats, even at doses 5 times higher than that administered IP (Fig. 3B and Table 1). A different pattern of inactivation after IP administration compared to that after oral absorption may be involved in this phenomenon.

It has been shown that a chronic treatment with minaprine caused a decrease in the maximum number of 5-HT_1 and 5-HT_2 binding sites without affecting K_d; the noradrenergic and dopaminergic binding parameters remained unchanged (6). In view of these data, it may be hypothesized that a subsensitivity of 5-HT receptors occurred also after our chronic treatment with minaprine, which may explain the decrease of efficacy of MKB inhibition after 25 days of treatment in K rats (Table 1).

We described earlier an expression of serotoninergic supersensitivity in a model of aggressive behavior: 5-HT agonists and uptake inhibitors induced a higher MKB inhibition in PCPA-treated and midbrain raphe-lesioned killer rats compared to spontaneous K rats (30), whereas type A MAOIs induced a similar MKB inhibition in the three groups of killer rats (18). The fact that type A MAOIs affect primarily intracellular 5-HT, which would not necessarily be released, may explain that these drugs do not display a higher efficiency on MKB in PCPA K and Ra K rats as shown with 5-HT agonists which act on the directly accessible supersensitive receptors, or with uptake inhibitors which block 5-HT in the synaptic cleft (18,30).

A lower MKB inhibition was observed with minaprine in PCPA K and Ra K rats compared to that in K rats. Although this drug was shown, at least ex vivo after IP administration, to be a

TABLE 4

EFFECTS OF SR 95191 ON MKB IN K RATS, PCPA K AND Ra K RATS

			Maximum	Latency	Duration	Efficacy	Locomotor Activity	
	Dose mg/kg						Counts per 60 min	
Rats	(IP)	N	%	min	min	%	30–90 min	90–150 min
K Rats	0	10	0	—	—	0	205 ± 75	110 ± 32
	5	16	56†	24	86	19.3	185 ± 69	103 ± 28
	10	10	100‡	15	345	54.6	193 ± 57	94 ± 30
PCPA K	0	10	0	—	—	0	212 ± 72	118 ± 36
	5	10	60*	30	120	24.6	220 ± 59	124 ± 40
Ra K	0	10	0	—	—	0	242 ± 80	128 ± 31
	5	10	50*	60	120	22.7	231 ± 70	132 ± 43

For legend see Table 2.

selective and reversible type A MAOI of mild potency (21), it may be hypothesized that the antimuricidal effect of minaprine is not related to its type A MAO inhibition:

1) the MKB inhibition occurred later than the MAO A inhibition (21); 2) the kinetic profile of MKB inhibition differed from that of other type A MAO inhibitors (18); 3) the effect of minaprine on MKB of PCPA K and Ra K rats is clearly different than that of other type A MAO inhibitors (18); 4) CM 30366, the main metabolite of minaprine (8), which had no MAO inhibitory properties, showed similar effects on MKB of PCPA K and Ra K rats as minaprine.

CM 30366 was found to have dopamine-like properties (44) and this drug had no effect on MAO activity in vitro or ex vivo (P. Worms, personal communication). The inhibition of MKB by CM 30366 is significantly lower in PCPA-treated and raphe-lesioned killer rats than in K rats. On the other hand, SR 95191 was shown to be a reversible and selective type A MAOI in vitro, as well as ex vivo (22,45). SR 95191 had similar effects on muricidal behavior in the three groups of killer rats. In this respect SR 95191, but not minaprine and CM 30366, behaved like other type A MAOIs (18). Moreover, the kinetic profile of MKB inhibition following SR 95191 administration showed parallelism with the type A MAO inhibition (22); the maximum of MKB inhibition was observed between 1 and 2 hours after drug injection and MKB returned to control values 6 hours later.

Locomotor activity was not reduced in the three groups of killer rats after administration of minaprine, CM 30366 or SR 95191. It may be concluded that the observed inhibition of MKB is not due to sedation of the rats. It seems also unlikely that MKB inhibition may be related to altered appetitive states induced by the drugs, since MKB inhibition by minaprine or CM 30366 is lower in PCPA K and Ra K rats compared to spontaneous K rats. Moreover, if food deprivation may facilitate the induction of MKB (1), hunger by itself is not determinant for MKB (24).

It was also reported that minaprine is acting through a dual serotoninergic and dopaminergic activating mechanism (5, 6, 11, 31) and that the MAO inhibitory effect of minaprine does not fully account for its pharmacological activities (11,21). It is noteworthy that PCPA treatment and midbrain raphe lesions decreased strongly the brain levels of 5-HT and its metabolite 5-HIAA (30). Since minaprine and CM 30366 displayed a lower MKB inhibition in PCPA K and Ra K rats as compared to K rats, it may be concluded that neither the weak inhibition of type A MAO activity by minaprine, nor the mechanism of action of CM 30366, could entirely compensate the 5-HT deficiency produced by PCPA treatment and raphe lesions, conditions where a supersensitivity of 5-HT receptors occurred (30).

It has been shown that specific lesioning of the 5-HT neurons in the raphe nucleus increased the striatal DA turnover rate (32). An inhibitory effect of 5-HT on DA release in the striatum has also been reported (10). This effect is blocked by minaprine (31). On the other hand, DA is thought to play an important role in the regulation of several types of aggressive behavior; it may facilitate affective aggression (2,12), while suppressing predatory aggression (4,16). Since minaprine and CM 30366 reinforce the dopaminergic neurotransmission, it seems likely that the inhibition of MKB by these two drugs occurs through a complex mechanism involving both serotoninergic and dopaminergic neurotransmission. Further studies are necessary to clarify their mechanisms of action. MKB of spontaneous killer rats and of serotonin-depleted killer rats appears to be an interesting model providing additional information on the mechanisms of action of new serotoninergic drugs.

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REFERENCES

1. Adamec, R. E.; Himes, M. The interaction of hunger feeding and experience in alteration of topography of the rat's predatory response to mice. Behav. Biol. 22:230–243; 1978.
2. Anand, M.; Gupta, G. P.; Bhargava, K. P. Modification of electroshock fighting by drugs known to interact with dopaminergic and noradrenergic neurons in normal and brain lesioned rats. J. Pharm. Pharmacol. 29:437–439; 1977.
3. Ask, A.-L.; Hogberg, H.; Schmidt, L.; Kiessling, H.; Ross, S. B. (+)-4-dimethylamino-2,alpha-dimethylphenethylamine (FLA 336 (+)), a selective inhibitor of the A form of monoamine oxidase in the rat brain. Biochem. Pharmacol. 31:1401–1406; 1982.
4. Baggio, G.; Ferrari, F. Role of brain dopaminergic mechanisms in rodent aggressive behavior: influence of (+)N-n-propyl-norapomorphine on three experimental models. Psychopharmacology (Berlin) 70:63–68; 1980.
5. Biziere, K.; Kan, J.-P.; Souilhac, J.; Muyard, J. P.; Roncucci, R. Pharmacological evaluation of minaprine dihydrochloride, a new psychotropic drug. Drug Res. 32:824–831; 1982.
6. Biziere, K.; Worms, P.; Kan, J.-P.; Mandel, P.; Garattini, S.; Roncucci, R. Minaprine, a new drug with antidepressant properties. Drugs Exp. Clin. Res. 11:831–841; 1985.
7. Da Prada, M.; Keller, H. H.; Kettler, R.; Schaffner, R.; Pieri, M.; Burkard, W. P.; Korn, A.; Haefely, W. E. Ro 11-1163, a specific and short-acting MAO inhibitor with antidepressant properties. In: Kamijo, K.; Usdin, E.; Nagatsu, T., eds. Monoamine oxidase—Basic and clinical frontiers. Amsterdam: Excerpta Medica; 1982:183–196.
8. Davi, H.; Dupont, P.; Jeanniot, J. P.; Roncucci, R.; Cautreels, W. The biotransformation of (^{14}C)minaprine in man and five animal species. Xenobiotica 11:735–747; 1981.
9. Di Chiara, G.; Camba, R.; Spano, P. F. Evidence for inhibition by brain serotonin of mouse killing behavior in rats. Nature 233:272–273; 1971.
10. Ennis, C.; Kemp, J. D.; Cox, B. Characterization of inhibitory 5-hydroxytryptamine receptors that modulate dopamine release in the striatum. J. Neurochem. 36:1515–1520; 1981.
11. Ferretti, P.; Algeri, S.; Benfenati, F.; Cimino, M.; Ferretti, C.; Garattini, S.; Lipartiti, M. Biochemical effects of minaprine on striatal dopaminergic neurons in rats. J. Pharm. Pharmacol. 36:48–50; 1984.
12. Geyer, M. A.; Segal, D. S. Shock-induced aggression: Opposite effects of intraventricularly infused dopamine and norepinephrine. Behav. Biol. 10:99–104; 1974.
13. Giacalone, E.; Kostowski, W. Lesions of midbrain raphe in the rat: Effect on level of biogenic amines in forebrain and spinal cord. Pharmacol. Res. Commun. 1:84–88; 1969.
14. Gibbons, J. L.; Barr, G. A.; Bridger, W. H.; Leibowtiz, S. F. Effects of parachlorophenylalanine and 5-hydroxytryptophan on mouse-killing behavior in killer rats. Pharmacol. Biochem. Behav. 9:91–98; 1978.
15. Gibbons, J. L.; Barr, G. A.; Bridger, W. H.; Leibowitz, S. F. Manipulations of dietary tryptophan: Effects on mouse killing and brain serotonin in the rat. Brain Res. 169:139–153; 1979.
16. Horovitz, Z. P.; Ragozzino, P. W.; Leaf, R. C. Selective block of rat mouse-killing by antidepressants. Life Sci. 4:1909–1912; 1965.
17. Horovitz, Z. P.; Piala, J. J.; High, J. P.; Burke, J. C.; Leaf, R. C. Effects of drugs on the mouse-killing (muricide) test and its relationship to amygdaloid function. Int. J. Neuropharmacol. 5:405–411; 1966.
18. Isel, F.; Ciesielski, L.; Gobaille, S.; Molina, V.; Mandel, P. 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: 97–104; 1988.
19. Johnston, J. P. Some observations upon a new inhibitor of monoamine oxidase in brain tissue. Biochem. Pharmacol. 17:1285–1297; 1968.

20. Kan, J. P.; Benedetti, M. S. Characteristics of the inhibition of rat brain monoamine oxidase in vitro by MD 780515. J. Neurochem. 36:1561–1571; 1981.
21. Kan, J.-P.; Mouget-Goniot, C.; Worms, P.; Biziere, K. Effect of the antidepressant minaprine on both forms of monoamine oxidase in the rat. Biochem. Pharmacol. 35:973–978; 1986.
22. Kan, J.-P.; Steinberg, R.; Mouget-Goniot, C.; Worms, P.; Biziere, K. SR 95191, a selective inhibitor of type A monoamine oxidase with dopaminergic properties. II. Biochemical characterization of monoamine oxidase inhibition. J. Pharmacol. Exp. Ther. 240:251–258; 1987.
23. Kantak, K. M.; Hegstrand, L. R.; Witman, J.; Eichelman, B. Effects of dietary supplements and a tryptophan-free diet on aggressive behaviour in rats. Pharmacol. Biochem. Behav. 12:173–179; 1980.
24. Karli, P. The Norway rat's killing response to the white mouse. An experimental analysis. Behavior 10:81–103; 1956.
25. Knoll, J.; Magyar, K. Some puzzling pharmacological effects of monoamine oxidase inhibitors. Adv. Biochem. Psychopharmacol. 5:393–408; 1972.
26. Kostowski, W.; Valzelli, L.; Kozk, W.; Bernasconi, S. Activity of desipramine, fluoxetine and nomifensine on spontaneous and p-CPA-induced muricidal aggression. Pharmacol. Res. Commun. 16: 265–271; 1984.
27. Lorens, S. A.; Guldberg, H. C. Regional 5-hydroxytryptamine following selective midbrain raphe lesions in the rat. Brain Res. 78:45–56; 1974.
28. Mandel, P.; Mack, G.; Kempf, E. Molecular basis of some models of aggressive behavior. In: Sandler, M., ed. Psychopharmacology of aggression. New York: Raven Press; 1979:95–110.
29. Molina, V. A.; Gobaille, S.; Mandel, P. Effects of serotonin-mimetic drugs on mouse killing behavior. Aggress. Behav. 12:201–211; 1986.
30. Molina, V. A.; Ciesielski, L.; Gobaille, S.; Isel, F.; Mandel, P. Inhibition of mouse killing behavior by serotonin-mimetic drugs: Effects of partial alterations of serotonin neurotransmission. Pharmacol. Biochem. Behav. 27:123–131; 1987.
31. Muramatsu, M.; Tamaki-Ohashi, J.; Usuki, C.; Araki, H.; Chaki, S.; Aihara, H. 5-HT_2 antagonists and minaprine block the 5-HT-induced inhibition of dopamine release from rat brain striatal slices. Eur. J. Pharmacol. 153:89–95; 1988.
32. Nicolaou, N. M.; Garcia-Munoz, M.; Arbuthnott, G. W.; Eccleston, D. Interactions between serotoninergic and dopaminergic systems in rat brain demonstrated by small unilateral lesions of the raphe nuclei. Eur. J. Pharmacol. 57:295–305; 1979.
33. Pucilowski, O.; Kostowski, W. Aggressive behavior and the central serotoninergic system. Behav. Brain Res. 9:33–48; 1983.
34. Salama, A. I.; Goldberg, M. E. Neurochemical effects of imipramine and amphetamine in aggressive mouse-killing (muricidal) rats. Biochem. Pharmacol. 19:2023–2032; 1970.
35. Sofia, R. D. Effects of centrally active drugs on four models of experimentally-induced aggression in rodents. Life Sci. 8:705–716; 1969.
36. Strolin Benedetti, M.; Boucher, T.; Fowler, C. J. The deamination of noradrenaline and 5-hydroxytryptamine by rat brain and heart monoamine oxidase and their inhibition by cimoxatone, toloxatone and MD 770222. Naunyn Schmiedebergs Arch. Pharmacol. 323:315–320; 1983.
37. Valzelli, L.; Garattini, S. Biochemical and behavioral changes induced by isolation in rats. Neuropharmacology 11:17–22; 1972.
38. Valzelli, L. 5-Hydroxytryptamine in aggressiveness. Adv. Biochem. Psychopharmacol. 11:255–263; 1974.
39. Valzelli, L.; Bernasconi, S.; Dalessandro, M. Effect of tryptophan administration on spontaneous and p-CPA-induced muricidal aggression in laboratory rats. Pharmacol. Res. Commun. 13:891–897; 1981.
40. Valzelli, L.; Galeato, E. Serotoninergic control of experimental aggression. Pol. J. Pharmacol. Pharm. 36:495–503; 1984.
41. Vergnes, M.; Mack, G.; Kempf, E. Lésions du raphé et réaction d'agression interspécifique rat-souris. Effets comportementaux et biochimiques. Brain Res. 57:67–74; 1973.
42. Vergnes, M.; Mack, G.; Kempf, E. Controle inhibiteur du comportement d'agression interspécifique du rat: Système sérotoninergique du raphé et afférences olfactives. Brain Res. 70:481–491; 1974.
43. Vergnes, M.; Kempf, E. Tryptophan deprivation: Effects on mouse-killing and reactivity in the rat. Pharmacol. Biochem. Behav. 14(Suppl. 1):19–23; 1981.
44. Worms, P.; Kan, J.-P.; Wermuth, C. G.; Biziere, K. Dopamine-like activities of an aminopyridazine derivative, CM 30366: A behavioral study. Naunyn Schmiedebergs Arch. Pharmacol. 334:246–252; 1986.
45. Worms, P.; Kan, J.-P.; Wermuth, C. G.; Roncucci, R.; Biziere, K. SR 95191, a selective inhibitor of type A monoamine oxidase with dopaminergic properties. I. Psychopharmacological profile in rodents. J. Pharmacol. Exp. Ther. 240:241–250; 1987.
46. Youdim, M. B. H.; Finberg, J. P. M. Monoamine oxidase inhibitor antidepressants. In: Grahame-Smith, D. G.; Cowen, P. J., eds. Psychopharmacology. 1. Preclinical pharmacology. Amsterdam: Excerpta Medica; 1983:38–70.