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Relationship Between Occurrence of Tremor/Convulsion and Level of β-Carbolines in the Brain After Administration of β-Carbolines Into Mice

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KAWANISHI, K., N. EGUCHI, T. HAYASHI AND Y. HASHIMOTO. *Relationship between occurrence of tremor/convulsion and level of β-carbolines in the brain after administration of β-carbolines into mice.* PHARMACOL BIOCHEM BEHAV **47**(3) 689–699, 1994. – Fifteen β-carboline derivatives, including those found in the South American hallucinogenic plant *Banisteriopsis caapi*, were injected IP and IVC into mice. Subsequent behavioral changes were observed and the levels of the compounds in brain tissue were determined.

It was found that following IP administration, tremors and/or convulsions were induced by β-carbolines having aliphatic alkyl groups, but not by those with carbonyl and oxo groups substituted at carbon-1 of the C ring. These effects were potentiated by the presence of a methoxy group at carbon-7 of the A ring, and their durations of actions were prolonged by 3,4-dihydro derivatives. When induced, tremors/convulsions correlated with levels of β-carbolines in the brain. The smaller ED_{50} values of β-carbolines that cause tremors/convulsions showed lower levels of β-carbolines in brain tissue.

β-Carbolines Tremor Convulsion Brain level of β-carboline

HARMINE and harmaline, the β-carboline alkaloids found in *Banisteriopsis caapi* and other plants, are well known to have hallucinogenic and tremorigenic properties (4,8). The tremors induced by harmine and harmaline in animals have been reported to involve serotonergic (10), noradrenergic (16), and GABAergic mechanisms (2). Harmine tremors have been attributed to the induction of an imbalance of catecholaminergic and serotonergic systems (3,9). The tremor-producing effects of some harmala and iboga alkaloids are reported to be more influenced by chemical structure than by lipid solubility (17). Tremors induced with harmine and harmaline have been correlated with their concentrations in the brain (12,14,17).

In the present study abnormal behaviors were observed in mice after administration of each of 15 natural and synthetic β-carbolines, and the levels of β-carbolines in brain tissue were determined.

METHODS

Materials

Norharman, harman, harmine, and harmaline (free bases) and their hydrochlorides were purchased from Sigma Co. (St. Louis). Hydrochlorides of harmol and harmalol were obtained from Fluka Fabrik (Switzerland). Harmol and harmalol (free bases) were prepared from their chlorides by using aq ammonia. 1-Propyl-β-carboline, 1-propyl-3,4-dihydro-β-carboline, 1-propyl-7-methoxy-β-carboline, and 1-propyl-7-methoxy-3,4-dihydro-β-carboline were synthesized by the method of Späth and Lederer (15) and identified by spectral data (6,7). Harmic acid, its methyl ester, harmalinic acid, harmine *N*-oxide, and ketotetrahydronorharmine were prepared by the method of Hashimoto and Kawanishi (6,7).

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Animals

Male *ddy* mice weighing 17–19 g were purchased from Japan SLC Co. Ltd. The animals were maintained on a 12-h light-dark schedule (lights on at 0700) at 24 ± 1°C. All drugs were administered to groups of 10 animals each for observation of behavior, and to 3 or 4 animals for measurement of levels of β-carbolines in brain tissue.

Experimental Procedure for Gross Behavior

Ten mice were housed in groups of 2 each in wire mesh cages (26 × 12.5 × 16.5 cm). Behavior was observed for 60–180 min commencing immediately after IP or IVC administration of drugs. For IP administration, hydrochlorides of β-carbolines were dissolved in distilled water. β-Carbolines (free bases) and acids were converted to chlorides and salts by adding the calculated amounts of 1 M HCl or 1 M KOH, respectively. They were then diluted with distilled water to make standard solutions. For IVC administration, the chlorides or salts were dissolved in saline to prepare final dilutions of solutions. IVC administration was conducted by injection of 3 μl (when the compound was less soluble, 5–6 μl was used) of drug solution of the appropriate concentration at a point 1 mm to the right of and 2 mm below the bregma, using a microsyringe adjusted with a stopper to a depth of 3 mm. The administration time was 8 s. Tremors of at least 2 min duration were considered to be a positive response. Hind-limb scratching and head twitching were regarded as a positive response if 10 such incidents were recorded.

ED_{50} values were calculated by the method of Litchfield and Wilcoxon (11).

Levels of β-Carbolines in the Brain After Administration of β-Carbolines

Each β-carboline (20 mg/kg) was administered IP to separate groups of three or four mice each. Brains were quickly removed 1, 2, 5, 10, 20, 30, or 60 min after drug administration and blotted between paper to remove excess fluid (for harmaline, additional doses were administered at 90 and 120 min, using groups of five or six mice). Each brain was homogenized with 8 ml of 0.1 N sulfuric acid containing quinine base for use as an internal standard for high-performance liquid chromatography (HPLC). Supernatant fractions were obtained by centrifugation at 3000 × *g* for 20 min and passed through a Diaion HP 20 (Nippon Rensui Co.) column (1.5 × 10 cm). The column was washed with 100 ml of distilled water and then β-carbolines and quinine were eluted with 100 ml of methanol. The eluates were evaporated to dryness in vacuo at 40°C and the residues were dissolved in methanol and filtered. The resulting filtrates were used for HPLC analysis.

Analysis of Levels of β-Carbolines in the Brain After Administration of β-Carbolines by HPLC

For filtrates of harmalol and harmine a model 6000A with a model 302 pump (Waters Associates Ltd., Milford, MA) was used as a solvent delivery system for HPLC, while for filtrates of all other β-carbolines a Model 803C manometric module with a Model 811 mixer (Gilson Medical Electronics, Middleton, WI) was used. Separation of harmol, harmalol, and harmine was achieved on a μ Bondasphere 5 μ C_{18} 100A (3.9 × 150-mm column) (Waters Ltd.) using methanol : water 40 : 60 containing 0.4% ammonium acetate and 0.5% sodium dodecyl sulfate run at 1 ml/min. 1-Propyl-7-methoxy-β-carboline and harmic acid methylester were separated on 5C 18 AR (4.0 × 150-mm column) (Nacalai Tesque Inc., Japan) using methanol : water 40 : 60 containing 0.4% ammonium acetate and 0.5% sodium dodecyl sulfate run at 1 ml/min. Norharman, harman, harmaline, and 1-propyl-7-methoxy-3,4-dihydro-β-carboline were separated using a mixture of 200 mM phosphate buffer pH 3.0 : methanol between 80 : 20 and 70 : 30 for each run at 1 ml/min. β-Carbolines and quinine were detected by fluorescence spectrophotometry at 340 nm for excitation and 460 nm for emission (F1000, Hitachi, Japan). An integrator C-R2A (Shimadzu, Japan) was used to calculate concentrations of β-carbolines.

RESULTS

Tremors, Convulsions, and Other Behavioral Changes Following IP Administration

Norharman (Ia) (Table 1) (10 to 100 mg/kg) caused 10/10 animals to lie on their bellies with head drop for 30 to 180 min. These doses, except 10 and 20 mg/kg, produced convulsions (convulsant ED_{50} in Table 1) which persisted for 10–30 min in each mouse (Fig. 1). Salivation and lacrimation resulted in 2/10 and 10/10 mice at 80 and 100 mg/kg, respectively. Deaths occurred following administration of 100 mg/kg in 4 mice during the period of observation. All mice given 70, 80, and 100 mg/kg were catatonic.

Harman (Ib) (Table 1) (10 mg/kg) produced convulsions (convulsant ED_{50} in Table 1) (Fig. 2) and marked scratching behavior. A dose of 20 mg/kg also induced convulsions and all mice exhibited head drop. At 50 mg/kg, convulsions were observed in 9/10 and salivation and lacrimation were apparent in 5/10 mice. Two out of 10 mice fell on their sides and all 10 mice eventually lay on their bellies with head drop.

1-Propyl-β-carboline (Ic) (Table 1) (10 mg/kg) caused no significant behavioral changes except for a hunching posture in all mice. At 20 mg/kg, convulsions were produced in 5/10 mice 2–7 min after administration, and rounding of the backs occurred in all mice (Fig. 3). At 50 mg/kg, the compound produced convulsion in all mice and jumping in 5/10 mice 1–3 min after administration.

1-Propyl-3,4-dihydro-β-carboline (IIc) (Table 1) (10 mg/kg) produced tremors in 3/10 and a Straub tail reaction in 3/10 mice (Fig. 4). A dose of 15 mg/kg caused tremors in 10/10 mice, and a dose of 20 mg/kg produced tremors and the Straub tail reaction in 10/10 mice for 45 min and screaming in 5/10 mice.

Harmol (Id) (Table 1) (20 mg/kg) caused hypoactive behavior in all mice and induced scratching in 2/10 persisting for 7 min. Scratching occurred in 8 mice for 20 min following administration of 50 mg/kg, but no tremors occurred.

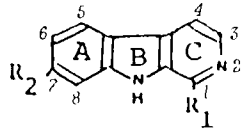
Harmalol (IId) (Table 1) (20 mg/kg) induced scratching in 9/10 mice for 10 min with hypoactivity 1–2 min after administration. The scratching occurred more often and longer than with harmol at 20 mg/kg. However, no other behavioral changes were apparent with harmalol at 50 mg/kg.

Harmine (Ie) (Table 1) (5–20 mg/kg) produced an increase in spontaneous activity with an unsteady gait. Marked tremors resulted about 5 min after administration. The incidence and duration of continuous tremors increased with increased doses (4–20 min) (tremorigenic ED_{50} in Table 1) (Fig. 5).

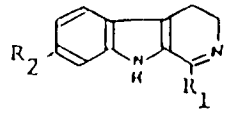
Harmaline (IIe) (Table 1) (2.5 mg/kg) induced scratching in 4/10 mice 2–4 min after administration. A significant stimulant effect on spontaneous behavior was induced at a dose of 5 mg/kg; 7/10 mice climbed the cages, and 3 of them

TABLE 1

RELATIONSHIP BETWEEN CHEMICAL STRUCTURE AND TREMOR/CONVULSION PRODUCING ACTIVITY IN MICE INTRAPERITONEAL ADMINISTRATION



(I)



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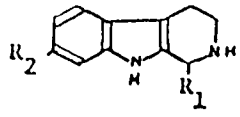

(III)

	R_1	R_2	ED_{50} mg/Kg (IP)	ED_{50} μg (IVC)
Norharman (Ia)	H	H	49.0 (40.2–59.8)*	not observed
Harman (IIb)	CH_3	H	23.0 (15.6–33.8)*	not observed
1-Propyl-β-carboline (Ic)	$CH_2CH_2CH_3$	H	20*†	>100‡
1-Propyl-3,4-dihydro-β-carboline (IIc)	$CH_2CH_2CH_3$	H	10–15†‡	50–100†‡
Harmol (Id)	CH_3	OH	not observed	not observed
Harmalol (IId)	CH_3	OH	not observed	50–100*†
Harmine (Ie)	CH_3	OCH_3	8.5 (6.6–11.0)‡	11.8 (9.5–14.6)‡
Harmaline (IIe)	CH_3	OCH_3	6.5 (5.0–8.4)‡	42.5 (35.1–51.4)‡
1-Propyl-7-methoxy-β-carboline (If)	$CH_2CH_2CH_3$	OCH_3	15†‡	80†‡
1-Propyl-7-methoxy-3,4-dihydro-β-carboline (IIf)	$CH_2CH_2CH_3$	OCH_3	3.8 (2.8–5.1)‡	54.5 (40.4–73.6)‡
Harmic acid (Ig)	COOH	OCH_3	not observed	
Harmalinic acid (IIg)	COOH	OCH_3	not observed	
Harmic acid methylester (Ih)	$COOCH_3$	OCH_3	not observed	not observed
Harmine-*N*-oxide (Ii)	CH_3	OCH_3	not observed	
Ketotetrahydronorharmine (IIIj)	O	OCH_3	not observed	

*Convulsion. †Approximate ED_{50}. ‡Tremor.

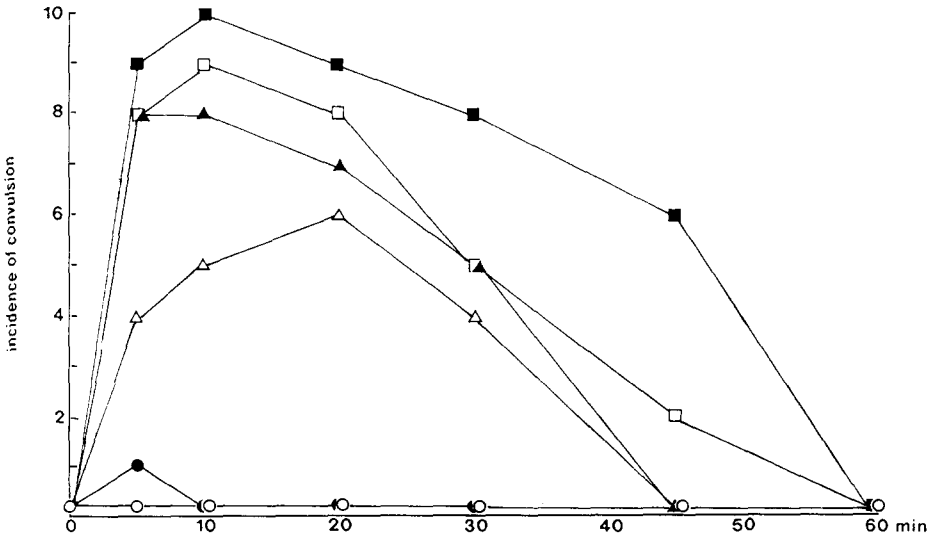

FIG. 1. Occurrence of convulsions induced by norharman in mice following IP administration. ○—○ 20 mg/kg, ●—● 30 mg/kg, △—△ 50 mg/kg, ▲—▲ 70 mg/kg, □—□ 80 mg/kg, ■—■ 100 mg/kg.

showed tremors 40 min after drug administration. The incidence and duration of tremors were potentiated with increased doses (tremorigenic ED_{50} in Table 1) (Fig. 6).

1-Propyl-7-methoxy-β-carboline (If) (Table 1) (10 and 20 mg/kg) caused tremors, and a dose of 50 mg/kg produced convulsions and jumping, which disappeared 40 min after administration (Fig. 7).

1-Propyl-7-methoxy-3,4-dihydro-β-carboline (IIf) (Table 1) produced dose-dependent tremors (tremorigenic ED_{50} in Table 1) (Fig. 8). Tremors were followed by convulsions and jumping after administration of 50 mg/kg, and these abnormal behaviors continued for 2 h.

Harmic acid (Ig) (Table 1) (20 mg/kg) produced a remarkable spontaneous hypoactivity and head drop in 10/10 mice. However, no specific postural effect was seen with the drug at 50 mg/kg.

Harmalinic acid (IIg) (Table 1) (20 mg/kg) caused all mice to become sedated with head drop.

Harmic acid methylester (Ih) (Table 1) (20 mg/kg) did not produce any marked behavioral change.

Harmine N-oxide (Ii) (Table 1) (20 mg/kg) (dissolved in 5% dimethylsulfoxide [DMSO]) produced no significant behavioral changes except for scratching, which was also seen with a control vehicle of 5% DMSO in 9/10 mice.

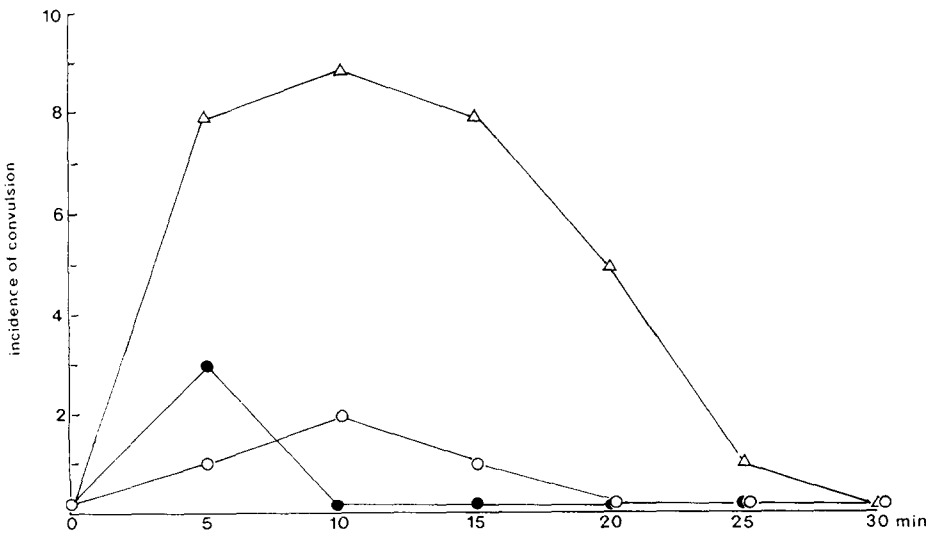

FIG. 2. Occurrence of convulsions induced by harman in mice following IP administration. ○—○ 10 mg/kg, ●—● 20 mg/kg, △—△ 50 mg/kg.

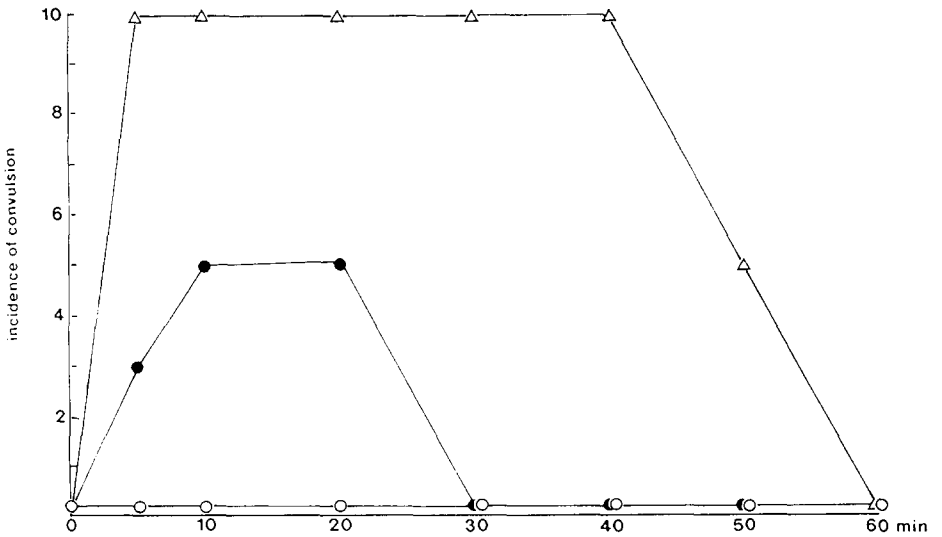

FIG. 3. Occurrence of convulsions induced by 1-propyl-β-carboline in mice following IP administration. ○ – ○ 10 mg/kg, ● – ● 20 mg/kg, △ – △ 50 mg/kg.

Ketotetrahydronorharmine (IIIj) (Table 1) (20 mg/kg) (dissolved in 10% ethanol) induced only scratching in 9/10 mice 2–5 min after administration with a duration of approximately 30 min. This effect was also seen in 9/10 mice 4–5 min after administration of the control vehicle.

Tremors, Convulsions, and Other Behavioral Changes Following IVC Administration

Norharman (Ia) (20, 50, and 100 μg) only induced a rotation to the left in 1/10 mice.

Harman (Ib) (50 μg) produced no remarkable changes, but 100 μg produced tremors in 1/10 mice.

1-Propyl-β-carboline (Ic) (50 and 100 μg) caused tremors in 0/10 and 1/10 mice 9.5 min after administration, respectively.

1-Propyl-3,4-dihydro-β-carboline (IIc) (20 μg) produced rotations to the left in 4/10 mice and a Straub tail reaction in 2/10 mice, but no tremors were produced. A dose of 50 μg caused tremors in 4/10 mice, and convulsions in 2 of these 4. A dose of 100 μg produced tremors in 8/10 mice, convulsions in 7/10, and jumping in four of these.

Harmol (Id) (20–100 μg) did not produce any significant effects on behavior.

Harmalol (IId) (50 μg) caused rotations to the left in 4/10 mice. Two of these 4 showed trembling, jumping, and scratching 15 min after administration of the drug. These behaviors persisted at intervals over a period of 120 min. At 100 μg harmalol produced convulsions in 9/10 mice with rotations to

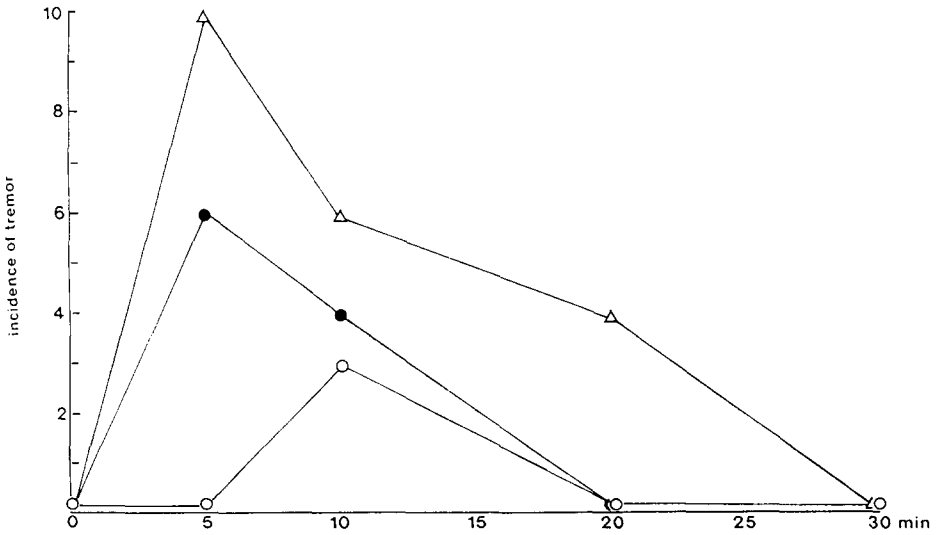

FIG. 4. Occurrence of tremors induced by 1-propyl-3,4-dihydro-β-carboline in mice following IP administration. ○ – ○ 10 mg/kg, ● – ● 15 mg/kg, △ – △ 20 mg/kg.

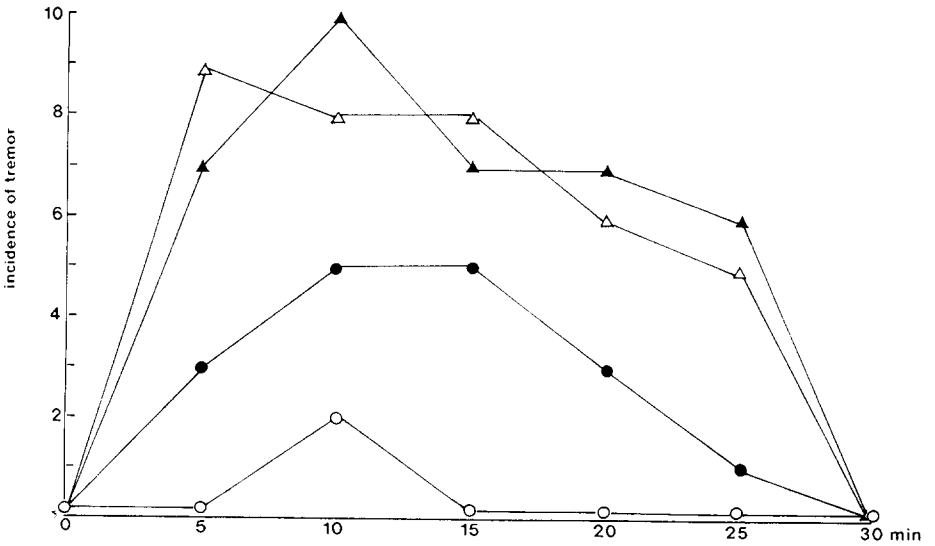

FIG. 5. Occurrence of tremors induced by harmine in mice following IP administration. ○—○ 5 mg/kg, ●—● 10 mg/kg, △—△ 15 mg/kg, ▲—▲ 20 mg/kg.

the left, squealing, scratching, and head twitch. Convulsions continued in 7 of these 9 mice over 120 min. Half of the mice died in 24 h.

Harmine (Ie) at doses of 7, 10, 15, and 20 μg induced tremors in 1/10, 4/10, 7/10, and 10/10 mice, respectively (tremorigenic ED_{50} in Table 1). Following administration of harmine at 15 and 20 μg, the mice rotated rapidly to the left with trembling. Administration of 100 μg caused tremors in all mice; 6/10 showed a left twisting of the forepart of their bodies, 2/10 showed the Straub tail reaction, and 1/10 jumped.

All mice given *harmaline* (IIe) at 20 μg showed remarkable hyperactive spontaneous behavior. The Straub tail reaction was apparent in 3/10 mice 1 min after administration. Administration of harmaline at 30 μg also caused hyperactive spontaneous behavior in all mice and continuous rotation to the left in 3/10. Tremors were observed in two of these three 10 min after administration. Five of 10 mice showed tremors 11 min after administration of 40 μg of harmaline (tremorigenic ED_{50} in Table 1). Administration of 50 μg caused tremors in 7/10, 5 of which rotated to the left and 1 of which walked backward to the right. Administration of 100 μg caused tremors in 10/10 and clonic convulsions in 5/10.

1-Propyl-7-methoxy-β-carboline (If) (40 and 80 μg) caused tremors in 3/10 and 5/10, respectively, and rotating to the left in 3/10 at both doses.

1-Propyl-7-methoxy-3,4-dihydro-β-carboline (IIf) (20, 40, and 80 μg) produced tremors in 1/10, 2/10, and 8/10 mice,

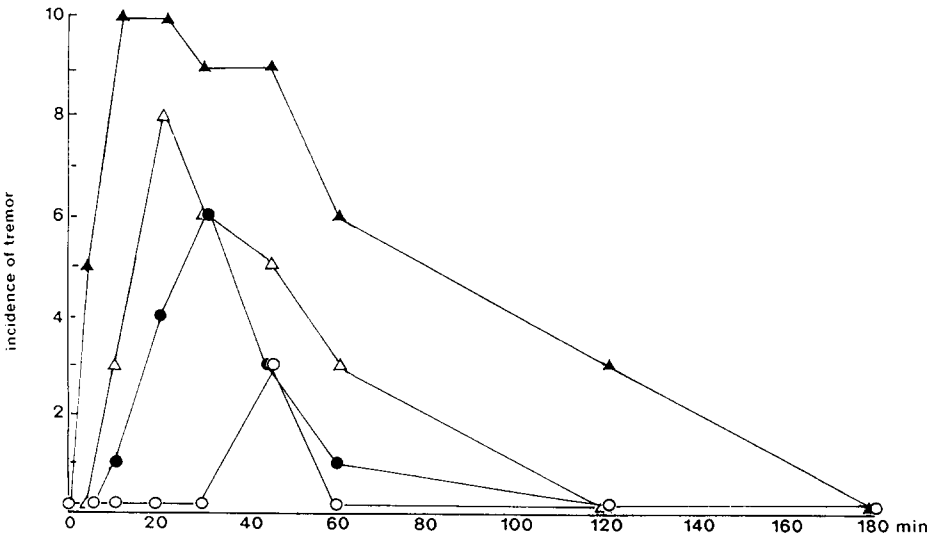

FIG. 6. Occurrence of tremors induced by harmaline in mice following IP administration. ○—○ 5 mg/kg, ●—● 7.5 mg/kg, △—△ 10 mg/kg, ▲—▲ 20 mg/kg.

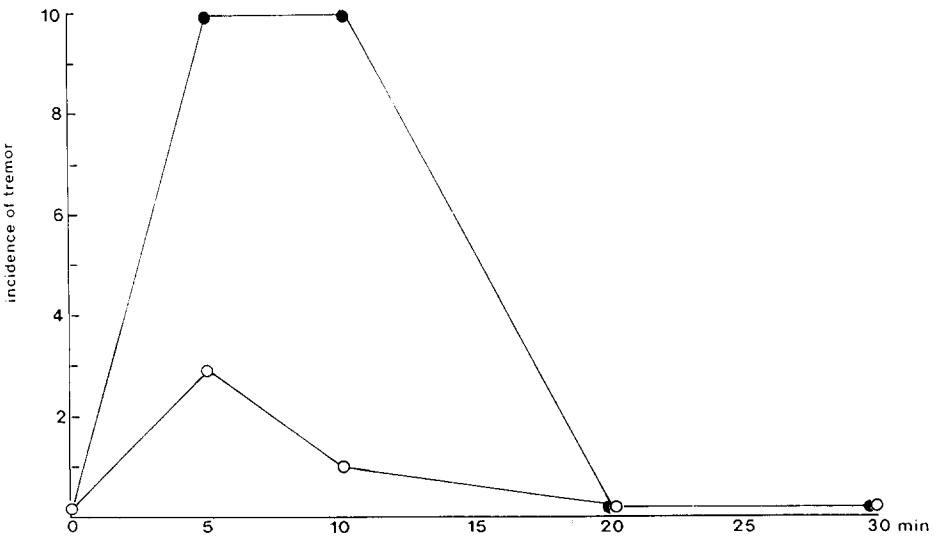

FIG. 7. Occurrence of tremors induced by 1-propyl-7-methoxy-β-carboline in mice following IP administration. ○ – ○ 10 mg/kg, ● – ● 20 mg/kg.

respectively. Tremors were induced with 80 μg, followed by convulsions in all mice with jumping seen in 4 of these 8 (tremorigenic ED_{50} in Table 1). These abnormal behaviors were not observed 60 min after administration.

Harmic acid methylester (Ih) (20 and 50 μg) produced no significant behavioral changes in any mice.

Levels of β-Carbolines in the Brain After Administration of β-Carbolines

Twenty mg/kg was chosen for the dose to determine the levels of β-carbolines distributed in the brain after administration of β-carbolines into mice. It was about the dose for tremorigenic ED_{50} responses (Table 1) and caused no deaths in the mice.

Norharman and harman were chosen from the drugs with no group substituted in the A ring, harmol and harmalol from the drugs with hydroxy groups at C-7 of the A ring, harmine and harmaline from the drugs with methoxy groups at C-7, 1-propyl-7-methoxy-β-carboline and its dihydro derivative as examples of β-carbolines with long chain alkyl groups at C-1 of the C ring, and harmic acid methylester as a drug which did not cause abnormal behavior. The time courses of distribution of β-carbolines in brain tissue, except for harmol and harmalol, are shown in Figs. 9–15 with the numbers of mice which caused tremors/convulsions.

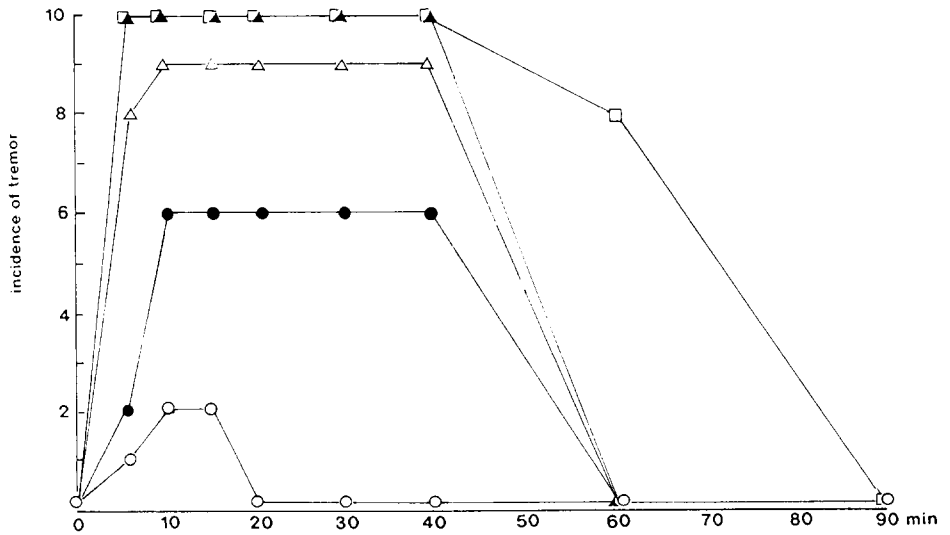

FIG. 8. Occurrence of tremors induced by 1-propyl-7-methoxy-3,4-dihydro-β-carboline in mice following IP administration. ○ – ○ 2 mg/kg, ● – ● 5 mg/kg, △ – △ 7.5 mg/kg, ▲ – ▲ 10 mg/kg, □ – □ 20 mg/kg.

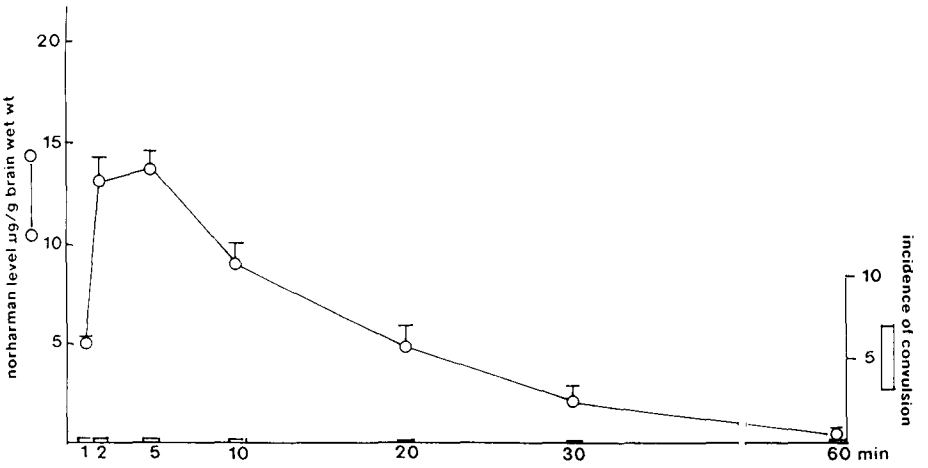

FIG. 9. Correlation of brain norharman levels with numbers of induced convulsions in a group of 10 mice after IP administration of norharman (20 mg/kg). Mean values of SD for 3 or 4 mice per group are shown.

Harmol was detected at 0.1–0.3 μg/g of wet brain tissue for 60 min after administration. Harmalol was not detected but apparently was metabolized to harmol, which was detected at 0.1–0.2 μg/g of wet brain for 60 min after administration of harmalol.

When harmine was administered, harmol was also detected (0.1–0.2 μg/g). When harmaline was administered, harmine and harmol in addition to harmaline were detected. The level of harmine found was approximately one fourth to one third of the level of harmaline, and the level of harmol was 0.1 μg/g.

When 1-propyl-7-methoxy-β-carboline was administered, 1-propyl-7-hydroxy-β-carboline was detected (1.9 μg/g as the maximum level at 5 min). When 1-propyl-7-methoxy-3,4-dihydro-β-carboline was administered, 1-propyl-7-methoxy-β-carboline and 1-propyl-7-hydroxy-β-carboline were detected (1–3 μg/g and 0.1–0.2 μg/g, respectively).

DISCUSSION

Behavioral changes induced by several natural and synthetic β-carbolines (Table 1) in mice were observed and their levels in brain tissue were determined.

A comparison of the ED_{50} values required to induce tremors/convulsions revealed that 1-propyl-7-methoxy-3,4-dihydro-β-carboline was the most potent, followed by harmaline and harmine. Norharman was the least active (Table 1).

It was found that peak levels of harman that occurred in

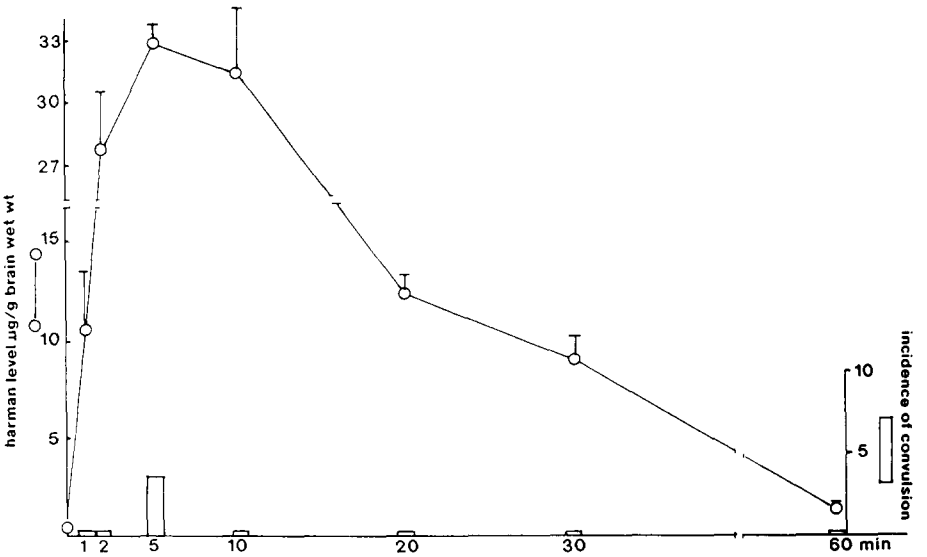

FIG. 10. Correlation of brain harman levels with numbers of induced convulsions in a group of 10 mice after IP administration of harman (20 mg/kg). Mean values of SD for 3 or 4 mice per group are shown.

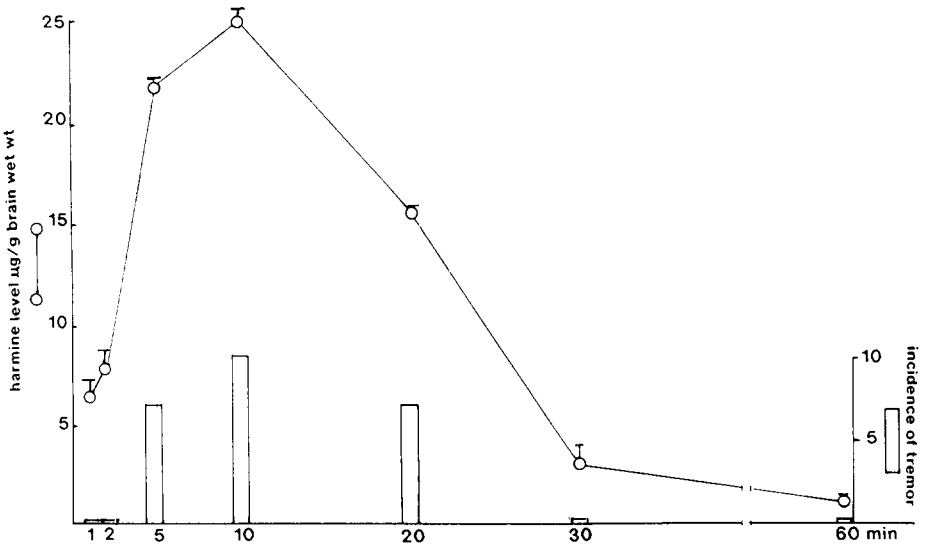

FIG. 11. Correlation of brain harmine levels with numbers of induced tremors in a group of 10 mice after IP administration of harmine (20 mg/kg). Mean values of SD for 3 or 4 mice per group are shown.

the brain were the highest of seven β-carbolines 5 and 10 min after their IP administration, followed by harmine, and the ones of harmaline were the lowest (Figs. 9–15).

The relationships between the tremorigenic/convulsant ED_{50} values and the levels of β-carbolines in the brain 5 min after IP administration of 20 mg/kg are shown in Table 1. The data suggest that the smaller ED_{50} values of β-carbolines correlated well with lower brain levels of the corresponding derivatives. The levels of β-carbolines distributed in the brain were consistent with their occurrence, duration, and intensity of tremorigenic and/or convulsant effects (Fig. 9–15).

The β-carbolines substituted with carboxy or oxo groups at C-1 of the C ring showed no abnormal behavior, although the levels of harmic acid methylester distributed in the brain were approximately equal to those of harmaline and 1-propyl-7-methoxy-3,4-dihydro-β-carboline.

Demethylation and dehydrogenation apparently occurred in the brain, since harmol, harmine, 1-propyl-7-hydroxy-β-carboline, and 1-propyl-7-methoxy-β-carboline were detected in the brain after administration of harmine, harmaline, 1-propyl-7-methoxy-β-carboline, and its dihydro derivative to mice.

These data suggest that β-carbolines must reach the brain to cause tremors/convulsions, but it is not necessary that they are present at high levels in the brain to produce intense tremors or convulsions of a long duration.

Therefore, it is assumed that β-carbolines in the brain may not act directly to produce tremors/convulsions, but their affinities to the tryptamine binding sites (13) and their inhibitory

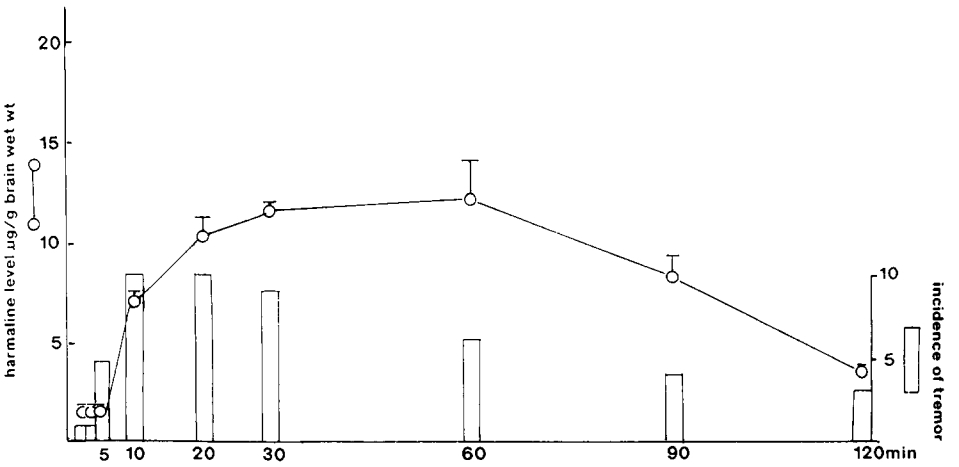

FIG. 12. Correlation of brain harmaline levels with numbers of induced tremors in a group of 10 mice after IP administration of harmaline (20 mg/kg). Mean values of SD for 3 or 4 mice per group are shown (except 60, 90, and 120 min for 5 or 6 mice per group).

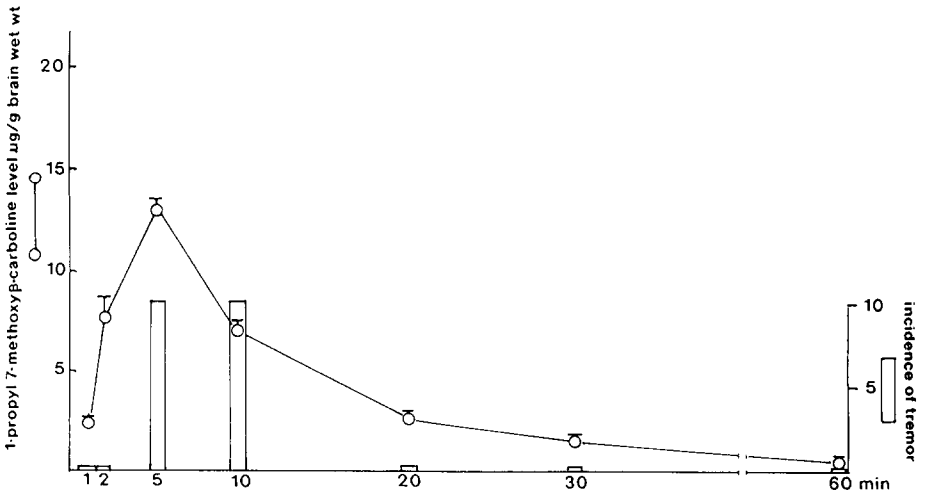

FIG. 13. Correlation of brain 1-propyl-7-methoxy-β-carboline levels with numbers of induced tremors in a group of 10 mice after IP administration of 1-propyl-7-methoxy-β-carboline (20 mg/kg). Mean values of SD for 3 or 4 mice per group are shown.

activities on serotonin uptake (1) and monoamine oxidase, selectively type A (5), may change the levels of amines and their metabolites in the brain. Harmic acid methylester would not affect on these parameters, since it distributed in the brain but did not induce any abnormal behavior.

Our findings suggest the following:

1. Induction of tremors and convulsions by β-carboline derivatives following IP administration in mice is highly dependent on chemical structures. For example, 1-propyl-7-methoxy-3,4-dihydro-β-carboline was the most potent in the 15 derivatives and norharman (aromatic unsubstituted β-carboline) was the least potent.
2. 3,4-Dihydro derivatives caused tremors of longer duration than aromatic derivatives.
3. The β-carbolines with carbonyl or oxo at carbon-1 of the C ring and the *N*-oxide did not produce any tremors/convulsions.
4. Onset time, duration, and intensity of tremors/convulsions induced by β-carbolines were consistent with their levels found in the brain.
5. The lower ED_{50} values of β-carbolines cause tremors/convulsions which correlated with lower levels of the β-carbolines found in the brain.
6. Demethylation and dehydrogenation of β-carbolines apparently occur in the brain.

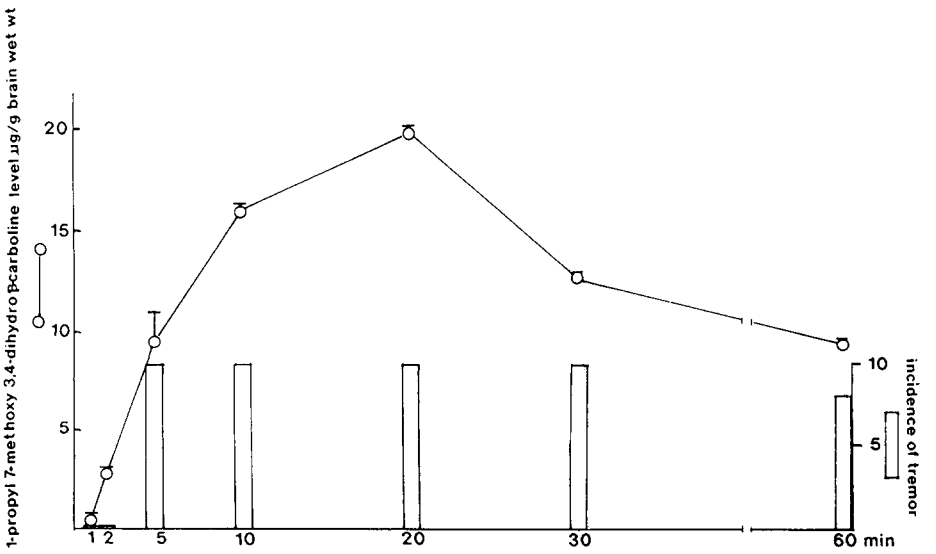

FIG. 14. Correlation of brain 1-propyl-7-methoxy-3,4-dihydro-β-carboline levels with numbers of induced tremors in a group of 10 mice after IP administration of 1-propyl-7-methoxy-3,4-dihydro-β-carboline (20 mg/kg). Mean values of SD for 3 or 4 mice per group are shown.

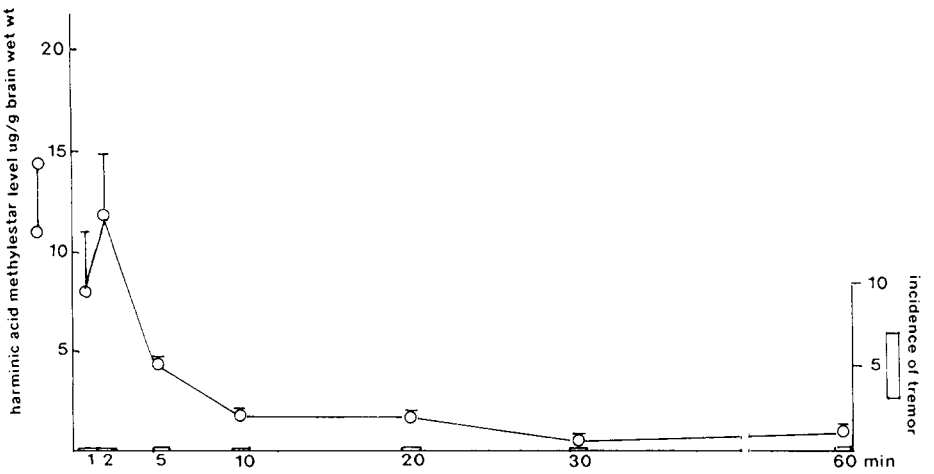

FIG. 15. Correlation of brain harmic acid methylester levels with numbers of induced tremors in a group of 10 mice after IP administration of harmic acid methylester (20 mg/kg). Mean values of SD for 3 or 4 mice per group are shown.

REFERENCES

1. Buckholtz, N. S.; Boggan, W. O. Inhibition by β-carbolines of monoamine uptake into a synaptosomal preparation: Structure-activity relationships. Life Sci. 20:2093-2100; 1977.
2. Costa, E.; Guidotti, A.; Mao, C. C.; Suria, A. New concepts of the mechanism of action of benzodiazepines. Life Sci. 17:167-186; 1975.
3. Costall, B.; Kelly, D. M.; Nayler, R. J. The importance of 5-hydroxytryptamine for the induction of harmine tremor and its antagonism by dopaminergic agonists assessed by lesions of the midbrain raphe nuclei. Eur. J. Pharmacol. 35:109-119; 1976.
4. Fuentes, J. A.; Longo, V. C. An investigation on the central effects of harmine, harmaline, and related β-carbolines. Neuropharmacology 10:15-23; 1971.
5. Fuller, R. W.; Hemrick-Luecke, S. K. Influence of selective reversible inhibitors of monoamine oxidase on the prolonged depletion of striatal dopamine by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine in mice. Life Sci. 37:1089-1096; 1985.
6. Hashimoto, Y.; Kawanishi, K. New organic bases from Amazonian *Banisteriopsis caapi*. Phytochemistry 14:1633-1635; 1975.
7. Hashimoto, Y.; Kawansihi, K. New alkaloids from *Banisteriopsis caapi*. Phytochemistry 15:1559-1560; 1976.
8. Hoffer, A.; Osmond, H. Indole hallucinogens derived from tryptophan. In: Hoffer, A.; Osmond, H., eds. The hallucinogens. New York: Academic Press; 1967:472-516.
9. Kawanishi, K.; Hashimoto, Y.; Fujiwara, M.; Kataoka, M.; Ueki, S. Pharmacological characteristics of abnormal behavior induced by harmine with special reference to tremor in mice. J. Pharmacobio-Dyn. 4:520-527; 1981.
10. Kelly, D. M.; Nayler, R. J. Mechanisms of tremor induced by harmine. Eur. J. Pharmacol. 27:14-24; 1974.
11. Litchfield, J. T.; Wilcoxon, F., Jr. A simplified method of evaluating dose-effect experiments. J. Pharmacol. Exp. Ther. 96:99-113; 1949.
12. Mori, K.; Kuga, T. Estimation of harmine and its derivatives by HPLC: Correlation of brain harmine levels with jumping behavior in rats. Jpn. J. Pharmacol. 43:33-41; 1987.
13. Rommelspacher, H.; Brüning, G.; Susilo, R.; Nick, M.; Hill, R. Pharmacology of harmalan (1-methyl-3,4-dihydro-β-carboline). Eur. J. Pharmacol. 109:363-371; 1985.
14. Singbartl, G.; Zetler, G.; Schlosser, L. Structure-activity relationships of intracerebrally injected tremorigenic indole alkaloids. Neuropharmacology 12:239-244; 1973.
15. Späth, F.; Lederer, F. Synthesen von 4-carbolinen. Chem. Ber. 2102-2111; 1930.
16. Yamazaki, M.; Tanaka, C.; Takaori, S. Significance of central noradrenergic system on harmaline induced tremor. Pharmacol. Biochem. Behav. 10:421-429; 1979.
17. Zetler, G.; Singbartl, G.; Schlosser, L. Cerebral pharmacokinetics of tremor-producing harmala and iboga alkaloids. Pharmacology 7:237-248; 1972.