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Cerebral Pharmacokinetics of Tremor-Producing Harmala and Iboga Alkaloids

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Abstract. Tremor-producing activity and concentration in brain were determined in mice for 4 harmala and 5 iboga alkaloids. All compounds were active, however, harmalol only after intracerebral injection. Kinetics of evasion from brain were first-order functions with most drugs, but revealed 2 compartments for harmalol and 3 for ibogaline. Tremor-producing activity was much more influenced by chemical structure than by lipid solubility. This points to specific receptors for indole compounds in tremorigenic brain structures.

Key Words
Harmaline
Harmalol
Harmane
Harmine
Ibogaine
Ibogaline
Iboxygaine
Indole alkaloids
Noribogaine
Pharmacokinetics
Tabernanthine
Tremor

The very large group of centrally-acting drugs comprises only relatively few tremor-producing compounds [cf. EVERETT, 1956]. The indole alkaloids we are dealing with have this potency and are still more interesting since some of them are hallucinogens [cf. HOFFER and OSMOND, 1967]. Chemical structure has been found to be of importance for cardiovascular and tremorigenic activity of iboga alkaloids [ZETLER, 1964; ZETLER *et al.*, 1968; ZETLER and SINGBARTL, 1970].

In our previous experiments on tremor these alkaloids were peripherally given, and thus it is possible that the quantitative differences found reflect inequalities of penetration into brain rather than those of true potency. CUBE *et al.* [1970] working with morphine-like analgesics were led to the same consideration. With this in mind we designed the present experiments on the possibility of receptors in brain for tremor-producing indole alkaloids.

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Materials and Methods

Animals

Male NMRI-mice weighing 22–26 g were purchased from P. Bäumler (Wolfratshausen), and kept at 22 °C. They were fed with Altromin pellets and tap water *ad libitum*.

Treatments

Tremor after s.c. injection was determined in single mice isolated immediately prior to treatment. We used 10 animals per dose and observed them 60 min at the most. Quantal responses were achieved considering an animal a reactor even if tremor lasted only seconds. All drugs were dissolved in 0.1 N sulfuric acid to bring the bases into solution, the volume of s.c. and i.v. injections was 0.1 ml/10 g. Many alkaloids remained in solution only at low pH and, therefore, i.v. doses were infused within 10 sec. Intracerebral injections were made using the technique described by HALEY and MCCORMICK [1957] and GREEFF and KASPERAT [1961]. Here the injection volume was 0.02 ml, however, there were often some losses by reflux of injected fluid. Control injections produced neither tremors nor convulsions or other reactions.

Extraction of Alkaloids

Each brain (without olfactory bulbs) was weighed and homogenized in 1.0 ml of 0.1 N sulfuric acid using a 5-ml handhomogenizer (model Dounce of B. Braun, Melsungen). The homogenate was mixed with 30 ml *n*-heptane/isoamyl alcohol (97/3 v/v) and the homogenizer rinsed with 2 ml of 0.1 N sodium hydroxide which was then added to the mixture (final pH $\sim$ 12.0). The glass-stoppered tubes were now turned with 45 rpm for 20 min and then centrifuged at 0 °C with 3,000 rpm for 10 min. 20 ml of the organic phase were added to 3 ml of 0.1 N sulfuric acid, shaken for 5 min and again centrifuged. The watery phase was used for quantitative determination. Noribogaine: 30 ml benzene crystallizable was used instead of heptane/isoamyl alcohol, and 12 g sodium chloride was added. Harmalol: The tissue was homogenized with 1.0 N sulfuric acid and extracted with 30 ml ethyl acetate plus 12 g sodium chloride (15 min at 45 rpm). The ethyl acetate was decanted, replaced by a new amount of 20 ml and the extraction repeated. Both ethyl acetate samples were thoroughly mixed, and then a volume of 20 ml was added to 3 ml of 1.0 N sulfuric acid and treated further as described above.

Recoveries were about 80 % with lowest values of 70 and 75 % for harmalol and noribogaine, respectively, and highest values with harmine (90 %).

Determination of Alkaloids

The Aminco-Bowman spectrofluorometer (American Instrument Co.) and the recorder Moseley 135 A (Hewlett-Packard) were used. Table I indicates the wavelengths of excitation and emission maxima of the alkaloids. Our figures for harmine and harmaline agree well with those described by UDENFRIEND *et al.* [1958] and VILLENEUVE and SOURKES [1966]. An internal standard curve was established for each alkaloid by adding known amounts of drug to fresh brain homogenates, and extracting it as described. If necessary, quenching was avoided by dilution 1 : 10 or 1 : 20.

Table I. Wavelengths of excitation and emission maxima

	Excitation, nm	Emission, nm
Harmane	300	430
Harmine	322	420
Harmaline	378	480
Harmalol	383	478
Ibogaine	300	360
Tabernanthine	296	368
Ibogaline	300	360
Iboxygaine	295	355
Noribogaine	292	350

Partition Coefficient

Partition coefficients were determined at room temperature with the method of HERZ *et al.* [1965] using as organic phase *n*-heptane which is suitable for work aiming at penetration through the blood-brain barrier [KURZ and APPIAH, 1969]. The watery phase was 1/15 M phosphate buffer (Soerensen) with the pH 7.4. For 'shaking', the glass-stoppered tubes were rotated at 45 rpm. Shaking for 20 min was sufficient to reach equilibrium.

Statistics

In general, arithmetic means and their confidence limits for $P = 0.05$ were calculated, an exemption (geometric mean) is indicated. The tremor-producing action after s.c. injection was determined with the method of LITCHFIELD and WILCOXON [1949] using 10 animals per dose and 3–5 doses per substance.

Drugs

The molecular weight (MW) of a compound is mentioned in parentheses. Harmane hydrochloride (MW 218; Carl Roth, Karlsruhe), harmine hydrochloride (MW 285; Fluka AG, Buchs/Switzerland), harmaline (MW 250; Carl Roth, Karlsruhe), harmalol hydrochloride (MW 273; EGA-Chemie, Steinheim), ibogaine hydrochloride (MW 347; Aldrich Chemical Co., Milwaukee, Wisc./USA), noribogaine (MW 292; J. R. Geigy, Basel), tabernanthine (MW 310; J. R. Geigy, Basel), ibogaline (MW 341; J. R. Geigy, Basel), iboxygaine (MW 326; J. R. Geigy, Basel), *n*-heptane p.a. (Merck), ethyl acetate p.a. (Merck), isoamyl alcohol p.a. (Merck), and benzene crystallizable p.a. (Merck). All concentrations mentioned refer to the bases.

Results

All alkaloids except harmalol produced tremor when given s.c. (table II). The tremor was coarse and interrupted by quiet episodes which could last even minutes. The highest doses of harmane (35 and 50 mg/kg)

Table II. Lipid solubility and tremor-producing dosage

	Distribution coefficient [1] $\bar{x} \pm s_{\bar{x}}$	Tremor-producing ED_{50}	
		μmol/kg s.c.	mg kg s.c.
Harmane	0.475 ± 0.006	102.0 (83.5–124.0) [2]	22.2
Harmine	0.305 ± 0.056	13.7 (11.2–17.2)	3.9
Harmaline	0.046 ± 0.002	12.8 (11.6–14.4)	3.2
Harmalol	0.006 ± 0.0003	293.0 ineffective!	80.0 ineffective!
Ibogaine	27.976 ± 0.602	34.8 (31.4–38.9)	12.1
Tabernanthine	11.770 ± 0.152	4.5 (3.9–5.2)	1.4
Ibogaline	0.866 ± 0.064	7.6 (7.0–8.5)	2.6
Iboxygaine	0.378 ± 0.021	80.4 (71.5–90.8)	26.2
Noribogaine	0.078 ± 0.018	176.0 (130.0–238.3)	51.4

[1] *n*-Heptane/phosphate buffer (1/15 M; pH 7.4).
[2] Confidence limits for P = 0.05.

and noribogaine (100 mg/kg) caused also salivation (harmane), running fits, and convulsions which killed 10% of the animals. Time factors of onset and duration of tremor were different as shown in table III for the s.c. ED_{95} of selected compounds.

Distribution coefficients varied greatly within both groups of alkaloids (table II). However, there was no correlation between this parameter and tremor-producing activity after s.c. application, although in both groups, the least active compounds also had lowest lipid solubility.

Intracerebral injection revealed that harmalol is not devoid of tremor-producing activity (table IV). Its power is, however, certainly lower than that of harmine or harmaline, and its action appears after a considerable delay.

A dose of 10 mg/kg of each alkaloid was given i.v. to obtain the kinetic parameters shown in table V (this dose was too low to produce tremor with harmane, harmalol, and noribogaine). Figure 1 demonstrates some characteristic results. A uniform distribution in the body would lead to a maximal cerebral concentration (y_{max}) of 10 μg/g. All drugs except harmalol were found to reach or surmount this level within the first minute after injection. Two maxima occurred with harmaline, one after 15 sec and a second one after 30 min as shown in the insert of figure 1, the difference between both values being statistically significant. It was possible

Table III. Time factors of tremor action and cerebral concentration of alkaloids at the moment of the end of tremor. *A* After i.v. injection (this dose was too low to produce tremor with harmane, harmalol and noribogaine). *B* After s.c. injection of ED_{95}

Alkaloid	mg/kg	Origin of tremor, min post-injection	End of tremor, min post-injection	Concentration in brain at the end of tremor, nmol/g wet weight
A				
Harmine	10	0.38 (0.34–0.43) [1]	25.1 (22.7–27.6) [1]	24.5 (29.0; 21.0) [2]
Harmaline	10	0.42 (0.38–0.45)	96.3 (90.5–102.1)	18.0 (19.2; 17.6)
Ibogaine	10	0.34 (0.30–0.38)	7.9 (7.5–8.4)	74.2 (77.4; 71.0)
Tabernanthine	10	0.23 (0.22–0.24)	51.8 (46.3–57.3)	9.4 (11.9; 7.1)
Ibogaline	10	0.98 (0.87–1.10)	40.5 (38.0–42.9)	4.7 (4.9; 4.7)
Iboxygaine	10	0.70 (0.52–0.88)	[3]	77.3 [4]
B				
Harmane	37.7	3.1 (2.9–3.3)	10.5 (8.8–12.3)	243.1 (232.0; 226.5)
Harmine	6.8	3.3 (2.7–3.9)	18.1 (14.4–21.8)	25.0 (29.0; 21.0)
Ibogaine	20.9	10.5 (7.2–13.8)	23.0 (14.4–39.9)	51.2 (49.7; 43.9)
Ibogaline	3.6	15.6 (13.8–17.4)	35.7 (29.1–43.7)	3.2 (4.1; 2.1)
Iboxygaine	60.0	10.4 (6.4–14.4)	36.3 (26.1–50.4)	128.5 (124.2; 131.9)

[1] Means and their confidence limits for P = 0.05. In case of end of tremor *B* geometric means because of large variability.

[2] These concentrations have been interpolated from mean time-concentration curves, and apply to the mean, and fiducial limits, of end of tremor.

[3] Tremor occurred only in 14 of 55 mice and lasted < 10 sec.

[4] Valid only for the 14 mice with tremor.

Table IV. Number of animals showing tremor after intracerebral injection of harmala alkaloids (5 mice/dose)

	3 μg	30 μg	100 μg	min [1]
Harmine	0	3	5	1.8 ± 0.4
Harmaline	0	3	5	2.0 ± 0.4
Harmalol	0	1	3	31.5 ± 2.7

[1] Time from injection till appearance of tremor ($\bar{x} \pm s_{\bar{x}}$).

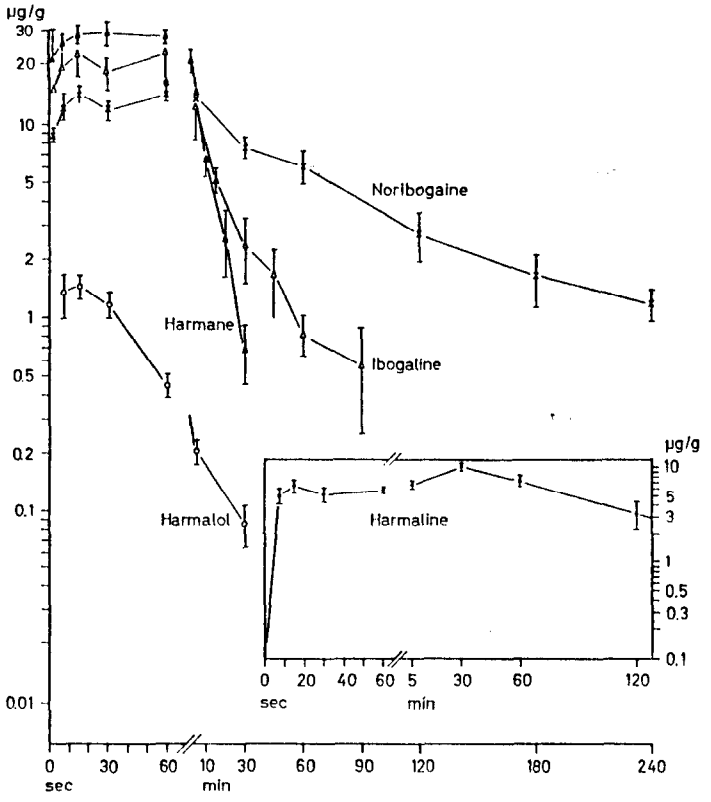


Fig. 1. Drug concentration in mouse brain after i.v. injection of 10 mg/kg of harmalol, harmaline, harmane, ibogaline, and noribogaine. Abscissa: time after injection (attention: first part of abscissa indicates seconds!). Ordinate: concentration in brain (μg/g wet weight). Points are means with their fiducial limits for $P = 0.05$.

that in this case the relatively long-lasting infusion (10 sec) was of importance. Therefore, the experiments were repeated with bolus injections (< 1 sec) well tolerated because of the low acidity of this solution. Again there were two maxima, concentrations being now somewhat higher and elimination slightly faster.

Elimination from brain was of very different speed, and for all alkaloids except both harmalol and ibogaline a first-order exponential function. The elimination curve of harmalol indicated 2 and that of ibogaline even 3 compartments. This view is justified by the fact that in both cases the k_e-values differ by a factor of > 2.5.

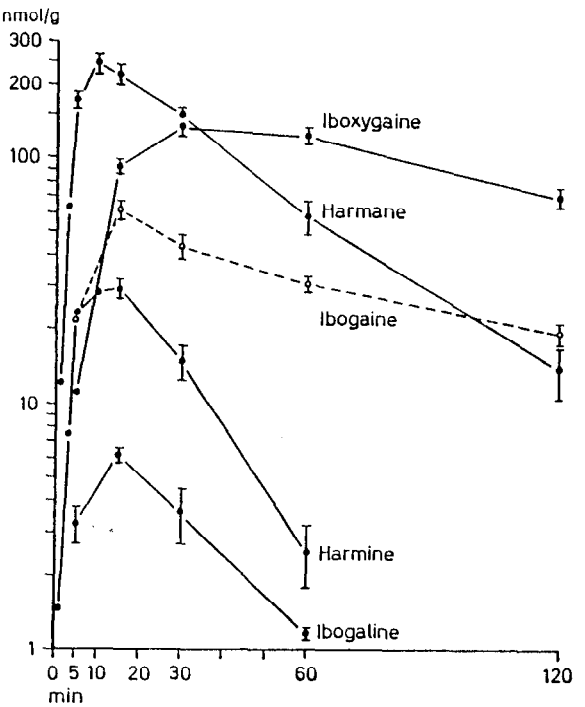


Fig. 2. Drug concentration in mouse brain after s.c. injection of the following equipotent doses (ED_{95}, mg/kg): harmane 37.7, harmine 6.8, ibogaine 20.9, ibogaline 3.6, iboxygaine 60.0. Abscissa: time after injection. Ordinate: concentration in brain (nmol/g wet weight). Points are means and standard error ($\bar{x} \pm s_{\bar{x}}$). Not shown are the following concentrations after 240 min: iboxygaine 11.5 ± 3.04, ibogaine 3.46 ± 0.45.

The elimination curves obtained in these experiments and in others with s.c. injection of the ED_{95} (fig. 2) allowed to interpolate the brain concentration at the mean moment of the end of tremor (table III). This functionally-defined parameter varied greatly with substances but was for a given drug of the same order of magnitude, no matter which dose and route of administration was utilized. Cerebral drug concentration at the end of tremor and the s.c. ED_{50} are closely correlated but independent from the distribution coefficient (table VI).

The experiments referred to in figure 2 are not suitable for analysis of kinetics. However, they were necessary to obtain functionally-defined cerebral concentrations (table III), and showed in general rapid absorption after s.c. injection. Invasion into brain was faster with the harmala than with the iboga alkaloids, which corresponds with the time factors for

Table V. Pharmacokinetic parameters as obtained in mouse brain after i.v. injection of 10 mg/kg

Alkaloid	y_{max} μg/g wet weight	t_{max} min	k_e min^{-1}	$t_{1/2}$ min
Harmane	29.1	0.19	0.1303	5.3
Harmine	32.1	0.37	0.0685	10.1
Harmaline	7.1; 10.3	0.25; 30.0	0.0130	53.4
Harmaline [1]	9.7; 12.9	1.0; 30.0	0.0144	48.2
Harmalol	1.4	0.25	4.16; 0.203	0.16; 3.42
Noribogaine	14.7	1.0	0.0105	66.0
Ibogaine	47.6	0.13	0.0120	57.9
Tabernanthine	28.6	0.2	0.0510	13.6
Ibogaline	22.9	1.0	0.213; 0.077; 0.014	3.25; 9.0; 50.0
Iboxygaine	24.6	0.5	0.0306	22.6

y_{max} = Maximal concentration in brain.
t_{max} = Time from end of injection till y_{max}.
k_e = Elimination rate constant.
$t_{1/2}$ = Half-life during evasion from brain.
[1] Bolus injection within < 1 sec.

Table VI. Ranking orders of parameters A (from table II), B (from table III), and C (from table II). r_S is Spearman's ranking order correlation coefficient

	A ED_{50} s.c. rank	B brain concentration at end of tremor rank	C distribution coefficient rank
Tabernanthine	1	2	2
Ibogaline	2	1	3
Harmaline	3	3	7
Harmine	4	4	6
Ibogaine	5	5	1
Iboxygaine	6	6	5
Harmane	7	7	4
r_S	0.96	0.107	
	$P < 0.005$	$P \gg 0.1$	

origin of tremor in these experiments (table III). It is obvious that work on tissue distribution of these alkaloids must be started earlier than 1 h after s.c. or i.p. injection [DHAHIR *et al.*, 1971].

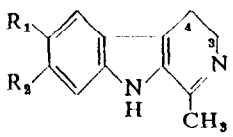
Discussion

All alkaloids used have tremor-producing potency. Too low dosage was the reason for our previous finding of inactivity of noribogaine [ZETLER, 1964]. Our positive results with harmane are in accord with those of YEN and DAY [1965] in mice but contrast with the negative findings of SIGG *et al.* [1964] and FUENTES and LONGO [1971] in rats. We found that harmalol is inactive when given peripherally, which confirms other authors [GUNN and SIMONART, 1930; POIRIER *et al.*, 1966; SOURKES and POIRIER, 1968; LAROCHELLE *et al.*, 1971]. Our present results prove that harmalol has indeed tremorigenic activity but does not penetrate through the blood-brain barrier to reach cerebral concentrations sufficiently high for action. The reason for this is the very low lipid solubility of this alkaloid (table II).

Lipid solubility is indeed an important factor for the initial concentration of the alkaloids in brain since there is a correlation between distribution coefficient and maximal brain concentration (Spearman's $r_S = 0.75$; $p < 0.025$; $n = 9$). Maximal brain concentration is, however, in our case indicative of a luxury supply rather than of pharmacological potency. The latter property can be assessed by the drug concentration at the end of tremor. This functional parameter is not correlated with the distribution coefficient but with the s.c. ED_{50} (table VI), which means that (a) our alkaloids have indeed different tremor-producing potency, and (b) differences between equiactive s.c. doses are not caused by the necessity to overcome unequal lipid solubilities. There is one exception: Tremor-end concentration of ibogaline is lower than that of tabernanthine, although s.c. ED_{50} of the former is higher than that of the latter. The distribution coefficient of ibogaline is, however, much smaller than that of tabernanthine, which makes a higher peripheral dose necessary. Furthermore, this example shows clearly that 'true' (i.e. intracerebral) potency does not depend on lipid solubility.

Intracerebral distribution after penetration of blood-brain barrier is perhaps a factor of unknown significance in our experiments. We conclude this from the great differences in latency after intracerebral injection

Table VII. Influence of chemical structure on tremor-producing activity



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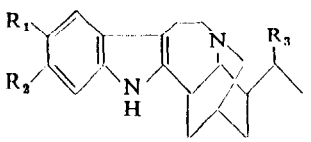

II

Alkaloid	R_1	R_2	R_3	CET [1] nmol/g	ED_{50} µmol/kg s.c. [2]	Distribution coefficient [3]
I						
Hamane [3]	H	H		243	102	0.475
Harmine [3]	H	OCH_3		25	14	0.305
Harmaline	H	OCH_3		18	13	0.046
Harmalol	H	OH		inactive	inactive	0.006
II						
Noribogaine	OH	H	H	[4]	176	0.078
Ibogaine	OCH_3	H	H	63	35	27.976
Tabernanthine	H	OCH_3	H	9	5	11.770
Ibogaline	OCH_3	OCH_3	H	4	8	0.866
Iboxygaine	OCH_3	H	OH	129	80	0.378

[1] Concentration in brain at the end of tremor (from table III).
[2] From table II.
[3] Double bond between C_3 and C_4.
[4] No information available.

(table IV). BRUINVELS [1969] has in fact shown for harmaline that neural tissues can prevent a drug from reaching tremorigenic brain areas. Such structures could be Nucleus caudatus and Substantia nigra [COX and POTKONJAK, 1971].

Intracerebral drug metabolism must also be considered since in rat brain a very small amount of a fluorescent metabolite appears after i.p. injection of harmine [VILLENEUVE and SOURKES, 1966]. However, complete fluorescence spectra taken from brain extracts made at the end of tremor did not indicate the existence of metabolites for any of our 9 alkaloids. Consequently, drug metabolism in brain is probably of no, or negligible, importance for the kinetics of elimination from brain. This leads to the conclusion that the additional compartments influencing elimination of harmalol and ibogaline may be extracerebral by nature.

The unusual shape of the invasion curve of harmaline may possibly point to an extracerebral compartment which first absorbs the drug as fast as brain, and then releases it leading thus to the second y_{max}-value after 30 min. The compartment was without influence during evasion which was a first-order exponential function. This peripheral compartment is perhaps the pancreas which, in rats, absorbed much more harmaline than other organs including brain, and released it much faster [VILLENEUVE and SOURKES, 1966].

Influences of chemical structure on pharmacological properties (table VII) are most obvious for the methoxy group which enhances tremorigenic potency whereas a hydroxy group has the opposite effect. The same structure-action relations exist for direct inhibition of the pacemaker of guinea-pig heart [ZETLER *et al.*, 1968]. This applies also to the fact that, for iboga alkaloids, one methoxy group in the position of R_2 (table VII) is of special value. Presence or absence of a double bond in harmala alkaloids is of minor importance.

It seems clear that the tremor-producing potency of our alkaloids depends more on chemical structure than on lipid solubility. Specific receptors for indole compounds are therefore postulated for brain areas important for generation of tremor.

References

BRUINVELS, J.: Comparison of intracisternally and intraperitoneally injected harmaline on body temperature and tremor in the rat. J. Pharm. Pharmacol *21:* 506–508 (1969).

COX, B. and POTKONJAK, D.: An investigation of the tremorgenic action of harmine in the rat. Europ. J. Pharmacol. *16:* 39–45 (1971).

CUBE, B. VON; TESCHEMACHER, H.; HERZ, A. und HESS, R.: Permeation morphinartig wirksamer Substanzen an den Ort der antinociceptiven Wirkung im Gehirn in Abhängigkeit von ihrer Lipoidlöslichkeit nach intravenöser und nach intraventrikulärer Applikation. Arch. Pharmakol. *265:* 455–473 (1970).

DHAHIR, H. I.; RICHARDS, A. B.; JAIN, N. C., and FORNEY, R. B.: Tissue distribution of ibogaine hydrochloride in rats. Toxicol. appl. Pharmacol. *19:* 420 (1971).

EVERETT, G. M.: Tremor produced by drugs. Nature, Lond. *177:* 1238 (1956).

FUENTES, J. A. and LONGO, V. G.: An investigation on the central effects of harmine, harmaline and related β-carbolines. Neuropharmacology *10:* 15–23 (1971).

GREEFF, K. und KASPERAT, H.: Vergleich der neurotoxischen Wirkung von Digitalisglykosiden und Geninen bei intracerebraler und intravenöser Injektion an Mäusen, Ratten und Meerschweinchen. Arch. exp. Path. Pharmakol. *242:* 76–89 (1961).

GUNN, J. A. and SIMONART, A. J.: The pharmacological actions of harmalol. Quart. J. Pharm. *3:* 218–237 (1930).

HALEY, T. J. and MCCORMICK, W. G.: Pharmacological effects produced by intracerebral injection of drugs in the conscious mouse. Brit. J. Pharmacol. *12:* 12–15 (1957).

HERZ, A.; TESCHEMACHER, H.; HOFSTETTER, A., and KURZ, H.: The importance of lipid-solubility for the central action of cholinolytic drugs. Int. J. Neuropharmacol. *4:* 207–218 (1965).

HOFFER, A. and OSMOND, H.: The hallucinogens (Academic Press, New York 1967).

KURZ, H. und APPIAH, A.: Beziehungen zwischen der Permeation von Arzneimitteln durch die Blut-Liquor-Schranke und ihrer Verteilung in verschiedenen Lipid/Wasser-Modellen. Arch. Pharmakol. *264:* 264–265 (1969).

LAROCHELLE, L.; BÉDARD, P.; POIRIER, L. J., and SOURKES, T. L.: Correlative neuroanatomical and neuropharmacological study of tremor and catatonia in the monkey. Neuropharmacology *10:* 273–288 (1971).

LITCHFIELD, J. T., jr. and WILCOXON, F.: A simplified method of evaluating dose-effect experiments. J. Pharmacol. exp. Ther. *96:* 99–113 (1949).

POIRIER, L. J.; SOURKES, T. L.; BOUVIER, G.; BOUCHER, R., and CARABIN, S.: Striatal amines, experimental tremor and the effect of harmaline in the monkey. Brain *89:* 37–52 (1966).

SIGG, E. B.; GYERMEK, L.; HILL, R. T., and YEN, H.: Neuropharmacology of some harmine derivatives. Arch. int. Pharmacodyn. *149:* 164–180 (1964).

SOURKES, T. L. and POIRIER, L. J.: Serotonin and dopamine in the extrapyramidal system. Adv. Pharmacol. *6A:* 335–346 (1968).

UDENFRIEND, S.; WITKOP, B.; REDFIELD, B. G., and WEISSBACH, H.: Studies with reversible inhibitors of monoamine oxidase: Harmaline and related compounds. Biochem. Pharmacol. *1:* 160–165 (1958).

VILLENEUVE, A. and SOURKES, T. L.: Metabolism of harmaline and harmine in the rat. Rev. canad. Biol. 25: 231–239 (1966).

YEN, H. C. Y. and DAY, C. A.: Evaluation of anti-tremor drugs in tremor-induced rodents. Arch. int. Pharmacodyn. *155:* 69–83 (1965).

ZETLER, G.: Einige pharmakologische Eigenschaften von 12 natürlichen und 11 partialsynthetisch abgewandelten Indol-Alkaloiden aus tropischen Apocynaceen des Subtribus Tabernaemontaninae. Arzneimittelforsch. *14:* 1277–1286 (1964).

ZETLER, G. and SINGBARTL, G.: Inhibition of cardiac effects of noradrenaline by eleven indole alkaloids, two azepinoindoles, quinidine, quindonium, and propranolol. Pharmacology *4:* 129–142 (1970).

ZETLER, G.; LENSCHOW, E. und PRENGER-BERNINGHOFF, W.: Die Wirkung von 11 Indol-Alkaloiden auf das Meerschweinchenherz *in vivo* und *in vitro*, verglichen mit 2 synthetischen Azepinoindolen, Chinidin und Quindonium. Arch. Pharmakol. exp. Path. *260:* 26–49 (1968).

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