Naunyn-Schmiedeberg's Arch. Pharmacol. 291, 201—212 (1975)

New Characteristics of Harmaline Inhibition of Intestinal Transport Systems

F. V. Sepúlveda and J. W. L. Robinson

Département de Chirurgie Expérimentale, Hôpital Cantonal Universitaire, Lausanne

Received July 3 / Accepted August 22, 1975

Summary. Harmaline strongly inhibits the uptake of phenylalanine by slices of guinea-pig intestine *in vitro*. The lowest concentration having a significant effect is 0.1 mM. The drug also inhibits the unidirectional flux of phenylalanine from the mucosal to serosal face of the tissue provided it is added to the solution bathing the mucosal surface. The unidirectional flux of sodium from the mucosa to the serosa was similarly reduced. Ion and water absorption in the perfused dog intestine *in vivo* is also diminished in the presence of harmaline. These results support the hypothesis, previously proposed in view of the rapid onset of harmaline inhibition of sodium-dependent uptake mechanisms in a variety of tissues, that harmaline interacts with the sodium-site of non-electrolyte carrier complexes.

The effect of harmaline on phenylalanine uptake by the intestine is duplicated by other psychotropic indole analogues. The actions of harmine and harmalol are similar to that of harmaline, despite great differences in the liposolubility of the different compounds. N:N-dimethyl-tryptamine is equally inhibitory, but serotonin is inactive. Mescaline and lysergic acid diethylamide also inhibit phenylalanine transport, but to a much lesser extent than harmaline.

Key words: Harmaline — Intestinal Transport — Hallucinogenic Drugs.

Harmaline is an alkaloid extracted from *Banisteriopsis caapi* (Hochstein and Paradies, 1957), a Colombian liana used by various indigenous tribes to prepare hallucinogenic concoctions (Uscátegui Mendoza, 1961). Apart from its psychotomimetic properties it recently aroused interest in the field of membrane transport, when it was shown to inhibit Na^+-K^+ ATPase in neural tissue and sodium movements in squid axon (Canessa *et al.*, 1973). More recently, harmaline was shown to inhibit sodium-dependent transport mechanisms in the small intestine and other epithelia (Sepúlveda and Robinson, 1974): It reduced both sugar and amino-acid uptake by small intestinal rings during short incubations, indicating that it acts at the luminal face of the epithelial cell. Harmaline also inhibited amino-acid, monosaccharide and PAH uptake by kidney cortex

Send offprint requests to: J. W. L. Robinson, Département de Chirurgie Expérimentale, Hôpital Cantonal Universitaire, CH-1011 Lausanne, Switzerland.

slices, and sugar and amino-acid accumulation in dog colonic mucosa. The common factor embracing all these transport systems is their dependence on the presence of sodium ions, so it was suspected that harmaline might interfere with the sodium-binding site of these transport mechanisms. This supposition was further supported by the finding that harmaline does not affect the Na^+-independent component of phenylalanine influx into guinea-pig intestinal rings and also that harmaline reduced the influx of sodium itself into this tissue, both in the presence and absence of non-electrolytes. Finally, it has recently been demonstrated that harmaline behaves as a fully competitive inhibitor of sodium influx into the guinea-pig intestinal mucosa (Sepúlveda and Robinson, 1975). The present paper describes certain additional characteristics of the mechanism of harmaline action on intestinal transport mechanisms, and compares the effect of harmaline in the intestine with that of other related psychotomimetic compounds.

Methods and Materials

Methods

The uptake of L-phenylalanine-^{14}C or β-methyl-D-glucoside-^{14}C by guinea-pig small intestinal rings was determined using methods described in detail elsewhere (Robinson, 1970; Luisier and Robinson, 1973). The rings were incubated at 37°C in oxygenated Krebs bicarbonate buffer containing the radioactive substrate, with or without the appropriate inhibitors. In experiments with some analogues, the incubations had to be performed at pH 6.3 in view of their solubilities. To this effect, the buffer was gassed with pure CO_2 until the required pH was attained. Incubations of 60 min were employed to assess the distribution ratio established at steady-state, and incubations of 5 min or less were used to gauge the initial velocity of uptake. Following the incubation, the rings were rinsed, blotted, weighed and dissolved in 30% KOH prior to counting in a liquid scintillation spectrometer, as described elsewhere (Robinson, 1970). Statistical evaluation of the results was performed by a two-way analysis of variance and by computation of the least significant difference between means at a given probability level, denoted as $D_{0.05}$, $D_{0.01}$, etc., in the tables (Pearce, 1965).

Transmural fluxes of phenylalanine and ions across sheets of guinea-pig ileum clamped under open-circuit conditions in thermostatically controlled flux chambers, of surface area 0.64 cm^2, were determined essentially as described earlier (Robinson *et al.*, 1973). Labelled phenylalanine, with or without harmaline, was added to one side of the tissue and the rate of appearance of the isotope in the opposite solution was assessed by taking 50 µl samples every 10 min for a period of 1 hr. Ion fluxes were computed using a triple-labelling technique which has been described in detail elsewhere (Robinson, 1975). ^{22}Na + ^{36}Cl were added to the Krebs bicarbonate buffer containing 0.2% glucose bathing one face of the tissue, and ^{24}Na was introduced on the other side, so that both unidirectional fluxes of sodium could be assessed on the same tissue sample. Tissues were mounted in pairs, the isotopes being reversed in the second chamber of each pair. Six chambers were studied in parallel, harmaline bathing the mucosal surface in one pair and the serosal surface in another pair. The ^{24}Na was counted as a β-emitter, a correction for the contamination by the other isotopes being assessed after disintegration of the ^{24}Na. The ^{22}Na and ^{36}Cl

were separated by counting in both β and γ counters, after decay of the contaminating ^{24}Na. Statistical evaluation was performed by an analysis of variance with replicates, the latter being provided by the two chambers of each pair.

Ion and water absorption *in vivo* by the dog ileum was determined using a closed circuit perfusion technique involving a flow-rate of 3.3 ml/min and a constant intraluminal hydrostatic pressure of 5 cm of water (Mirkovitch *et al.*, 1974). Dogs were used for this experiment owing to the difficulties in working with anaesthetised guinea-pigs. The loop was perfused for 1 hr with Krebs bicarbonate buffer containing 0.2% glucose, and then for a further hour with the medium containing 4 mM harmaline. To correct for the reduction in absorption capacity that occurs during prolonged perfusion of the ileum of the anaesthetised dog, a series of control loops was perfused for two successive hours without harmaline. The results were then evaluated by means of an analysis of co-variance taking into consideration the drop in absorption in the control series with time (Lison, 1968).

Materials

L-phenylalanine-(U)-^{14}C was obtained from New England Nuclear, Boston; β-methyl-D-glucoside-glucose-(U)-^{14}C was bought from Calbiochem, Los Angeles; ^{22}Na and ^{36}Cl, in the form of sodium chloride, originated from the Radiochemical Centre, Amersham; ^{24}Na was purchased from the Eidgenössisches Institut für Reaktorforschung, Würenlingen. Harmaline hydrochloride, harmalol hydrochloride, and serotonin-creatinine sulphate were purchased from Fluka, Buchs, harmine hydrochloride from Sigma, St. Louis, and N:N-dimethyl-tryptamine from Koch-Light, Colnbrook. Mescaline and amphetamine were kindly supplied by Dr. J. P. Bertschinger from the stocks of the Eidgenössisches Gesundheitsamt, Bern, and lysergic acid diethylamide (Lysergide) was a gift of Sandoz A.G., Basel.

Results

The sensitivity to harmaline of the initial rate of phenylalanine entry into guinea-pig intestinal rings is illustrated in Fig. 1. A significant inhibitory effect of the drug is already registered at a harmaline concentration of 0.1 mM. The curve can be linearised by the probit transformation, and iterative analysis, performed as described previously (Robinson, 1972), indicates a most probable asymptote for the curve of 0.234. The fit in this case is good ($t = 48.3$; $r = 0.9994$). The existence of a finite asymptote suggests that harmaline is not a fully-competitive inhibitor of phenylalanine transport, a point that has been discussed in greater detail elsewhere (Sepúlveda and Robinson, 1975). It is worth pointing out that the asymptotic value of 0.234 is in close agreement with the value for uptake of 1 mM phenylalanine during 5-min incubations in Na^+-free choline-substituted buffer of 0.225 μmoles/g. fresh tissue (cf. Table 2 in Sepúlveda and Robinson, 1974), an uptake that was insensitive to harmaline, but sensitive to competitive inhibition by similar amino-acids. This observation consequently infers that the entire Na^+-dependent component of phenylalanine entry can be inhibited by harmaline at sufficient concentrations of the drug.

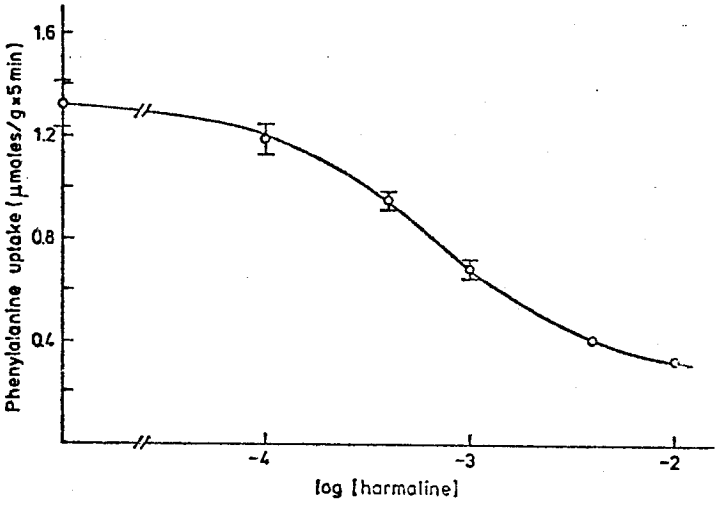

Fig. 1. Dose-response curve of the inhibition by harmaline of phenylalanine uptake by guinea-pig intestinal rings. Incubations for 5 min performed in 1 mM phenylalanine in Krebs bicarbonate buffer in the presence of different molar concentrations of harmaline. Results are the means of 6 experiments, presented ± SEM (at the two highest concentrations, the errors are smaller than the size of the symbols). The curve can be linearised by the probit transformation, and the most likely asymptote of the curve is found by iteration to be 0.234 μmoles/g fresh tissue × 5 min

Table 1. Irreversibility of the action of harmaline on β-methyl-glucoside uptake by guinea-pig intestinal rings

First incubation		Washing	β-methyl-glucoside uptake (μmoles/g fresh tissue)
Buffer alone		10 min	0.870
0.5 mM phloridzin		10 min	0.883
4 mM harmaline		10 min	0.392
Buffer alone		30 min	0.818
0.5 mM phloridzin		30 min	0.765
4 mM harmaline		30 min	0.284
	$D_{0.05}$		0.121
	$D_{0.01}$		0.163
	$D_{0.001}$		0.217

Tissues were subjected to the first incubation for 10 min, then washed for 10 or 30 min in Krebs bicarbonate buffer alone. Finally, the uptake of 1 mM β-methyl-glucoside was determined in a third incubation for 5 min in Krebs bicarbonate buffer with the sugar. Results are the means of 6 experiments; statistical evaluation by a random-block analysis of variance.

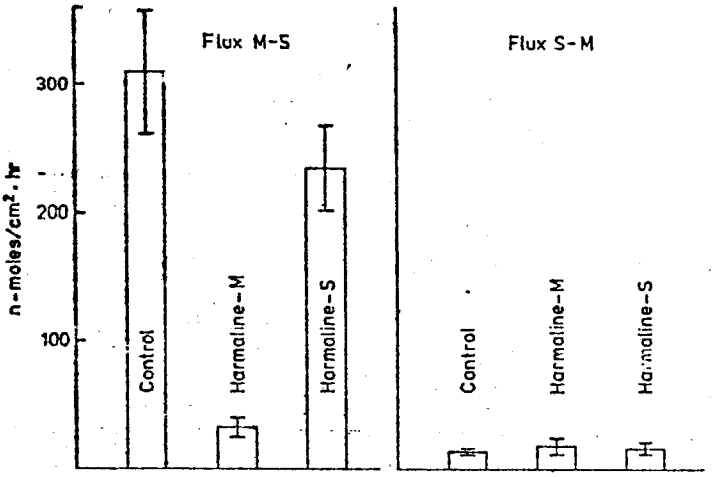

Fig. 2. Influence of harmaline on the unidirectional fluxes of phenylalanine (1 mM in Krebs bicarbonate buffer) across guinea-pig ileum. Harmaline (4 mM) was added to only one side of the tissue, and a significant inhibition of the mucosal-to-serosal (M-S) flux was only registered when the inhibitor was added to the mucosal solution. The drug had no effect on the serosal-to-mucosal (S-M) fluxes. Results are the means ± SEM of 7 determinations

The reversibility of the action of harmaline was examined by preincubating intestinal rings in a solution of harmaline in the absence of substrate, washing the tissues by means of a second incubation at 37°C in buffer, and then studying the rate of uptake of substrate in the absence of harmaline. The results in Table 1 compare the actions of harmaline and phloridzin, a well-known competitive inhibitor of monosaccharide entry into the intestinal epithelial cell. The results confirm that the effect of phloridzin is reversible (Alvarado, 1970), insofar as the inhibitor can be removed during an intermediate incubation, whereas the effect of harmaline is essentially irreversible, since it persists despite the intervening incubation.

If harmaline acts at the luminal surface of the epithelial cell, as suggested by our earlier experiments (Sepúlveda and Robinson, 1974, 1975), it should affect ion or non-electrolyte fluxes across the mucosa only when added to the mucosal medium, provided its rate of penetration across the tissue is relatively low. It can be seen from Fig. 2 that harmaline very strongly inhibits phenylalanine flux across guinea-pig ileum when added to the medium bathing the luminal face of the tissue, but its effect when added to the serosal medium is insignificant. Furthermore harmaline does not influence the serosal-mucosal flux of phenylalanine across this tissue. The fluxes of sodium and chloride in the presence and absence of har-

Table 2. Influence of harmaline on unidirectional ion fluxes across guinea-pig ileum

Flux (μEq/cm^2 · h)	Control	Harmaline-M	Harmaline-S
Sodium M-S	10.3 ± 0.68	6.3 ± 0.49*	10.0 ± 0.64**
Sodium S-M	10.1 ± 0.63	6.6 ± 0.45*	8.4 ± 0.55**
Sodium net	0.2 ± 0.63	0.3 ± 0.36	1.6 ± 0.53**
Chloride M-S	6.6 ± 1.15	7.0 ± 1.10	7.9 ± 0.86
Chloride S-M	5.0 ± 1.23	7.1 ± 1.00	3.2 ± 0.76**

The tissue was bathed with Krebs bicarbonate buffer containing 0.2% glucose under open-circuit conditions. Harmaline was added to the mucosal (M) or serosal (S) face of the tissue at a concentration of 4 mM. The results are the means of nine experiments, in each of which two determinations of the unidirectional fluxes of sodium and one measurement of each unidirectional flux of chloride were made by means of a triple-labelling technique (see methods). M-S refers to the flux from mucosal to serosal medium, and S-M to the opposing flux. * Indicates a significant difference with the control series at the 1% level (according to a two-way analysis of variance with replicates), and ** indicates a significant difference at the 5% level with the harmaline-M series. No difference between control and harmaline-S was ever significant.

maline are shown in Table 2. Harmaline added to the mucosal medium inhibits both unidirectional sodium fluxes, but the addition of harmaline to the serosal medium has no effect. The mucosal-serosal flux of chloride is the same under all conditions, but the serosal-mucosal flux of chloride is apparently smaller when the harmaline is added to the serosal medium, though in fact only the difference between the values for harmaline-M and harmaline-S is statistically significant.

The effect of harmaline on transport processes in the dog ileum *in vivo* is illustrated in Table 3. Although a reduction in absorption occurs during the course of a prolonged perfusion, addition of harmaline to the perfusate causes a significantly greater decrease in the absorption of water, sodium and chloride than occurred during the control perfusions.

The inhibition provoked by harmaline was compared with that of other tryptamine derivatives. Harmine, which differs from harmaline only in its degree of saturation, also inhibits the initial velocity of uptake and the steady-state distribution ratio of phenylalanine (Table 4). Harmalol, in which the methoxy group of harmaline has been replaced by a hydroxyl group, exerts similar effects. Despite the similarities in structure of these compounds, they have very different lipid solubilities (Zetler *et al.*, 1972), but no relationship appeared to exist between their liposolubility and their actions in the intestine. This result, incidentally, argues against an unspecific effect of harmaline at the level of the lipid structure of the membrane.

Table 3. Inhibition of water and ion transport in the dog ileum *in vivo* by harmaline

	Control dogs ($n = 8$)		Treated dogs ($n = 16$)		Statistical analysis	
	First period	Second period	First period	Second period	$F_{1,21}$	P
Water	6.1 ± 0.78	4.5 ± 0.45	4.6 ± 0.52	2.7 ± 0.23	15.8	< 0.01
Sodium	0.88 ± 0.097	0.68 ± 0.063	0.68 ± 0.073	0.40 ± 0.033	17.2	< 0.01
Potassium	0.025 ± 0.0042	0.018 ± 0.0051	0.024 ± 0.0027	0.012 ± 0.0013	3.81	> 0.05
Chloride	0.83 ± 0.083	0.62 ± 0.059	0.62 ± 0.059	0.39 ± 0.025	10.9	< 0.01

An intestinal loop was perfused for 1 hr with Krebs bicarbonate buffer containing 0.2% glucose. In the "treated dogs", 4 mM harmaline was added to the perfusate during the second hour of perfusion, whereas in the "control dogs", the loops were perfused for a second hour with the same solution. The results were then evaluated by an analysis of covariance, and the significance of the influence of harmaline is given in the last columns. The values are expressed in ml/g dry tissue · hour in the case of water absorption, and in mEq/g dry tissue · hour in the case of the ions.

Table 4. Influence of harmine and harmaol on phenylalanine uptake by guinea-pig intestinal rings

Drug added	Phenylalanine uptake (μmoles/g fresh tissue)	
	2 min	60 min
None	0.759	6.89
2 mM harmaline	0.421	1.38
2 mM harmine	0.637	1.97
2 mM harmalol	0.590	3.44
$D_{0\cdot05}$	0.061	0.82
$D_{0\cdot01}$	0.084	1.15
$D_{0\cdot001}$	0.116	1.59

The tissues were incubated for either 2 min or 1 hr in 1 mM phenylalanine in Krebs bicarbonate buffer gassed in advance with CO_2 to reduce the pH 6.3. The results are the means of six experiments.

Table 5. Effect of serotonin and N:N-dimethyl-tryptamine on phenylalanine uptake by guinea-pig intestinal rings

Drugs added	Phenylalanine uptake (μmoles/g fresh tissue)
None	10.39
4 mM harmaline	1.32
2 mM N:N-dimethyl-tryptamine	1.94
4 mM serotonin	8.66
4 mM harmaline + 4 mM serotonin	1.36
2 mM N:N-dimethyl-tryptamine + 4 mM serotonin	2.11
$D_{0\cdot05}$	1.08
$D_{0\cdot01}$	1.47
$D_{0\cdot001}$	1.99

Guinea-pig intestinal rings were incubated for 1 hr in 1 mM phenylalanine in Krebs bicarbonate buffer, containing the drugs indicated. The results are the means of 5 experiments.

It has been proposed that drugs of the tryptamine class derive their hallucinogenic activity from competition with serotonin in the central nervous system (Aghajanian and Freeman, 1968). It seemed therefore of interest to test the influence of serotonin itself in the intestine, and also to see whether it was capable of modifying the mucosal effect of harmaline. The results in Table 5 show that serotonin has only a very small effect on phenylalanine transport, and it does not modify the action either of harmaline or of N:N-dimethyl-tryptamine. The latter drug is approximately as powerful as harmaline in inhibiting phenylalanine transport in the enterocyte.

Table 6. Influence of various hallucinogenic drugs on phenylalanine uptake by guinea-pig intestinal rings

Drug added	pH	Phenylalanine uptake (μmoles/g fresh tissue)	
		5 min	60 min
None	7.4	2.05	10.48
1 mM harmaline	7.4	1.05	2.11
1 mM amphetamine	7.4	2.01	9.11
1 mM mescaline	7.4	1.85	9.19
None	6.3	1.96	10.52
1 mM harmaline	6.3	1.15	2.29
1 mM lysergide	6.3	1.54	4.62
$D_{0\text{-}cs}$		0.21	1.20
$D_{0\text{-}cl}$		0.28	1.62
$D_{0\text{-}con}$		0.37	2.14

The tissues were incubated for either 5 min or 1 hr in 1 mM phenylalanine in Krebs bicarbonate buffer. For the comparison with lysergide, it was necessary, to dissolve the drug, to saturate the solution with CO_2 in order to reduce the pH to 6.3. The results are the means of 6 experiments.

Finally, the influence of certain other well-known hallucinogenic drugs was examined (Table 6). Amphetamine was ineffective as an inhibitor of phenylalanine transport in the guinea-pig intestine, and mescaline had only a very weak action at the concentration used. In an auxiliary experiment with higher concentrations, the uptake of phenylalanine during a 60-min incubation was inhibited by $49.3 \pm 5.7\%$ by 10 mM mescaline, in comparison with an inhibition of $77.6 \pm 1.7\%$ by 1 mM harmaline ($n = 3$). Finally, lysergide, which had to be tested at a pH of 6.3 because of its solubility, very significantly diminished phenylalanine uptake although its effect was not as potent as that of harmaline. The fact that it is active during both short and long incubations indicates that its mode of action may be similar to that of harmaline.

Discussion

The characteristics of the inhibition of intestinal transport systems by harmaline and certain related indole derivatives do not resemble those of other known inhibitors. Earlier work showed that sodium-dependent non-electrolyte transport systems in a number of tissues were affected, though Na^+-independent intestinal transport was not inhibited (Sepúlveda and Robinson, 1974). It was postulated that harmaline must act at the level of the brush-border membrane of the epithelial cell, since its inhibitory effect could be extrapolated to zero time. This surmise is upheld by the results in the present study, since the drug inhibits trans-

mural fluxes of phenylalanine only when added to the mucosal bathing medium, and at high concentrations reduces phenylalanine influx into the tissue to the level observed in the absence of sodium in the incubation medium. The findings *in vivo* provide further support for this concept. Secondly, harmaline was found to inhibit sodium influx, as well as the concomitant uptake of non-electrolytes, and it was suggested that harmaline interacts with sodium-sites of the carriers responsible for the sodium-dependent transport of non-electrolytes. The present results, indicating that transmural sodium flux is also sensitive to harmaline provided the drug is added to the mucosal medium, are in agreement with this hypothesis. Recent kinetic studies have demonstrated that harmaline is indeed a fully competitive inhibitor of sodium influx into guinea-pig intestinal rings (Sepúlveda and Robinson, 1975). The fact that harmaline is apparently not a fully competitive inhibitor of phenylalanine uptake is not inconsistent with this view, since the most recent analyses of the kinetics of sodium-dependent non-electrolyte transport have suggested a form of allosteric interaction between the two substrates on a multifunctional carrier matrix (Alvarado and Mahmood, 1974). This would specifically preclude the existence of kinetics of the fully competitive type to describe the interaction between an inhibitor binding to the sodium site and a substrate whose site is allosterically transformed by the binding of sodium.

Harmaline has also been described by Canessa *et al.* (1973) as an inhibitor of the sodium-dependent reaction in the Na^+-K^+-ATPase of neural tissue. These investigators also tested the effects of a similar series of drugs on this enzyme in squid axon membranes, and found the following order of inhibitory effectiveness of the different compounds: lysergide > harmine = harmalol > harmaline > mescaline, whereas serotonin had no effect. This order of potencies does not agree with ours, where harmaline was the most effective inhibitor.

Finally, harmaline is known to be a powerful hallucinogenic drug (Naranjo, 1967), and is probably responsible, at least in part, for the psychotomimetic activity of extracts from plants of the genus, *Banisteriopsis*. Various compounds with psychotropic activity have been isolated from members of this genus (Schultes, 1957; Deulofeu, 1967), and it was originally believed that harmine was responsible for the hallucinogenic properties of extracts of *Banisteriopsis caapi* (Mors and Zaltzman, 1954). More recent work has divulged that both harmaline and harmine are present in this plant (Hochstein and Paradies, 1957). In addition, N:N-dimethyl-tryptamine has been identified as the active principle of another hallucinogenic species of the same genus (Poisson, 1965). The fact that the same group of alkaloids, and also mescaline and lysergide, possess psychotomimetic activity and the ability to interact with sodium sites in

brush-border membranes and in the Na^+-K^+-ATPase enzyme complex begs the question as to whether there could be any relationship between these two actions.

Acknowledgements. This work was supported by grants from Zyma S. A., Nyon, and from the Fonds National Suisse. We are indebted to Dr J.-P. Bertschinger, Service Fédéral de l'Hygiène Publique, Berne, for the gift of drugs and for organising the necessary permits, and to Sandoz A.G., Basel, for supplying the lysergic acid diethylamide. We are grateful to Mmes H. Capt and P. Ganguillet and Mlle D. Mettraux for their skilful technical assistance.

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