Psychotropic Properties of the Harmala Alkaloids

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The use of plant materials containing harmala alkaloids is probably very old. *Peganum harmala*, a zygophyllaceous plant, the seeds of which contain harmine (1), harmaline (2), and harmalol (3), is thought to be native to Russian Turkistan or Syria, and has been used throughout the Middle East both as a spice and as an intoxicant. Its medical and psychotropic properties are known in India, where it was probably taken by the Moslems, and where the seeds may now be purchased in bazaars (4). It is also believed that it was the Arabs who took the plant along the African Mediterranean and into Spain, where it may be found growing wild at present.

The species of *Banisteriopsis* that constitute a source of harmala alkaloids are used in an area lying between the rain forests of South America and the Andes. This is approximately the area designated as the "montaña" in the classification of South American cultures. It consists of a tropical elevated territory along the headwaters of the Amazon and Orinoco Rivers, where live some of the least known Indian groups.

Of much interest is the recent discovery of substances closely related to the harmala alkaloids in animals. One of these is adrenoglomerulotropine, a hormone of the pineal body, the chemical identity of which has been indicated as 2, 3, 4, 9-tetrahydro-6-methoxy-1-methyl-1Hpyrido (3, 4, 6) indole (5). This substance is identical to 6-methoxytetrahydroharman which has been shown to be formed *in vivo* from 5-methoxytryptamine and acetaldehyde (6). 6-Methoxytetrahydroharman is an isomer of tetrahydroharmine, one of the alkaloids in *Banisteriopsis* (7), and in the African *Leptactinia densiflora* (8). One more substance, 6-methoxyharmalan, has been shown to derive, at least *in vitro*, from melatonin (9), which in turn results from the methylation of acetylserotonin. The enzyme which makes this methylation possible, hydroxyindole-0-methyltransferase (HIOMT), has only been found in the pineal body. (See Fig. 1.)

6-Methoxyharmalan is an isomer of harmaline differing in the position of the methoxy group, which is attached to the same point of the ring as the phenolic group in serotonin or the methoxy group in ibogaine, a demonstrated hallucinogen (10). (See Fig. 2.)

As will be seen in the rest of the paper, I have found both synthetic 6-methoxyharmalan and 6-methoxytetrahydroharman to be hallucinogenic (11), a fact which invites speculation on the possible role of the metabolites on the psychoses. It is suggestive that the highest concentrations of serotonin have been found in the pineal glands of schizophrenics, and that 6-methoxyharmalan is a powerful serotonin antagonist.
Fig. 1.

Fig. 2.
It may be noted that the above reported finding constitutes the first demonstration of an endogenous hallucinogen, twenty years after the motion of a psychotoxic metabolite was proposed by Hoffer, Osmond and Smythies (12).

Lastly, one may wonder whether the pineal body-associated by Tibetan traditions with higher states of consciousness-may not actually play a part in the regulation of attention or the rhythm of sleep and wakefulness. An indirect indicated of this is the demonstration of increased pineal HIOMT activity in rats kept in constant darkness for six days (13).

Studies carried out some 30 years ago by Gunn et al., showed that some synthetic beta-carbolines had similar pharmacological properties, which in turn resembled those of quinine (14). Thus, both quinine and the harman derivatives were toxic to protozoa, inhibited the contraction of the excised muscle of the frog, caused relaxation of most smooth muscle, but contraction of uterine muscle, and caused convulsions followed by paralysis in mammals.

The only compound in this chemical group reported to have hallucinogenic properties, to my knowledge, is harmine (15), which may be regarded as identical to telepathine, yageine, and banisterine, and constitutes most of the alkaloid content in the Banisteriopsis extracts. Yet the question poses itself as to whether the qualitative similarity of harman derivatives, as evidenced by many pharmacological effects, would also apply to the psychological syndrome produced. For instance, Gunn finds that harmaline is twice as active as harmine, judging from the lethal doses of both compounds for the rabbit, and from their toxicity to protozoa. I have indeed found harmaline to be hallucinogenic at dosage levels above 1 mg./kg. i.v. or 4 mg./kg. by mouth, which is about one half the thrash-old level for harmine. It may be interesting to note at this point that the onset of effects of harmaline or other derivatives is about one hour after ingestion by mouth, but almost instantaneous after intravenous injection, if circulation time from elbow to brain is taken into account. In this, harmaline resembles the chemically related tryptamines and differs from the slow-acting phenylethylamines.

Tetrahydroharmine, the reduction product of harmaline, is another substance studied by Gunn and shown to be similar to its more saturated homologs, but three times less active than harmaline.

Racemic tetrahydroharinine, up to the amount of 300 mg. by mouth, was administered by us to one volunteer, who reported that at this dosage level there were subjective effects similar to those he experienced with 100 mg. of harmaline. More trials would be required to assess the mean effective dosage of tetrahydroharmine as a hallucinogen, but this single experiment suggests that racemic tetrahydroharmine is about one-third as active as harmaline, corresponding to Gunn's estimation on the basis of lethal dosage.

The effect of relocating the methoxy group of harmaline was not tested by Gunn but was of special interest here, in view of a possible function of the 6-methoxy homolog in the body. 6-Methoxyharmalan was indeed shown to be hallucinogenic, as was anticipated, subjective effects becoming apparent with approximate oral dosages of 1.5 mg./kg. The ratio between threshold doses of harmaline and its 6-methoxy analog is 3:2, 6-methoxyhannalan being the more active.

6-Methoxytetrahydroharmalan, probably identical with pineal adrenoglomerulotropine, was also shown to be psychoactive, elicits mild effects at a dosage level of 1.5 mg./kg. The relative activities of the two 6-methoxyharmans are approximately 1:3, the harmalan being more active than its unsaturated homolog, which confirms once more Gunn’s statement as to the relationship between double bonds and pharmacological effect.

It would seem premature to make any statement as to whether there is a qualitative difference in the subjective reaction to the different carbolines tested. Such appeared to be the case, in that experiences with
the 6-methoxy compounds happened to be of a less hallucinogenic nature in the strict sense of the word, their
effect being more akin to a state of inspiration and heightened introspection. Among the 7-methoxy
compounds, harmaline seemed to cause more withdrawal and lethargy than harmine, but both substances
showed a highly hallucinogenic quality in the visual domain. However, more systematic study would be needed
to confirm differences such as these, in view of the variability which exists even between consecutive
experiences of the same individual with the same chemical. This is well known for LSD-25, and was quite
marked in four of the seven subjects to whom harmaline was administered more than once. Yet it seems clear
that the various beta-carbolines are similar enough in their effect to be told apart from mescaline, as was
shown by the comments of persons to whom mescaline, harmaline and some other harman derivative were
administered on consecutive -occasions. The third compound, the nature of which was not known to the
experimental subjects, was invariably likened to harmaline rather than to mescaline. The same can be said
of instances in which harmaline was administered on a second or third occasion without divulging the drug's
identity. Regardless of the differences between consecutive harmaline experiences, these were classified
together as distinct from that of mescaline.

It is quite possible that further research with a larger number of subjects may demonstrate qualitative
differences of a subtle kind between the different carbolines, analogous to those shown for variously
substituted phenylisopropylamines (16, 17). Nevertheless, it may be adequate for the, time being to regard
the effects of harmaline as an approximately valid indication of -a syndrome shared, with minor variations, by
compounds of similar structure.

This information that I am presenting here on the effects of harmaline is based on the reactions of 30
volunteers to whom the drug was administered as a hydrochloride, either by mouth or intravenously, under
standard conditions. One aspect of these was the absence of all information regarding effects other than those
primarily psychological in nature.

As part of the Interest lay in knowing the difference between the harmaline syndrome and that of mescaline,
both drugs were administered to each volunteer on different occasions.

In the case of every one of the 30 subjects it was evident to the observer that both the subjective and
behavioral reactions of the person were quite different for the two drugs, and this was corroborated without
exception -by the subjects themselves. Yet the quality of the difference was not clearly the same in all
instances, so that it is hard to find regularities to which no exception can be, mentioned. Recurring differences
between harmaline and mescaline can be observed however, and in what follows, the most salient of these are
cited.

Physical sensations in general are more a part of the harmaline intoxication than of that produced by mescaline
(or similar substances). Parasthesias of the hands, feet or face are almost always present with the onset of
effects, and are usually followed by a sensation of numbness. These symptoms are most marked when the
alkaloid is injected intravenously, in which case some subjects have likened them to those experienced under
ether anesthesia. Distortions of the body image, which are quite frequent with mescaline or LSD-25, were very
exceptional with harmaline. Instead, subjects indicated isolated physical symptoms such as pressure in the
head, discomfort in the chest, or enhancement of certain sensations, as those of breathing or blinking.

Nausea was reported by 18 subjects and this sometimes led to intense vomiting. It was usually associated with
dizziness or general malaise, which would in turn appear or disappear throughout a session in connection with
certain thoughts or stimuli.

In the domain of perception, one of the most noticeable differences -between the drugs is in the visual
appearance of the environment. While distortions of forms, alterations in the sense of depth and changes in
the expression of faces are of frequent occurrence under most hallucinogens, these phenomena were
practically never seen with harmaline. The same was true in regard to color enhancement, or perception of apparent movement - flowers breathing, shapes dancing and so on- frequently seen with LSD-25. With harmaline, the environment is essentially unchanged, both in regard to its formal and its aesthetic qualities. Phenomena which most frequently occur with open eyes are the superposition of images on surfaces such as walls or ceilings, or the viewing of imaginary scenes simultaneously with an undistorted perception of surrounding objects. Such imagery is not usually taken for reality but there was an exception to this in the case of a man who saw a cat climbing a wall, then turning into a leopard, when in fact, not even the cat existed. 

Other recurrent visual phenomena were a rapid lateral vibration in the field of vision and double or multiple contours in objects, especially when these were in motion or when the subject's eyes turned away from them. Some described lightning-like flashes.

With closed eyes, imagery was abundant and most often vivid and bright colored, with a predominance of red-green or blue-orange contrasts. Long dream-like sequences were much more frequent for harmaline than for mescaline. Certain themes, such as felines, negroes, eyes, and flying are frequent and have been reported elsewhere (18).

Perception of music was not altered or enhanced with harmaline as is the case with mescaline or LSD-25. Yet noises became very prominent and generally bothersome. Buzzing sounds in the head were reported by more than half of the subjects.

Synaesthesias were not reported, and the sense of time was unaltered.

Many of the differences between harmaline and mescaline may be related to the facts that the effect of the former on the emotions is much less than that of mescaline, and thinking is affected only in subtle ways, if at all. Concern with religious or philosophical problems is frequent, but there is not the aesthetic or empathetic quality of the mescaline experience. Thus, the typical reaction to harmaline is a closed-eye contemplation of vivid imagery without much further effect than wonder and interest in its significance, which is in contrast to the ecstatic heavens or dreadful hells of other hallucinogens. Despite this lesser effect of harmaline on the intensity of feelings, qualitative changes do occur in the emotions, which may account for the pronounced amelioration of neurotic symptoms evidenced by 8 of our 30 subjects, as detailed in a separate report (19).

Desire to communicate is slight under the effect of harmaline, since other persons are felt to be a part of the external world, contact with which is usually avoided. Possibly related to this withdrawal is the extreme passivity which most subjects experienced in regard to physical movement. Most of them lay down for 4 to 8 hours and reported a state of relaxation in which they did not feel inclined to move a muscle, even to talk. In view of this observation, it is hard to understand how the Indians, according to some authors (20), engage in dancing or even whip one another under the effects of caapi.

Summing up, harmaline may be said to be more of a pure hallucinogen - than other substances whose characteristic phenomena are an enhancement of feelings, aesthetic experiences, or psychotomimetic qualities such as paranoid delusions, depersonalization, or cognitive disturbances. Moreover, harmaline appears to be more hallucinogenic than mescaline (the most visually acting drug in its chemical group), both in terms of the number of images reported and their realistic quality. In fact some subjects felt that certain scenes which they saw has really happened, and that they had been as disembodied witnesses of them in a different time and place. This matches the experience of South American shamans who drink ayahuasca for purposes of divination.

The remarkable vividness of imagery viewed under the effect of harmaline, together with phenomena such as double contours and persistence of after images, had led us to suspect a peripheral, i.e. retinal, effect of the drug, and this was tested by the recording of electroretinograms in cats. The suspicion was confirmed, in that
harmaline causes a definite increase in the alpha wave and a decrease in the beta wave of the electroretinogram, both of which become apparent before any change is observed in the brain cortex.

It would be beyond the scope of this paper to deal with electrophysiological studies, but I will briefly mention some recent results we have obtained in cat experiments at the University of Chile, which add to the general picture of the harmaline intoxication:

(1) Electrocorticograms recorded in chronically implanted cats showed either electrocortical desynchronization or synchronization in correspondence with the animal's behavior, alternating between arousal and lethargy. In addition to this spindle bursts of high voltage and low frequency were observed in all instances and these did not seem to be related to the animal's behavior.

(2) Experiments performed in cats with a chronically isolated forebrain showed even more clearly the above mentioned spindle bursts in the brain cortex, and regular wave bursts of high voltage in the pontine reticular formation, which we have not seen described under other pharmacological conditions. These cats were behaviorally overactive.

These facts may be interpreted as an indication that harmaline acts as a stimulant on the midbrain reticular formation. The direct action of harmaline on the brain cortex is hard to interpret and seems more that of a depressant, but this is counteracted in the intact animal by the arousing influence of the reticular formation. The neurophysiological picture matches well that of traditional yagé "dreaming", in that the state we have described involved lethargy, immobility, closed eyes and generalized withdrawal from the environment, but at the same time an alertness to mental processes, and an activation of fantasy.

REFERENCES

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