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Harmaline Effects on the Sensory-Motor Reactivity: Modifications of the Acoustic Startle Pattern

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PELLET, J., M. WEISS AND M.-J. GOURDON. *Harmaline effects on the sensory-motor reactivity: Modifications of the acoustic startle pattern.* PHARMACOL BIOCHEM BEHAV **19**(3) 527–534, 1983.—The effects of harmaline, an indoleamine and a MAOI, were tested on the acoustic startle pattern. EMG measures of the startle reflex, the pinna reflex as well as the characters of the vertex evoked responses to brief intense tone bursts (60 msec, 110 dB, 8000 Hz) were simultaneously studied in 4 alert guinea-pigs. The basic experimental design was a 4 by 4 latin square, with the treatments being given at 2 day intervals. The four harmaline-HCl treatments were isotonic saline, 0.25, 5.0, and 10.0 mg/kg. Compared with saline baselines, all the doses resulted, throughout the 60 min session, in overall high significant depressions of the startle reflex, the pinna reflex and the initial wave of the acoustic evoked potential at the vertex. In contrast, harmaline had little or no influence on amplitude and latency of the late wave of the vertex response. The effects of harmaline on the general behavior of the guinea-pig are also reported. These results may support an involvement of serotonergic systems in the modulation of the sensory-motor reactivity at the brainstem level. Nevertheless , the probably more complex cortical processes involved in startle responsivity do not appear univocally affected by the indoleamine drugs such as harmaline.

Harmaline Acoustic startle reflex Acoustic pinna reflex Vertex potentials Guinea-pig
Sensory-motor reactivity Indoleamine hallucinogens

INDOLEAMINE hallucinogens have biphasic dose-response effects on sensory-motor reactivity [9]. Low doses of LSD, psilocybin or DMT produce an increase in acoustic startle reflex, whereas high doses depress startle [9–12]. The indoleamine compound Harmaline (H) induces auditory and visual hallucinations [34]. Some behavioral and electrographic studies [5, 15, 19, 39, 46] have already been carried out on animals to elucidate mechanisms of H-induced hallucinations, but the sensory-motor reactivity does not seem to have been systematically examined after H administration. The main purpose of this study was to explore the H effects on acoustic startle. If H acted as other indole-related drugs, the same dose-dependent biphasic effects should be expected. However, H is also a reversible monoamine oxydase inhibitor (MAOI) [17,41]; it is therefore conceivable that the drug could act in the same way as the MAOI pargyline which is known to markedly decrease acoustic startle [9]. In both cases, an involvement of the serotonergic (5-HT) systems in the modulation of the sensory-motor reactivity can be suggested on the basis of the inhibitory effects of indole hallucinogens and MAOI on the 5-HT neurons in the raphe: LSD [1–3, 44], pargyline [2], harmaline [49]. This view is consistent with reports that the behavioral actions of LSD [9,43] and H [26,42] are mediated, at least in part, by the 5-HT system. However, dissociations between the effects of hallucinogenic drugs on behavior and 5-HT raphe unit activity have been observed [44].

In the neuropharmacological literature [9], findings concerning acoustic startle reactions are predominantly obtained, in the rat, from measures of the whole body motor response (jump), the main overt element of the startle pattern [20,29]. In this work, we describe a method for studying the startle pattern in chronic animals by recording simultaneously the head jerk, the pinna reflex (or Preyer reflex), [7, 13, 18, 20] and the startle-related vertex potentials [24, 25, 27]. Guinea-pigs are used because of their exagerated tendency to startle in response to acoustic stimuli [7,33]. Moreover, characteristics of the startle and pinna reflexes [13, 18, 33] and the auditory potentials [14, 21, 25] are well known in the guinea-pig.

The main effects of H on the startle pattern are compared to the H-induced alterations of the EEG [15, 19, 39, 46] and referred to the tremorogenic actions of the harmala-alkaloids [5, 28, 42, 46, 48].

METHOD

Surgical Procedure

At least 3 days before the experiment proper, electrodes were implanted in naive male guinea-pigs (500–600 g) under Thiopental anaesthesia (IP: 40 mg/kg). Two silver wire electrodes (0.2 mm in diameter) insulated up to tip were placed epidurally to record the vertex response [24,25]. Extradural electrodes (stainless steel screws) were also fixed for EEG recordings. Pairs of multi-stranded teflon insulated wires (0.5 mm in diameter) were inserted in nuchal and auricular muscles.

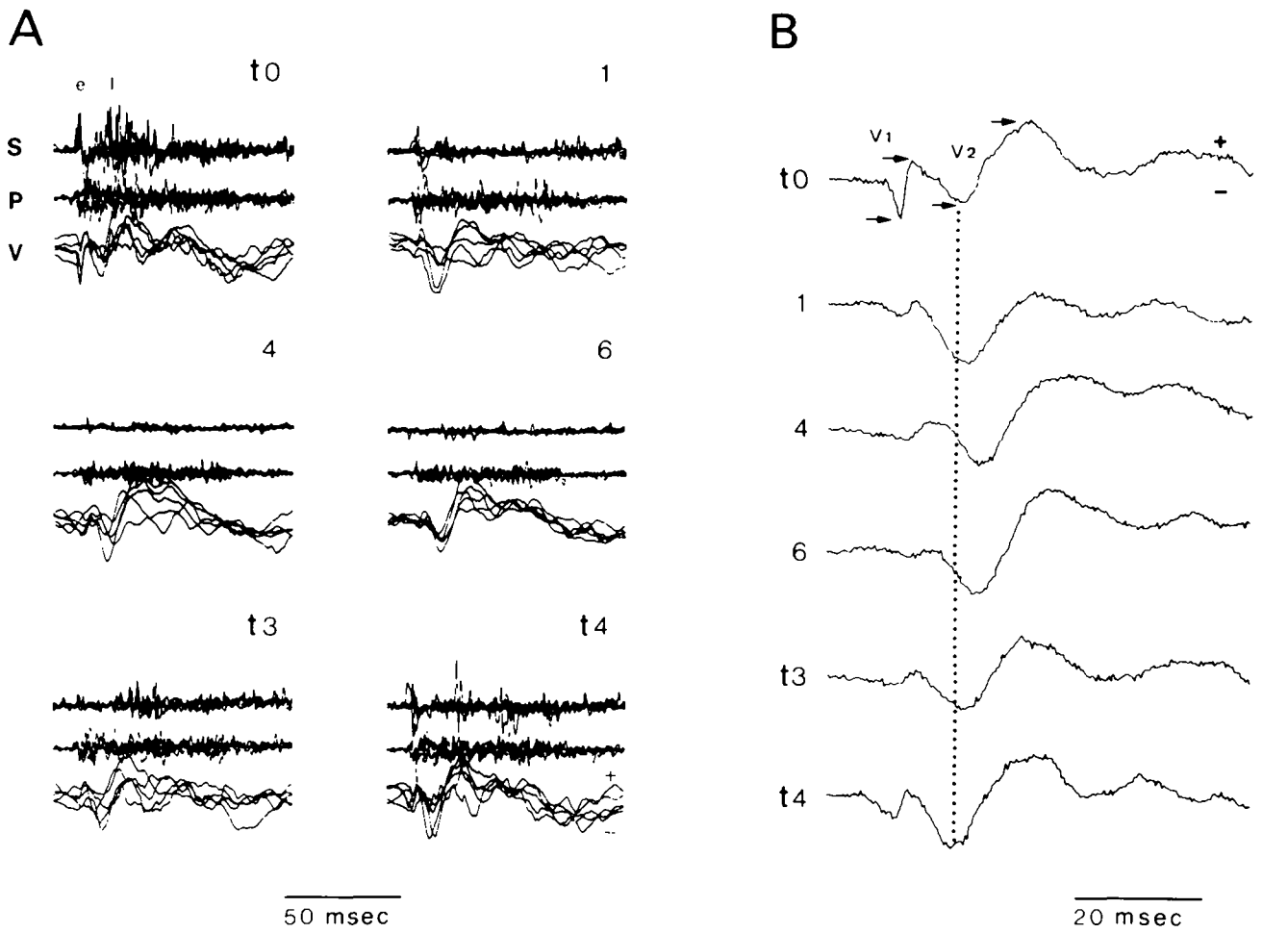

FIG. 1. Typical alterations in acoustic startle pattern produced by harmaline in guinea-pig. A. Electrographic tracings: Electromyography of the body startle (S) recorded in the nuchal muscles. Electromyography of the pinna reflex (P, Preyer reflex) recorded in the auricular muscles. Auditory evoked responses recorded from the vertex (V). Awake unrestrained guinea-pig. The sound-burst (60 msec, 8000 Hz, 110 dB) stimulus occurs at trace onset. Recordings t0, 1, 4, 6, t3, t4: simultaneous S, P, V electrographic CRO tracings of the responses to 5 successive stimulations (60 sec ISI) which constitute a block of trials. These recordings were obtained during the same test session under identical stimulation and amplification procedures. t0: control block before harmaline injection (10 mg/kg IM): 1: first block, 10 min after injection. 4: 4th block, 40 min after harmaline injection: 6: 6th block, 60 min after injection. t3: block 3 hours after the beginning of the session. t4: block at the end of the session, after 4 hours. Note in 4–6 the disappearance of the early (e) component and the late (l) component of the startle response and a marked depression of the pinna reflex. Concerning the vertex potential alterations, see Fig. 1B for details. B. Sequence of auditory evoked potentials recorded from the vertex during the same harmaline session (10 mg/kg IM): Vertex potentials (V) averaged from Fig. 1A. The stimulus onset occurs at the beginning of each trace, and negativity is in the downward direction. Each recording is the average (CAT 400) of the 5 responses during a block. Same blocks as in Fig. 1A: the upper trace (t0) shows the initial (V1) and late (V2) vertex potentials taken before harmaline, and tracings 1-4-6-t3-t4 show the vertex responses taken 10, 40, 60 min, 3 and 4 hours after the injection. Note that the early negative wave (V1), virtually disappears within the 20 min after the drug injection and remains diminished for more than three hours. On the opposite, the late wave (V2) does not present clear change in amplitude under harmaline. The peak latency of the V2 wave is slightly increased (15–20%) after 40–60 min. Recovery occurs after 4 hours for both waves.

Apparatus

During the testing, the animals were restrained in a small wire mesh cage. EEG and EMG were continuously monitored on a polygraph and recorded on tape. The EMG responses and the vertex potentials were, moreover, displayed on a storage CRO. The vertex potential was fed into a Mnemotron CAT 400 and written out on an X-Y plotter.

The cage was enclosed in a sound-attenuated observation box. The animal's head was at 30 cm from a loudspeaker. Startle stimuli were brief intense tone bursts (60 msec, 110 dB-RMS, 8000 Hz). Throughout the testing, a steady white noise (85 dB-RMS) was maintained in order to obtain sensitization [9].

Experimental Design and Testing

The four animals were given four sessions. The basic design was a 4 by 4 latin square with the treatments being given at least at intersession intervals of two days. The four treatments were: isotonic saline (placebo session), 2.5, 5.0 or 10 mg/kg harmaline-HCl (experimental sessions).

At the beginning of a test session (Fig. 2), each guinea-pig was allowed 10 min of adaptation in white noise before re-

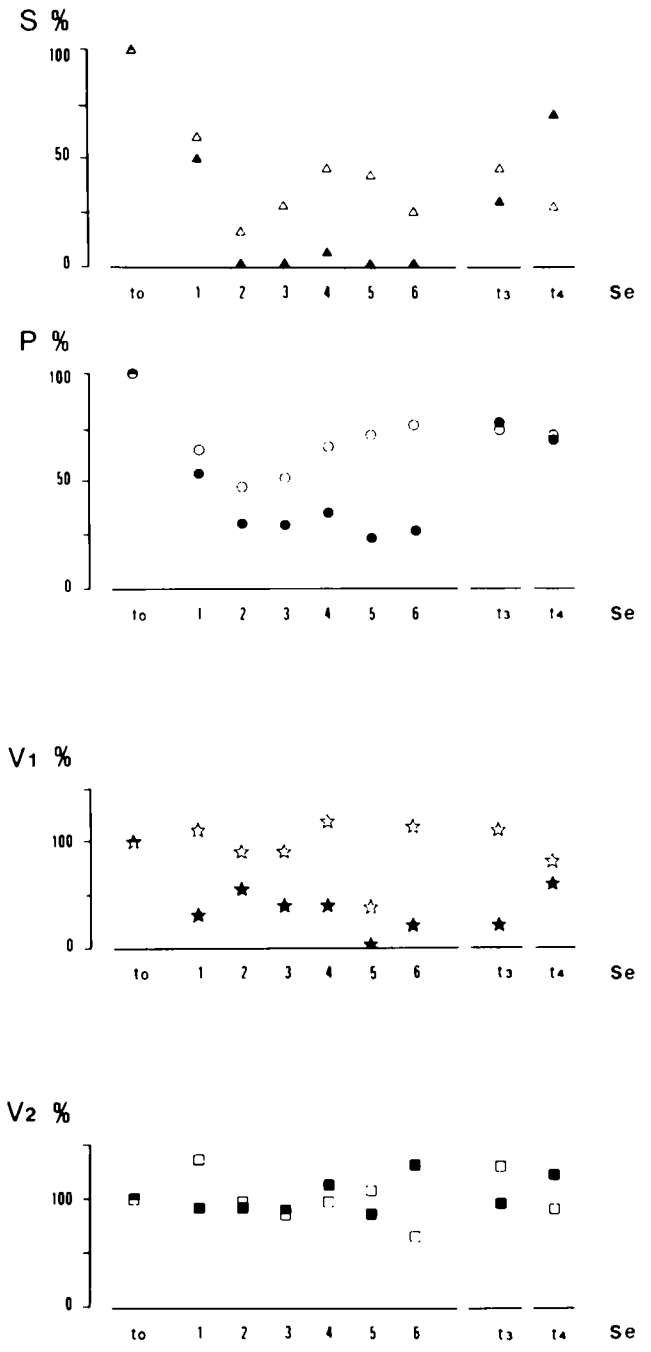

FIG. 2. Example of quantitative changes in amplitude of the startle reflex (S), the pinna reflex (P) and the vertex potentials (V1, V2) after harmaline administration. The four graphs are constructed with data obtained from a typical guinea-pig; the electrographic records can be seen in Fig. 1. As in Fig. 1, the control saline session (open symbols) was the last one, and it occurred eight days after the 10 mg/kg harmaline session (solid symbols) which was the first one. Abscissa represent the session (Se) which consisted of a control block (t0) of five trials (60 sec ISI), six post-injection test blocks of five trials each (60 min period), two recovery blocks after three and four hours (t3, t4). The ordinates are mean percentage of response amplitude of the four indexes of reactivity (S, P, V1, V2) obtained for the two conditions. For each test and recovery blocks, the mean responses are plotted as the percentage of the average response amplitude recorded for the control block.

ceiving the first control block (t0 in Figs. 1, 2) of 5 startle stimulations with a 60 sec ISI. The animal was then immediately IM injected and, after 10 min presented with six 5-stimulation blocks with a 60 sec ISI (1–6 in Fig. 2) and a five min interval between blocks. Recuperation was tested 3 hours (t3) and 4 hours (t4) after H-administration.

Data Analysis

Latencies and morphological characteristics of the components of each startle response were determined from the CRO photographs of the 5-stimulation blocks (Fig. 1A). The head-jerk response and the pinna response were quantified by measuring in millimetric units the magnitude of pen deflection on the head and ear EMG records: i.e., the maximum amplitude of the early responses (e) with a peak latency of 10–15 msec (Fig. 1A, S and P). The amplitudes of the two main waves of the auditory vertex response (Fig. 1B, V1 and V2) were measured from the average evoked potentials of each block of 5 stimulations. Startle and vertex response amplitudes of test trials (1 to 6) were calculated for each animals, and at each session, as a percentage of the average amplitude of the five responses obtained before drug or saline injection (t0).

RESULTS

The Acoustic Startle Pattern

The startle reflex (S) and the pinna reflex (P). Before drug administration (t0) the animals presented a widespread muscular reaction to the loud sound. This response was similar to that classically described in the white rat [20] and in the guinea-pig [7,13]: lifting of the head, twitching of the ears, jumping of the whole body, and secondary crouching posture. The EMG records from the nuchal and auricular muscles showed two components (Fig. 1A, S and P): a first sharp increase in activity with a latency of 10 msec from the stimulus onset, and with a duration of about 10 msec. This early response (e, in Fig. 1A), the startle reaction proper, was followed by a late (l, in Fig. 1A) response, the orienting reaction, lasting 50–100 msec. The present work is only concerned with the brief, short latency nuchal and ear responses. The head jerk can be considered as the main element of the body response and is herein referred to as startle reflex (S). The clonic movement of the ears is referred to as the pinna reflex (P).

The startle-related potentials at the vertex (V). In the absence of drug, the vertex electrode yielded in the four animals a relatively constant, reproducible response consisting in 2 main waves (Fig. 1 A–B, t0). An initial vertex-negative wave (V1) with a latency of 8–10 msec, and a peak amplitude of 50–100 microV at 10–12 msec, was followed by a biphasic negative-positive wave (V2) which occurred in a latency range of 15–20 msec, with a maximal negative deflection at about 20–25 msec, and which showed large amplitude fluctuations. A peak to peak measurement was made on the negative-positive secondary wave in order to quantify V2 (Fig. 1, B–t0). The maximal amplitude of the initial vertex wave, with respect to the anterior baseline, was used for quantitative analysis.

The Effects of Harmaline on the Startle Pattern

Depression of the startle reflex. Figure 3-S presents the mean amplitude of the startle response, following injection of H (solid triangles) or saline (open triangles), over six blocks

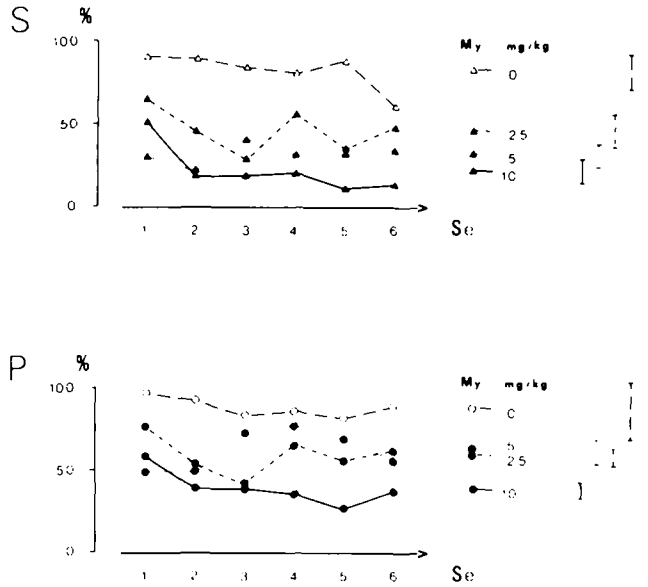

FIG. 3. Time course of depression of the startle reflex (S) and the pinna reflex (P) under harmaline. The mean amplitude variations of the startle response (S) and the pinna response (P) are illustrated over the six test blocks of five trials each (60 min overall duration), after injection of either 2.5, 5, 10 mg/kg of harmaline (solid symbols) or saline (open symbols). The treatment was based on four guinea-pigs which were tested under each of the three different doses and saline, by means of a latin square design. Abscissa: six test blocks (1–6) of the harmaline or placebo sessions (Se). Ordinates: mean response amplitudes expressed as percentages (%) of the baseline startle or pinna responses. Each point on the curves represents the mean value of 20 measures of the startle or pinna responses corresponding to the application of a test block (5 stimulations) on the 4 animals. Mean values of each curve are given with ±SEM on the right of the panels (My, N=120).

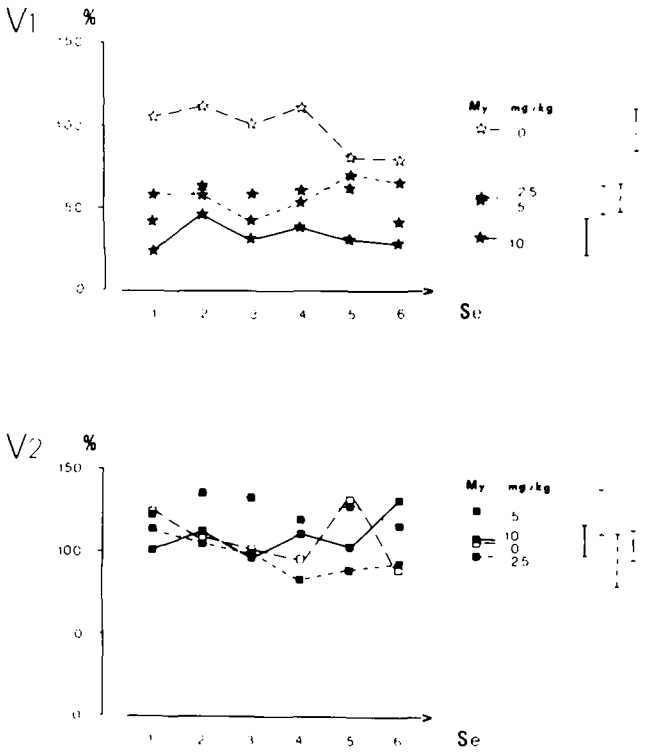

FIG. 4. Time course of variations in the initial wave (V1) and the late wave (V2) of the auditory vertex potential under harmaline. The upper graph represents the mean amplitude V1 response, the lower graph represents the mean ampitude V2 response over six blocks of five trials each after injection of either 2.5, 5, 10 mg/kg harmaline (solid symbols) or saline (open symbols). Legend is same as in Fig. 3.

(1–6) of five trials each. All treatments resulted in a substantial startle size decrease during the 6 successive 10 min periods of the sessions (Se). An analysis of variance performed on these pooled data indicated that the treatment effect was significant, $F(3,9)=6.78$; $p<0.02$. Compared to control trials, H doses of 2.5, 5 and 10 mg/kg depressed the startle size in 53, 68 and 78% respectively. Over the placebo sessions, repetitive stimulus exposure resulted in a relatively light habituation as witnessed by the about 20% decrease in startle mean amplitude (Fig. 3, upper curve). A significant decrement within placebo-session (60%) occurred in only one animal (Fig. 2, S, open triangles).

All doses of H significantly decrease the startle amplitudes (sign test, [40]), as compared with those of the saline controls ($p<0.001$). Moreover, the startle amplitude was also significantly depressed ($p<0.003$) when the dose was increased from 2.5 to 10 mg/kg. However, comparisons of the amplitude decreases did not statistically differ ($p<0.08$) between the 2.5–5 mg/kg groups and between the 5–10 mg/kg groups. Therefore, only a crude dose-related depression of startle could be assessed. The analysis of variance revealed that the drug × trials interaction was not statistically significant. It means, for the 3 doses, a very rapid onset of the depressive effect—about 10 min after H injection—; this effect outlasted one hour. With doses of 5 or 10 mg/kg a total inhibition of the startle (and of the orienting reaction) may occur in the 2–6 blocks (Fig. 2).

Depression of the pinna reflex. Figure 3-P shows the mean amplitude of the pinna response over the 60 min after injection of saline (open circles) or various doses of H (solid circles). Figures 1 and 2 present the data from one guinea-pig under placebo and 10 mg/kg of H. The analysis of variance made on the pooled data indicated a reliable drug depressant effect, $F(3,9)=7.98$; $p<0.01$. Relatively to control trials, H at 2.5, 5.0 and 10 mg/kg depressed the pinna reflex 42, 39 and 61%, respectively (Fig. 3). The depression occurred in all the subjects with a mean amplitude reduction of 50%, except for one guinea-pig which presented but a 30% reduction of control size. The habituation process could only account for a small fraction of the overall reduction of the pinna reflex because the mean placebo-session decrement was about 10% of the pretreatment baseline (Fig. 3, upper curve).

All the doses of H significantly decreased the pinna reflex amplitude as compared with the saline controls: at the 10 mg/kg and 2.5 mg/kg doses the overall harmaline-saline differences were highly reliable (sign test; $p<0.001$); with the 5 mg/kg dose a smaller but reliable difference could be noted ($p<0.01$). Comparisons of the reflex amplitude decreases between the 2.5–5 mg/kg groups did not differ statistically (Fig. 3). However, the pinna reflex size decreased significantly ($p<0.001$) when the doses were increased from 2.5–5 mg/kg to 10 mg/kg. Just like the startle reflex depression, the H-induced depression of the pinna reflex was, therefore, imperfectly dose-related.

TABLE 1

EFFECTS OF THE DIFFERENT DOSES OF HARMALINE ON THE STARTLE PATTERN AND ON GENERAL BEHAVIOR IN GUINEA-PIG

Behavioral Indexes/ Injected doses	Saline	Low dose of harmaline (2.5 mg/kg)	Moderate dose of harmaline (5.0 mg/kg)	High dose of harmaline (10 mg/kg)
Startle reflex	baseline	55% decrease	70% decrease	80% decrease
Pinna reflex	baseline	40% decrease	40% decrease	60% decrease
Vertex potentials: V1 wave	baseline	40% decrease	45% decrease	70% decrease
Vertex potentials: V2 wave	baseline	no effect	NS increase	no effect
Head tremor at 10–12 Hz	—	none	Intention tremor only	Intention and resting tremor
Arousal level	drowsiness	drowsiness and quiet wakefulness	quiet wakefulness and active wakefulness	Active wakefulness only
Motor activity	scarce	scarce	small increase	clear increase followed by catatonic postures
Hallucinatory-like behavior	—	not visible	not visible	not visible

At all the doses used, H produced an almost immediate (10 min after injection) decrease in the pinna reflex size which persisted during the 60 min sessions. An overall variance analysis, using drugs and trial as within-subjects factors did not show any significant drug × test-time interaction, $F(15,45)=1.76$; $p<0.10$). The pinna reflex returned to saline baseline within 3 hours, i.e., faster than the recovery of the startle reflex (Figs. 1, 2). Another difference with the startle reflex is that H did not completely suppress the pinna response, even at the maximal dose, whatever the test-time (Fig. 2) or the subject.

Harmaline effects on the vertex responses. (1) The initial component (V1): The three doses of H produce a consistant and sustained decrease in the V1 wave size (Fig. 4). The overall effect of the drug treatment was highly significant, $F(3,9)=17.21$; $p<0.001$). At 10 mg/kg the V1 component may completely disappear during periods of maximal depressions of the startle reflex and pinna reflex (Fig. 1B). Figure 4-V1 shows the dose-response curves, expressed as the mean percentage changes from the pre-injection baseline, during the 60 min post-injection period, for the three H doses (solid stars) and saline (open stars). H at 2.5, 5.0 and 10 mg/kg depressed V1 wave 42, 45, 67% respectively.

The three doses of H significantly decreased the V1 amplitude as compared with the saline controls (sign test, $p<0.001$). The V1 amplitude was moreover reliably depressed ($p<0.001$) when the doses were increased from 2.5–5.0 mg/kg to 10 mg/kg, but no significant differences were observed in the comparisons between the effects of the low and moderate doses (Fig. 4). The lack of significant dose × post-time interaction reflected the fact that 10 min after injection H clearly depressed V1 wave even with the lower dose. One hour later the depressant effect was still noted. We never observed apparent V1-peak latency variations.

(2) The late component (V2): Concerning the second biphasic wave of the vertex potential (Figs. 1B, 2-V2, 4-V2), the analysis of variance and the sign test revealed non-significant differences between the four treatments. At the 5 mg/kg dose H seemed to increase the V2 amplitude (26%) but not in a statistically reliable manner. With the maximal dose, a weak increase (10–20%) of the V2 peak latency was noted in three animals (Fig. 1B). The variability of the V2 morphology did not show any relevant change after H administration (Fig. 1A, V).

Harmaline Effects on General Behavior (Table 1).

The guinea-pigs injected with H (2.5 to 10 mg/kg) did not show the behavioral syndromes induced by drugs acting on the brain 5-HT system in mammals [22, 23, 43]. We did not observe the aberrant patterns of behavior which have been proposed as indexes of the hallucinogenic activity of LSD [22,43] or H [46] in cats. Moreover, at the dose levels we used, H did not induce serious neurovegetative disturbances or abnormal EEG hypersynchrony [46]. However, guinea-pigs presented the two typical symptoms [15,46] of H intoxication: increase in arousal—EEG and motor activations—and tremor—nuchal EMG rhythmic activity at 10–12 Hz. Versus saline condition, the low and moderate doses produced a change in arousal level [35] characterized by: a decrease amount of drowsiness and an increase in quiet wakefulness at 2.5 mg/kg; an increase amount of active wakefulness at 5.0 mg/kg. With the 10 mg/kg dose a clear increase in motor activity lasted for about 30 min and then progressively diminished, leading to catatonic-like postures. Sustained tremor was a constant sign at the maximal dose. At moderate dose, tremor was noted in three subjects and was only evident when the animals were moving. A low dose of harmaline had no tremorogenic effect. (Table 1).

DISCUSSION

Harmaline Effects on the EMG Components of the Startle Pattern

The Startle Reflex. Experimental data [9] suggest that the 5-HT raphe system exerts a tonic inhibitory action upon sensory-motor reactivity: e.g., 5-HT depletion induces an increase of startle. It is hypothetized [9] that the raphe modulates acoustic startle through a 5-HT postsynaptic inhibition of the pontine reticular formation (PRF) startle circuit [31]. As expected, H depressed startle with the same potency as the other hallucinogenic indoleamines [9–12] when sufficiently high doses are used. As LSD, DMT or Psilocin [9], H should act like 5-HT agonist on the postsynaptic receptor sites in the startle circuit. Yet, a direct depression of firing in PRF after H administration is not demonstrated, and H has not been hitherto considered as a specific 5-HT agonist. The only well established biochemical action of H is a MAO inhibition [17] which increases brain level of 5-HT. Therefore, at high (tremorogenic) doses, H probably depresses startle through an increased 5-HT transmission at the brainstem startle circuit, in the same way as the MAOI pargyline [9].

At low doses, hallucinogenic indoles enhances startle [9] by acting preferentially on the presynaptic raphe 5-HT-cells through autoreceptor activation [3]. A decrease in activity of the 5-HT raphe cells, and hence a decreased 5-HT transmission, brings about an increase in activity of their target cells in the startle system through a disinhibitory process [9–12]. This functionally 5-HT like antagonist presynaptic effect is presumed to be overriden by additional postsynaptic actions at high doses. If so, indole hallucinogens have biphasic dose-response effects on sensory-motor reactivity because high doses increase 5-HT transmission, thereby depressing startle, whereas low doses decrease 5-HT transmission and thus potentiate startle. Recently we reported that H markedly decreases the firing of 5-HT neurons in the midbrain raphe when administered systemically in the rat [49]. But, contrary to what was expected from the LSD analogy [10,32] we observed neither a sustained enhancement of startle at reasonably low H doses nor an initial excitation preceding the depressive effect at higher doses. If we admit that the lower dose was really a small one (absence of tremor and EEG modification, except activation), then H did not act on startle in the same way as other hallucinogens. In contrast with indoleamine non-MAOI hallucinogens, H may primarily affect the postsynaptic brainstem startle areas. Consequently, high or low doses would involve the same action i.e., MAO inhibition leading to an increase in 5-HT transmission and a decrease in the startle amplitude.

The pinna reflex. This reflex is generally only considered as part of the startle pattern in rodents [13,29]. In the present study, the pinna reflex was shown to have the same latency (10 msec) as the head startle and, therefore, pinna and startle reflexes could be mediated by similar brainstem circuits and different motor paths. Moreover, H alters the pinna reflex in the same direction as the startle reflex proper. However, the drug has more potent actions on the startle reflex (Table 1). Considering the difference in drug sensitivity and also in habituation during the placebo experiments (20% vs. 10%) between the two reactivity tests, we believe that the brainstem circuits, and the neurotransmitter systems which modulate them, might be somewhat different. Pinna reflex could then provide an interesting, easy quantifiable, test for comparative psychopharmacological studies. In this prospect, investigations on the neural substrate of the pinna reflex will be useful.

Harmaline Effects on the Cortical Components of the Acoustic Startle Pattern

In various species including man, it is well established that the nonspecific EEG response recorded near the vertex [4, 24, 25, 36] can be considered as the cortical component of the startle pattern [16, 27, 30, 37, 38]. The late V2 wave studied here has close similarities with the cortical evoked potential described by Kern *et al.* [24,25] in guinea-pigs and proposed as model for the human vertex response. It is therefore puzzling that H, which markedly depressed the EMG component of the startle, has no obvious action on amplitude or latency of the V2 wave, more especially as alterations of the vertex potential amplitude under an indoleamine hallucinogen (Psilocybin) have been previously reported in monkey [4].

According to Buchwald *et al.* [6], the long-latency vertex potentials (20–30 msec) in the cat—presumably similar to our V2 potential in the guinea-pig—would be generated through a diffuse forebrain system receiving "auditory information in parallel from the brainstem, rather than serially from the primary geniculo-cortical pathway." Consequently, we can conclude that H has only a very slight action on the information processing in the unspecific secondary auditory path [36].

In contrast, the transmission in the primary geniculocortical system seems to be preferentially depressed by H, if we admit that the initial component V1 is equivalent to the middle-latency (10±2 msec) vertex wave of Buchwald *et al.* [6] and mainly reflects the auditory cortex primary evoked response [25,47] which is volume-conducted to the vertex (far-field potential).

Previous data [8] suggested that the brainstem startle reflex circuit may receive both auditory afferents from the ascending path, and descending facilitatory specific impulses from the primary acoustic cortex through a collicular relay. We demonstrate in this study that the primary cortical potential drops drastically under H; consequently, the substantial decrease of the startle response could be explained both through a direct depressant action of the drug at the brainstem level and, indirectly, through the suppression of facilitatory influences arising from the acoustic cortex.

To sum up, our results may support an involvement of the 5-HT system in the modulation of the sensory-motor reactivity; nevertheless, the cortical processes underlying the startle responsivity do not appear univocally affected by the indoleamine drugs such as harmaline.

REFERENCES

1. Aghajanian, G. K., W. E. Foote and M. H. Sheard. Action of psychotogenic drugs on single midbrain raphe neurons. *J Pharmacol Exp Therap* **171**: 178–187, 1970.
2. Aghajanian, G. K., A. W. Graham and M. H. Sheard. Serotonin containing neurons in brain: depression of firing by monoamine oxydase inhibitors. *Science* **169**: 1100–1102, 1970.
3. Aghajanian, G. K. and R. Y. Wang. Physiology and pharmacology of central serotonergic neurons. In: *Psychopharmacology, a Generation of Progress*, edited by M. A. Lipton, A. Di Mascio and K. F. Killam. New York: Raven Press, 1978.

4. Bermont, F. and J. Bert. Etude des effets électrophysiologiques de la psilocybine chez un cercopithecinae, papio papio. *Electroencephalogr Clin Neurophysiol* **27:** 48–56, 1969.
5. Brailowsky, S., S. Walter, G. Vuillon-Cacciuttolo and T. Serbanescu. Alcaloïdes indoliques induisant ou non un tremblement: effets sur l'épilepsie photosensible du papio papio. *C R Seanc Soc Biol (Paris)* **169:** 1190–1193, 1975.
6. Buchwald, J. S., C. Hinman, R. J. Norman , C.-M. Huang and K. A. Brown. Middle- and long-latency auditory evoked responses recorded from the vertex of normal and chronically lesioned cats. *Brain Res* **205:** 91–109, 1981.
7. Burham, R. W. Repeated auditory stimulation of the startle response in the guinea-pig. *J Psychol* **7:** 79–89, 1939.
8. Buser, P., J. St. Laurent and Ch. Menini. Intervention du colliculus inférieur dans l'élaboration et le contrôle cortical spécifique des décharges cloniques au son chez le chat sous chloralose. *Exp Brain Res* **1:** 102–126, 1966.
9. Davis, M. Neurochemical modulation of sensory-motor reactivity: acoustic and tactile startle reflexes. *Neurosci Biobehav Rev* **4:** 241–263, 1980.
10. Davis, M. and M. H. Sheard. Effects of lysergic acid diethylamide (LSD) on habituation and sensitization of the startle response in the rat. *Pharmacol Biochem Behav* **2:** 675–683, 1974.
11. Davis, M. and M. H. Sheard. Biphasic dose-response effects of N-N-dimethyltryptamine on the rat startle reflex. *Pharmacol Biochem Behav* **2:** 827–829, 1974.
12. Davis, M. and J. K. Walters. Psilocybin: biphasic dose-response effects on the acoustic startle reflex in the rat. *Pharmacol Biochem Behav* **6:** 427–431, 1977.
13. Dodge, R. and C. M. Louttit. Modification of the pattern of the guinea-pig's reflex response to noise. *J Comp Psychol* **6:** 267–285, 1926.
14. Dum, N., V. Schmidt and H. Von Wedel. Scalp distribution of the auditory evoked brainstem potentials in the guinea-pig during monaural and binaural stimulation. *Hearing Res* **5:** 271–284, 1981.
15. Fuentes, J. A. and V. G. Longo. An investigation on the central effects of harmine, harmaline and related B-carbolines. *Neuropharmacology* **10:** 15–23, 1971.
16. Gastaut, Y. Les pointes négatives évoquées sur le vertex. Leur signification psychophysiologique et pathologique. *Rev Neurol* **89:** 382–399, 1953.
17. Gerardy, J. La monoamine-oxydase et son inhibition. *J Pharm Belg* **35:** 133–142, 1980.
18. Gerstner, H. Die Schallstärkeschwelle des Preyerschen Ohrmuschel-reflexes als quantitatives Hörprüfverfahren am Meerschweinchen. *Pflugers Arch* **246:** 265–273, 1942.
19. Himwich, H. E., W. G. Van Meter and H. F. Owens. An EEG analysis of psychotomimetic drugs. In: *Neuropsychopharmacology*, edited by P. B. Bradley and P. Deniker. New York: Elsevier, 1959, pp. 329–333.
20. Horlington, M. A method for measuring acoustic startle response latency and magnitude in rats: detection of a single stimulus effect using latency measurements. *Physiol Behav* **3:** 839–844, 1968.
21. Huang, C.-M. A comparative study of the brainstem auditory response in mammals. *Brain Res* **184:** 215–219, 1980.
22. Jacobs, B. L. An animal behavior model for studying central serotonergic synapses. *Life Sci* **19:** 777–786, 1976.
23. Jacobs, B. L., M. E. Trulson and W. C. Stern. Behavioral effects of LSD in the cat: proposal of an animal behavior model for studying the actions of hallucinogenic drugs. *Brain Res* **132:** 301–314, 1977.
24. Kern, E. B., D. Thane, R. Cody and R. G. Bickford. Neurogenic components of the averaged response evoked by clicks in guinea-pigs. *Mayo Clin Proc* **44:** 886–899, 1969.
25. Kern, E. B., D. Thane, R. Cody and R. G. Bickford. Vertex-response thresholds to pure tones in guinea-pigs. *Arch Otolaryngol* **90:** 315–325, 1969.
26. Kim, J. S., R. Hassler, M. Kurokawa and I. J. Bak. Abnormal movements and rigidity induced by harmaline in relation to striatal acetylcholine, serotonin, and dopamine. *Exp Neurol* **29:** 189–200, 1970.
27. Klingberg, F. and L. Pickenhain. Veranderungen des ECG, der kortikalen hervorgerüfenen Potentiale und der Startle-Reaktionen bei Ratten wahrend der Ausarbeitung eines bedingten Fluchtreflexes. *Acta Biol Med Ger* **12:** 552–567, 1964.
28. Lamarre, Y., C. de Montigny, M. Dumont and M. Weiss. Harmaline-induced rhythmic activity of cerebellar and lower brainstem neurons. *Brain Res* **32:** 246–250, 1971.
29. Landis, C. and W. A. Hunt. *The Startle Pattern*. New York: Farrar and Rinehart, 1939.
30. Larsson, L.-E. Sensitization of the startle blink and non-specific electroencephalographic response. *Electroencephalogr Clin Neurophysiol* **12:** 727–733, 1960.
31. Leitner, D. S., A. S. Powers and H. S. Hoffman. The neural substrate of the startle response. *Physiol Behav* **25:** 291–297, 1980.
32. Miliaressis, T. E. and J. St. Laurent. Effets de l'amide de l'acide lysergique-25 sur la réaction de sursaut chez le rat. *Can J Physiol Pharmacol* **52:** 126–129, 1974.
33. Miller, J. D. and F. S. Murray. Guinea-pig's immobility response to sound: threshold and habituation. *J Comp Physiol Psychol* **61:** 227–233, 1966.
34. Naranjo, P. N. Psychotropic properties of the harmala alkaloids. In: *Ethnopharmacologic Search for Psychoactive Drugs*, edited by D. H. Efron, B. Holmstedt and N. S. Kline. New York: Raven Press, 1979.
35. Pellet, J. Etude électropolygraphique et comportementale des états de veille et de sommeil chez le cobaye (cavia porcellus). *C R Seanc Biol (Paris)* **160:** 1476–1482, 1966.
36. Picton, T. W. and S. A. Hillyard. Human auditory evoked potentials. II. Effects of attention. *Electroencephalogr Clin Neurophysiol* **36:** 191–199, 1974.
37. Sakano, N. and L. Pickenhain. Relationship between the auditory evoked cortical response and the startle reflex in man. *Physiol Behav* **1:** 215–217, 1966.
38. Sakano, N. and L. Pickenhain. Evoked response and startle blink to strong acoustic stimuli of different signal meaning. *Psychophysiology* **5:** 1–14, 1968.
39. Schmitt, H. Action de l'harmine et de l'harmaline sur l'électroencéphalogramme du lapin. *Arch Int Pharmacodyn Ther* **162:** 84–92, 1966.
40. Siegel, S. *Nonparametric Statistics for the Behavioral Sciences*. New York: McGraw-Hill, 1956.
41. Singh, P., L. J. Poirier and R. Boucher. Effect of monoamine oxidase inhibitors on the concentrations of dopamine and serotonin in the striatum of the cat with and without unilateral brainstem lesions. *Can J Physiol Pharmacol* **45:** 897–904, 1967.
42. Sjölund, B., A. Björklund and L. Wiklund. The indolaminergic innervation of the inferior olive. 2. Relation to harmaline induced tremor. *Brain Res* **131:** 23–37, 1977.
43. Sloviter, R. S., E. G. Drust, B. P. Damiano and J. D. Connor. A common mechanism for lysergic acid, indolealkylamine and phenethylamine hallucinogens: serotonergic and mediation of behavioral effects in rats. *J Pharmacol Exp Ther* **214:** 231–238, 1980.
44. Trulson, M. E., J. Heym and B. L. Jacobs. Dissociations between the effects of hallucinogenic drugs on behavior and raphe unit activity in freely moving cats. *Brain Res* **215:** 275–293, 1981.
45. Vergnes, M. and E. Kempf. Tryptophan deprivation: effects on mouse-killing and reactivity in the rat. *Pharmacol Biochem Behav* **14:** Suppl 1, 19–23, 1981.
46. Villablanca, J. and F. Riobo. Electroencephalographic and behavioral effects of harmaline in intact cats and in cats with chronic mesencephalic transection. *Psychopharmacologia* **17:** 302–313, 1970.
47. Walloch, R. A. Cortical evoked potentials recorded from the guinea-pig without averaging. *Acta Otolaryngol* **80:** 7–12, 1975.

48. Weiss, M. Influence du système olivo-cérébello-bulbaire sur les neurones moteurs de la moelle lombaire chez le chat après administration d'harmaline. *Arch Ital Biol* **116:** 1–15, 1978.

49. Weiss, M. and J. Pellet. Raphe-cerebellum interactions. I. Effects of cerebellar stimulation and of harmaline administration on single unit activity of midbrain raphe neurons in the rat. *Exp Brain Res* **48:** 163–170, 1982.