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Mescaline Increases Startle Responding Equally in Normal and Raphe-Lesioned Rats[1]

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GEYER, M. A., G. J. ROSE AND L. R. PETERSEN. *Mescaline increases startle responding equally in normal and raphe-lesioned rats.* PHARMAC. BIOCHEM. BEHAV. **10**(2) 293–298, 1979.—To test the possible involvement of serotonin-containing cells of the midbrain in mediating the effects of mescaline on startle responding, electrolytic lesions were made in either the dorsal or median raphe nucleus in rats. Decreases in either striatal or hippocampal tryptophan hydroxylase activity confirmed the effectiveness of the lesions. One week later, startle was measured in response to 30 air-puff stimuli for each rat. Median, but not dorsal, raphe lesions increased startle magnitudes throughout the test session. The following day each group was divided into matched halves and were given 60 trials, 30 minutes after intraperitoneal injection of either saline or 10 mg/kg mescaline. Despite the large differences in baseline startle among the groups, mescaline produced comparable 25% increases in startle magnitudes in both sham- and raphe-lesioned animals. This result fails to support the hypothesis that increased startle responding produced by mescaline is mediated by the midbrain raphe nuclei.

Startle Mescaline Serotonin Raphe nuclei Lesions Tryptophan hydroxylase

SEVERAL lines of evidence suggest that central serotonergic systems may play an important role in mediating some of the behavioral effects of hallucinogens such as lysergic acid diethylamide (LSD) or mescaline. These compounds are known to reduce the rate of turnover of brain serotonin [9] and to inhibit competitively the high affinity binding of serotonin in brain homogenates [7,8]. Given systemically, LSD, mescaline, and related compounds specifically inhibit the firing of serotonergic cells in the midbrain raphe nuclei [1]. The observations that hallucinogens still inhibit raphe firing after transection of the ascending pathways [23], and that either LSD or serotonin inhibits firing when applied iontophoretically to the raphe cells led to the suggestion that some hallucinogens may have a direct action on the somata or dendrites of raphe neurons [24]. More recent findings indicate that this cell body autoreceptor effect may predominate at relatively low doses and be overridden at higher doses by the additional effect of the indoleamine hallucinogens as serotonergic agonists on the neuron postsynaptic to the raphe system [24].

One behavioral measure that is known to be sensitive to manipulations of serotonin and to hallucinogens is the rat startle response. Serotonin infusions into the lateral ventricles or bilaterally into the hippocampi reduce startle amplitude [16,22], while depletions of brain serotonin by lesions of the raphe nuclei [12,21], parachlorophenylalanine (PCPA) [10,11], para-chloroamphetamine (PCA) [14], tryptophan-free diets (Markham, Rose, and Mandell, unpublished observations) or 5,7-dihydroxytryptamine [6] (Petersen, Rose and Geyer, unpublished observations) increase startle responding. This augmentation of startle following serotonin depletion is now thought to be due primarily to impairment of the mesolimbic serotonergic pathway originating in the median raphe nucleus and projecting to such limbic structures as the hippocampus and septal nuclei [20,21].

A variety of hallucinogens have been shown to augment startle responding at reasonably low doses. We have shown that mescaline (10 mg/kg) or 2,5-dimethoxy-4-methylamphetamine (DOM; 0.5–1.0 mg/kg) increases startle responses to tactile stimuli [16]. Davis and his coworkers have demonstrated that the acoustic startle response is similarly potentiated by LSD at 20–160 μg/kg [13] and psilocybin at 1.0 mg/kg [15]. They have suggested that these effects may be attributable to a direct inhibitory effect of the drugs on the raphe neurons, since higher doses of LSD attenuated the behavioral effects. This attenuation is ascribed to the serotonergic agonist effects that are presumed to predominate at the higher doses. Furthermore, in rats with large lesions of the midbrain raphe nuclei, no LSD-induced increase in startle could be detected above the elevated response level produced by the lesions themselves [13]. Although the relatively small LSD effect may have been masked by the lesion effect, as they acknowledged, this result is at least consistent with the hypothesis that the enhancement of startle responding by hallucinogens is related to their inhibition of raphe unit firing. The present experiment was designed to test this hypothesis further by determining whether the increase in startle responding produced by mescaline is precluded by midbrain raphe lesions.

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Since the enhancement of tactile startle responding is produced by lesions of the median raphe (B8) but not the dorsal raphe (B7) [21], we made selective lesions of B7 or B8 in separate groups of rats and tested them with mescaline or saline eight days later. To determine an appropriate dose of mescaline for this experiment we first conducted a dose-response study in non-lesioned rats.

METHOD

Animals

For the dose-response study, 40 male Sprague-Dawley rats weighing 225–250 g were obtained from Hilltop Laboratories (Scottdale, PA) and housed in groups of five with free access to water and Purina Rat Chow®. For the lesion experiment, 70 similar animals weighing 175–200 g were obtained and housed individually. At the time of behavioral testing, therefore, the groups had comparable weights. Seven days were provided to each group for acclimation to the animal room before behavioral testing or surgery. The animal room was maintained at 25 ± 2°C and kept on a 12/12 hour light-/dark cycle.

Lesion Procedure

Electrolytic lesions (2 mA cathodal current, 12 sec) were made as previously described [20] at the following coordinates [28]: B7, AP 0.1, DV −0.6; L 0; B8, AP 0.1; DV −2.6, L 0. The B8 electrodes were lowered at an angle of 36 degrees from the back, through part of the cerebellum, to avoid damage to B7. Control animals were treated similarly except that the electrodes were stopped 1 mm above the target and no current was applied. Four animals died after surgery, leaving 22 rats in each of the three groups (B7, B8 and control).

Apparatus

Two separate stabilimeter devices were used to measure startle amplitudes. Each stabilimeter consisted of a cylindrical Plexiglas cage 8.2 cm in diameter and adjustable in length, surrounded by a 12.5 × 23.0 × 25.5 cm Plexiglas frame. Within this frame the cage was sandwiched between four rubber cylinders, two located above the cage and two below it. A microphonic transducer, positioned between the bottom of the cage and the frame, detected cage movement. Each stabilimeter was housed in a 29.5 × 39.5 × 55.0 cm sound-attenuated, illuminated, and ventilated box.

Air-puff stimuli, 20 msec in duration, were administered through a 6.2 mm pipe located 10 mm above the center of the cage. The cylindrical shape and adjustable length of the cage assured that the stimulus would strike the animal's back, evoking defensive startle reactions of fairly consistent topography. During the 250 msec interval following stimulus onset, the maximum voltage produced by the microphonic transducer was recorded by a sample-and-hold circuit. This signal was then amplified, digitized (0 to 1999) via an analogue-to-digital converter, and simultaneously recorded on magnetic tape and printed on paper tape.

Procedure

Seven days after arrival (dose-response study) or surgery (lesion study) each animal was brought to the laboratory for an hour prior to being placed in a stabilimeter for baseline testing. After a 5 min warm-up period, 30 air-puff stimuli (37.5 psi) were presented on a 15 sec fixed-interval schedule.

The 40 non-lesioned rats were divided into 4 matched groups of 10 rats each on the basis of each animal's mean startle response amplitude over the 30 baseline trials. The following day each group was injected intraperitoneally (IP) with either isotonic saline (1 ml/kg) or 5, 10, or 20 mg/kg mescaline sulfate. These doses were selected on the basis of previous studies with doses ranging from 2.5 to 40 mg/kg. Thirty minutes after injection each animal was returned to the same stabilimeter for a 5 min warm-up period followed by 60 air-puff stimuli at 15 sec intervals. Pilot studies indicated that mescaline was equally effective in increasing startle when injected from 10 to 45 minutes before testing.

The 66 lesioned rats remaining after surgery were treated similarly. Each lesion group was divided into matched halves of 11 animals each on the basis of their baseline scores and tested the following day 30 min after IP injections of either isotonic saline or 10 mg/kg mescaline sulfate. Thus the test for an interaction between raphe lesions and mescaline was made eight days after surgery. This point in time was selected to allow adequate degeneration of forebrain serotonergic terminals following the lesion, while minimizing time for the development of supersensitivity. The 10 mg/kg dose of mescaline was chosen on the basis of the dose-response study which showed the threshold for a mescaline effect on startle to be about 5 mg/kg and doses of 10 and 20 mg/kg to produce comparable behavioral effects (Fig. 1). This dose is also known to inhibit firing in some raphe neurons reliably [1,23] and is within the typical human dose range [31].

Lesion Verification

Histological and biochemical confirmations of the lesion damage were done as described previously [20]. Briefly, the animals were sacrificed 23 days after surgery; the midbrain was examined histologically with cryostat sections; and the hippocampus and striatum were assayed for soluble tryptophan hydroxylase activity [27]. Tyrosine hydroxylase activity is not affected in any forebrain region by raphe lesions of this type [23].

Statistical Analyses

The enzyme and startle response data were analyzed by one- (lesion or drug) or two- (lesion and drug) factor analysis of variance (ANOVA). Specific comparisons between group means were made with Dunnett's *t*-test [32]. Some of the data were also analysed after combining all the lesioned animals, irrespective of the intended manipulation, by a multivariate correlation analysis using the SPSS statistical program [30].

RESULTS

Startle Responding

Figure 1 presents the results of the dose-response study in non-lesioned animals. Mescaline produced a significant increase in overall startle magnitude, $F(3,36)=3.6$, $p<0.025$. Specific comparisons attributed this effect to the 37% increases in startle produced by the 10 and 20 mg/kg doses, Dunnett's t's $(36,4)=2.8$ and 2.9, $p<0.025$. Higher doses were not tested because hindlimb motor ataxia is noticeable above 25 mg/kg (D. S. Segal, personal communication).

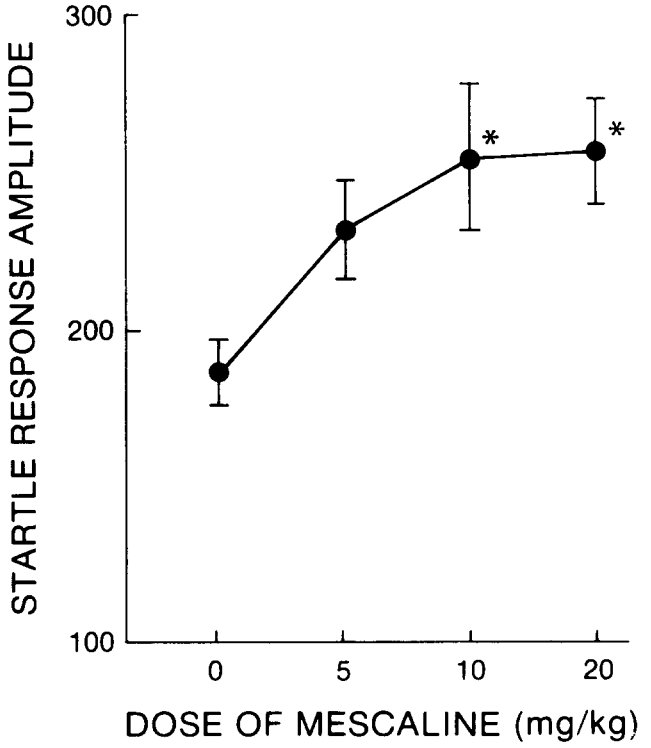

FIG. 1. The startle response amplitude over all 60 trials is presented for non-lesioned animals treated with either isotonic saline or 5, 10, or 20 mg/kg mescaline sulfate. Each point represents the mean ± SEM of 10 animals. *=significantly greater than saline controls by Dunnett's t; $p<0.025$.

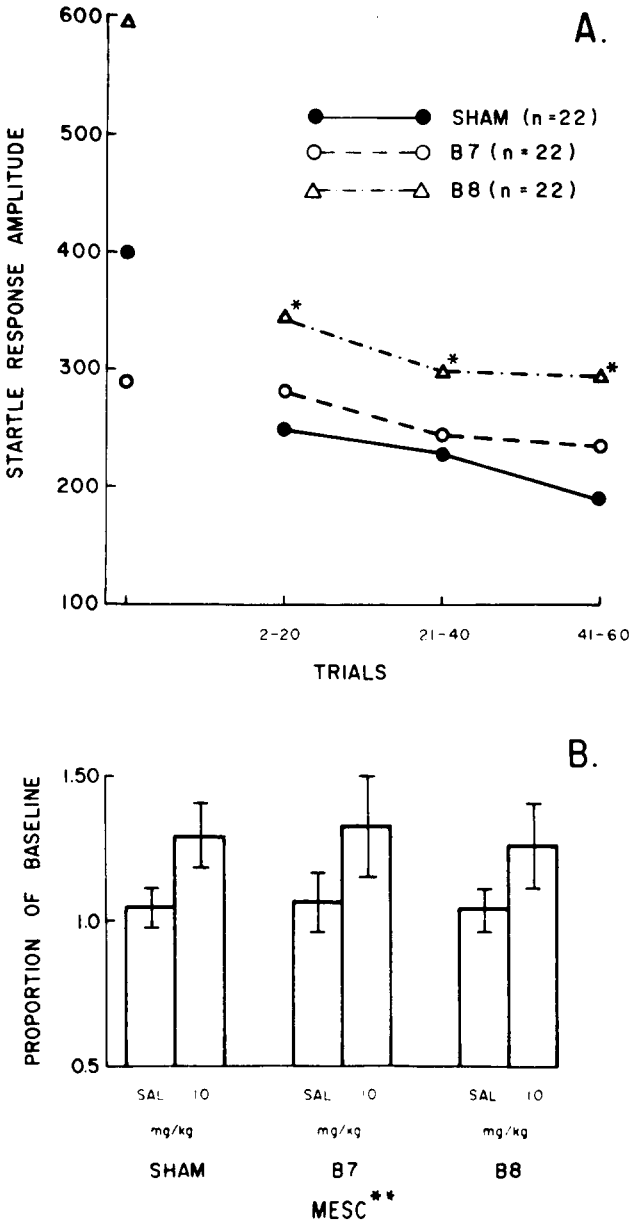

FIG. 2. A: The mean startle response amplitudes for the first response and responses 2 through 20, 21 through 40, and 41 through 60 are shown for sham-, B7-, and B8-lesioned rats. *=significantly greater than control; $p<0.05$. B: Each bar represents the mean ± SEM of 11 animals given either saline or 10 mg/kg mescaline 30 min before testing. The data are expressed as the proportion each rat's averaged startle response on test day was of his averaged response on the baseline (preceding) day. Given saline, all animals responded comparably on the two days. After mescaline a similar 25% increase above baseline was obtained in all three lesion groups, despite the differences between these groups shown in Fig. 2A. **=ANOVA: mescaline significantly greater than saline across all groups for both raw data and the proportion to baseline, $p<0.05$; no significant interaction between lesion and drug was found.

As expected from our previous work [21], median raphe lesions increased startle responding substantially on the baseline day, while dorsal raphe lesions had no significant effect (Fig. 2A). The overall one-way ANOVA showed a significant effect of the lesions on startle response magnitudes over the 30 baseline trials, $F(2,60)=7.7$, $p<0.01$. Specific comparisons indicated that this effect was due to the 44% increase in responding following B8 lesions, Dunnett's t $(60,3)=3.6$, $p<0.001$. Furthermore, a significant correlation coefficient of +0.58 ($N=42$; $p<0.001$) was found between the startle response means and the histologically determined estimates of percent damage to B8, while no such correlation was observed between startle behavior and B7 damage. Similarly, the expected inverse correlation between startle and hippocampal, but not striatal, tryptophan hydroxylase activity was also significant, $r=-0.44$, $N=42$, $p<0.005$.

Figure 2A presents the mean startle response amplitudes in blocks of 20 trials for all three lesion groups on the test day. The overall two-way ANOVA, with lesion and drug as factors, confirmed the B8 lesion-induced increase in startle for each 20-trial block and the initial trial as well, $F(2,60)=4.1$ to 7.2, $p<0.025$. In confirmation of the dose-response study, the injection of mescaline (10 mg/kg) also significantly increased startle responding over all 60 trials, $F(1,60)=4.4$, $p<0.005$ (Fig. 2B). This effect was most marked during the last two blocks of 20 trials, $F(1,60)=6.9$ and 5.6, $p<0.025$.

The purpose of the present experiment was to determine

whether raphe lesions might preclude or affect in some other manner the potentiation of startle produced by mescaline. Given that both mescaline and the lesions resulted in significant increases in startle, the major statistic of interest is the interaction term in the overall ANOVA. No drug-by-lesion interaction was found either for individual trial blocks or the overall means, $F(2,60)=0.5$, $p>0.1$; this result indicates that the effect of mescaline was not altered by raphe lesions. Inspection of Fig. 2B, in which these results are presented as proportions of the baseline scores, reveals that mescaline produced comparable 25% increases in startle responding in each of the lesion groups, when compared either with the matched group of saline-injected rats or with each animal's baseline score. Note also that the response of saline-injected animals was quite similar to their baseline scores.

Histology

Figure 3 shows the typical range of damage to the raphe nuclei following the lesions. In the 22 dorsally lesioned rats the estimated percent damage to B7 [19] ranged from zero (2 animals) to 95% with a mean of 46.6 ± 4.5% (Fig. 3A). For the median raphe lesions, the percent damage to B8 ranged from 20 to 100, with a mean of 62.7 ± 4.6% (Fig. 3B).

Tryptophan Hydroxylase Activity

The depletions in striatal and hippocampal tryptophan hydroxylase activity produced by the B7 and B8 lesions are shown in Table 1. As expected, B7 lesions reduced activity in the striatum without affecting the hippocampus, while B8 lesions primarily reduced hippocampal tryptophan hydroxylase activity. Although the B8 lesions also reduce striatal enzyme activity, this effect was not correlated with the percent damage to B8 (Table 1); rather, it is attributable to the incidental damage to ventromedial B7 caused by the electrode track, (Fig. 3B) [20]

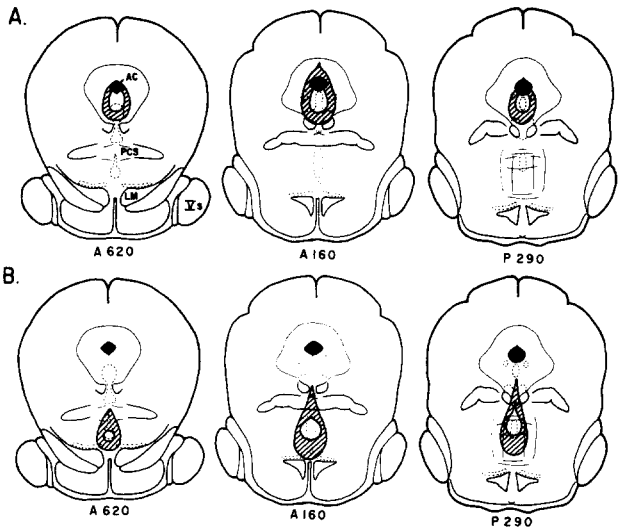

FIG. 3. These drawings show the extent of damage to the raphe nuclei produced by lesions of (A) the dorsal or (B) the median raphe nucleus. The cross-hatched area depicts the maximal damage produced by the largest lesions in each group, while the central area within the cross-hatching depicts the minimal area of damage observed with these lesions. The diagrams are modified from König and Klippel [4]. PCS=superior cerebellar peduncle; LM=medial lemniscus; AC=aqueduct of sylvius; Vs=fifth nerve. The dashed lines represent the most prominent clusters of serotonergic perikarya within the raphe nuclei, as mapped previously [19].

DISCUSSION

Our results suggest that the enhancement of tactile startle responding produced by 10 mg/kg mescaline in rats may not depend on any direct effect mescaline may have on midbrain raphe nuclei. In rats with electrolytic lesions of the serotonergic perikarya in either the dorsal or median raphe and concomitant reductions in tryptophan hydroxylase activities in either the striatum or the hippocampus, mescaline increased startle response magnitudes to the same degree that it did in sham-operated control rats (Fig. 2B). Despite the marked augmentation of tactile startle responding after median but not dorsal raphe lesions, mescaline still produced a further 25% increase in startle magnitude in B8-lesioned animals. It should be noted that this use of percent-of-baseline scores presumes a multiplicative model of behavior, rather than a strictly additive model. In terms of absolute differences, the increase in startle produced by mescaline was considerably larger in B8-lesioned rats than in controls. The results shown in Fig. 2B suggest that mescaline magnified the pre-existing response level to the same extent in all groups, rather than adding a fixed increment in response level to each group. In support of the multiplicative model, a positive correlation of 0.615 ($n=11$; $p<0.05$) was found in the mescaline control group between the baseline scores and the

TABLE 1

FOREBRAIN TRYPTOPHAN HYDROXYLASE ACTIVITIES AFTER RAPHE LESIONS

Region	Dorsal Raphe Lesions				Median Raphe Lesions			
	% Shams*	Correl.†	t‡	$p<$	% Shams	Correl.	t	$p<$
Striatum	52	−0.60	3.9	0.001	63	n.s.	n.s.	
Hippocampus	104	n.s.	3.0	0.01	13	−0.71	7.5	0.001

*Shams averaged 29.8 pmoles/mg protein/30 min in the striatum, $F(2,57)=8.4$, $p<0.01$, and 23.3 pmoles/mg protein 30 min in the hippocampus, $F(2,57)=39.4$, $p<0.001$.

†Pearson's correlation coefficients are shown for the linear correlation between the histological estimates of damage to B7 or B8 and the tryptophan hydroxylase activities. N=60 pairs each.

‡Dunnett's t-score is shown for the difference in enzyme activities between each lesion group and the shams.

increments in startle produced by mescaline. This result is reminiscent of the many reports that the subjective effects of hallucinogens in humans depend primarily on the pre-existing status of the individual [29].

It is conceivable that the raphe neurons remaining after our partial lesions (or the neurons they innervate) had become super-sensitive within the eight days between surgery and testing and that they were thus able to mediate the normal response to mescaline. That the hyperactivity produced by raphe lesions is apparent within 24 hours of surgery and remains for at least one month makes this explanation seem unlikely [25]. Furthermore, a similar experiment with the phenylethylamine hallucinogen, DOM (1.0 mg/kg) three weeks after raphe lesions gave no indication of a potentiated effect of the drug (M. A. Geyer, G. J. Rose and L. R. Petersen, unpublished observations).

An earlier study [13], using large combined lesions of the raphe nuclei and auditory rather than tactile stimuli, suggested that the LSD-induced enhancement of acoustic startle may depend upon an intact raphe system; no further increase in startle was found in raphe-lesioned rats upon administration of LSD. The dramatic augmentation of startle produced by the lesions alone mitigated against any definitive interpretation of their study because of the possibility that a ceiling effect precluded detection of the relatively slight increase normally produced by LSD. Further studies will be required to resolve this question. Unlike mescaline, LSD has no significant effect on tactile startle over the first 60 trials; rather, LSD appears to impair the habituation of tactile startle when the test is extended to 240 trials so that appreciable habituation is evident in controls [19].

Another consideration is that combined lesions of both midbrain raphe nuclei such as were used by Davis and Sheard[13], may be required to preclude the effects of hallucinogens on startle. Electrophysiological studies have suggested that phenylethylamine hallucinogens inhibit dorsal but not median raphe neurons while indoleamine hallucinogens inhibit all raphe neurons [1]. Yet the effects of phenylethylamines on startle are more similar to the effects of median than dorsal raphe lesions. However, recent studies using quantitative cytofluorimetric measures of intracellular serotonin levels [18] in which the identity of the scattered serotonergic cells of B8 can be verified histochemically, demonstrate that indoleamine and phenylethylamine hallucinogens affect B7 and B8 neurons similarly [17]. Despite the fact that B7 lesions have no effect on startle, it is logically possible that mescaline's effect in B8-lesioned animals was mediated by its inhibition of B7 neurons.

The disruptive effects of LSD on appetitively reinforced operant behavior have been reported to be potentiated by depletions of serotonin, either by PCPA [4], 5,7-dihydroxytryptamine [3] or combined raphe lesions [5]. More recent work has shown this effect to be related in part to motivational effects of serotonin depletion [26] and may reflect processes that are different from those involved in the startle response.

Our current data confirm our previous report [20,21] that B8, but not B7, lesions decrease hippocampal tryptophan hydroxylase activity and increase startle response magnitudes, and that these two phenomena are significantly correlated on an individual-animal basis. As indicated in Fig. 2A, this augmentation of startle following B8 lesions was apparent on the very first trial, on both the baseline and test days. This result is consistent with the hypothesis that median raphe-lesioned rats are generally hyper-reactive, and inconsistent with the suggestion that such lesions either impair habituation or increase sensitization, since the latter two processes should only affect subsequent responses [12].

In summary, either mescaline or lesions of the median raphe nucleus increase tactile startle in a manner consistent with an augmentation of behavioral reactivity. Since lesions of either the dorsal or median raphe nuclei neither preclude nor potentiate this behavioral effect of mescaline, it would appear that mescaline increases tactile startle by affecting neuronal systems other than those of the midbrain raphe.

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