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Mescaline: excitatory effects on acoustic startle are blocked by serotonin$_2$ antagonists

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Abstract. The ability of serotonin$_2$ (5-HT$_2$) antagonists to block the excitatory effects of mescaline on the acoustic startle reflex were analyzed. Mescaline (20 mg/kg) caused a consistent increase in the amplitude of the acoustic startle reflex. This effect was blocked in a dose-related fashion by the 5-HT$_2$ antagonist ritanserin (ED_{50} dose = 0.25 mg/kg IP). In contrast, even a high dose of ritanserin (2.0 mg/kg) did not block the excitatory effects of amphetamine on startle. Other 5-HT$_2$ antagonists (ketanserin, cinanserin, LY 53857) also blocked mescaline's effect, whereas the 5-HT$_1$ antagonist pindolol (5 mg/kg) did not. These results support the hypothesis that the behavioral effects of hallucinogens are mediated by agonist actions at 5-HT$_2$ receptors.

Key words: Mescaline – Startle – Ritanserin – Serotonin – Ketanserin – Amphetamine

Behavioral effects of hallucinogenic drugs have most frequently been ascribed to actions on brain serotonin neurons. The finding that indole hallucinogenic drugs decrease serotonin turnover (Freedman 1961; Rosecrans et al. 1967) and preferentially and directly depress serotonergic raphe cell firing rates (Aghajanian et al. 1969; Aghajanian et al. 1972) led to the demonstration that hallucinogens could cause a net decrease in 5-HT transmission (Gallager and Aghajanian 1975). These findings, coupled with the fact that serotonin inhibited neuronal firing rates when applied locally onto sensory or limbic brain cells (Haigler and Aghajanian 1974a), lead to the influential hypothesis that the behavioral effects of hallucinogens might be caused by a disinhibition of sensory and limbic areas (Aghajanian and Haigler 1974). However, it was realized early on that this "disinhibition hypothesis" might not be completely adequate, since phenethylamine hallucinogens such as mescaline or 2,5-dimethoxy-4-methylamphetamine (DOM) did not consistently depress raphe cell firing (Haigler and Aghajanian 1973; Trulson et al. 1981). Because of this, electrophysiological studies turned their focus onto areas where indole and phenethylamine hallucinogens had similar effects. It was found that both classes of hallucinogens increased the facilitatory effects of 5-HT or NE on motorneurons which were known to be innervated by 5-HT and NE (McCall and Aghajanian 1980). However, these effects were not produced by the non-hallucinogen lisuride (McCall and Aghajanian 1980) which nonetheless does markedly depress raphe cell firing (Rogawski and Aghajanian 1979). Since these effects occurred in animals depleted of 5-HT it was hypothesized (McCall and Aghajanian 1980) that the hallucinogens might act at post-synaptic receptors such as the binding sites labelled by ^{3}H-5-HT and ^{3}H-LSD in radioligand binding studies (Bennet and Snyder 1976). In addition, other studies showed that both indole and phenethylamine hallucinogens increased reactivity of cells in the locus coeruleus to tactile stimulation (Aghajanian 1980), whereas non-hallucinogens such as amphetamine did not. Taken together, these studies provided electrophysiological evidence for sites in the brain where indole and phenethylamine hallucinogens might have the common action of increasing sensory and motor reactivity.

At about the same time, other investigators reported that the depressant effects of indole hallucinogens on raphe cell firing did not correlate temporally with their prominent behavioral effects (Trulson et al. 1981) and did not show tolerance (Trulson et al. 1977; Trulson and Jacobs 1979; Lee and Geyer 1980) as has been reported for their hallucinogenic actions in humans (Cholden et al. 1955; Isbell et al. 1956; Balestrieri and Fontanari 1959). In addition, a large number of studies indicated that the behavioral effects of both indole and phenethylamine hallucinogens could be blocked by 5-HT antagonists (Browne and Ho 1975; Tilson et al. 1975; Winter 1975; 1978; Kuhn et al. 1978; Commissaris et al. 1980a; Appel et al. 1982; Colpaert and Janssen 1983; Dwoskin and Sparber 1983; Glennon et al. 1983b; Mokler et al. 1983; Trulson et al. 1983; Heym et al. 1984; Colpaert et al. 1985; Glennon and Hauck 1985; Mokler et al. 1985; Nielsen et al. 1985; Sietnieks 1985). Because these same antagonists were ineffective in blocking the pre-synaptic actions of indole hallucinogens (Haigler and Aghajanian 1974b), the behavioral effects of hallucinogens, like the electrophysiological effects on motor neurons, were more easily ascribed to actions on postsynaptic 5-HT receptors. This conclusion was corroborated by the finding that destruction of presynaptic stores of 5-HT via neurotoxins or 5-HT synthesis inhibitors not only did not prevent behavioral actions of hallucinogens but instead actually lead to greater effects, as one would expect if their actions were mediated by postsynaptic receptors made supersensitive via 5-HT depletion (Brown and Ho 1975; Stoff et al. 1976; Commissaris et al. 1980b; Appel et al. 1982).

More recently the 5-HT$_2$ receptor has been explicitly hypothesized to be critical in the actions of hallucinogens (Glennon et al. 1984). This hypothesis was based on a) a high correlation between the 5-HT$_2$ binding affinities and hallucinogenic potency in humans of 15 different indole and phenethylamine compounds (Glennon et al. 1984); b) a high correlation between the 5-HT$_2$ binding affinities and

potency in drug discrimination tests of 22 different indole and phenethylamine compounds (Glennon et al. 1984); c) a high correlation between the potency of these compounds to serve as discriminative cues in drug discrimination tests and their hallucinogenic potency in humans (Glennon et al. 1983a) and d) the consistent finding that 5-HT antagonists such as ritanserin or ketanserin, which have higher affinity for 5-HT_2 versus 5-HT_1 binding sites, blocked the discriminative cue of either indole or phenethylamine hallucinogens (Glennon et al. 1983; Colpaert et al. 1985; Nielsen et al. 1985).

Recent electrophysiological evidence lends strong support to this hypothesis since a) 5-HT_2 antagonists selectively block the increased reactivity of locus coeruleus neurons produced 3y hallucinogens (Rasmussen and Aghajanian 1986) and b) the potency of various phenethylamine hallucinogens in producing this effect correlates with their order of potency in binding to 5-HT_2 binding sites (Rasmussen et al. 1986).

Given the importance of this hypothesis for understanding brain systems involved in hallucinogenic activity, the present study evaluated whether 5-HT_2 antagonists would selectively block the excitatory effect of the hallucinogen, mescaline, on another behavior, the acoustic startle response. The startle response is a relatively simple reflex that is mediated by a brainstem and spinal cord neural pathway (Davis et al. 1982). Both indole and phenethylamine hallucinogens increase the amplitude of the startle response (Davis and Sheard 1974a, b; Miliaressis and St Laurent 1974; Walters 1977; Geyer et al. 1978; Geyer et al. 1979; Braff and Geyer 1980). The phenethylamine hallucinogen mescaline was chosen as the test drug, since phenethylamines generally have a higher affinity for 5-HT_2 binding sites than for 5-HT_1 binding sites compared to indoleamine hallucinogens like LSD which bind at both sites (Glennon et al. 1984; Shannon et al. 1984; Engel et al. 1986) and it has been hypothesized that actions of hallucinogens at 5-HT_2, not 5-HT_1 receptors, could account for the behavioral and psychological effects of both classes of hallucinogens (Aghajanian et al. 1987). The dose-response effects of ritanserin were analyzed first since this compound has high selectivity for 5-HT_2 binding sites (Leysen et al. 1985). Selected doses of ketanserin, cinanserin and LY 53857 were also used, since each of these compounds are known to bind to 5-HT_2 receptors (Cohen et al. 1983; Leysen et al. 1982). To evaluate the role of 5-HT_1 receptors in mescaline's action, the effects of the 5-HT_1 antagonist pindolol were tested (Engel et al. 1986). To evaluate the specificity of the interactions between the 5-HT_2 antagonist and mescaline, the effect of ritanserin was tested against amphetamine, which increases acoustic startle by actions involving dopamine (Davis et al. 1975; Kehne and Sorenson 1978).

Methods

Animals. A total of 160 male albino Sprague-Dawley rats (Charles River Co.) weighing between 300 and 400 g were used. The rats were housed in group cages of five rats each and maintained on a 12 h:12 h light/dark schedule. Food and water were continuously available. All subjects were drug-naive at the start of the experiment.

Apparatus. The apparatus used to measure startle has been described previously (Cassella and Davis 1986). Briefly, five separate stabilimeters were used to record the amplitude of the startle response. Each stabilimeter consisted of an $8 \times 15 \times 15$ cm Plexiglas and wire mesh cage suspended between compression springs within a steel frame. Cage movement resulted in displacement of an accelerometer where the resultant voltage was proportional to the velocity of displacement. Startle amplitude was defined as the maximum accelerometer voltage that occurred during the first 200 ms after the startle stimulus was delivered and was measured with a specially designed sample and hold circuit interfaced to a PDP-11 computer. The stabilimeters were housed in a dark, ventilated, sound attenuating chamber. Each cage was located 10 cm from a high frequency speaker (Radio Shack Supertweeter). The startle stimulus was a 50 ms burst of white noise having a rise-decay time of 5 ms. Background white noise, provided by a white noise generator, was 55 db. Sound level measurements were made within the cages with a General Radio Model 1551-C sound level meter (A-scale).

Procedure. Prior to drug testing, groups of rats were placed in the startle test cages and 5 min later presented with 30 noise bursts at a 20-s interstimulus interval. Three different intensities were used (95, 105, and 115 dB), with ten noise bursts at each intensity, presented in an irregular, balanced sequence across the session. Mean startle amplitudes across the 30 noise bursts were used to divide the rats into several groups with similar means before the main experiment began. Previous work has shown this matching procedure to be most appropriate for startle studies, since there are wide variations among individual startle levels but a high degree of consistency in startle amplitude from one day to the next (Davis and Wagner 1969).

The general design used for drug testing was identical in all experiments. Two or 3 days after matching, two matched groups of five rats each were injected with a particular pretreatment drug (e.g., ritanserin) and two other matched groups of five rats each were injected with its vehicle (e.g., DMSO) in their home cages. Fifteen minutes later, half of the drug-pretreated animals were injected with the test drug (e.g., mescaline) and half with its vehicle (e.g., saline). Immediately after the second injection the rats were placed in the startle test cages and presented with a total of 120, 105 dB noise bursts at a 20-s interstimulus interval. Two days later the same procedures were repeated. In this case, however, rats previously injected with the test drug (e.g., mescaline) were now injected with its vehicle and vice versa. Thus, each rat served as its own control with respect to the test drug, whereas the pretreatment drug varied between rats. Each rat was tested only twice, once with the test drug and once with its vehicle.

Using this design the effects of pretreatment with either DMSO or ritanserin (2.0 mg/kg) were evaluated using mescaline (20 mg/kg) as the test drug. This dose of mescaline is known to produce a reliable increase in both tactile (Geyer et al. 1979) and acoustic (Davis, unpublished) startle. As a control, a similar experiment was done using *d*-amphetamine (4.0 mg/kg) as a test drug at a dose that increases startle by a comparable degree to the increase produced by mescaline. A third experiment compared the effects of several pretreatment doses of ritanserin (0.125, 0.25, 0.5) versus DMSO in blocking the excitatory effects of mescaline (20 mg/kg). The last series of experiments evaluated whether other 5-HT_2 antagonists (cinanserin–10 mg/kg; ketanserin–3.0 mg/kg, Lilly 53857–3.0 mg/kg) would block the ability of mescaline (20 mg/kg) to increase startle. A

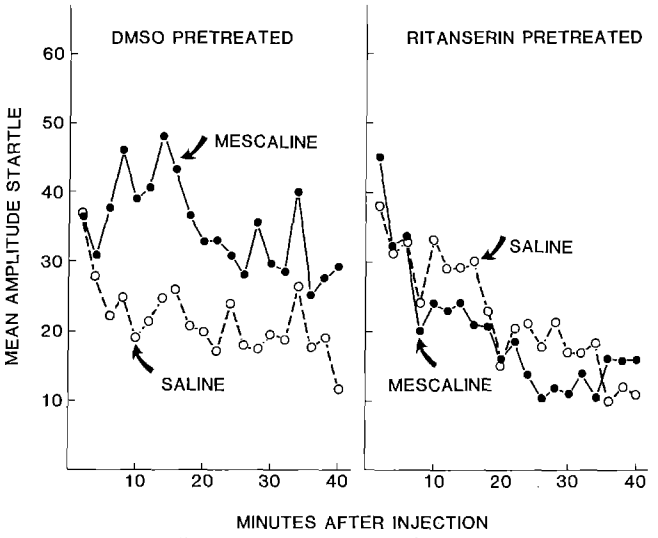

Fig. 1. Mean amplitude startle response after injection with saline or mescaline (20 mg/kg) 15 min after pretreatment with either ritanserin (2.0 mg/kg – *right panel*) or its vehicle, DMSO (*left panel*). Each point represents the mean startle amplitude over blocks of six successive stimuli (2-min periods)

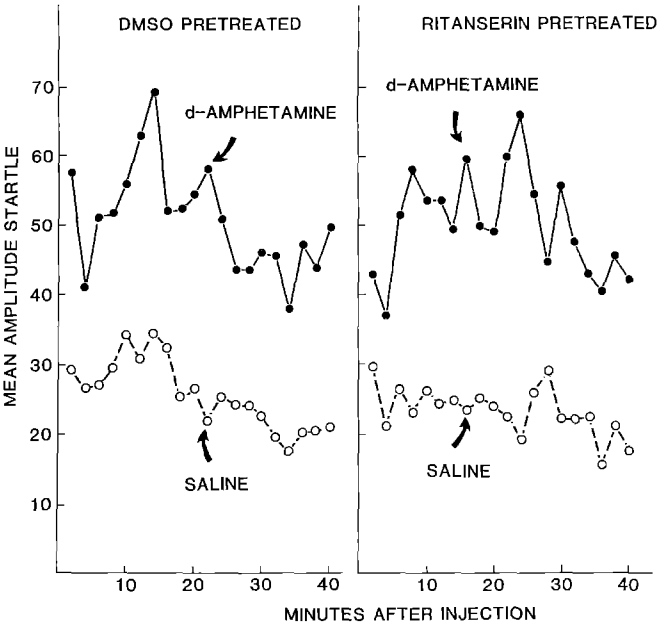

Fig. 2. Mean amplitude startle response after injection with saline or *d*-amphetamine (4 mg/kg) 15 min after pretreatment with either ritanserin (2.0 mg/kg – *right panel*) or its vehicle, DMSO (*left panel*). Each point represents the mean startle amplitude over blocks of six successive stimuli (2-min periods)

high dose of pindolol (5 mg/kg) was used as a control, since pindolol has been shown to have selectivity for 5-HT_1 versus 5-HT_2 sites (Engel et al. 1986) and has been shown to block behavioral effects of some 5-HT agonists (Trickelbank et al. 1984).

Drugs. The following drugs were used: dimethyl sulfoxide (DMSO–Sigma); mescaline HCl (Sigma); *d*-amphetamine sulfate (Sigma); cinanserin HCl (a gift from E.R. Squibb & Co.); ketanserin (a gift from Janssen); ritanserin (a gift from Janssen); Lilly 53857 (a gift from Eli Lilly & Co.); pindolol (Sigma). Ketanserin, ritanserin, and pindolol were dissolved in DMSO, all other compounds were dissolved in saline. All injections were given intraperitoneally at a volume of 1 ml/kg body weight.

Results

Figure 1 shows the mean amplitude startle response after injection of either saline (dotted) or mescaline (solid) in rats pretreated 15 min earlier with either DMSO (left panel) or 2.0 mg/kg ritanserin (right panel). Figure 2 shows comparable data using *d*-amphetamine as the test drug. Figure 1 indicates that mescaline increased startle in rats pretreated with DMSO but not in animals pretreated with ritanserin. An overall analysis of variance, using the mean amplitude startle response combined across the 40 min test session as a score for each animal, with saline versus mescaline as a within-subjects factor and DMSO versus ritanserin as a between-subjects factor, found a significant pretreatment by test drug interaction [$F(1,18)=7.29$, $P<0.02$], indicating that the magnitude of the mescaline effect on startle conditions. Subsequent individual *t*-tests revealed a significant excitatory effect of mescaline after pretreatment with differed between the DMSO and ritanserin pretreatment DMSO [$t(9)=2.85$, $P<0.02$] but not after pretreatment with ritanserin [$t(9)<1$].

In contrast, Fig. 2 shows that even this high dose of ritanserin did not prevent *d*-amphetamine from increasing startle. An overall analysis of variance on these data found a highly significant effect of *d*-amphetamine [$F(1,18)=62.79$; $P<0.001$] but no pretreatment by test drug interaction [$F(1,18)<1$]. Subsequent *t*-tests revealed that *d*-amphetamine still significantly increased startle after pretreatment with ritanserin [$t(9)=4.72$, $P<0.001$].

In the dose response study, the mean amplitude startle responses after injection with saline were 22.5, 22.2, 25.5, 24.2 and 22.7 after pretreatment with DMSO, 0.125, 0.25, 0.5 or 2.0 mg/kg ritanserin, respectively. Comparable startle levels after injection with mescaline were: 34.6, 34.3, 32.1, 26.8 and 20.0. An overall analysis of variance using mescaline versus saline as a within-subjects factor and pretreatment dose of ritanserin as a between-subjects factor found a significant excitatory effect of mescaline [$F(1,55)=13.81$, $P<0.001$] and, most importantly, a significant pretreatment dose by test drug interaction [$F(4,55)=3.29$, $P<0.02$], which was linearly related to the pretreatment dose of ritanserin [*F*-linear $(1,55)=12.44$, $P<0.001$]. Hence, ritanserin blocked the excitatory effect of mescaline in a dose-related fashion but had no apparent effect on baseline startle levels.

The dose-related blockade of mescaline by ritanserin is illustrated in Fig. 3, which shows the mean percent difference between mescaline and saline conditions, combined across the entire test session, after pretreatment with either DMSO or various doses of ritanserin. Data shown for the 2.0 dose were obtained in the first experiment shown in Fig. 1 and were included in the overall dose-response analysis. Using these per cent scores an overall analysis of variance found a significant dose related decrease in mescaline's facilitatory effect on startle that was linearly related to the pretreatment dose of ritanserin employed [*F*-linear $(1,55)=8.89$, $P<0.01$].

Figure 4 shows the mean amplitude startle response,

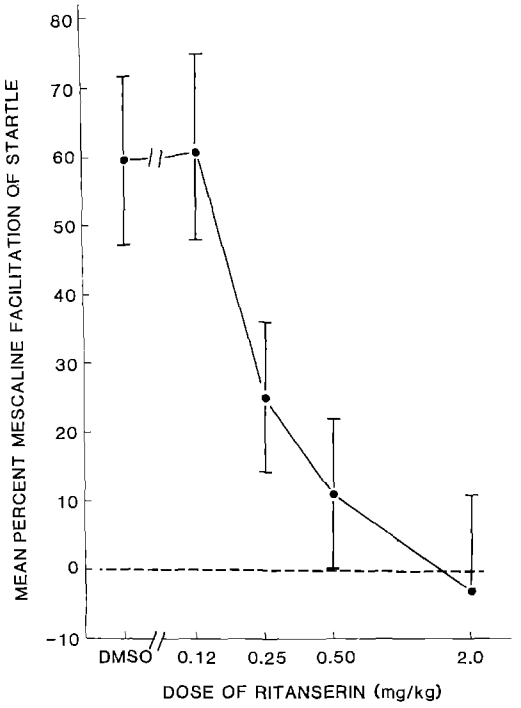

Fig. 3. Mean percent excitation (±SEM) of startle by mescaline, averaged across all 120 stimuli (i.e., across the entire 40-min test session), after injection of DMSO or various doses of ritanserin given 15 min before testing

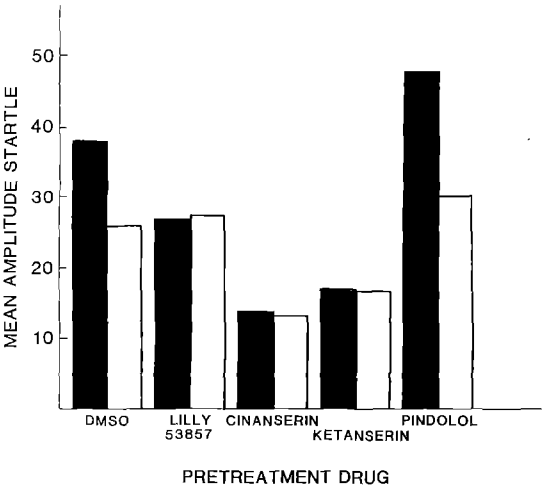

Fig. 4. Mean amplitude startle response after injection of mescaline (20 mg/kg) or saline, averaged across all 120 stimuli (i.e., across the entire 40-min test session), after pretreatment 15 min earlier with the 5-HT-2 antagonists Lilly 53857 (3.0 mg/kg); cinanserin (10 mg/kg); or ketanserin (3.0 mg/kg) or the 5-HT-1 antagonist pindolol (5 mg/kg). ■ Mescaline, □ Saline

combined across the entire test session, in the saline versus mescaline conditions after pretreatment with either cinanserin, ketanserin, Lilly 53857, or pindolol. For each of the four pretreatment drugs a separate control group of ten rats was pretreated with DMSO. However, since an overall analysis of variance on these four control groups did not find any difference in either their overall startle levels [$F(3,36)=1.33$], or the magnitude of the mescaline enhancement of startle [$F(3,36)<1$], these control groups have been combined for statistical and graphic purposes and labelled "DMSO" pretreated in Fig. 4. An overall analysis of variance on the main data indicated a significant pretreatment drug effect [$F(4,75)=5.36$, $P<0.001$], a significant excitatory effect of mescaline [$F(1,75)=11.90$, $P<0.01$] and, most importantly, a significant pretreatment by test drug interaction [$F(4,75)=4.26$, $P<0.01$]. Subsequent individual t-tests indicated that the mescaline minus saline difference scores in the cinanserin, ketanserin, and Lilly 53857 groups differed significantly from the DMSO groups (all $Ps<0.05$) as well as from the pindolol-pretreated group (all $Ps<0.01$), which itself did not differ statistically the DMSO pretreated group.

Finally, it might be noted that at these doses, ketanserin and cinanserin ($P<0.05$) depressed baseline startle levels (i.e., as judged by the groups injected with saline as the test drug) but Lilly 53857, like ritanserin, did not.

Discussion

The present experiment indicated that the 5-HT_2 antagonists ritanserin, ketanserin, LY 53857, and cinanserin blocked the excitatory effects of mescaline on the acoustic startle reflex. In contrast, ritanserin did not block the excitatory effects of amphetamine on startle which is believed to be mediated by actions on central dopamine transmission (Davis et al. 1975; Kehne and Sorenson 1978). Moreover, pindolol, which has a higher affinity for 5-HT_1 than 5-HT_2 receptors (Engel et al. 1986) did not block mescaline's effect on startle, at a dose that has been shown to block the behavioral syndrome produced by 8-OH-DPAT (Trickelbank et al. 1984).

Both cinanserin (10 mg/kg) and ketanserin (3 mg/kg) depressed baseline startle levels. However, this depressant effect cannot account for the blockade of mescaline and does not seem attributable to 5-HT_2 receptor antagonism, since the 5-HT_2 antagonists ritanserin and LY 53857 completely blocked the excitatory effect of mescaline at doses that produced no depression of startle baseline.

Taken together, the present data support the hypothesis of Glennon et al. (1984 – see introduction) that the behavioral effects of mescaline may result from agonist-like actions at 5-HT_2 receptors. At the present time the location of the 5-HT receptors that mediate the excitatory effects of mescaline on startle are not known. They are not on the dorsal or median raphe nuclei since lesions of these nuclei do not prevent mescaline from increasing startle (Geyer et al. 1979). It is unlikely that they are located on neurons within the startle pathway itself, since very low densities of 5-HT_2 binding sites in nuclei within the startle pathway have been reported (Pazos et al. 1985). Future studies using local infusion of 5-HT_2 agonists or antagonists into areas containing high densities of 5-HT_2 binding sites may elucidate the location of the relevant 5-HT_2 receptors in mediating mescaline's excitatory effect on startle.

Electrophysiological studies have shown that hallucinogenic drugs indirectly increase reactivity of cells in the locus coeruleus (Aghajanian 1980) and that the potency of a series of phenethylamines in producing this effect correlates highly with their affinity to 5-HT_2 binding sites (Rasmussen et al. 1986). Moreover, the effects of either LSD or mescaline can be blocked by 5-HT_2 antagonists (Rasmussen and Aghajanian 1986). It is possible that the excitatory effects of hallucinogens on startle could ultimately result from their actions on norepinephrine transmission, since norepinephrine appears to modulate startle (e.g., Adams and Geyer

1981; Astrachan et al. 1983; Kehne and Davis 1985). Future studies looking at the effect of norepinephrine depletion on mescaline's excitatory effect on startle would be needed to test this possibility.

Electrophysiological studies have also shown that hallucinogens enhance the facilitatory effect of 5-HT or NE on motor neurons. Normally, 5-HT or NE have no effects on motor neurons by themselves but they markedly facilitate the excitatory effects of glutamate (McCall and Aghajanian 1979; White and Neuman 1980). By themselves, most hallucinogens do not alter motorneuron excitability but they do increase the ability of 5-HT or NE to facilitate excitation produced by glutamate (McCall and Aghajanian 1980). Previous work has shown that NE or 5-HT (Davis et al. 1980; Astrachan and Davis 1981) or NE or 5-HT agonists (Davis et al. 1980; Astrachan and Davis 1981; Astrachan et al. 1983; Davis et al. 1986) increase startle amplitude after local infusion in the vicinity of the motorneurons in the spinal cord. Future studies looking at interactions between hallucinogens and intrathecal infusions of 5-HT or NE or their agonists, as well as the effects of 5-HT_2 antagonists in this situation, could evaluate the role of these mechanisms in mediating the excitatory effects of hallucinogens on startle.

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