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Short communication

Phenethylamine hallucinogens in the locus coeruleus: potency of action correlates with rank order of 5-HT_2 binding affinity

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The rank order of potency for the physiological effects of three phenethylamine hallucinogens in the locus coeruleus (LC) was identical to that previously shown for their 5-HT_2 binding affinity ((−) DOB > DOM > (+)DOB). The behaviorally inactive positional isomer of DOB, SL-7161, did not significantly affect LC unit activity. These results offer insight into structure-activity relationships at 5-HT_2 receptors and support earlier findings that the actions of hallucinogens displayed in the LC are mediated via 5-HT_2 receptors.

DOM; DOB; SL-7161; 5-HT_2 receptors; Locus coeruleus; Hallucinogens

1. Introduction

The locus coeruleus (LC) is one of the few places in the rat brain where indoleamine and phenethylamine hallucinogens have been demonstrated to have a common electrophysiological action. In anesthetized rats systemic administration of both types of hallucinogens has been shown to suppress the spontaneous activity of LC neurons while simultaneously facilitating the activation of LC neurons by sciatic nerve stimulation (Aghajanian, 1980; Rasmussen and Aghajanian, in press). The common action of the two types of hallucinogens in the LC appears to be mediated by 5-HT_2 receptors since selective 5-HT_2 antagonists reverse the effects of hallucinogens on the LC. In order to further examine the nature of the 5-HT_2 receptor mediation of the effects of hallucinogens on the LC and to examine the structure-activity relationship of 5-HT_2 agonists on the LC we compared the effects of DOM (1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane) and of several analogs of DOM on the LC. The analogs of DOM used in this study were the S(+) and R(−) optical isomers of DOB (1-(2,5-dimethoxyphenyl)-4-bromo-2-aminopropane), which are potent hallucinogens in man (Anderson et al., 1978), and SL-7161 (1-(2,5-dimethoxy-3-bromophenyl)-2-aminopropane) a positional isomer of DOB that is essentially inactive both behaviorally (Glennon et al., 1982) and at 5-HT_2 binding sites (Glennon et al., 1986).

2. Materials and methods

Male Sprague-Dawley rats (Charles River) weighing 255-335 g were used in these experiments. The animals were anesthetized with chloral hydrate (400 mg/kg i.p.); supplemented doses of anesthetic were administered through a lateral tail vein as needed. Body temperature was maintained at 35-37°C by a heating pad. Rats were mounted in a stereotaxic apparatus and a cisternal drainage was performed to help prevent tissue swelling. A burr hole was made 1.2 mm posterior to lambda and 1.1 mm lateral to the midline. The electrodes

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used in this study were single barrel glass micropipettes that were broken back to a tip diameter of 2-3 μm, filled with a 2 M NaCl solution containing 2% pontamine sky blue, and had impedances measuring 1-2 MΩ. Procedures for locating the LC and for extracellular single-unit recordings were the same as those described previously (Aghajanian et al., 1977). Once the LC was located, four stabilizing pins (No. 0 Clay Adams insect pins) were inserted 1.5-2 mm apart in the brain in a square pattern around the recording site. The pins served to reduce local pulsations and other movements. For histological confirmation of LC recording sites, the electrode tip locations were marked at the end of each experiment by passing current through the electrode. Drugs were administered i.v. via a lateral tail vein and the effective dose for 50% suppression of firing (ED_{50}) was calculated from the log-probit method (cumulative doses of 2, 4, 8, 16, 32 and 112 μg/kg; n = 3-11 cells/dose). In order to insure a large enough sample of the higher doses used in this study (since LC units could only be recorded for a finite period, typically 20-30 min) the initial dose administered to some cells was 16 μg/kg. To normalize the distribution of the data, statistical tests were performed on geometric means (Fleming et al., 1972). Therefore, all mean values reported in the text are geometric means. Differences in ED_{50}s were compared with a one-way ANOVA coupled with the Newman-Keuls test. The contralateral sciatic nerve was stimulated with a bipolar hook electrode (0.1-0.8 mA, 0.25 Hz, Harvard Subminiature Electrode). Post-stimulus time histograms were collected before and 3-5 min after the administration of a total of 16 μg/kg of the test drug. Evoked spikes were taken from the first 250 ms of each post-stimulus time histogram. Differences in evoked LC unit activity were analyzed with a matched-sample t-test comparing the number of

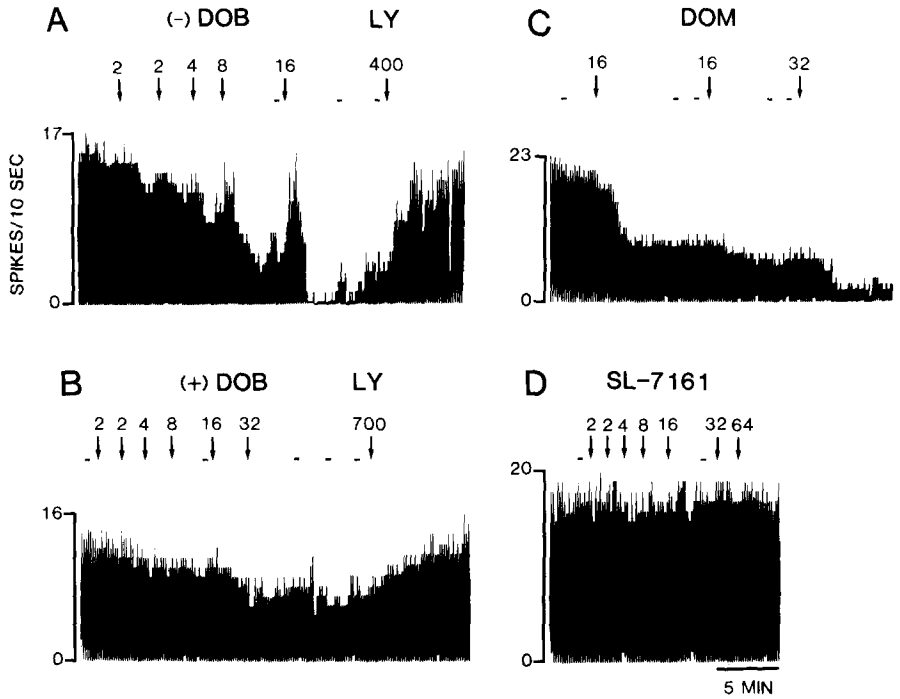


Fig. 1. Effects of (−)DOB (A), (+)DOB (B), DOM (C) and SL-7161 (D) on LC unit activity. Drugs were given by slow i.v. infusion (arrows, numbers refer to dose in μg/kg). Bars represent periods of sciatic nerve stimulation. Note that in (A) and (B) the administration of the selective 5-HT_2 antagonist LY 53857 (LY) completely reversed the action of the hallucinogen. Also note that in (A) the unit being recorded became so sensitive to peripheral stimuli that administration of more drug (8 and 16 μg/kg doses, administered via a lateral tail vein) caused a large but transient increase in activity.

spikes evoked by 10 sciatic nerve stimulations before and after drug administration. Doses of (+)DOB hydrochloride, (−)DOB hydrochloride, DOM hydrochloride (NIDA) and SL-7161 oxalate were calculated as the salt. DOB and SL-7161 were synthesized in the laboratory of one of the authors (R.A.G.) as previously described (Glennon et al., 1980; 1986).

3. Results

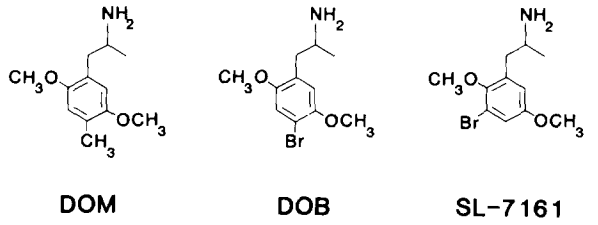
All three hallucinogenic compounds produced a dose-dependent suppression of LC unit activity (figs. 1 and 2). The ED_{50}s for the suppression of LC unit activity for (−)DOB (means ± S.E.M.; 5.0 ± 0.5 μg/kg; n = 10), DOM (15.8 ± 0.5 μg/kg; n = 9) and (+)DOB (35.5 ± 1.1 μg/kg; n = 7) had the same rank order of potency as the known 5-HT_2 binding potency of the compounds (i.e. (−)DBO > DOM > (+)DOB). All three ED_{50}s were significantly different from each other.

All three hallucinogens at a cumulative dose of 16 μg/kg also produced a significant increase in evoked LC activity, and the percent increase in evoked LC activity for (−)DOB (means ± S.E.M.; 44 ± 1.9; n = 8), DOM (25 ± 2.5; n = 6) and (+)DOB (12 ± 1.5; n = 6) had the same rank order as the ED_{50} for suppression of the spontaneous activity (i.e. (−)DOB > DOM > (+)DOB), and thus the same rank order of potency as the 5-HT_2 binding affinity of the compounds.

The behaviorally inactive positional isomer of DOB, SL-7161, did not significantly suppress LC unit activity (figs. 1 and 2; no ED_{50} could be calculated) nor significantly increase evoked LC activity (means ± S.E.M.; percent change = −4 ± 5.3; n = 6).

4. Discussion

These data add support to previous results that the action of hallucinogens on the LC are media-



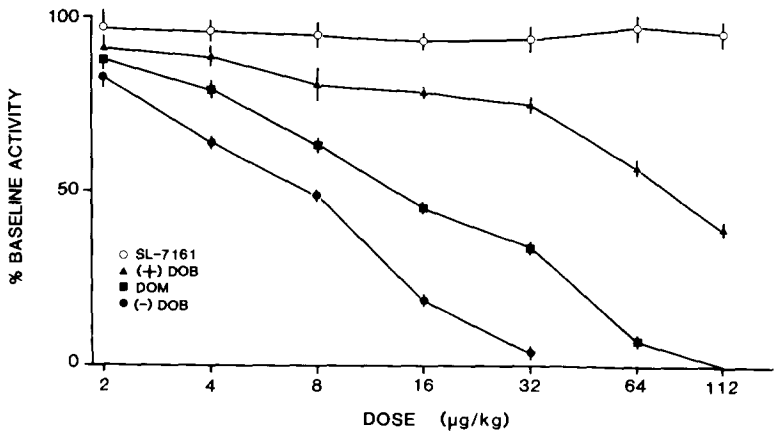


Fig. 2. Structure of DOM, DOB and SL-7161 and the effects of systemic administration of these compounds on LC unit activity in anesthetized rats. Each point represents the geometric mean of 3-11 cells, and vertical bars are S.D. of the geometric mean.

ted via 5-HT_2 receptors since the rank order of potency of the compounds used in this study both for suppressing spontaneous LC unit activity and for facilitating LC evoked activity is the same ranke order of potency for affinity at 5-HT_2 binding sites (i.e. (−)DOB > DOM > (+)DOB; Glennon et al., 1986). These results also support the hypothesis that hallucinogens act as 5-HT_2 agonists (Glennon et al., 1984) since this dual action on the LC (i.e. decrease in spontaneous activity and increase in evoked activity) is unique to psychedelic hallucinogens (Aghajanian, 1980; Rasmussen and Aghajanian, in press) and the more potent a compound is as a hallucinogen, the higher its 5-HT_2 binding affinity, and the more potent its actions on the locus coeruleus.

These results also show that substituents at the phenethylamine 4-position are important in determining activity at 5-HT_2 receptors since the potency of DOM can be enhanced by substituting a bromine at this carbon, whereas moving this 4-position bromine to the 3-position renders the compound inactive at 5-HT_2 receptors (fig. 2; Glennon et al., 1986). These results also indicate that for DOB the α-methyl group of the sidechain is more beneficial to activity when in the R(−) rather than the S(+) configuration. In addition, the chiral center of DOB corresponds to the 5-position of the LSD molecule; interestingly, the most behaviorally active isomer of LSD also possesses the R-configuration at this position (cf. Glennon, 1979).

It should also be mentioned that these actions of hallucinogens on LC neurons are not direct ones since the effects of these drugs given systemically are not mimicked by their iontophoretic application onto LC cell bodies (Aghajanian, unpublished observations). In addition, there are few if any 5-HT_2 receptors in the LC (Pazos et al., 1985). This implies that the hallucinogens are acting on afferents to the LC, afferents that are affected directly, or indirectly, by 5-HT_2 receptors.

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