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MESCALINE-LIKE ACTIVITY OF 2-AMINO-7-HYDROXYTETRALIN

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SUMMARY

2-Amino-7-hydroxytetralin has sleep effects in rats like mescaline and D-LSD, and it showed cross-tolerance with mescaline, as did D-LSD. These properties had been predicted by total valence electron calculations.

Molecular orbital calculations (1-4), including total valence electron calculations (3-4), and stereochemical analysis (4-6) suggested congruities among D-lysergic acid diethylamide (LSD), indolealkylamines, and mescaline-like substances. These studies could account for the observations that these hallucinogenic compounds of ostensibly dissimilar structure show cross-tolerance (7-13) [not attributable to metabolic disposition (13)] and therefore may act at the same or similar sites in the nervous system. We proposed (4) that the conformation common to these different hallucinogens is 2-aminotetralin (i.e., 2-amino-1,2,3,4-tetrahydronaphthalene, Fig. 1), a proposal that is supported by recent studies using radioimmunoassay (14) and by observations on the mescaline-like activity of the trans isomer of the cyclopropylamine analogue of mescaline (15). As high electron donor ability correlated with hallucinogenic activity (1-4) it was predicted (4) that 2-aminotetralins with electron-donating groups (e.g., methoxy or hydroxy groups) on the aromatic ring would have mescaline-like activity; in fact, owing to their rigid structure, which fixes the position of the amino group, it was also predicted that they would be more potent hallucinogens than mescaline (4) Molecular orbital analysis also suggested that hal-

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lucinogenic activity of some methoxylated phenylisopropylamines (16) can be correlated with high donor ability from the 3-position and low donor ability from the 1-position of the aromatic ring (K. P. Dressler, in preparation); these correspond to the f-position and 9-position, respectively, of aminotetralin (Fig. 1).

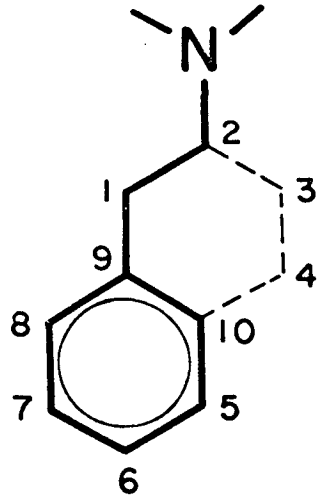

FIG. 1

To test this prediction, the electroencephalographic effects of 2-amino-7-hydroxytetralin were compared with those of mescaline and LSD in normal rats and in rats made tolerant to mescaline.

Methods

The methods have been described in detail (17). Adult female Sprague-Dawley rats (250-300 g) were used in the experiments. For cortical electroencephalographic recordings, chronic electrodes consisting of stainless-steel screws were implanted in the skull over the frontal cortices. After the rats had recovered from surgical procedures, the electroencephalogram from the relatively unrestrained freely moving rats in individual cages, was recorded with a 10-channel modified Grass model 7 polygraph.

Results

Table 1 shows that 2-amino-7-hydroxytetralin had the same effects on sleep as did mescaline and LSD and, like LSD, showed cross-tolerance with mescaline (Table 1).

TABLE 1

The effect of some compounds on sleep and rapid eye movement (REM) sleep in normal rats and in rats given mescaline, 30 mg/kg every six hours for three days and then 60 mg/kg every six hours for two additional days. All drugs were given by intraperitoneal injection. Numbers of rats are shown in parenthesis. Values are means ± s.d.

Drug	Previous Treatment	Onset of sleep (min)	Onset of REM sleep (min)
Mescaline (60 mg/kg)	none(5)	173±20*	221±44[§]
	mescaline(5)	39±24*	67 30[§]
LSD (200 µg/kg)	none(4)	68±7*	198±27.1*
	mescaline(5)	36±9*	129±46.6*
2-amino-7-hydroxytetralin (37.5 mg/kg)	none(3)	58±30[†]	128±13[§]
	mescaline(5)	11±6[†]	48±7[§]

*$p<0.001$ [§]$p<0.01$ [†]$p<0.05$

Discussion

These results support the proposed conformation of mescaline(4). They also show that quantum mechanics can be helpful in predicting the biological activity of chemical substances even when tested in whole animal. Previous studies of 2-aminotetralin and some of its derivatives focused on their steric resemblance to lysergic acid derivatives (18-21) and revealed their amphetamine-like activities (22-26). Consideration of the electronic as well as the steric characteristics of 2-aminotetralins suggested a biological activity that was not previously observed or intuitively obvious.

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