Mechanisms of Action of Indole and Phenylalkylamine Hallucinogens

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Introduction

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Although the effects of hallucinogenic drugs have been recognized throughout the ages, extensive scientific investigation was prompted only in recent times by the synthesis and characterization of lysergic acid diethylamide (LSD) by Hofmann in 1943 (Hofmann, 1970). Important recent studies in this area are listed in Table 1. The suggestion that LSD may act via brain serotonin (5-HT) functions was made independently by Gaddum (1953) and Woolley and Shaw (1954), based on smooth muscle interactions. Prominent effects on animal operant behavioral models were described by Appel, Freedman, and colleagues (Appel, 1968) several decades ago.

The use of electrophysiological techniques by Aghajanian and co-workers (1975) supported the concept that LSD acted as a 5-HT agonist to suppress discharge of brainstem raphe neurons by acting at neurosomal autoreceptors. Jacobs and colleagues (1978), and later work by Aghajanian's group (1975), demonstrated that the autoreceptor effect of LSD was not sufficient to explain the hallucinogenic activity. Only a few laboratories have dealt more broadly with investigation of various classes of hallucinogenic agents. Domino's group (1964) is one of these. He has demonstrated the more generalized behavioral disruption of deliriant hallucinogens such as atropine and PCP when compared to the psychedelics. The literature on clinical research with hallucinogens is derived mainly from studies done from 1950 to 1970 by Hollister (1984) and a few others. Due to later restrictions, carefully controlled human research on hallucinogenic mechanisms has been rare in the last decade.

TABLE 1. Milestones in Hallucinogenic Drug Research.*

1. Synthesis, description of human effects of LSD by Albert Hofmann in 1943.
2. Gaddum; Woolley and Shaw: LSD induces CNS effects by antagonizing 5-HT neurotransmitter function, 1953, 1954.
3. Appel, Freedman and colleagues: Operant behavior of rats disrupted in a distinctive pattern by indolealkylamine and phenalkylamine hallucinogens, 1960's.
4. Aghajanian and coworkers: LSD was a potent suppressor of 5-HT raphe cell discharge by agonistic action at autoreceptors, early 1970's.
5. Jacobs and colleagues: Autoreceptor activity of LSD was not sufficient to explain hallucinogenic action, late 1970's.
6. Domino and others: Contrasted effects of deliriant hallucinogens (atropine-type, PCP) with those of the psychedelics, 1960's, 1970's.
7. Hollister and others: Clinical research on hallucinogens performed in the 1950's, 1960's.
8. Recent experimental research (Appel; Glennon; Jacobs; Rech): Psychedelics act at a certain subset(s) of 5-HT receptors in forebrain (as well as hindbrain?) to alter CNS functions.

*See selected references below.

Current animal research with the psychedelics has led to a consensus that these agents act at a certain type (or types) of brain 5-HT receptors to disturb a balance in the functioning of these systems that is necessary for normal sensory and other cognitive processings.

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