BRIEF REPORTS

Influence of Environmental Context on Tolerance to LSD-Induced Behavior in Primates

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Introduction

Traditional theories of drug tolerance and dependence have generally stressed the physiological consequences of chronic drug administation. However, substantial evidence indicates that environmental contingencies exert profound effects on drug action. It has become increasingly clear that the behavioral outcome of chronic pharmacological stimulation is a function of both the characteristics of the drug and the context in which the drug is given (Siegel 1979; Poulos et al. 1981; Eikelboom and Stewart 1982; Demellweek and Goudie 1983).

Contextual influences have been particularly well characterized with respect to central nervous system depressants, primarily opiates, alcohol, and sedative-hypnotics. However, such modulation is not limited to these drug classes. Both addictive as well as nonaddictive agents (e.g., haloperidol) (Poulos and Hinson 1982) have been found to be susceptible to contextual modulation.

One class of drugs that has not previously been examined in this regard is the hallucinogens. A rapid partial tolerance develops to the hallucinogenic effect of most hallucinogens, notably *d*-lysergic acid diethylamide (LSD). As yet, the mechanism responsible for this tolerance is unknown.

Experimental animal models have recently been developed that correlate with certain aspects of hallucinogen action in humans, including the rapid development of tolerance (Davis et al. 1984). Interestingly, despite the development of tolerance to hallucinogen-related behavior in animals, tolerance fails to develop to LSD-induced suppression of raphe cell firing (Trulson and Jacobs 1979). This is surprising, as the raphe response has been suggested to be a mechanism by which hallucinogens exert their psychotomimetic effect. The dichotomy between the neural and behavioral consequences of LSD raises a question concerning the possible involvement of mechanisms that are not directly effected by LSD in the development of tolerance to hallucinogens.

The purpose of this study was to examine one possibility by determining whether or not tolerance to the behavioral effects of LSD was specific to the environment in which the drug was given. The paradigm used for the study was observation of open field behavior in members of two stable nonhuman primate social colonies.

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Acute administration of LSD and other hallucinogens to selected members of primate social colonies induces several significant behavioral changes. Importantly, rapid development of tolerance to certain LSD-induced behaviors can be demonstrated with repeated administration of the hallucinogen (Schlemmer and Davis 1983).

Methods

Two stable social colonies of adult stumptail macaques (*Macaca arctoides*) served as subjects in the study. In the first experiment, a colony of one male and three females received treatment (Group 1), and in the second experiment, another colony of four females served as subjects (Group 2). Both colonies were routinely housed in a large group cage, 1.75 × 3.0 × 5.25 m, 24 hr a day. Each colony received a generous supply of food (Purina Monkey Chow) each morning and had continuous access to water throughout the study.

The study was set up in a counterbalanced design. In the first experiment (Group 1), all four monkeys received an intramuscular injection of *d*-LSD, 0.01 mg (base)/kg, 15 min prior to observation for 5 consecutive days. On the first 2 days, the animals remained in their large home group cage. Immediately prior to the injection of LSD on the third day, each monkey was removed from the group cage and placed in a smaller individual cage in a different room. This constituted the environmental shift. All four individual cages were in close proximity in the same room so that each monkey could see and hear all other members of the colony, but could not touch any other animal. The monkeys remained in the individual cages 24 hr a day from the time of injection on day 3 until the completion of the observation session on day 5. The monkeys were then returned to their group cage, where they remained for a 2-week drug washout period. The experiment was then repeated; however, this time the monkeys remained in their home group cage throughout the 5-day LSD treatment period.

The second experiment (Group 2) was conducted in an identical manner as the first experiment, with the exception that all four colony members first received LSD treatment for 5 days in their group cage. This was followed 2 weeks later by a 5-day LSD treatment, during which the environmental shift from the group cage to individual cages occurred on day 3.

Beginning 15 min after drug injection, a 60-min behavioral observation session was conducted by one or two experienced observers. The interrater reliability was high ($r > 0.95$), as determined in previous studies. During each session, the observer quantified and recorded the behavior of each member of the colony in rotation in accordance with a checklist of 48 social, solitary, and abnormal behaviors for this species using the focal sampling technique (Schlemmer and Davis 1983). Although LSD induced behavioral changes consistent with those previously reported in this species (Schlemmer and Davis 1983), three are reported here—limb jerks, body shakes, and visual scanning. *Limb jerks* are involuntary myoclonic spasms of the extremities, usually the legs. In this species, limb jerks are only induced by hallucinogens and are not seen upon acute administration of other psychoactive nonhallucinogenic substances (Schlemmer and Davis 1983). A *body shake* resembles the response of a dog after emerging from water ("wet dog shake"). It begins with vigorous, momentary shaking of the head, then continues down the body. *Visual scanning* (checking) is the number of obvious changes in visual field as determined by head and eye movements. Other behavioral changes noted were inappropriate for the analysis because (1) changes in social behavior could not be assessed in individually caged monkeys, (2) drug treatment scores were reduced to, or near, zero, resulting in a "floor" effect, or (3) other solitary behaviors were not significantly affected by LSD.

Because the study was a counterbalanced design, data from the two groups were combined for the statistical analysis. Data were analyzed using a two-way analysis of variance. The least significant difference method was used to determine significance between means.

Table 1. Effect of Environmental Context on LSD-Induced Behavior in Monkeys

Behavior	Test day	Experimental condition	
		No change	Change
Limb jerks	1	19.4 ± 4.7	23.2 ± 6.7
	3	1.4 ± 0.8[a]	3.6 ± 2.1[a]
Body shakes	1	10.4 ± 2.0	7.7 ± 2.0
	3	6.1 ± 0.5[a]	5.6 ± 1.2
Visual scanning	1	54.9 ± 5.7	42.0 ± 5.1
	3	34.9 ±4.2[a]	58.5 ± 3.4[a]

The mean number of responses (± SEM) for all subjects (n = 8) under each of the two experimental conditions. In the no change condition, monkeys remained in the same environment throughout the treatment period; in the change condition, the monkeys were placed in a new environment on day 3 of the treatment period.

[a] $p < 0.01$ when compared to the respective score on day 1 of treatment.

Results

Table 1 sumarizes the results of the study for the three primary behaviors that met our criteria—limb jerks, body shakes, and increased visual scanning. The data are presented as the mean (± SEM) of all eight subjects for the two experimental conditions. When there was no change in the environment (NC condition), tolerance was evident for each behavior, as indicated by the significant decline from day 1 to day 3. The pattern of results, however, was different when the environment was changed. Tolerance again developed in the limb jerks, but there was no significant change in body shakes, and the degree of visual scanning was actually reversed in this situation. That is, in contrast to the decrease in visual scanning (tolerance) seen when the monkeys remained in their home cage (NC), visual scanning increased when the environment shift occurred (C).

Discussion

These results suggest that the effect of environmental context on tolerance to LSD-induced behaviors is a function of the particular response measure. There appears to be a pharmacological specificity in the extent to which LSD-related behaviors were modified by the drug-associated context. The hallucinogen-specific behavior of limb jerks showed little evidence of situational specificity. Conversely, increased visual scanning, which is induced by several classes of psychotomimetic drugs, was sensitive to environmental change. That is, tolerance that developed to this response during repeated administration in a consistent environment was disrupted when the environment was changed. The fact that tolerance initially developed to all of the drug-induced behaviors, and that the visual scanning response was modulated by context, appears to rule out the possibility that LSD-induced sensory disturbance were responsible for the lack of modulaton seen with the limb jerk.

It is surprising that the limb jerk response was not influenced by the environmental shift, because other elementary responses, such as the tail flick withdrawal reflex, are sensitive to similar manipulations (Advokat 1980). Within the conditions of this paradigm, LSD appears to be unique with respect to other drugs examined so far, in that tolerance to this behavioral response, which characterizes hallucinogens in monkeys, is not specific to the context of drug administration.

More importantly, if the limb jerk response in monkeys is indeed reflective of the hallucinogenic response in humans, the findings of this study would suggest that contextual or situational tolerance does not appear to provide an explanation for the mechanism of tolerance to the hallucinogenic effect of these agents in humans. It remains to be seen if these impressions can be verified clinically. However, it is unlikely that these results will be forthcoming in the foreseeable future, due to the difficulties in conducting such studies.

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Relationship of Limbic Dopamine Levels to Amphetamine- and Anticholinergic-Induced Hyperactivity in the Rat

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Limbic dopamine receptors are considered to be the important target site for antipsychotic drugs. Accordingly, increased selectivity for limbic dopamine receptors is generally considered to be a desired goal in the design of antipsychotic drugs. Although the relationship of limbic dopamine neurons to pharmacological antipsychotic clinical efficacy is speculative, studies at the basic research level using laboratory animals have shown consistently that when limbic dopamine terminals are selectively destroyed by 6-hydroxydopamine (6-OHDA), psychomotor stimulant drugs no longer produce their characteristic behavioral hyperactivity effects (Kelly

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