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BRIEF REPORT

The Effects of Chronic Mescaline Administration on Operant Behavior in the Pigeon

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A dose of 6.5 mg/kg mescaline which acutely abolishes fixed-ratio appetitive responding in pigeons becomes progressively less disruptive with repeated administration. When responding reaches about 60% of baseline (in about 3 weeks) no further tolerance occurs. A dose of 3.5 mg/kg mescaline acutely lowers responding to about 60% of baseline and repeated administration of this dose continues to produce approximately the same response deficit. Discontinuation of both doses results in an immediate return to baseline levels of responding. Two possible mechanisms underlying this two-stage action of mescaline seen in this and other studies are discussed. The endogenous hallucinogen hypothesis of schizophrenia is considered in light of the existence of tolerance-resistant hallucinogenic drug effects.

Until recently, repeated administration of hallucinogenic compounds to man (Isbell *et al.*, 1961; Wolbach *et al.*, 1962) or to animals (Freedman *et al.*, 1958; Appel and Freedman, 1968) was almost universally reported to result in a progressive diminution and eventual abolition of the psychological and behavioral effects produced initially. These findings of tolerance development have been considered to effectively refute the endogenous hallucinogen model of schizophrenia first proposed by Osmond and Smythies (1952).

However, over the past several years a growing number of workers has discovered paradigms in which tolerance fails to develop to effects of a variety of hallucinogenic compounds including amphetamine (Segal and Mandell, 1974; Segal, 1975), cocaine (Post and Kopanda, 1975), *N,N*-dimethyltryptamine (DMT) (Cole and Pieper, 1973; Gillin *et al.*, 1973), LSD (Hamilton, 1960; Stoff *et al.*, 1974), and mescaline (Smythies *et al.*, 1966; Bridger *et al.*, 1973).

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Smythies *et al.* (1966) reported that a dose of mescaline which initially disrupted rats' performance of a conditioned avoidance response (CAR) actually facilitated their responding later in the same test session. In addition, they found that repeated administration of this dose eventually produced only facilitation--tolerance developing to the disruptive effect; no tolerance developing to the facilitating effect. Furthermore, these investigators found that a low dose of mescaline which acutely facilitated CAR performance retained its facilitating effect when given repeatedly; this dose also facilitated acquisition of the CAR both acutely and when given several times before presentation of the task.

Studies of the effects of chronic hallucinogen administration on appetitive behavior in rats have uniformly reported tolerance to occur to the disruptive effects within a few days (Freedman *et al.*, 1958; Appel and Freedman, 1968; Silva *et al.*, 1968; Bailey and Pradhan, 1972). However, in the only study involving a species other than the rat, Cole and Pieper (1973) found persistence of the DMT-induced inhibition of fixed-ratio appetitive responding in squirrel monkeys with repeated administration.

Whether or not tolerance develops to hallucinogenic drug action evidently depends on the particular combination of drug, behavior, and animal species under investigation. By characterizing those paradigms in which tolerance does or does not develop, we may acquire insight into the mechanisms of hallucinogenic drug action and the applicability of the endogenous hallucinogen model of schizophrenia. In this study we have examined the effects of chronic mescaline administration on fixed-ratio appetitive responding in the pigeon, a species which has been successfully employed in research with other hallucinogens (Becker *et al.*, 1967; Siegel, 1969) and which is widely used in studies of appetitive operant behavior.

Fourteen male White Carneaux pigeons obtained from the Palmetto Pigeon Plant were used. The birds were maintained at between 75-80% of their free-feeding weight and were individually housed in a room with a 12-hour light-dark cycle. The experimental chambers were standard one-key, Grayson-Stadler pigeon chambers. All pigeons were trained to peck the key for reinforcement (2 sec of food availability) on an FR 35 schedule, after which they were placed in the chambers for 30 min each day and the number of responses recorded.

The experimental design is represented in Table 1. The pigeons were randomly divided into four groups after 8 days of training. All injections were given into the breast muscle once daily 15 min before testing. In addition to the electronic recording of key-pecks, the birds were visually observed during the sessions and their gross behavior recorded. Only one pigeon from the 3.5 mg/kg group was continued beyond Day 15; his pre- and post-drug response rate was representative of the other animals in that group.

The first injection of mescaline produced a dose-dependent disruption of

TABLE 1

Experimental Design

Group	Days 1-4	5-8	9-15	16-39	40-45	46-52
1 (N = 3)	Baseline (no injection)	Baseline 1 cc/kg saline	1.0 mg/kg mescaline			
2 (N = 4)	↓	↓	1.5 mg/kg mescaline			
3 (N = 4)	↓	↓	3.5 mg/kg mescaline	3.5 mg/kg mescaline (N = 1)	1 cc/kg saline	3.5 mg/kg mescaline
4 (N = 3)	↓	↓	6.5 mg/kg mescaline	6.5 mg/kg mescaline	1 cc/kg saline	6.5 mg/kg mescaline

performance (Fig. 1). There was no significant alteration of the response rate for any bird injected with either of the lowest doses (1.0 and 1.5 mg/kg) after acute or repeated administration.

The chronic effects of 3.5 and 6.5 mg/kg are depicted in Fig. 2. The 3.5 mg/kg dose resulted in an initial decrease in responding to about 60% of baseline ($P < 0.01$). This reduced level of responding was maintained throughout the first week of drug administration. The one pigeon continued beyond this point remained at about the 60% level throughout the entire drug course, and immediately recovered to baseline when saline was substituted on Day 40. Reinitiation of drug administration on Days 46-52 produced a reduction in response rate comparable to that observed in the original drug course.

The dose of 6.5 mg/kg initially abolished responding (Fig. 1; $P < 0.01$). During the next 3 weeks responding steadily increased, stabilizing at about 60% of baseline for the remainder of the drug course (Fig. 2). Saline injection

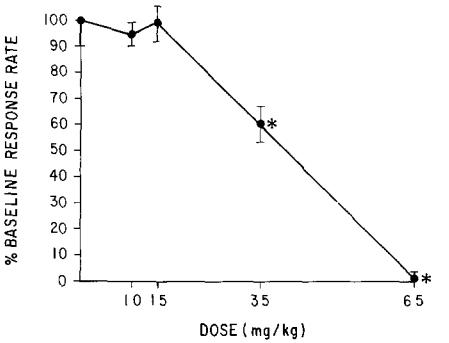

Fig. 1. Dose-dependent effects of mescaline on the acute (one session) disruption of appetitive fixed-ratio responding in pigeons. * = Significantly less than baseline ($P < 0.01$); brackets indicate ± SEM.

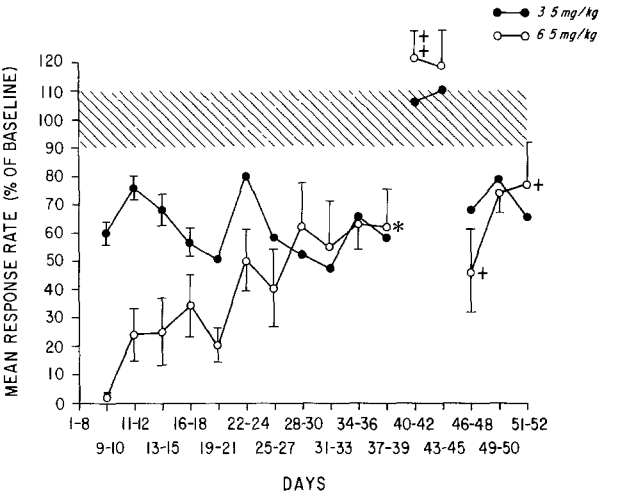

Fig. 2. Effects of daily administration of two doses of mescaline on appetitive fixed-ratio responding in pigeons. Mescaline was injected (im) for 39 days followed by 6 days of saline, after which mescaline was reintroduced for 8 days. Diagnonal band indicates mean ± *SD* for baseline responding; brackets indicate ± *SEM*. * = Significantly less than baseline ($P < 0.02$) and significantly greater than initial effect of 6.5 mg/kg mescaline ($P < 0.01$); + = significantly less than baseline ($P < 0.05$); ++ = significantly greater than late (Days 37-39) mescaline effect ($P < 0.05$).

on Day 40 resulted in an immediate return to baseline response levels ($P < 0.05$). One subject increased to 70% over baseline; this pigeon accounts for the relatively high mean response level during this period observed in Fig. 2. Drug readministration on Days 46-52 resulted in a response rate comparable to the level of responding achieved late in the original drug course, but markedly greater than that produced by this dose on Day 9. No overlap in response rate occurred between the first week of drug administration (Days 9-15) and either the final week of the original drug course (Days 32-39) or the final 4 days of mescaline readministration (Days 49-52).

The effects of mescaline on gross behavior were observed only in subjects injected with doses of 3.5 or 6.5 mg/kg and consisted primarily of spontaneous headshakes [similar in appearance to the headshakes seen in mice with tactile stimulation to the pinnae or with hallucinogenic drug administration (Corne and Pickering, 1967)] and periods in which the subjects remained immobile with eyes partially or completely closed and feathers ruffled. These behaviors were most prevalent during the first two to three drug days, occurring almost 100% of the time in the 6.5 mg/kg group and about 20% of the time in the 3.5 mg/kg group. After a few days their rate of occurrence was reduced to about 60 and 5%, respectively, and persisted at this reduced level for the remainder of the drug course and during the drug

readministration period (Days 46-52). Also, during the first two to three drug days (Days 9-11) each member of the 6.5 mg/kg group exhibited ataxia when walking and were seen to occasionally sway and stumble even while standing still. Ataxia was not observed after the first few days and was not seen in the lower dose groups.

In order to rule out persistent effects of mescaline on food motivation, a separate study was performed in which daily mescaline injections (6.5 mg/kg) were given to food-deprived pigeons 15 min before a full food cup was presented to them in their home cages. The amount of food consumed during a 30-min period was compared to a control (saline) group over several days. Although on Day 1 food consumption in the mescaline group was lowered to 50% of controls, on Day 2 the drug group actually consumed 75% more than controls, and thereafter food intake was essentially identical to controls. Consistent with these results is our observation that when supplemental feeding was required immediately after a test session (in order to maintain 75-80% free feeding weight), the subjects ate the food as vigorously as they did when not drugged. At the time of removal from the chambers, they were still clearly under the influence of mescaline, as evidenced by a uniformly low response rate throughout the test session and by continued headshaking and stuporous appearance.

A dose of 6.5 mg/kg of mescaline which initially abolishes responding becomes progressively less disruptive with repeated administration. When responding reaches approximately 60% of baseline (in about 3 weeks), no further tolerance occurs. At a dose of 3.5 mg/kg, mescaline lowers responding to about 60% of baseline and repeated administration of this dose continues to produce approximately the same level of responding.

These results are comparable to those of Smythies *et al.* (1966) and of Bridger *et al.* (1973) in that tolerance develops to the effects of high doses of mescaline until its effect is equivalent to that of a lower dose, after which no further tolerance occurs. Similarly, low doses maintain their effect on performance with repeated administration. These parallels are apparent despite the fact that a low dose is facilitory to rats performing a CAR and inhibitory to pigeons in an FR appetitive paradigm.

Bridger *et al.* (1973) have suggested that complete tolerance develops to one effect of mescaline (elicited by a high dose), thereby "unmasking" a second tolerance-resistant effect (elicited by a low dose). Our results are consistent with this interpretation. However, in contrast to the inhibition-facilitation dichotomy observed by Smythies' and Bridger's groups, in the present study the two effects would be acting independently to produce the same end-result: inhibition. The fact that in our study complete tolerance rapidly developed to the ataxic and anorectic effects and partial tolerance occurred to the other gross behavioral effects described above indicates that mescaline has several actions, tolerance developing to some but not to others.

An alternate explanation of the two-stage mescaline action is that mescaline produces a single disruptive effect in pigeons performing a FR appetitive response and partial tolerance (subserved by behavioral, functional, and/or distributional mechanisms) develops to this effect with repeated administration of the drug. Although Bridger *et al.* (1973) do not consider partial tolerance to a single effect as a possible explanation for their results, it is conceivable that the inhibitory effects observed with high doses of mescaline reflect excessive activation of the mechanism subserving the facilitation induced by the low dose. Partial tolerance would decrease the effective dose and the excitation to a level comparable with response requirements, thus resulting in improved performance.

The final week of drug readministration (Days 46-52) indicates that whatever tolerance mechanisms were activated during the original drug course are still effective after a drug-free period of at least 7 days. This is consistent with Smythies and Sykes' finding (1964) of some tolerance to mescaline persisting 2 weeks after the last dose.

In this paper we report a paradigm in which tolerance-resistant effects of an hallucinogenic drug are observed; the salient features which distinguish such paradigms from those in which tolerance develops remain to be elucidated. It is apparent, however, that under certain circumstances effects of hallucinogenic drugs may persist with repeated exposure to the drug. An endogenously produced hallucinogenic substance could, therefore, conceivably continue to disrupt brain function over extended periods of time, resulting in a long, chronic course of schizophrenia.

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