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# Drug-Induced Stimulus Control and the Concept of Breaking Point: LSD and Quipazine

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**Abstract.** Discriminative stimulus control was established in rats ($N = 12$) with LSD (100 µg/kg) and saline using a two-lever response choice task and an FR10 schedule of water reinforcement. Subjects were then tested once per week with either LSD or quipazine (3 mg/kg) and every other week the test ratio was doubled, i.e., each drug was tested at ratios of 10, 20, 40, and 80. In contrast with LSD, which maintained stimulus control at all ratios, LSD-appropriate responding following quipazine declined significantly at FR80. In addition, five of eight subjects tested with quipazine failed to complete the FR80 in 15 min. In subsequent experiments, the breaking point, here defined as the number of LSD-appropriate responses prior to emission of ten responses on the saline-appropriate lever, was determined for LSD and for quipazine. Mean values ($N = 12$) for LSD and quipazine were $161 \pm 28$ and $65 \pm 19$, respectively.

**Key words:** Breaking point – LSD – Progressive-ratio – Quipazine – Stimulus control

Despite a generally good correlation between the discriminative stimulus properties of indoleamines and phenethylamines in the rat and their hallucinogenic activity in man, there are some drugs which mimic one another in the rat yet differ in their ability to induce hallucinations in human subjects (Winter 1980). For example, quipazine substitutes for lysergic acid diethylamide (LSD) in rats trained with the latter drug (Kuhn et al. 1978; Winter 1979) but extensive clinical tests have failed to reveal hallucinogenic activity (J. Villarreal, personal communication).

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Hodos (1961) described a progressive ratio procedure in which an animal was required to emit a progressively increasing number of responses in order to obtain food. The ratio at which response rate fell below some preset criterion was termed the terminal ratio or breaking point. Hodos suggested that the breaking point provides a quantitative measure of the strength of a reinforcer. The progressive ratio procedure was subsequently employed in studies of intracranial electrical stimulation (Hodos 1965) and the reinforcing properties of self-administered drugs (Yanagita 1973). The present experiments apply the concept of breaking point to cross tests of quipazine in rats trained with LSD and saline.

## Material and Methods

All subjects were CFN strain rats (Carworth Farms, Wilmington, MA, USA). They were housed in pairs and had free access to dry food in the home cage. With the exception of weekends, water intake was limited to that obtained during experimental session.

Twelve rats were trained with LSD (100 µg/kg) and saline in a two-lever response choice task (Hirschhorn and Winter 1971) using a fixed-ratio 10 (FR10) schedule of reinforcement. During discrimination training, LSD was administered on Monday, Wednesday, and Friday; saline was injected on Tuesday and Thursday. The distribution of the first ten responses between the two levers was recorded each day. LSD-induced stimulus control was presumed to be present when, in five consecutive sessions, eight or more of the initial ten responses were upon the appropriate lever.

Cross tests of quipazine (3 mg/kg) in LSD-trained subjects were conducted on Fridays so long as previous performance in the same week did not fall below a criterion of 80% correct responding. During cross tests, no responses were reinforced and the cross test sessions were terminated after completion of the ratio in effect. With the exception of the quipazine cross test at FR10, for which the preceding LSD session was used as a control, quipazine cross tests alternated on a weekly basis with LSD control sessions. Thus, one-half of the subjects were tested in the following sequence: quipazine (QP)-FR10; LSD-FR20; QP-FR20; LSD-FR40; QP-FR40; LSD-FR80; QP-FR80. The remaining subjects were tested with quipazine before LSD at every ratio after 10. Response distribution at the higher ratios was

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not a criterion for continued testing but the criterion of 80% correct choices on Monday through Thursday was applied throughout.

Upon completion of the progressive ratio series, subjects were tested as follows. After pretreatment with either quipazine or LSD, rats were allowed to lever press in extinction until ten responses had been emitted on the saline lever. In these tests, the breaking point is the number of drug-appropriate responses emitted prior to reaching the criterion of ten saline-appropriate responses. For one-half of the subjects, the order of breaking point determination was LSD-QP and for the other half, the order was reversed.

Comparisons of LSD-appropriate responding following quipazine and LSD at each ratio in the progressive ratio series and of breaking points were made by means of the sign test for paired observations. D-LSD tartrate (NIDA, Rockville, MD, USA) and quipazine (Miles Laboratories, Elkhart, IN, USA) were dissolved in 0.9% saline and injected IP 15 min before testing in a constant volume of 1 ml/kg body wt.

## Results

When LSD and quipazine were tested in the progressive ratio series ($N = 8$), the degree of LSD-appropriate responding was not significantly different for the two drugs at ratios of 10, 20, and 40 (FR10: LSD = 100%, QP = 89%; FR20: LSD = 100%, QP = 94%; FR40: LSD = 98%; QP = 86%). However, at FR80 all subjects treated with LSD completed the FR80 during the 15-min session but only three of eight did so following quipazine. The three subjects gave 54% of their responses on the LSD lever as compared with 95% for the LSD sessions at FR80. For all eight subjects, regardless of completion of the ratio, the mean percentage of LSD-appropriate responses was 71% following quipazine (LSD control = 96%; $P = 0.01$) and the mean number of LSD-appropriate responses was 33 (LSD control = 77; $P = 0.01$).

The implications of the failure of all subjects to complete the FR80 following quipazine were confirmed by breaking point determinations. Prior to the emission of ten saline-appropriate responses, subjects trained with LSD ($N = 12$) and tested in extinction with LSD emitted a mean of 161 (SE = 28) responses on the LSD lever. In contrast, the same group responded 65 (SE = 19) times on the LSD-appropriate lever following quipazine ($P = 0.05$), Despite this difference in breaking points, the distribution of the first ten responses remained quite similar (LSD: 9.82; quipazine: 9.42).

## Discussion

The data obtained from the progressive ratio series indicate that conclusions regarding the stimulus properties of LSD and quipazine may be altered as a function of cross test conditions. Thus, the ability of quipazine to mimic LSD closely at low test ratios is diminished at FR80. Furthermore, the values for breaking point for stimulus control by LSD and quipazine are quite different. Although it remains to be established that comparison of drugs using progressive ratios or a knowledge of breaking points for stimulus control will improve the correlation between stimulus properties in animals and clinical effects in man, there are no obvious experimental barriers to examination of this question. Indeed, it is hoped that such experiments will add a new dimension to the already impressive body of knowledge regarding drug-induced stimulus control.

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