European Journal of Pharmacology, 96 (1983) 317–320
Elsevier

Short communication

TOLERANCE DEVELOPS TO LSD WHILE THE DRUG IS EXERTING ITS MAXIMAL BEHAVIORAL EFFECTS: IMPLICATIONS FOR THE NEURAL BASES OF TOLERANCE

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Received 13 October 1983, accepted 19 October 1983

M.E. TRULSON and T. CRISP, *Tolerance develops to LSD while the drug is exerting its maximal behavioral effects: implications for the neural bases of tolerance*, European J. Pharmacol. 96 (1983) 317–320.

Tolerance to a test dose of 50 mg/kg of LSD occurred within 0.5-1.0 h following an initial dose of 10 mg/kg of the drug, using limb flicking and abortive grooming as behavioral indices in the cat. These findings represent an example of very rapidly developing drug tolerance using a behavioral index. These data are discussed within the context of hypotheses concerning the neurochemical bases of tolerance to LSD.

LSD Cats Limb flick Tolerance Hallucinogens Animal model

1. Introduction

A very pronounced and rapidly occurring tolerance develops to the psychic effects of lysergic acid diethylamide (LSD) in humans following repeated drug administration (e.g., Abramson et al., 1956). Similarly, tolerance to the behavioral effects of LSD occurs quickly in animals (e.g., Trulson and Jacobs, 1977). The neurochemical bases for this tolerance effect is not known; however, it has been established with certainty that the tolerance involves changes within the central nervous system (CNS), rather than increased peripheral metabolism of the drug (Trulson and Jacobs, 1977).

LSD produces characteristic behavioral responses in a variety of animal species, including mice, rats, cats and monkeys. Our laboratory has employed the cat as the experimental animal in most of our behavioral studies of the effects of LSD. Drug administration to cats elicits a constellation of behavioral signs consisting primarily of limb flicking, abortive grooming, head shakes, excessive grooming, staring, and investigatory and hallucinatory-like responses (Trulson and Jacobs, 1977). Limb flicks and abortive grooming are the most sensitive and reliable behavioral indices of the central action of hallucinogenic drugs and were therefore used for the quantitative behavioral analyses in the present study (Trulson and Jacobs, 1977). The limb flick and abortive groom are useful model behaviors for studying the actions of LSD, particularly when precise quantitative data are desired. These behaviors display the following characteristics: (1) they are elicited only by LSD and related hallucinogens, with few possible exceptions (White et al., 1981) (2) they parallel the major characteristic of the action of LSD in humans; (3) they are not simply due to drug-induced somatosensory alterations, but are reflective of more complex central processes (Trulson and Crisp, 1982); and (4) they show the characteristics of dose-dependency, sensitivity to doses near the human range, and are robust, reliable and easy to quantify.

In the present study, we systematically investigated the time-course for the onset of tolerance to LSD in the cat, with the expectation that these findings might provide some insight into the nature of the central mechanism mediating this tolerance effect.

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2. Materials and methods

Adult male (n = 5) and female (n = 7) cats (2.8 = 4.0 kg) were individually housed in standard stainless steel cat cages in a room kept at constant temperature (22 ± 2°C) and on a 12:12 h light dark cycle (lights on, 8:00 a.m.). The cats were administered saline (0.5 ml/kg i.p.) or LSD (50 mg/kg i.p.) in a counter-balanced design at 7-day intervals for a total of 28 days to establish baseline data. Thus, each cat received 2 saline injections and 2 LSD injections. Following each injection, behavioral observations were made by experimenters who were unaware of the treatment. Each of the behavioral effects described above was tallied; however, quantitative data will be presented only for the limb flick and abortive groom responses, due to the reasons described above. Seven days after completing the baseline observations, the cats were pretreated with a single injection of saline or 10 mg/kg (i.p.) of LSD followed by an additional 50 mg/kg dose of LSD either 0.5, 1.0, 2.0, 6.0 or 24 h later. Behavioral observations were taken for one h following the test dose (50 mg/kg) of LSD. For statistical analysis, the means and standard error for the number of limb flicks and abortive grooms were obtained for each time point, and compared to saline baseline (i.e., saline followed by 50 mg/kg of LSD) using two tailed t-tests, following a two-way analysis of variance (ANOVA) for time and drug treatment (i.e., saline plus 50 mg/kg of LSD versus 10 mg/kg of LSD plus 50 mg/kg of LSD).

3. Results

A two-way ANOVA revealed a significant time effect for limb flicking ($P < 0.05$) for animals that were pretreated with 10 mg/kg of LSD and then given a test dose of 50 mg/kg (table 1). There was also a significant drug by time interaction ($P < 0.05$). The limb flick response showed a significant tolerance effect at 0.5 h following the 10 mg/kg LSD pretreatment (table 1). The magnitude of tolerance for limb flicks gradually increased over time, reaching levels of −48.1%, −51.3%, −74.2% and −91.5% at 1, 2, 6 and 24 h following a dose of 10 mg/kg, respectively (table 1). A two-way ANOVA for abortive grooming also revealed a significant time effect ($P < 0.05$) and drug by time interaction ($P < 0.05$). While the rate of abortive grooming was decreased by 28.8% at 0.5 h following the initial dose of 10 mg/kg of LSD, this difference was not statistically significant (table 1). However, by 1 h postinjection, abortive grooming

TABLE 1

Onset of tolerance to LSD in the cat [c].

Behavior	Drug (dose, mg/kg)	Inter-LSD injection interval (h)					
		0	0.5	1.0	2.0	6.0	24
Limb flick	Saline + LSD (50)	41.3 ± 4.6	39.6 ± 3.5	46.8 ± 4.9	40.9 ± 3.7	43.4 ± 3.1	32.5 ± 4.1
	LSD (10) + LSD (50)	39.2 ± 3.8	30.2 ± 2.9 [a]	24.3 ± 2.4 [b]	19.9 ± 3.4 [b]	11.2 ± 2.1 [b]	3.2 ± 0.9 [b]
% Change		(−5.1%)	(−23.7%)	(−48.1%)	(−51.3%)	(−74.2%)	(−91.5%)
Abortive groom	Saline + LSD (50)	4.9 ± 2.0	5.2 ± 1.6	4.3 ± 1.7	4.0 ± 1.9	5.6 ± 2.2	6.1 ± 2.4
	LSD (10) + LSD (50)	5.3 ± 1.3	3.7 ± 0.5	2.6 ± 0.9 [a]	1.9 ± 0.7 [b]	0.9 ± 0.5 [b]	0.2 ± 0.2 [b]
% Change		(+8.2%)	(−28.8%)	(−39.5%)	(−52.5%)	(−85.9%)	(−95.2%)

[a] Significantly different from saline value, $P < 0.05$, t-test.

[b] $P < 0.01$.

[c] Cats received a single injection of saline (0.5 ml/kg i.p.) or 10 mg/kg of LSD, and then a test dose of 50 mg/kg of LSD 0, 0.5, 1.0, 2.0, 6.0 or 24 h later. The frequency of occurrence of limb flicking and abortive grooming were recorded during the h immediately after the test dose. Data are presented as mean hourly occurrences ± S.E.M. for 12 cats.

showed a significant decrease of 39.5% ($P < 0.05$). Abortive grooming then showed progressive decreases in frequency of −52.5%, −83.9% and −95.2%, respectively, following a test dose of 50 mg/kg of LSD at 2, 6 and 24 h after the initial dose of LSD (10 mg/kg) (table 1).

4. Discussion

The present data demonstrate that partial tolerance to a test dose of LSD (50 mg/kg) following a single injection of 10 mg/kg of LSD develops very rapidly. A significant tolerance develops within 30 min using the limb flick as a behavioral index, and within 1 h using the measure of abortive grooming. This confirms our previous notion that the limb flick is the most sensitive index for the action of LSD (Trulson and Jacobs, 1977).

Rapid development of tolerance has been reported to occur for other drugs as well. For example, tolerance to the analgesic effects of morphine has been reported to occur within 24 h after a single injection (Kayan and Mitchell, 1972). Similarly, tolerance to the behavioral effects of barbiturates has been reported to occur within 26 h after a single dose (Jaffe and Sharpless, 1965). In addition, tolerance to the 'running fit' elicited by levorphanol occurs even more rapidly, showing a significant effect within 12 h (Goldstein and Sheehan, 1969). The tolerance observed in the present study does not appear to represent a case of tachyphylaxis or 'behavioral tolerance', since the effect occurs betwen 0.5 and 1 h, a time when cats display their maximal response to either 10 or 50 mg/kg of LSD (Trulson and Jacobs, 1977). Since tolerance to LSD is not mediated by increased peripheral metabolism of the drug, as discussed above, this phenomenon obviously involves changes within the CNS.

LSD appears to exert its behavioral effects by binding to specific CNS receptors (Peroutka and Snyder, 1979) which are related to both serotonergic and dopaminergic receptors. We have not observed changes in LSD binding to occur this rapidly following repeated LSD treatment (Trulson and Jacobs, 1979). Thus, a change in the binding of LSD to its receptor is unlikely to account for the rapid development of tolerance. That is, adding 50 mg/kg of LSD 30 min after administering a dose of 10 mg/kg of LSD is not likely to decrease the amount of LSD around the relevant receptor sites, nor alter the binding characteristics of LSD to its receptor.

In a recent study of the ontogeny of the behavioral effects of LSD in the cat, we observed a total lack of tolerance development following repeated LSD treatment in young kittens (Trulson and Howell, 1983). These latter findings suggested that the primary site of action for LSD in exerting its characteristic behavioral effects, such as limb flicking and abortive grooming, may be different from the site mediating the tolerance effect. The present data are consistent with such an hypothesis. If the primary behavioral effects and tolerance are indeed mediated by different neurochemical mechanisms, then one might expect to see on-going behavioral changes induced by LSD treatment, while tolerance begins to develop concurrently.

In conclusion, the present data demonstrate that a significant tolerance to the behavioral effects of LSD in the cat develops within 30 min. These findings, together with previous data, suggest that the neurochemical bases for tolerance development is quite different from that mediating the primary behavioral effects.

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