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Lack of Synergism and Cross Tolerance Between Tactile Stimulus- and LSD-Induced Limb Flicking in the Cat

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TRULSON, M. E. AND T. CRISP. *Lack of synergism and cross tolerance between tactile stimulus- and LSD-induced limb flicking in the cat.* PHARMAC. BIOCHEM. BEHAV. **17**(3) 589–591, 1982.—The hypotheses that LSD-induced limb flicking, as well as tolerance to this behavioral effect following repeated drug administration, are due to alterations in somatosensory thresholds were tested by examining the rate of limb flicking to LSD alone, saline plus water on the limbs, or LSD plus water on the limbs, and by comparing the limb flick rate with water on the limbs in drug tolerant versus non-tolerant conditions. Cats exhibited the same rate of limb flicking in response to water on the limbs regardless of whether they were pretreated with saline of LSD. Furthermore, there was no significant difference in the tactile stimulus-induced rate of limb flicking in the tolerant versus non-tolerant states. These data suggest that LSD-induced limb flicking is not simply a function of drug-induced altered somatosensory thresholds, but is apparently reflective of more complex neural processes.

Synergism Cross tolerance Tactile stimulus LSD Limb-flicks Cat

SEVERAL years ago Jacobs, Trulson and Stern [1] introduced an animal behavioral model for studying the actions of hallucinogens. It was reported that administration of lysergic acid diethylamide (LSD), 2,5-dimethoxy-4-methylamphetamine (DOM), psilocin, mescaline, and N,N-dimethyltryptamine (DMT) to cats elicits a number of behaviors such as limb flicking, abortive grooming, investigatory and hallucinatory-like responses [1, 2, 7, 8]. The utility of this behavioral syndrome is greatly enhanced by the fact that these model behaviors are rarely seen following saline administration; show a dose-dependent increase in frequency; are reproducible across time; are easily quantified; and are sensitive to doses near the human range [2]. While recent studies have indicated that these model behaviors are not totally specific for hallucinogenic drugs [3, 4, 5, 6]; J. L. Marini, personal communication) this behavioral syndrome continues to be useful in studying drug action.

Of these model behaviors, the limb flick has proven to be the most sensitive and reliable index of drug action, because it is virtually never seen following saline administration, and occurs with a high frequency following drug treatment. Furthermore, the limb flick is the easiest behavior to observe and quantify, and most closely parallels the parameters of the actions of hallucinogens in humans such as the duration of action and onset and duration of tolerance [8].

The limb flick is a species-specific behavior normally used exclusively for removing foreign substances from the limbs, and thus is intimately associated with tactile stimuli. Hallucinogen-induced limb flicking, therefore, has face validity as a model for hallucinogens in that it is a bizarre response for the context in which it occurs, i.e., in the absence of any foreign substance on the limb. Since the paw of a cat is virtually always in contact with some surface, one could argue that the hallucinogen-induced increase in the rate of limb flicking is due to an increase in the sensitivity of the limbs.

One of the most dramatic effects of LSD administration is the nearly complete tolerance that develops to its repeated administration. For example, when a naive cat is given a dose of 50 μg/kg of LSD it will exhibit approximately 40 limb flicks per hour. If the same dose of LSD is re-administered 24 hours later, only 1–3 limb flicks per hour are typically observed [8]. If the LSD-induced increase in limb flick rate is related to altered somatosensory function, as suggested above, then tolerance to LSD may also be mediated by altered somatosensory thresholds. To test these hypotheses, we examined the limb flick rate in response to LSD, saline plus a foreign substance (water) on the limbs, and LSD plus water on the limbs. In addition, we compared the limb flick rate in response to water on the limbs in naive cats and those made tolerant by repeated administration of LSD.

METHOD

Experiment 1

Six naive male (N=3) and female (N=3) (2.3–3.8 kg) cats were used. On Day 1, each cat received an injection of saline (0.5 ml/kg, IP) and was placed in a cage which contained a metal pan floor covered with 2 cm of water at room tempera-

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TABLE 1

RATE OF LIMB FLICKING INDUCED BY A TACTILE STIMULUS, LSD, AND THE COMBINED EFFECT OF A TACTILE STIMULUS AND LSD

Day	Treatment	Mean limb flick rate/ 30 min ±S.E.M.*
1	Saline plus water on limbs; Trial 1	36.3 ± 5.7
1	Saline plus water on limbs; Trial 2	30.7 ± 3.8
2	Saline plus water on limbs; Trial 1	34.9 ± 4.2
2	Saline plus water on limbs; Trial 2	31.3 ± 3.1
3	LSD (50 μg/kg)	24.9 ± 2.0
11	LSD (50 μg/kg)	26.1 ± 2.2
19	LSD (50 μg/kg) plus water on limbs	39.4 ± 4.6

*No two values differ significant from each other, $p>0.05$, Newman-Keuls tests, N=6 per group.

TABLE 2

EFFECT OF REPEATED LSD TREATMENT ON TACTILE-STIMULUS INDUCED LIMB FLICKING

Day	Treatment	Mean limb flick rate/30 min±S.E.M.
1	water on limbs; Trial 1	29.1 ± 6.4
1	water on limbs; Trial 2	25.3 ± 4.9
2	water on limbs; Trial 1	20.7 ± 4.1
2	water on limbs; Trial 2	22.9 ± 2.9
3	LSD (50 μg/kg)	17.2 ± 1.8
4	LSD (50 μg/kg)	1.5 ± 1.0*
4	water on limbs; Trial 1	15.0 ± 3.9
4	water on limbs; Trial 2	11.4 ± 4.1
5	water on limbs; Trial 1	18.2 ± 3.4
5	water on limbs; Trial 2	14.6 ± 4.2

*Differs significantly from all other values, $p<0.05$, Newman-Keuls tests, N=6 per group.

ture, and the number of limb flicks during a 30 min period was tabulated. Two hours later, the trial was repeated in exactly the same manner. On Day 2, an identical protocol was followed as on the previous day, in order to assess the stability of the measures across time. On Day 3, each cat received LSD (50 μg/kg, IP), and the number of limb flicks was tabulated for 30-minutes post-injection, using a dry chamber. On Day 11, each cat again received LSD (50 μg/kg) to assess the stability of responsiveness to LSD over time (7 days intervened between injections to allow time for all tolerance effects to disappear [8]). On Day 19 (again allowing time for tolerance to dissipate), the cats received LSD (50 μg/kg) and then were placed in chambers containing 2 cm of water on the floor, as described above, and the number of limb flicks during a 30-minute period was tabulated.

Experiment 2

Six naive male (N=3) and female (N=3) cats (2.1–3.6 kg) were used. On Day 1, each cat was placed in a cage which contained a metal pan floor covered with 2 cm of water at room temperature, and the number of limb flicks during a 30-minute period was tabulated as described above. Two hours later, the trial was repeated in exactly the same manner. On Day 2, an identical protocol was followed as on the previous day. On Day 3, each cat received LSD (50 μg/kg), and the number of limb flicks was again tabulated for 30-minutes post-injection in a dry chamber. Immediately following this 30-minute period, the cats were placed in cages with water covering the floor, as described above, and the number of limb flicks during two 30-minute trials separated by two hours was tabulated. Finally, on Day 5, the cats were placed in cages with water covering the floor, as described above, and the number of limb flicks during two 30-minute trials separated by two hours was again tabulated.

RESULTS

The limb flick rate in response to water on the paws was very stable across trials, ranging from 30.7 to 36.3 flicks per 30 minutes in Experiment 1 (Table 1) and 20.7 to 29.1 flicks per 30 minutes in Experiment 2 (Table 2). In agreement with previous studies, initial administration of 50 μg/kg of LSD elicited 17.2 to 26.1 flicks per 30 minutes (Tables 1 and 2). The combined effect of LSD plus water on the limbs had no significantly greater effect than either water on the limbs or LSD alone (Table 1). Also in agreement with prior studies, re-administration of 50 μg/kg of LSD 24 hours after the initial dose elicited only 1.5 flicks per 30 minutes, i.e., nearly complete tolerance had developed (Table 2). Despite this virtually complete tolerance to LSD-induced limb flicking, however, the cats continued to flick at approximately the same rate in response to the presence of water on their paws (Table 2).

DISCUSSION

The present data demonstrate that LSD-induced limb flicking in the cat is not due to drug-induced altered somatosensory thresholds, since cats exhibited the same rate of limb flicking in response to water on the limbs regardless of whether they were pretreated with saline or LSD. Furthermore, the profound tolerance that develops to LSD-induced limb flicking following its repeated administration is not due to an alteration in tactile sensitivity. The cats continued to flick at approximately the same rate in response to water on the paws during LSD tolerance as during the non-tolerant condition. Our previous studies have shown that tolerance following a single injection of LSD at a dose of 50 μg/kg persists for approximately 5 days [8] and, therefore, no response to LSD would have been expected on Day 5 in Experiment 2.

The lack of synergism and cross tolerance between tactile stimulus and LSD-induced limb flicking in the cat suggests that drug-induced limb flicking is apparently not merely a function of somatosensory alterations and, therefore, may be reflective of more complex neural processes. Future neurochemical and neurophysiological studies should help elucidate the neural mechanisms by which hallucinogens (and other drugs) elicit the limb flick response.

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