Ontogeny of the Behavioral Effects of Lysergic Acid Diethylamide in Cats

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The ontogeny of the behavioral effects of lysergic acid diethylamide (LSD) was examined in cats between the ages of 4 and 112 days postpartum. The kittens showed little LSD-induced behavioral change prior to 14 days of age. By the age of 21 days, however, the kittens exhibited many of the behavioral signs characteristic of LSD-induced behaviors in adult cats. These behaviors include limb-flicking, abortive grooming, head-shakes, grooming, and investigatory responses. In general, these behaviors began at a low frequency of occurrence, then increased rapidly with advancing age, reaching adult values by approximately 35–40 days of age, and remained relatively constant through 112 days postpartum. The time course for the behavioral effects following an acute injection of LSD showed the adult pattern, i.e., persisting for approximately 8 hr post-injection, from their earliest appearance during ontogeny. Young kittens (21–42 days of age) were resistant to the development of tolerance following repeated administration of the drug. LSD was capable of eliciting certain behaviors, such as head-shakes and grooming, well in advance of the age at which they normally appear spontaneously. This indicates that the neuronal and musculature substrata are developed for the performance of these behaviors long before the kitten naturally employs them.

The potent hallucinogenic properties of lysergic acid diethylamide (LSD) were initially described by Albert Hofmann in 1943. Since then, the phenomenology of LSD-induced hallucinosis in humans has been extensively described by a number of investigators (Cholden, Kurland, & Savage, 1955; Isbell, Belleville, Fraser, Wikler, & Logan, 1956; Savage, 1975). The effects of LSD in humans include visual hallucinations, large and rapid changes in mood, a distorted time sense, depersonalization, difficulty in thinking, a dreamlike feeling, synesthesia (a mixing of the senses), dizziness, nausea, tremors, weakness, blurred vision, and a tingling sensation of the skin. The behavioral effects of LSD in animals have also received monumental attention, and literally thousands of studies have dealt with this issue. These effects have been described in a wide variety of animal species including insects (Witt, 1975), fish (Turner, 1956), mice (Corne & Pickering, 1967), rats (Butters, 1966; Hamilton, 1960; Trulson, Ross, & Jacobs, 1976; Winter & Flataker, 1956), rabbits (Gormezano & Harvey, 1980), cats (Jacobs, Trulson, & Stern, 1977; Siegel & Jarvik, 1975), dogs (Hardman, Haavik, & Seevers, 1973), monkeys (Evarts, 1956; Jonas & De C Downer, 1964), and even elephants (Siegel & Jarvik, 1975). Although LSD-induced behavioral effects have been well studied across phylogeny, virtually no

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attention has been devoted to the study of the behavioral effects of LSD during ontogeny for a given species.

A study of the ontogeny of the behavioral effects of LSD is important for several reasons. First, the drug is frequently used by young humans so that knowledge of the comparative effects of the drug in adult vs younger individuals is important, especially since virtually all neurochemical and neurophysiological studies of the effects of the drug have been conducted on adult animals. Second, a study of the ontogeny of the behavioral effects of LSD may help to understand the mechanism of action of the drug, since ontogenetic changes in drug action can be correlated with neurochemical, neurophysiological, and anatomical changes in the developing brain. Third, LSD is generally considered the prototypic hallucinogen, possessing both phenylethylamine and indoleamine moeities so that a description of the ontogeny of the behavioral effects of LSD may be useful in predicting similar patterns for other hallucinogens. Finally, general principles of drug action may emerge through the study of a variety of drugs during ontogeny.

In the present study, we investigated the ontogeny of the behavioral effects of LSD in the cat. The cat was chosen as the test animal for the following reasons: It possesses a very rich behavioral repertoire, so that many behavioral changes may be monitored during ontogeny; extensive experimentation has been conducted concerning neurochemical, neurophysiological and neuroanatomical development in the cat so that it may be possible to relate drug-induced behavioral effects to changes in these various measures of brain development; the behavioral effects of LSD in the adult cat have been described in detail, so there is a wealth of data available to indicate what behaviors should be made the focus of the study (Jacobs et al., 1977; Trulson & Jacobs, 1976; Trulson & Jacobs, 1977); and the life span of the cat is conducive to such a study, since the interval between birth and adulthood is short enough to conduct such a study in a reasonable amount of time, but long enough to permit the detection of small changes using test intervals of several days.

Methods

Pregnant cats were individually housed in standard laboratory cages in a room kept at constant temperature (22 ± 2°C), maintained on a 12:12-hr light-dark cycle (lights on 8:00 a.m.), and were checked for births twice daily. Behavioral observations were made with the kittens placed in pairs in their home cage, since previous studies have demonstrated that kittens show no significant distress in a familiar environment with a littermate present, even though the mother has been removed (Rheingold & Eckerman, 1971). In addition, kittens were observed together as a litter with the mother present during the first 2 weeks postpartum. Groups of kittens were administered saline or LSD tartrate (10, 50, or 200 μg/kg, i.p.) at ages 4, 7, 14, 21, 25, 30, 42, 49, 56, 70, 84, and 112 Days postpartum. Doses of LSD were counterbalanced within kittens over time. Subgroups of kittens at various ages that received 50 μg/kg of LSD were given a second LSD injection (50 μg/kg) 24 hr after the initial injection, to test for tolerance development. Five to 28 days intervened between consecutive sessions with the same kittens (except for the tolerance studies). Our previous studies have demonstrated that any tolerance dissipates within 5 days (Trulson & Jacobs, 1977). Each kitten received a total of five to eight LSD injections. A total of 71 kittens were used (35 female; 29 male; sex was not determined on seven kittens). A group of adult cats (12–26 months of age) that had never received LSD treatment was tested for its responsiveness to 50 μg/kg of LSD as well as for tolerance development to the same dose of the drug 24 hr later. The average number of kittens receiving each dose at each age was 16.2 (range = 12–19).

In all studies, behavior was continuously monitored and recorded on a standard scoring sheet for 1 hr post-injection and then for the second 30-min period of each succeeding hour until all behavioral changes had largely subsided (i.e., had returned to within 10% of baseline levels). Testing kittens at room temperature was not a problem, since LSD, particularly at moderate to high doses, elevates body temperature (Trulson & Jacobs, 1979). Furthermore, cats obtain homeothermy within a few days after birth. Quantitative data (i.e., frequency of occurrence per hr) were obtained for the following behaviors: limb-flicking (lifting the forepaw or hindpaw and then rapidly snapping or flicking the limb outward from the body); abortive grooming (orienting to the body surface as if to groom but not emitting the consummatory grooming bite, lick, or scratch or emitting such a response in mid-air); grooming (rubbing the head with the forepaw, licking and scratching the body surface); head-shakes; staring (fixation of the gaze in one direction for more than five seconds); investigatory responses (pawing or sniffing at objects or in corners, chasing the tail, or batting at pieces of food, etc.); hallucinatory-like behavior (looking around at the floor, ceiling, or walls of the cage and appearing to track objects visually; or hissing at, batting at, or pouncing at unseen objects); yawning; vocalization; rubbing (against the cage); and treading (or kneading) of the forepaws. All of the above behaviors have been well-described in previous studies of the effects of LSD in adult cats (Jacobs et al., 1977; Trulson & Jacobs, 1976, 1977). Other behaviors, such as stereotyped movements, rigidity, tremor, and sympathomimetic signs, were recorded in a qualitative fashion.

Since the limb-flick response has been shown to be the most sensitive and reliable index of the action of LSD in adult cats (Trulson & Crisp, 1982b), particular attention was given to this behavior. Because the limb-flick is a response used by non-drugged cats to remove foreign substances from the paws, subgroups of kittens at various ages were tested for their response to water on their paws. The following test procedure was used. The kittens were placed in pairs in a flat pan containing 1 cm of water at room temperature and the number of limb-flicks during a 15-min test period was recorded.

The behaviors that were recorded quantitatively were statistically analyzed using two-way analyses of variance (ANOVA) for dose of LSD and age. These analyses were followed by 2-tailed *t*-tests for differences between individual data points. We measured the percentage of kittens displaying a significant response to LSD for each behavior in various age groups using the criterion that the frequency of occurrence of that behavior, following LSD administration, was greater than two standard deviations from the mean frequency for all saline-treated kittens at that particular age. The statistical significance of differences in the frequency of occurrence of each behavior following LSD administration on Day 1 vs Day 2 in the tolerance study was evaluated using 2-tailed *t*-tests for each age group examined.

Results

Administration of LSD to kittens produced a constellation of behavioral signs that has been previously described in detail for the adult cat. However, the onset of the assorted behaviors varied considerably with age, and the drug dose had dramatically different effects at various ages. The general behavioral effects of LSD on young kittens will be described first and then the various LSD-induced behaviors characteristic of adult cats will be described sequentially. There were no significant differences in the behavioral response of male vs female kittens following LSD treatment.

The kittens showed little LSD-induced behavioral change prior to 14 days postpartum, and no notable behaviors were observed following saline administration prior to

the age of 14 days. During the first 2 weeks of life, the kittens showed only nursing behavior and largely uncoordinated movements of the limbs. Only one behavior, head-shakes, showed a significant increase in frequency of occurrence following LSD injection. The frequency of head-shakes was significantly increased above the saline baseline of 0 by 50 μg/kg of LSD at 7 days of age (2.7 ± .9; $p < .05$; 2-tailed t-test). By 14 days of age, the frequency of head-shakes was significantly increased above the saline baseline of 0 by both the 50-μg/kg dose (9.4 ± 1.9; $p < .01$; t-test), and the 200-μg/kg dose (3.0 ± 1.0; $p < .05$; t-test) of LSD.

The other dramatic change in behavior following LSD administration to kittens less than 2 weeks of age was the occurrence of rigidity and tremor, which appeared following administration of the highest dose tested (200 μg/kg). This behavior was very prominent between the ages of 4 and 14 days. Administration of LSD at this high dose to young kittens consistently resulted in an extension of the hindlimbs caudally and extension of the forelimbs laterally while the animal was lying on its ventral surface. There was also a noticeable tremor in all extremities as well as the body as a whole. This behavior persisted for several hours (i.e., 4-6 hr) post-injection. The two lower doses of the drug (10 and 50 μg/kg) did not elicit these behaviors.

By the age of 21 days postpartum, the kittens displayed many of the behavioral signs characteristic of LSD-induced behaviors in adult cats. In general, these behaviors began at a low frequency of occurrence, then increased rapidly with advancing age. The various behavioral signs will now be described individually.

Limb-Flick

Using a two-way ANOVA for dose of LSD and age postpartum, the limb-flick reponse showed a significant age effect from 4 to 112 days of age ($p < .05$); however, the dose effect was not statistically significant when measured across this time interval ($p > .05$). The low (10-μg/kg) and high (200-μg/kg) doses of LSD produced no significant increase in the limb-flick rate above saline baseline until 30 days of age (Fig. 1). At 30 days postpartum, 10 μg/kg of LSD produced a mean of 7.1 ± .4 flicks/hr ($p < .05$; t-test), and the limb-flick rate remained relatively constant between 7.1 and 10.6 flicks/hr between ages 30 and 112 days (Fig. 1). All 16 of the kittens tested at a dose of 10 μg/kg of LSD showed a significant increase in the limb-flick rate above saline baseline levels between 30 and 112 days of age, with the exception of one that showed no significant change at the age of 30 days. None of the kittens showed a significant increase in the limb-flick rate prior to 21 days of age, and only 13% (2/16) showed a significant increase in rate at 25 days of age. The intermediate dose of LSD used (50 μg/kg) produced no significant increase in the mean limb-flick rate between ages 4 and 14 days (Fig. 1). However, 11% (2/19) of the individual kittens showed a significant increase above saline baseline at 14 days of age.

At 21 days of age, 32% (6/19) of the kittens tested showed a significant increase in limb-flick rate, and at 25 days of age, 47% of the kittens (9/19) showed a significant increase in limb-flick rate at 50 μg/kg of LSD (14.1 ± 1.6 vs 1.2 ± .2 flicks/hr for saline baseline; $p < .05$). The rate of limb-flicking in response to 50 μg/kg of LSD then rapidly increased and 76% (13/17) of the subjects showed a significant increase in rate at 30 days of age (27.2 ± 2.6 vs 2.4 ± 1.8 flicks/hr for saline baseline; $p < .01$). By 35 days of age, all kittens tested (17/17) showed a significant behavioral response (49.9 ± 4.7 vs .9 ± .5 flicks/hr; $p < .001$). The rate of limb-flicking in response to 50 μg/kg of LSD remained relatively constant between 35 and 112 days of age (except for significant decreases of approximately 20% on Days 49 and 56; see Fig. 1).

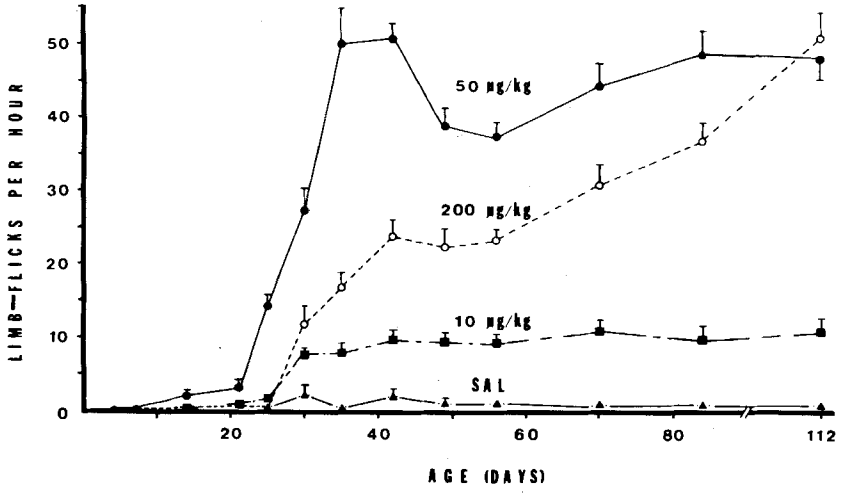

Fig. 1. Dose-response relationships for LSD-induced limb-flicking during ontogeny. Cats were given intraperitoneal injections of saline (.5 mL/kg) or LSD (10, 50, or 200 µg/kg), and their behavior was scored for 1 hr post-injection. Note that saline produced very few limb-flicks, irrespective of age. LSD-induced limb-flicking appeared between 21 and 30 days and increased rapidly to adult levels. LSD-induced limb-flicking remained relatively constant between 35 and 112 days for the 10- and 50-µg/kg doses while the rate of limb-flicking continued to rise steadily throughout this time period for the 200-µg/kg dose.

The rate of limb-flicking in response to a high dose of LSD (200 µg/kg) was slower to develop than the response to the low and intermediate doses (Fig. 1). There was no significant increase in the rate of limb-flicking in response to 200 µg/kg of LSD until 30 days postpartum (11.6 ± 2.4 vs 2.4 ± 1.8 flicks/hr on saline baseline; $p < .05$). The rate of limb-flicking with the high dose of LSD steadily increased between 30 and 112 days of age and still appeared to be on the rise at the latter time point (50.7 ± 3.7 vs .4 ± .3 for saline baseline; $p < .001$). None of the kittens (0/15) showed a significant increase in limb-flick rate at 25 days of age, while 73% (11/15) showed a significant increase at 30 days and all animals tested ($N = 12$) showed a significant increase in limb-flick rate between 35 and 112 days postpartum.

Since the limb-flick response has proven to be the most reliable and reproducible index of the action of LSD (as described above), we tested the tolerance effect of repeated LSD administration using the limb-flick as a behavioral measure. When 50 µg/kg of LSD was readministered to 25-day-old kittens, they showed no tolerance (17.8 ± 2.7 flicks/hr vs 14.1 ± 1.6 on Day 1; see Fig. 2). When the tolerance effect was retested on 30-day-old kittens, a significant tolerance was observed (27.2 ± 2.6 flicks/hr on Day 1 vs 13.9 ± 3.9; $p < .05$; t-test). The tolerance gradually became more pronounced throughout the period between 30 and 112 days of age, reaching an adult level of virtually complete tolerance at 112 days of age (Fig. 2). A group of adult naive cats (12-26 months of age, $N = 12$) displayed 41.2 ± 4.6 limb-flicks/hr following their initial injection of 50 µg/kg of LSD, and displayed the typical adult tolerance effect when given a second dose of LSD (50 µg/kg) 24 hr later (1.1 ± .7 limb-flicks/hr; $p < .01$).

Examination of the development of forelimb-vs-hindlimb response to 50 µg/kg of LSD revealed that the forelimb response appeared first during ontogeny (Fig. 3). Twenty-one percent (3/14) of the animals showed forelimb flicks at the age of 14 days, while none of the kittens displayed hindlimb flicks at this age. At 21 days of age, 43% (6/14) of the kittens tested with 50 µg/kg of LSD showed forelimb flicks, while only 7% (1/14)

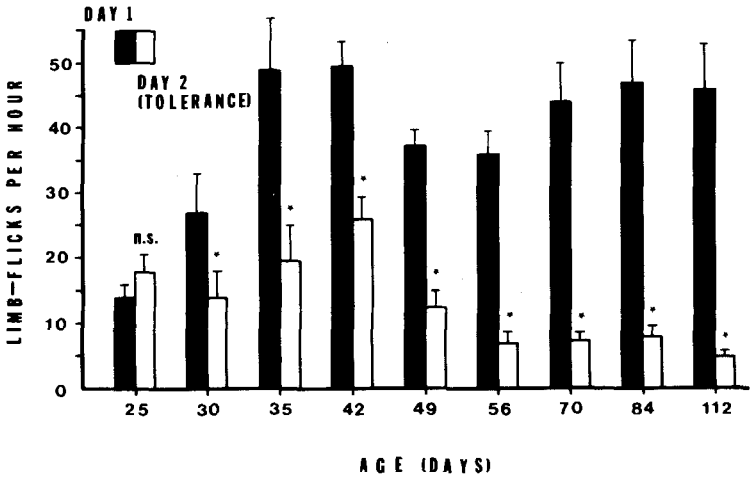

Fig. 2. Development of tolerance to LSD during ontogeny. Kittens were given 50 μg/kg of LSD (i.p.) on Day 1 (black bar) and were administered a second 50-μg/kg dose of LSD 24 hr later (white bar). The behavior was monitored for 1 hr post-injection. Note the progressively larger tolerance effect across ontogeny.

showed any hindlimb flicks. Virtually the same observations were made at 25 days of age (Fig. 3). By 30 days of age, however, 70% (11/14) of the kittens tested displayed forelimb flicks while only 14% (2/14) showed any hindlimb flicks. This represents a forelimb/hindlimb ratio of approximately 10:1 in terms of frequency. The ratio of forelimb/hindlimb flicks decreased with age, reaching the typical adult level of approximately 2:1 by 112 days of age (Fig. 3).

When kittens of various ages were tested for their response to water on their paws, the rate of increase in the limb-flick response closely paralleled the development of the

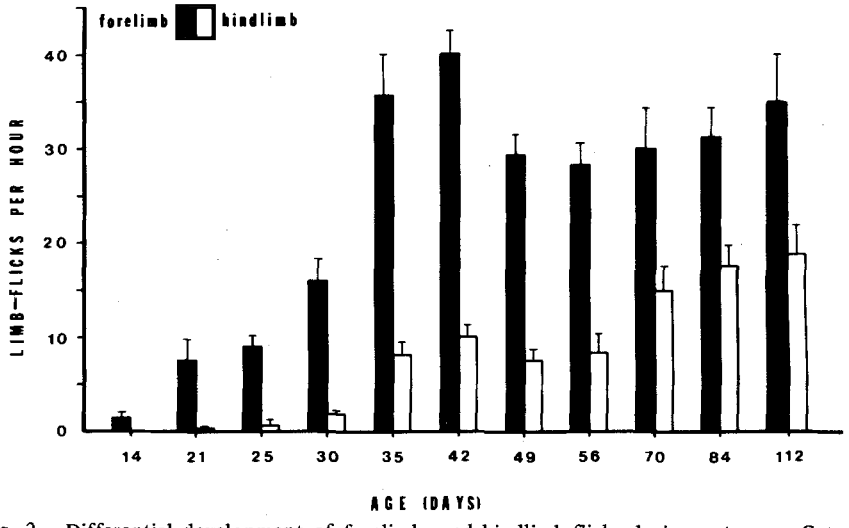

Fig. 3. Differential development of forelimb- and hindlimb-flicks during ontogeny. Cats were given LSD (50 μg/kg, i.p.) and their behavior was monitored for 1 hr post-injection. Note that the forelimb flick (black bar) appears prior to the hindlimb flick (white bar) and that the ratio of forelimb/hindlimb flicks decreases from approximately 10:1 to 2:1 across ontogeny. The latter value is comparable to that observed in adult cats in our previous studies.

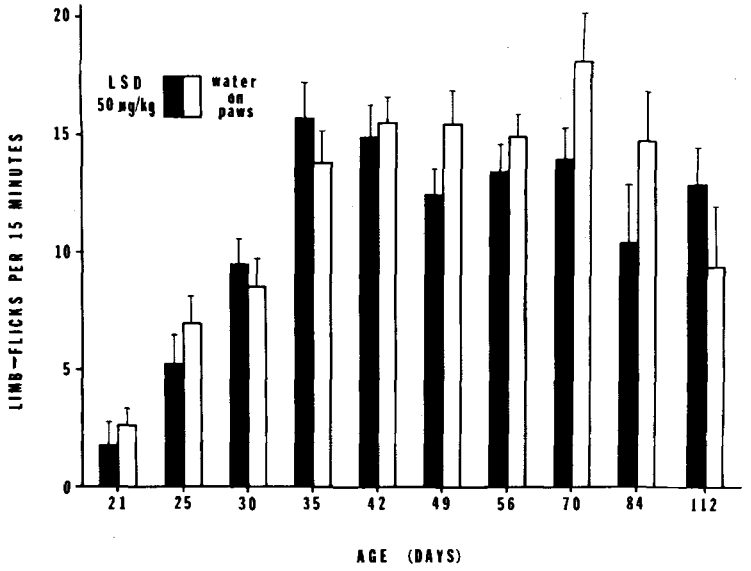

Fig. 4. Correspondence between LSD- (50 µg/kg) induced limb-flicking and limb-flicking due to the presence of water on the paws. Note that the rate of development of limb-flicking under the two conditions develops in parallel. There were no significant differences between the rate of limb-flicking under the two conditions at any age investigated.

limb-flick response to 50 µg/kg of LSD (Fig. 4). In addition, the forelimb and hindlimb flick in response to water on the paws closely paralleled the development of LSD-induced fore- and hindlimb flicking.

The time course for the persistence of the limb-flick response induced by LSD administration (50 µg/kg) was similar to the adult pattern from its earliest appearance during ontogeny. While the magnitude of the response varied between 13.3 flicks/hr for a subgroup of kittens at 21 days of age to 44.2 flicks/hr for 112-day-old animals, the limb-flick response persisted at a rate significantly above saline baseline for at least 8 hr in groups of animals at 21, 30, 42, 56, 84, and 112 days postpartum (Fig. 5). The time course for the occurrence of limb-flicks at doses of 10 µg/kg (3–4 hr) and 200 µg/kg (>12 hr) of LSD also closely paralleled the adult values.

Abortive Grooming

A second emergent behavior that has been well-described in adult cats following LSD administration is abortive grooming. Analyses of variance revealed a significant age effect for this behavior ($p < .05$) and a marginally significant dose effect ($p < .06$), using saline as a dose of 0. Abortive grooming was virtually never seen in saline-treated animals at any age (Fig. 6). LSD produced no significant increase in this behavior until 30 days of age, when all three doses of LSD (10 µg/kg: 2.4 ± .3 occurrences/hr; 50 µg/kg: 3.5 ± .5 occurrences/hr; and 200 µg/kg: 4.1 ± .6 occurrences/hr) produced a significant increase in the incidence of abortive grooming above the saline baseline of 0. The largest increase in abortive grooming occurred at 35 days of age (10 µg/kg: 3.1 ± .4 occurrences/hr; 50 µg/kg: 9.7 ± .9 occurrences/hr; and 200 µg/kg: 4.3 ± .4 occurrences/hr). Between 42 and 112 days of age, the rate of occurrence of LSD-induced abortive grooming leveled off at the adult values (10 µg/kg: approximately two occurrences/hr; 50 µg/kg: 2.5–4.3 occurrences/hr; and 200 µg/kg: 2.0–2.6 occurrences/hr) (Fig. 6).

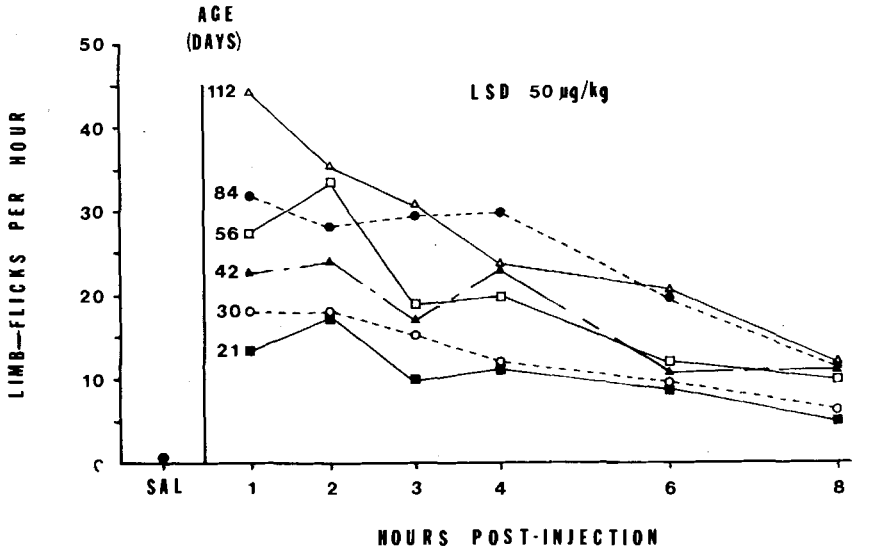

Fig. 5. Time course for the increase in LSD-induced limb-flicking during ontogeny. The time course for the persistence of the limb-flick response following 50 µg/kg of LSD was very similar between 21 and 112 days of age; i.e., the response persisted for at least 8 hr above the saline baseline from its earliest appearance during ontogeny.

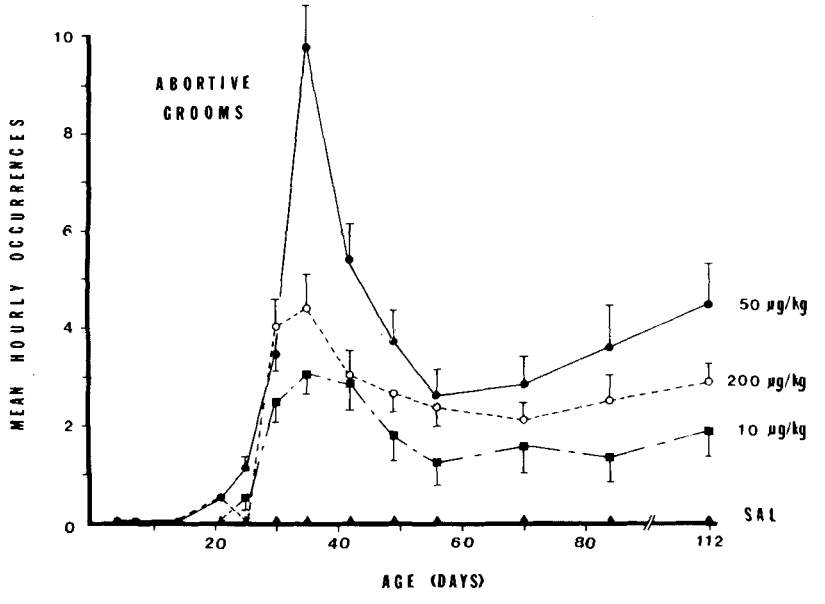

Fig. 6. Dose-response relationships for LSD-induced abortive grooming during ontogeny. Cats were given intraperitoneal injections of either saline (.5 mL/kg) or LSD (10, 50, or 200 µg/kg), and their behavior was monitored for 1 hr post-injection. Saline injections produced no abortive grooming, irrespective of age. LSD-induced abortive grooming first appeared at approximately 25 days of age, then rapidly increased in frequency of occurrence between 25 and 42 days of age. Abortive grooming remained relatively constant at the adult levels between 42 and 112 days of age. The 50-µg/kg dose of LSD elicited the largest behavioral response, while the 10-µg/kg dose produced the smallest response, and the highest dose (200 µg/kg) produced an intermediate response.

Head-Shakes

A two-way ANOVA revealed a strong LSD dose effect and age effect for the frequency of occurrence of head-shakes ($p < .001$) (Fig. 7). Of all the major behaviors investigated in the present study, head-shakes appeared at the earliest point during ontogeny. A significant increase in head-shakes occurred at 7 days postpartum, following administration of the 50-μg/kg dose of LSD (2.7 ± .8 vs 0 on saline baseline). Thirty-two percent (6/19) of the kittens showed a significant behavioral response at this time. The frequency of LSD-induced head-shakes steadily increased, reaching an adult level of 25-32/hr at ages 35-112 days postpartum. Head-shakes began to occur following saline administration after 25 days of age (2.4 ± .6/hr), then gradually increased over time, reaching an adult level of approximately 5-6/hr by age 56-112 days. No significant increase in the rate of head-shaking following 10 μg/kg of LSD occurred until 21 days of age (6.2 ± 1.4 vs 1.0 ± .5 for saline baseline; $p < .05$). The rate of occurrence of head-shakes increased over time, reaching a maximal adult level of 11-13 at ages 49-112 days postpartum. A significant increase in the rate of head-shaking following the high dose of LSD (200 μg/kg) occurred at 14 days of age (3.1 ± 1.0 vs 0 on saline baseline), then increased rapidly to a maximum adult level of 30-35 head-shakes/hr between the ages of 35 and 112 days of age (Fig. 7).

Grooming

A two-way ANOVA revealed a strong age effect for the development of grooming behavior ($p < .001$), but no significant dose effect, using saline as a dose of 0 (Fig. 8). The kittens showed no significant increase in the rate of spontaneous functional grooming

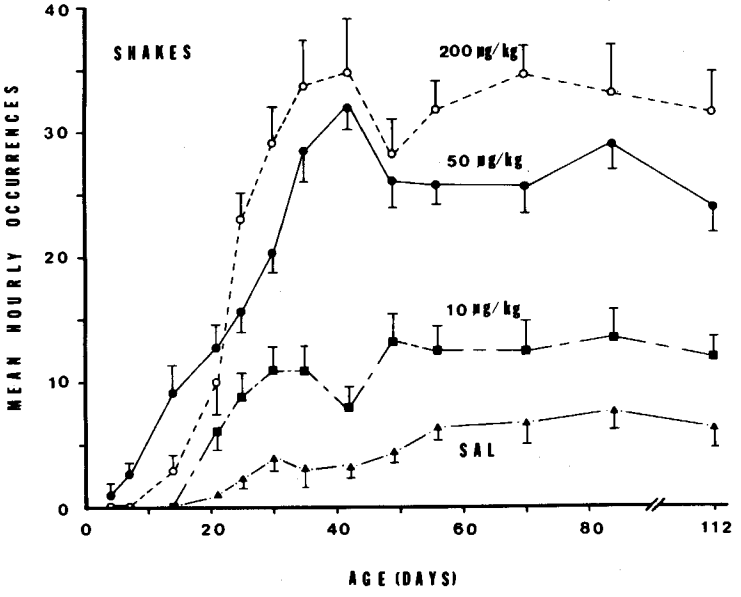

Fig. 7. Dose-response relationships for LSD-induced head-shakes during ontogeny. Cats were given intraperitoneal injections of either saline (.5 mL/kg) or LSD (10, 50, or 200 μg/kg), and their behavior was monitored for 1 hr post-injection. The curves follow a clear dose-response relationship, i.e., the lowest dose of LSD (10 μg/kg) produced the smallest behavioral change, followed by the intermediate dose (50 μg/kg), which in turn is followed by the highest dose (200 μg/kg). Note that LSD-induced head-shakes appear much earlier during ontogeny than those following saline administration.

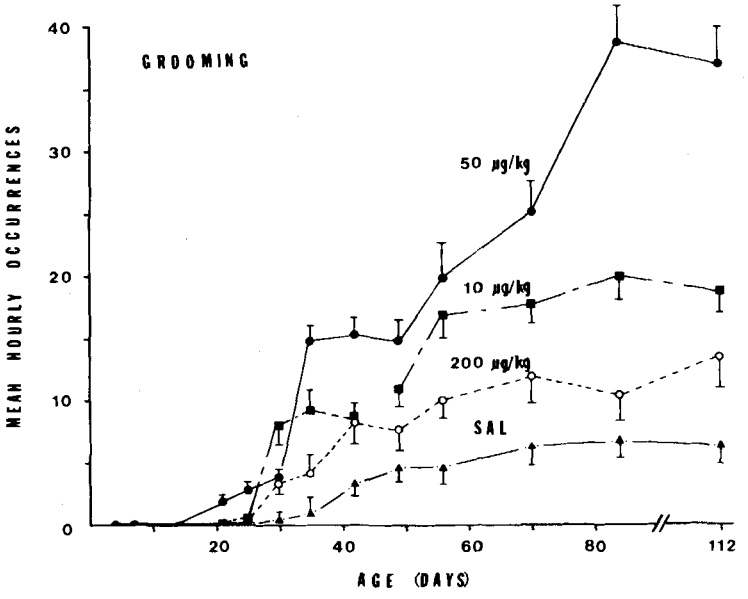

Fig. 8. Dose-response relationships for LSD-induced grooming during ontogeny. Cats were given intraperitoneal injections of either saline (.5 mL/kg) or LSD (10, 50, or 200 µg/kg), and their behavior was monitored for 1 hr post-injection. The curves do not follow a clear dose-response relationship. That is, the intermediate dose of LSD (50 µg/kg) produced the largest increase in grooming, while the highest dose (200 µg/kg) produced the smallest increase, and the lowest drug dose (10 µg/kg) produced an intermediate response. Note also that LSD-induced grooming appears much earlier during ontogeny than that which occurred following saline administration.

until 42 days of age, when they exhibited 3.5 ± .7 grooms/hr following saline administration. The rate of grooming gradually increased over time, reaching the typical adult level of approximately 5-7 episodes of spontaneous grooming/hr. The rate of grooming was significantly increased by 50 µg/kg of LSD at 25 days of age (2.9 ± .4 vs 0 for saline) ($p < .05$). The rate of grooming following the 50-µg/kg dose of LSD then rapidly increased to a maximum adult level of approximately 40/hr between ages 84 and 112 days (Fig. 8). The lowest dose of LSD (10 µg/kg) showed a rapid increase in the rate of grooming between the ages of 25 (0) and 30 (8.2 ± 2.6 vs .3 ± .3 on the saline baseline). The rate of occurrence of grooming then gradually increased to a maximum of 15-20 occurrences/hr between the ages of 56 and 112 days (Fig. 8). Grooming in response to the highest dose of LSD tested (200 µg/kg) was slowest to develop, showing a significant increase of 3.4 ± .6 vs .3 ± .3 on the saline baseline ($p < .05$) at Day 30 postpartum. The frequency of grooming in response to the high dose of LSD then gradually increased over the next several days, reaching a maximum of 10-13 occurrences/hr between the ages of 56 and 112 days (Fig. 8).

Investigatory Responses

These responses were very difficult to quantitate in kittens. In general, kittens showed none of these behaviors prior to approximately age 42 days. After that, following LSD administration, many of the kittens engaged in investigatory or play behavior for a large portion of the observation period. Therefore, while the frequency of occurrence of these behaviors was low, the total amount of time spent engaged in investigatory or play behavior was very large. The kittens would frequently emit several limb-flicks, abortive

grooms, head-shakes, or grooms during the course of an extended investigatory or play behavior period.

Hallucinatory-Like Responses

These responses were virtually never seen in any of the kittens at any of the doses of LSD tested.

Other Behaviors

None of the other behaviors scored quantitatively, i.e., vocalization, rubbing, kneading the forepaws, and yawning showed any significant changes from the saline baseline during the course of the experiment. Most of the animals showed some sympathomimetic signs (e.g., vomiting, piloerection, dilated pupils, salivation) at all ages at the high (200-μg/kg) dose of LSD employed. However, these behaviors were rarely seen in response to the 50-μg/kg dose and were never seen following administration of the lowest dose of the drug (10 μg/kg).

Discussion

The present study apparently represents the first systematic investigation of the ontogeny of the behavioral effects of LSD in any animal species. The time course for the appearance of the various LSD-induced behaviors varied considerably. Head-shakes was the first behavior to show a significant increase in frequency of occurrence following LSD treatment, exhibiting a significant increase above the saline baseline at 7 days of age. LSD-induced limb-flicking, abortive grooming, and grooming first appeared at 21 days of age. Interestingly, each of the above four behaviors (head-shakes, grooming, limb-flicking, and abortive grooming) could be elicited by LSD at a much earlier age than the behavior would occur spontaneously, i.e., following saline administration. This indicates that kittens are capable of emitting these various behaviors long before they do so spontaneously.

The absence of the spontaneous occurrence of limb-flicking and abortive grooming is not surprising in view of the fact that these two behaviors occur with an extremely low frequency (i.e., nearly 0) in saline-treated adult cats (Jacobs et al., 1977; Trulson & Jacobs, 1976, 1977). However, the occurrence of head-shakes and grooming represent quite a different phenomenon. Kittens show no significant amount of spontaneous head-shaking until age 25 days postpartum, while LSD elicits a comparable number of head-shakes at 7 days of age. The case of functional grooming showed just as dramatic an effect. Kittens began to show a significant amount of grooming at age 42 days, while LSD (50 μg/kg) elicited a significant amount of grooming at 21 days postpartum. Thus, an important principle emerges from these observations: the neurological substratum for behaviors such as grooming in cats is developed well in advance of the time that they begin to utilize the behavior. This absence of spontaneous grooming behavior in young kittens may be attributable to the fact that kittens are groomed by their mothers until the time of weaning, which occurs at approximately 6 weeks.

The large number of episodes of grooming, head-shakes, and abortive grooming seen in the older kittens represents a general disjunctiveness of behavior characteristic of a cat given LSD, as reported in our previous papers (Jacobs et al., 1977; Trulson & Jacobs, 1976, 1977). That is, following LSD treatment, the animals seem unable to engage in any kind of sustained behavioral activity, but rather move constantly from one category of behavior to another.

The limb-flick is the best behavioral index because it is elicited only by hallucinogens (with few possible exceptions) (Marini, Jacobs, Sheard, & Trulson, 1981; Trulson & Crisp, 1982a; White, Holohean, & Appel, 1981). Its occurrence parallels the major characteristics of the action of LSD in humans (Trulson & Jacobs, 1977); it is not simply due to drug-induced somatosensory alterations, but is reflective of more complex central processes (Trulson & Crisp, 1982b); and this behavioral index is dose-dependent, sensitive to doses near the human range, robust, reliable, and easy to quantify (Jacobs et al., 1977). Therefore, the limb-flick response was given a considerable amount of attention in the present study. The development of the LSD-induced limb-flick response closely paralleled the development of limb-flicks that occurred in response to water on the paws. Therefore, kittens apparently show no limb-flicks in response to LSD treatment prior to 21 days of age, owing to a lack of maturation of the neuronal and/or musculature substrate for this response (Levine, Hull, & Buckwald, 1980). The limb-flick is a species-specific behavior normally used for removing foreign substances, such as water, from the paws, and this response appears to develop at 21-25 days postpartum. Furthermore, the ability to execute limb-flicks occurs first during ontogeny for the forepaws. LSD produced no significant number of hindlimb flicks until 35 days postpartum. In addition, the forelimb/hindlimb flick ratio was initially approximately 10:1 (i.e., at 30 days), but gradually decreased to approximately 2:1 (the adult value) by 70 days of age. Thus, the maturation of the hindlimb flick response is considerably slower than the forelimb flick response.

Previous studies with adult cats have shown that LSD-induced behavioral changes (in particular, the limb-flick response) following a 50-μg/kg dose persist for 8–12 hr postinjection (Trulson & Jacobs, 1977). The present data revealed that LSD-induced limb-flicking in kittens persisted for the same duration of time (i.e., 8–12 hr) from their earliest appearance during ontogeny (21 days of age). While the magnitude of the behavioral response increased with age, the time course remained the same (Fig. 5).

These findings suggest that the binding of LSD to its CNS receptor, as well as the pharmacokinetics of the drug, are well developed at a very early age. LSD has been shown to bind to a specific CNS receptor, which is similar, but not identical, to dopamine and serotonin receptors (Peroutka & Snyder, 1979; Trulson & Jacobs, 1979). Studies on the pharmacokinetics of LSD in adult animals have demonstrated that the drug is rapidly absorbed and reaches the brain quickly—a finding in agreement with the present behavioral effects of LSD, which occurred within approximately 5 min of injection. LSD then reaches the liver and bile and is secreted into the intestines (Sankar, 1966). The half-life of LSD in the adult cat is approximately 2 hr (Trulson & Jacobs, 1977), which is compatible with the time course for the behavioral effects in adult cats. The same half-life would appear to occur in young kittens, since the time course for the behavioral effects so closely parallels that seen in adults.

A developmental study of serotonin concentration in various regions of cat brain revealed a sharp rise in serotonin levels between the ages of 14 and 25 days (when we began to observe most of the behaviors induced by LSD in the present study) (Pscheidt & Himwich, 1966). Interestingly, these sharp increases were seen in such regions as the caudate, thalamus, cortex, hippocampus, and hypothalamus, all of which are areas rich in serotonin nerve terminals (Fuxe, 1965; Steinbusch, 1981). The pons-medulla, which contains the serotonergic cell bodies, as well as nerve terminals (Dahlstrom & Fuxe, 1964; Leger & Wiklung, 1982; Poitras & Parent, 1978), on the other hand, showed constant levels of serotonin from the age of 1 day to adulthood (1000 days). This suggests that serotonin cell bodies are all present at birth, but that the nerve terminals develop later, an hypothesis that is supported by additional neurochemical data (Lidov & Molliver, 1982).

Postsynaptic serotonin receptors, however, appear to be present prior to the development of the nerve terminals (Bennett & Snyder, 1976). This would be expected to result in supersensitivity of the serotonergic receptors (Trulson, Eubanks, & Jacobs, 1976), an hypothesis which receives support from our data using the high dose of LSD (200 μg/kg) in young kittens (i.e., less than 2 weeks of age). The high dose of LSD produced forelimb and hindlimb extension and rigidity, as well as tremor throughout the body. These behavioral signs are reminiscent of the "serotonin syndrome" observed in rats, cats, and other species given high doses of serotonin agonists, including LSD (Trulson et al., 1976). Receptor supersensitivity may also account for the large peak in abortive grooming observed at Day 35 (Fig. 6); however, one would then have expected 10 μg/kg of LSD to be more effective in younger kittens, which was not the case.

LSD has also been shown to act on dopamine receptors in the CNS (Trulson, Stark, & Jacobs, 1977; Von Hungen, Roberts, & Hill, 1975). No dopamine-related stereotyped behaviors were observed in the kittens following any dose of the LSD tested; however, the presence of the "serotonin syndrome" induced by the high dose of LSD in young kittens may have masked any dopamine-related stereotypy. High doses of LSD produced dopamine-related stereotyped behaviors in adult rats as well as cats. Many of the kittens showed sympathomimetic signs such as vomiting, piloerection, pupillary dilation, and salivation, particularly at the highest dose of the drug tested, and these signs may be attributable to dopaminergic actions. The dopamine agonist, apomorphine, has been shown to elicit limb-flicks and related behaviors in adult cats without significantly altering serotonergic activity (Trulson & Crisp, 1982a). Thus, it appears that the limb-flick and related behaviors can be elicited by an action at either postsynaptic serotonin or dopamine receptors, and LSD, which acts as an agonist at both types of receptors, is particularly efficacious in eliciting these behaviors.

One of the most important findings of the present study is the lack of tolerance to repeated administration of LSD in young kittens. LSD ingestion by humans produces a marked tolerance to the psychic effects of the drug after a single dose of 100 μg, and a complete tolerance develops after three to four consecutive daily doses (Cholden et al., 1955). This tolerance completely disappears within 4–5 days after drug withdrawal. Very little information is available concerning possible neural mechanisms for this tolerance effect. The only well-established fact regarding LSD tolerance is that it is not attributable to increased peripheral metabolism of the drug, but clearly involves changes within the CNS (Trulson & Jacobs, 1977; Winter, 1971). In the present study, approximately half of the kittens tested showed a significant behavioral response to LSD (50 μg/kg) at 25 days. When the same dose of LSD was readministered to these kittens 24 hr later, they showed no tolerance (Fig. 2). At 30 days postpartum, 76% of the kittens tested showed a significant increase in limb-flick rate following LSD treatment, and these kittens showed a significant tolerance when tested 24 hr later. The tolerance effect gradually became more pronounced throughout the time period between 30 and 112 days of age, reaching an adult level of virtually complete tolerance at 112 days of age (Fig. 2). It is important to point out that these kittens received multiple injections of LSD during ontogeny.

In a previous study (Trulson & Howell, 1983), we evaluated in more detail the development of resistance to tolerance in kittens by injecting groups of naive kittens with 50 μg/kg of LSD every 24 hr for 5 consecutive days, beginning at age 25, 30, or 42 days. This study revealed that no significant tolerance developed during the treatment regimen when the injections were initiated at 25 days of age. When the kittens received the first injection of LSD at 30 days of age, no significant tolerance occurred until the fifth consecutive daily injection. This is in sharp contrast to the significant tolerance that develops to LSD following a single injection at 30 days when the kittens had previously been ex-

posed to the drug (Fig. 2). When naive kittens received the first LSD injection at 42 days of age, five consecutive daily injections were required to demonstrate a significant tolerance, in contrast to the significant tolerance which occurs following a single injection of the drug in animals 42 days of age that had previous exposure to LSD.

These data clearly demonstrate that prior exposure to the drug greatly accelerates the maturation of the tolerance mechanisms, and also suggest that the neural mechanism for mediating the behavioral response is separate from that which mediates the tolerance effect. This latter hypothesis is supported by the observation that, in adult cats, tolerance to LSD develops while the initial dose is still exerting its primary effect, i.e., a significant tolerance to 50 μg/kg of LSD is observed within 30 min following an initial injection of 10 μg/kg (Trulson & Crisp, 1983).

The significance of these tolerance studies is greatly enhanced by the finding that, while adult humans exhibit tolerance to LSD following a single dose, daily LSD treatment in children (5-12 years old) with various neurological and psychiatric disorders, over periods of several weeks, produced little, if any, tolerance (Bender, 1970). Therefore, a direct parallel exists for the dissociations between the behavioral effects of LSD and tolerance development during ontogeny in cats and humans.

The dose-response observations in the present study provided some unexpected results. Previous studies with adult cats revealed dose-dependent increases in the frequency of occurrence of limb-flicking and abortive grooming at 10, 50, and 200 μg/kg doses of LSD (Jacobs, Trulson, Stark, & Christoph, 1977). However in the present study, the 50-μg/kg dose was most effective in eliciting these behaviors while 10 μg/kg was least effective, and the 200-μg/kg dose produced an intermediate frequency of occurrence of these behaviors. This may be attributable to an appearance of competing behaviors (rigidity, tremor) following the high dose of LSD employed in young kittens. Indeed, by 112 days of age, the 200-μg/kg dose of LSD produced approximately the same behavioral response as the 50-μg/kg dose, particularly in the case of limb-flicks (Fig. 1). Thus, we might expect the previously established dose-response relationships to appear had these animals been retested at a later time.

The situation is quite different in the case of grooming behavior. Spontaneous grooming behavior first appeared during ontogeny at approximately the time of weaning, i.e., at 42 days of age. The rate of spontaneous grooming increased to saline-treated adult levels of 6-8 occurrences/hr between Days 70-112 (Fig. 8). This value agrees well with the data previously reported for adult cats (Jacobs et al., 1977). It is important to note that no attempt was made to measure the duration of each grooming episode in the present study. Rather, only the number of occurrences of grooming per unit time was examined. In prior studies, we determined that the adult cat spends 67% of its nonsleeping, nonresting time engaged in grooming behavior (Trulson, 1976). The large increase in grooming behavior following LSD administration appears to be due to the general disjunctiveness of behavior following drug administration. Thus, the overall amount of time spent grooming does not appear to be increased by LSD treatment, but, rather, each grooming bout is shorter in duration, so the frequency of occurrence of grooming shows a large increase following LSD treatment. In the present study, the intermediate dose of LSD (50 μg/kg) produced the largest increase in grooming behavior, particularly at the higher age levels (Fig. 8), at which the rate of occurrence reached approximately 40/hr. This is considerably higher than that observed in most of our prior studies for a comparable dose of LSD (approximately 20/hr). Thus, the frequency may decrease after 112 days of age. The lowest dose of LSD tested (10 μg/kg) produced a rate of grooming behavior that leveled off at 15-20 occurrences/hr between ages 56 and 112 days (Fig. 8). This rate is comparable to that observed in previous studies with adult cats (Jacobs et al.,

1977). The highest dose of LSD tested (200 μg/kg) produced the smallest increase in grooming above the saline baseline, leveling off at a rate of 8-12/hr between 42 and 112 days of age. This rate of grooming following 200 μg/kg of LSD agrees well with values obtained for adult cats in our previous studies. Thus, the only apparent aberrant response to LSD with regard to grooming behavior was the large increase between 84 and 112 days of age, following the intermediate dose of the drug.

Head-shakes was the only behavior in the present study to display both well-defined age and dose-response effects (Fig. 7). The rate of head-shaking steadily increased from 0 occurrences at 14 days of age to 6-8 occurrences/hr following saline administration between 56 and 112 days. This value agrees well with that observed in our prior studies with adult cats (Jacobs et al., 1977). Head-shakes in response to 10 μg/kg of LSD followed a similar pattern of development, leveling off at adult values of 12-14/hr between Days 49 and 112, in agreement with previous values obtained for this dose of LSD in adult cats. Similarly, the 50-μg/kg dose of LSD produced significant increases in the rate of head-shaking, reaching a maximum value of 25-30 occurrences/hr between 35 and 112 days. These values also agree very well with those observed in previous studies with adult cats. The results with the highest dose of LSD tested, however, were quite different from values observed in adult animals. The rate of head-shaking rapidly increased between 7 and 35 days of age, reaching a maximum of approximately 35 head-shakes/hr (Fig. 7). Previous studies with adult cats revealed that the animals emitted approximately 7-15 shakes/hr following 200 μg/kg of LSD. While it is not known what this particular group of kittens would have shown at a later stage of development, there does seem to be a downward trend in the frequency of occurrence of head-shakes between 70 and 112 days of age in the present study (Fig. 7).

Behaviors such as investigatory responses and hallucinatory-like responses proved to be very difficult to quantify in the present study. This is due to the fact that kittens are very active after 42 days of age and frequently appear to be constantly engaged in investigatory or play behavior. Thus, many kittens would have a very low frequency score for investigatory behavior when in fact this type of activity dominated their behavior. Adult cats, on the other hand, exhibit short, well-defined episodes of investigatory behavior. Hallucinatory-like responses were very rarely seen during the present study; however, this behavior occurs with a very low frequency in adult cats as well (Jacobs et al., 1977). Typical values from our previous studies with adult animals ranged from 1-3 occurrences/hr of hallucinatory-like responses at doses of 10 and 50 μg/kg of LSD, and this behavior was virtually never seen following the highest dose of LSD tested (200 μg/kg).

In a previous study of the effects of LSD on the sleep cycle during ontogeny in kittens, Shimizu and Himwich (1968) reported that low doses of the drug (10-20 μg/kg) significantly decreased total sleep time. This may account, at least in part, for the increased frequency of occurrence of certain behaviors following LSD treatment. That is, if the kittens are awake a greater proportion of the time, they are more likely to engage in some form of active behavior.

To our knowledge, the only other systematic study of the behavioral effects of an hallucinogen during ontogeny in the cat is a recent report on the effects of phencyclidine (PCP) by Levine, Clausen, and Butcher (1981). They reported that PCP (1-2 mg/kg), administered every other day to kittens between the ages of 5 and 39 days, resulted in a large increase in the frequency of rostro-caudal forelimb movements and hindlimb abduction between 5 and 21 days of age, and in ataxic locomotion and rigidity between the ages of 21 and 39 days of age. While the mechanism of action of PCP appears to be quite different from that of LSD (Menon, Clark, & Vivonia, 1980), the above-described behavioral effects of PCP bear a considerable resemblance to the behavioral effects induced in young kittens by high doses of LSD in the present study.

In conclusion, the present data reveal an orderly progression of the characteristic behavioral effects of LSD during ontogeny in the cat. LSD is capable of eliciting certain behaviors, such as head-shakes, grooming, etc., well in advance of the age at which they normally appear spontaneously. Therefore, the neuronal and musculature substrata for the performance of these behaviors are developed long before the kitten naturally employs them. This may be attributable to the fact that the mother satisfies the needs that these behaviors would serve until relatively late in development. Alternatively, LSD may mimic the effects of transmitter release in those systems involved in the mediation of these behaviors prior to sufficient innervation. Perhaps the most important finding in the present series of studies is the fact that the primary behavioral effects of LSD occur in kittens before the tolerance mechanism is functional and that prior exposure to the drug greatly enhances the development of this tolerance mechanism (Trulson & Howell, 1983). These findings should stimulate new research into the mechanisms mediating tolerance to LSD.

Notes

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