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Maternal Responsiveness in the Squirrel Monkey Following Chronic Administration of Δ^9-THC[1]

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KAPLAN, J. N. *Maternal responsiveness in the squirrel monkey following chronic administration of Δ^9-THC.* PHARMAC. BIOCHEM. BEHAV. 11(5) 539–543, 1979.—Mother squirrel monkeys were orally administered gradually increasing doses of Δ^9-THC (from 0.5 to 5.0 mg/kg) 5 days/wk from 2 wk to approximately 6 mo after birth. After having received a dose of 5.0 mg/kg for an average of 3.5 mo, drug-treated mothers were then compared with control mothers in terms of their responsiveness both to their own and to unrelated infants. In contrast to the control mothers whose response pattern clearly showed differentiation of their own and other infants, the mothers that received Δ^9-THC responded in much the same manner to the alien infant as they did to their own infant. The results show that the behavior of the THC-exposed mothers was not attributed simply to a general reduction in their responsiveness toward their offspring or to an overall reduction in their own state of arousal. Rather, the results suggest that chronic ingestion of Δ^9-THC caused the mothers to be less disturbed by separation from their infants and/or produced some degree of perceptual distortion that prevented them from responding selectively to the different infants.

Δ^9-THC Chronic ingestion Maternal responsiveness Squirrel monkey

AN EXTENSIVE literature now exists for both lower animals and man on the behavioral consequences of marihuana and its major psychoactive ingredient Δ^9-tetrahydrocannabinol (Δ^9-THC). Both acute and chronic effects have been described in detail, including the development of tolerance to the drug (e.g., [12]. One area of research that has been neglected, however—and one which would appear to be extremely important—concerns the influence of this drug on social relationships established early in life. Such relationships play a key role in the development of emotional stability and social adjustment in both man and monkey. Conditions that interfere with these relationships are known to have adverse results [1].

One of the most significant figures in the social-emotional development of an individual is its mother, and it is not unlikely that psychoactive drugs such as Δ^9-THC taken by the mother could affect the quality of her caretaking activities. There has been an increased usage of such drugs in recent years by females, particularly those in the age range most likely to have children [12]; therefore, a better understanding of the risk to the child would appear warranted.

Although the author is unaware of any studies on how maternal care is affected by Δ^9-THC, there is sufficient evidence of the drug's general effects on behavior to suggest that marihuana could alter maternal behavior sufficiently to result in neglect of the infant. For example, its sedative-like effects, observed both in man and lower animals [4, 5, 6], could produce less than optimal concern for an infant. Reports from human subjects regarding sensory-perceptual distortions and an inability to think in a clearly organized manner following Δ^9-THC intake also suggest that maternal care might be adversely affected [3, 5, 10].

The present study was conducted to provide information on maternal responsiveness in squirrel monkeys who had received Δ^9-THC on a chronic basis throughout the first six months of their infants' lives. Tests were conducted after a lengthy period of chronic treatment rather than after acute exposure, because any alterations in maternal care after such treatment would probably have a greater impact on the infant in terms of its emotional-social development.

METHOD

Subjects

Fourteen pairs of mother and infant squirrel monkeys (*Saimiri sciureus*, Bolivian type) from our breeding colony were used as subjects. All adults had at least one infant previously and none had been used in any drug study before this experiment. Seven pairs were assigned at random to the

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group receiving Δ^9-THC and the other seven pairs served as the control group. Each pair was removed from its multianimal breeding group after an infant was born, then housed separately in a standard primate cage for the duration of the study. All pairs were housed in the same animal room which was maintained at a temperature of approximately 26°C and was on a 12-hr light/dark schedule, lights on at 0700 hr. Infants in the drug and control groups consisted of 3 males/4 females and 2 males/5 females, respectively.

Drug Administration

Δ^9-THC was administered to mothers 5 days per week, Monday through Friday, from two weeks after birth until tests of maternal behavior were completed and infants ranged between 26 and 30 weeks old. The drug was supplied by the NIDA as a 10 mg/ml solution dissolved in sesame oil and was administered by oral intubation with a commercial stainless steel curved animal feeding tube (18 ga × 5 cm). The time of administration was kept constant and occurred at 1100 hr, approximately 3 hr after the animals had been fed their morning meal. A dose of 0.5 mg/kg was administered initially and was then increased weekly by 0.5 mg/kg until a dose of 5.0 mg/kg was achieved. This latter dose was then maintained for the remainder of the experiment. The seven mothers that served as controls were intubated on the same schedule and with equivalent volumes of sesame oil as the drug-treated mothers. The stock solution of the drug was diluted with laboratory grade sesame oil (Fisher Scientific) whenever necessary in order to administer volumes of 0.5 ml to each animal at the different doses.

Maternal Tests

Tests of maternal responsiveness were conducted over a two-week period and began when infants ranged between 24 and 28 weeks old. They were conducted in a room 5.5 × 4.0 × 3.5 m high, in which the floor had been divided into zones for recording an animal's location (see Fig. 1). Infants were presented in Plexiglas containers measuring 20 cm on a side, located in the corners of one end of the room. The containers had several small holes drilled in the top for ventilation. Containers differing in opacity were used for the purpose of modifying the difficulty with which mothers could discriminate their infants, a parameter which was thought might differentiate drug-treated and untreated mothers. Infants invariably vocalized when they were placed in the containers and, therefore, the clear containers afforded mothers both visual and auditory cues, compared with the opaque containers that prevented visual exposure. We have previously demonstrated that mothers untreated with drugs can discriminate their infants on the basis of auditory cues alone, although to a lesser extent than when both visual and auditory cues are available [9].

Mothers were tested under four separate conditions in which either their own infant or an alien infant was presented alone in either a clear or opaque (painted gray) container. Thus, the test conditions were: (1) own infant/clear container, (2) own infant/opaque container, (3) alien infant/clear container, and (4) alien infant/opaque container. A second container identical to the one in which an infant was placed was left empty and was presented at the same time in the opposite corner of the room (see Fig. 1). The alien infant that was used as a stimulus was similar in age (within 2 weeks) to a mother's own infant and belonged to one of the other

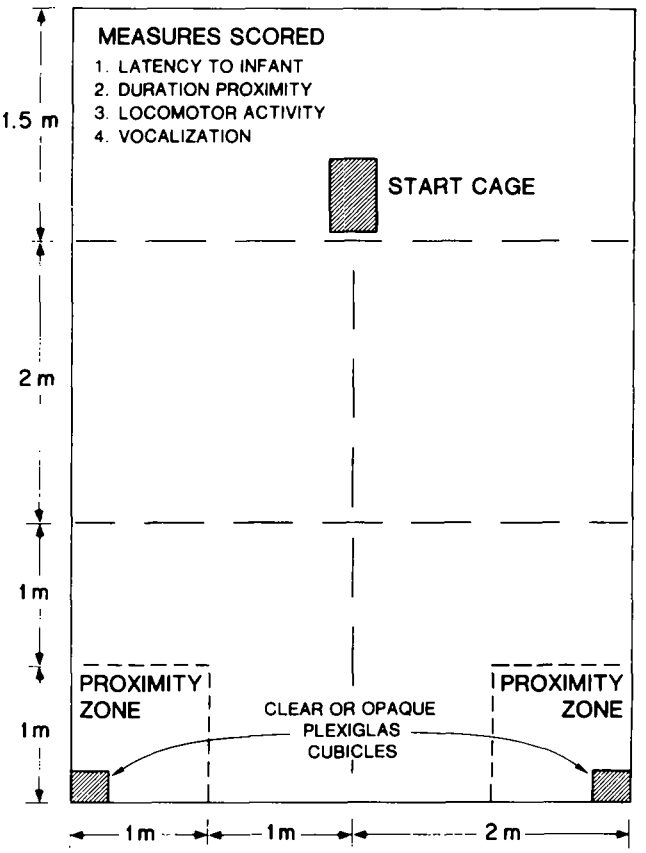

FIG. 1. Floor plan of room used for tests of maternal responsiveness and response measures that were scored.

mothers from the same treatment group. Because of the disproportionate number of males and females in the two groups, and because we wished to test mothers with alien infants that were close in age to their own infants (to eliminate the possibility that differences in the responses of mothers could be due to differences in the ages of the infants), it was not possible to control the gender of the alien infants in the test conditions (i.e., that for all mothers the alien infant was either the same as or different from their own infant). However, since previous work in our laboratory has shown that responsiveness toward an unrelated infant is not affected by that infant's gender [9], this factor would not appear to be important under the present circumstances. Thus, the gender of the alien infant with respect to a mother's own infant varied from mother to mother, although the identity of this infant remained the same for a given mother throughout her testing.

Six trials, each 5 min in duration, were administered for each condition. Three trials were conducted approximately 2 hr after drug/vehicle administration and three trials were conducted approximately 22 hr after drug/vehicle administration. This schedule was selected so that a comparison could be made between effects that occurred shortly after administration (i.e., 2 hr postdrug) with those that occurred after a longer period of time (i.e., 22 hr postdrug). All four conditions were presented consecutively in a single session on a given day, one trial per condition. The sequence of conditions was randomized for each session, and the side of

the room in which infants were presented was selected at random on each trial.

Before the start of each session, the mother to be tested was separated from her infant and moved to a holding area outside the test room. The stimulus infant was then transferred to the test room and placed inside the appropriate container. The mother was brought into the test room in a small transport cage and released from a designated starting line at the end of the room opposite the infant (see Fig. 1). At the end of the 5-min trial, the mother was returned to the transport cage and placed outside the room until the next condition was set up with the appropriate infant and container. Four measures of the mother's behavior were obtained during trials: (1) latency from the start of a trial to enter a 1-m proximity zone surrounding the container housing the infant, (2) duration of time spent in the proximity zone, (3) locomotor activity based on the number of lines crossed within four 2-m quadrants marked off on the floor of the room, and (4) frequency of vocalization.

Statistical Analyses

A three-factor analysis of variance (ANOVA) with repeated measures on two factors (conditions and time of testing) was conducted for each category of maternal behavior and evaluated in terms of overall differences between (1) the two groups, (2) the two periods of testing after drug administration, and (3) the four test conditions [17]. The minimum criterion for statistical significance was 0.05. Statistically significant results obtained with ANOVA were then followed by additional t-tests for making appropriate comparisons (e.g., between conditions).

RESULTS

During the initial stages of Δ^9-THC administration and/or when the dose of the drug was increased, some mothers appeared to display signs of intoxication which included a decrease in general activity and occasional vomiting. However, by the time maternal tests were conducted, none of the THC-exposed mothers displayed such behavior and, following drug administration, could not be distinguished from control mothers by observers who had no knowledge of the treatment of the different animals.

In contrast to this apparent development of tolerance to certain easily noticed effects of Δ^9-THC, the results of our maternal tests indicated that chronic administration of the drug was not without other, more subtle, effects. The results of ANOVAs for each of the parameters of maternal responsiveness obtained in these tests were similar and indicated that mothers receiving Δ^9-THC responded in much the same way to the alien infant as they did to their own infant. Untreated mothers, however, displayed clear differential responses to the two types of infants (Fig. 2). These differences between the two groups are suggested by the F values for the Group × Conditions interaction obtained in the ANOVAs, which were statistically significant for the measures of vocalization $F(3,36)=6.52$, $p<0.01$, and latency to infant $F(3,36)=3.45$, $p<0.05$. ANOVAs also showed that overall, the conditions differed for both groups of mothers combined (vocalization, $F(3,36)=9.96$, $p<0.01$; latency to infant, $F(3,36)=22.80$, $p<0.01$; duration proximity, $F(3,36)=21.36$, $p<0.01$; locomotor activity, $F(3,36)=4.00$, $p<0.05$), but that neither time of testing after drug/vehicle administration nor differences between the groups summed over all conditions were significant factors for any of the measures scored.

More detailed analyses of the differences between the two groups of mothers in their responses to own and alien infants were carried out by comparing scores for each group of mothers with respect to the magnitude of their responses to the two types of infant stimuli for each behavioral category. This was done by using t-tests for repeated measures after combining scores for the clear and opaque conditions and for the 2-hr and 22-hr postdrug sessions. The results of these tests showed that the control mothers responded more vigorously to their own infant compared with the alien infant on each of the four behavioral measures that were scored; vocalization, $t(6)=3.32$, $p<0.02$; latency to infant, $t(6)=3.79$, $p<0.01$; duration proximity, $t(6)=4.39$, $p<0.01$; locomotor activity, $t(6)=3.43$, $p<0.02$. In contrast, mothers that received Δ^9-THC showed a greater response to their own infant only in terms of latency to infant, $t(6)=2.67$, $p<0.05$. However, this was still significantly less than that displayed by the control mothers as determined by comparing the two groups on difference scores obtained for the two types of infants, $t(12)=2.25$, $p<0.05$.

In general, both groups of mothers responded more to infants when infants were presented in clear containers. Differences between the clear and opaque conditions were significant for both groups of mothers for the measures of latency to infant, $t(6)=4.53$, $p<0.01$ for Δ^9-THC group and $t(6)=3.68$, $p<0.02$ for control group, and duration of proximity, both $ts(6)>3.5$, $ps<0.02$, but not for the measures of vocalization and locomotor activity.

DISCUSSION

The results of this study show that chronic intake of Δ^9-THC can cause a lack of differential responsiveness toward their own and alien infants on the part of mother squirrel monkeys. The behavior of THC-treated mothers, however, cannot be attributed simply to a general reduction in their responsiveness toward their offspring or to an overall reduction in their own state of arousal. These mothers reached their infants as quickly at the start of a trial and also displayed similar levels of activity as untreated mothers.

The major distinguishing feature of the drug-exposed mothers compared to controls was that they responded in a similar fashion both to their own and to unrelated infants, instead of responding selectively as is typical. This occurred both in 2-hr and 22-hr tests following drug administration, indicating that such behavior was not due to an acute effect of the drug. A lack of selective response was particularly noticeable in the results on vocalization, but occurred on the other behavioral measures as well. Only the latency data provided statistical evidence of selective responding by THC-treated mothers, but this was still significantly below that displayed by untreated mothers.

One possible explanation for these findings is that the THC-treated mothers were less disturbed by separation from their infants than mothers who were not given the drug. Normally, physical separation of squirrel monkey infants from their mothers produces strong protest on the part of both members of the pair, exemplified most by an elevation in distress related vocalizations [8]. Such a reaction was quite evident in the control mothers of the present study, at least in terms of their differential respon-

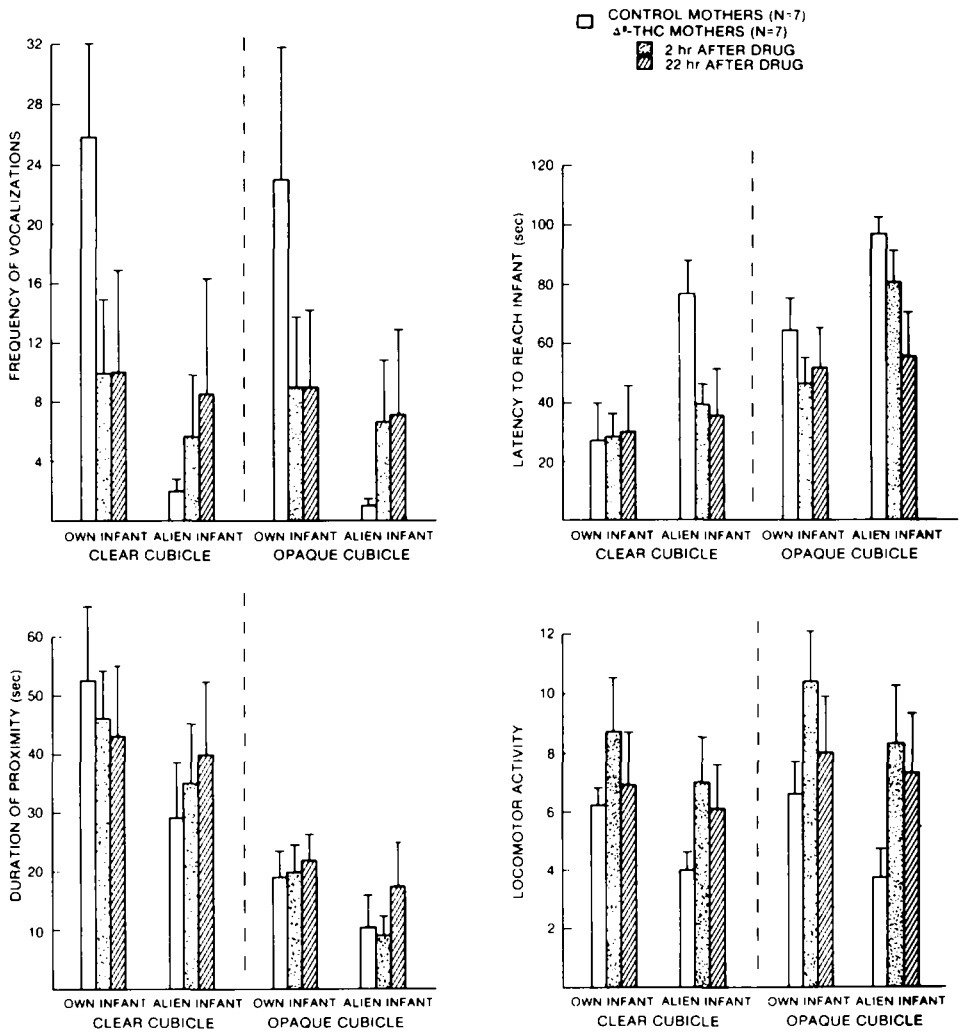

FIG. 2. Mean ± S. E. scores per trial of maternal responses to own and unrelated infants following a schedule of chronic oral administration of Δ^9-THC to mothers for a period of approximately 6 months after birth. Infants were presented in either clear or opaque containers during tests to provide conditions that differed in the degree of sensory exposure, and tests were conducted at both 2 hr and 22 hr after drug administration to mothers. Scores of control mothers represent mean for combined trials 2 hr and 22 hr after vehicle administration.

siveness to their own and alien infants. Mothers that received Δ^9-THC, on the other hand, displayed much less distress, as measured by the frequency of vocalizations emitted in tests with their own infants. However, one problem with this interpretation is that these same mothers also vocalized more frequently than control mothers in response to the alien infant, which would seem to indicate that a simple reduction in separation-induced distress cannot explain the data completely.

Thus, if Δ^9-THC did have an effect on reducing such distress under the present conditions, it would appear that other mechanism(s) were probably involved as well. One possible contributing factor is that some degree of perceptual distortion occurred in the THC-exposed animals which prevented them from responding selectively to the different infants. For example, these mothers may have had difficulty sorting out relevant from irrelevant information under the given test conditions, and thus responded inappropriately to the available cues. On the basis of such an interpretation, the data on vocalization, which we have previously shown to be a good measure of infant identification by mother squirrel monkeys [9], would suggest that the THC-treated mothers were deficient in recognizing their own infants.

It is also possible that the differences between THC-treated and control mothers was due to differences in behavior or other qualities of stimulation on the part of infants from the two groups, instead of to the direct action

of the drug on the mothers. Δ^9-THC and its metabolites are transferred to the infant squirrel monkey in the mother's milk [2] and, therefore, it might be expected that some sensory/behavioral quality of the infants receiving the drug in this manner would differentiate them from unexposed infants. Moreover, since in all cases mothers were tested with alien infants that were from the same treatment condition, the relative lack of selectivity by the THC-exposed mothers may have been the result of a common characteristic shared by the infants in the drug-treated group. Although this possibility cannot be completely discounted, it seems unlikely on the basis of observations made in our laboratory in which no differences were found between unexposed infants and those consuming the drug via their mother's milk on measures of physical growth and developmentally-related behaviors (unpublished data). However, certain cues which might have differentiated exposed and unexposed infants and for which no data were obtained (e.g., olfactory cues) would need to be evaluated specifically in order to assess their role in affecting maternal responsiveness under the present test conditions. It should be pointed out, however, that to trained observers the infants of both groups looked and responded alike when presented in the plastic containers during tests. With respect to olfactory cues, none of the mothers of either group was observed to sniff at, or around, the containers that housed the infants, suggesting that such cues had little bearing on the mothers' responses in this test situation.

A major problem in studying the chronic effects of Δ^9-THC is determining the extent of tolerance to the drug with repeated administration. Several reports on both human and animal subjects have indicated that rapid behavioral tolerance to Δ^9-THC develops under certain conditions [7, 11, 13, 14]. However, all of the studies that have demonstrated tolerance have examined nonsocial behaviors, and the degree to which such results would generalize to the more complex and spontaneous behaviors that occur in a social milieu, such as was the case in the present experiment, is not clear. For example, in a study with socially living rhesus monkeys, it was found that administration of Δ^9-THC at 2.4 mg/kg/day over several months, produced tolerance to the initial suppressive effects of the drug, but also a subsequent increase in social aggression [16].

Thus, in the present study, it is possible that any drug-related changes in maternal care could have been altered during the course of chronic treatment. Unfortunately, systematic daily observations of mothers and infants were not conducted as part of this experiment and clarification of this point remains to be determined. It is important to point out, however, that throughout the six-month period while mothers and infants were housed as pairs in cages, drug-treated mothers were not conspicuously different from control mothers in either their routine caretaking activities or with regard to changes representing the normal sequence of maternal behavior [15]. Nonetheless, under formal test conditions, as demonstrated here, some aspects of maternal responsiveness were clearly affected by chronic administration of Δ^9-THC.

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