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Maternal Marijuana Smoking Alters Respiratory Timing in the Fetal Lamb

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SZETO, H. H., D.-L. WU, Y. CHENG, P. Y. CHENG AND J. A. DECENA. *Maternal marijuana smoking alters respiratory timing in the fetal lamb.* PHARMACOL BIOCHEM BEHAV 43(4) 1227–1231, 1992.—The effect of single and repeated maternal marijuana smoke exposure on fetal breathing movements (FBMs) was investigated in 13 fetal lambs in the third trimester. These animals were surgically instrumented for long-term intrauterine recording of diaphragmatic electromyogram (EMG). Maternal inhalation of marijuana smoke [1.84% tetrahydrocannabinol (THC)] increased FBMs and resulted in a more continuous and regular breathing pattern. There was a significant increase in the number of breaths/h ($p < 0.01$) and the incidence of FBMs ($p < 0.001$) in the second hour. Breathing activity returned to presmoke level by the third hour. Duration of the longest breathing epoch was significantly increased from 16.8 ± 3.3 min to 31.9 ± 5.2 min ($p < 0.005$). Instantaneous breathing rate was much more stable in the second hour after marijuana exposure ($p < 0.01$). Inhalation of placebo smoke did not result in any significant change in either overall breathing activity or continuity and stability of the breathing rate. The effects of marijuana smoke on fetal breathing were not observed after repeated smoke exposure. These results suggest that tolerance develops rapidly to the respiratory stimulating effect of marijuana smoke in the fetus.

Marijuana Cannabis Respiration Breathing Fetus Tolerance

AVAILABLE clinical evidence suggests that while marijuana use during pregnancy does not seem to result in significant developmental anomalies or impairments there is an increased incidence of shortened gestation and lower birth weights (16,29). There is also evidence that marijuana exposure may be associated with increased tremors and startles and abnormal sleep cycling in the neonate (12,23). Despite these clinical reports, our understanding of the maternal and fetal responses to maternal marijuana use remains rather limited.

The investigation of the effects of marijuana smoke in an animal model has been greatly hampered by the lack of a convenient method to introduce marijuana smoke to an alert animal. Further, the large number of cannabinoids in marijuana, many of which are pharmacologically active and may interact with each other, has made it difficult to justify studying the effects of individual cannabinoids by parenteral or oral routes. The recent development of a simple system for introducing marijuana smoke to conscious sheep (2) has made it possible for us (27) and other investigators (6,7,20) to systematically investigate the effects of marijuana smoking on various maternal and fetal physiological parameters. The data from these studies demonstrate that marijuana causes sedation and cardiorespiratory depression in the mother (6,7,20). In the fetus, however, marijuana exposure resulted in activation of the fetal electroencephalogram (EEG) (27). Because fetal respiratory activity is closely associated with EEG (9), this current study was designed to examine the effects of single and repeated marijuana smoke exposure on fetal breathing activity.

METHOD

Animal Preparation

Thirteen fetal lambs were surgically instrumented for long-term intrauterine recording of fetal breathing movements (FBMs) between 115–120 days of gestation (term being ~145 days). The surgical procedures were described previously (2,24). For monitoring of FBMs, a pair of stainless steel electromyographic (EMG) electrodes was implanted in the diaphragm through an incision in the thoracic wall and a polyvinyl catheter was placed in the fetal trachea. A polyvinyl catheter was also placed in the distal aorta to permit collection of arterial blood for blood gas determinations. The EMG leads and catheters were tunneled SC to the maternal flank and stored in a pouch. Intraoperatively, 2 g ampicillin was placed in the amniotic cavity and 1 g in the peritoneal cavity of the ewe. In addition, a silicon rubber T-tube was implanted in the maternal trachea to facilitate inhalational exposure to marijuana/placebo smoke.

Study Design

Ewes were allowed at least 5 days for recovery after surgery before they were randomized to either the placebo or mari-

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juana treatment group. Only fetuses with arterial pH > 7.3, PCO_2 < 50 mm Hg, and PO_2 > 16 mm Hg were included in the study. Fetal diaphragmatic EMG and tracheal pressure were recorded with the ewe standing or lying quietly in a cart. The ewe had access to food and water throughout the study period. FBMs were recorded for 2 h prior to smoke exposure. Over a 10-min period, the ewe "smoked" either a marijuana (n = 8) or placebo (n = 8) cigarette supplied by the National Institute on Drug Abuse containing either 1.84 or 0% tetrahydrocannabinol (THC), respectively. The cigarettes were prehumidified and burned in a small Plexiglas cylinder hung around the ewe's neck (2). During inhalation, the cigarette smoke is mixed with residual and inspired air and delivered to the lower trachea and bronchial systems. Recording of FBMs continued for 3 h after smoke inhalation. In five animals, exposure to marijuana was repeated once every third day. The effect of exposure to marijuana smoke was studied again after the second and third exposure.

Data Acquisition and Processing

Diaphragmatic EMG (bandpass filtered, 100 Hz–1 kHz) and tracheal pressure were recorded on a Gould 2800S analog recorder (Gould, Inc., Cleveland, OH). The amplified, filtered signals were also recorded concurrently onto FM tape (TEAC XR-310; TEAC Corp., Montebello, CA) for storage and off-line analysis. Analog-to-digital conversion of the diaphragmatic signal (256 Hz) was accomplished with a board (DT-2801A; Data Translation; Marlboro, MA) resident in an AST 386 microcomputer. Automated recognition of diaphragmatic EMG bursts was accomplished using a template recognition algorithm (26).

Analysis of Fetal Breathing Pattern

Fetal breathing pattern is different from postnatal breathing pattern in that FBMs occur intermittently and do not become continuous until after birth. These breathing movements tend to occur in epochs, interspersed with periods of quiescence or apnea that can be as long as 30 min (25,26). In addition, there is a high degree of variability in instantaneous breathing rate during these breathing epochs. Thus, a complete quantitative description of the fetal breathing pattern requires not only a measure of total respiratory activity but also of the continuity and regularity of the breathing pattern. The necessary techniques were recently published by our laboratory (25,26). Briefly, respiratory output was measured by the total number of diaphragmatic EMG bursts per hour. Continuity of the breathing pattern was assessed by durations of the breathing epochs. A breathing epoch was arbitrarily defined as a series of consecutive breaths whose interbreath intervals were all less than 10 s, with a minimum of three breaths occurring within 9 s. The incidence of FBM was calculated as [(sum of all epoch durations/total time) × 100%]. Instantaneous breathing rate was computed as 60/[interbreath interval (in s)]. The regularity of the breathing pattern was assessed by examining the rate of change in instantaneous breathing rates. A stable cluster was defined as a series of at least three breaths whose instantaneous rates differed by <20% between successive breaths.

Statistical Analysis

It has previously been shown that these breathing parameters undergo significant developmental changes throughout the third trimester in the fetal lamb (25). Thus, the effects of marijuana/placebo smoke inhalation were compared with presmoke values with the same animal serving as its own control. For each study, the total number of individual breaths, FBM incidence, and longest epoch duration were determined for 2 h before and 3 h after smoke inhalation. Time course of action was characterized in hourly blocks after smoke inhalation and the peak response determined for each animal. All data are presented as mean ± SEM. Hourly data were analyzed using analysis of variance (ANOVA) with repeated measures. Peak effect in each animal was compared to control values using the paired-t test.

RESULTS

Spontaneous breathing activity was observed in all fetal lambs prior to placebo/marijuana smoke inhalation, with the total number of breaths averaging 2,082 ± 222/h. These breaths occurred in epochs separated by long apneic periods, as illustrated in Fig. 1A. Epoch durations were quite variable within and between animals, and the duration of the longest epoch averaged 19.6 ± 2.9 min. The overall incidence of FBMs was found to be 38.7 ± 3.4%. Instantaneous breathing rate within these epochs were highly variable, and only 55.5 ± 4.1% of the breaths occurred in stable or regular clusters. There was no significant difference in the control presmoke breathing pattern between the marijuana and placebo smoke groups.

Maternal inhalation of marijuana smoke increased fetal breathing activity and resulted in a more continuous and stable breathing pattern (see Fig. 1B). There was a significant increase in both the number of breaths/h (p < 0.01), as well

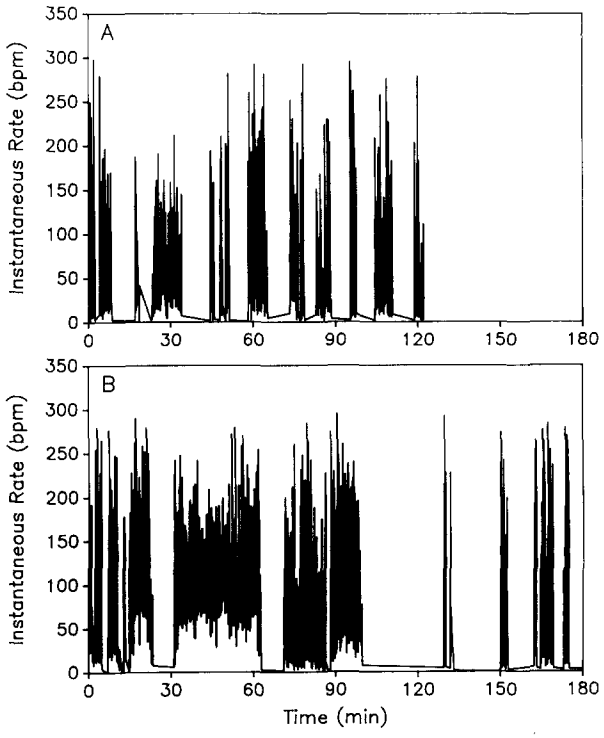

FIG. 1. Instanteous fetal breathing rate plotted as a function of time before (A) and after (B) maternal inhalation of marijuana smoke containing 1.84% tetrahydrocannabinol (THC) in a representative animal.

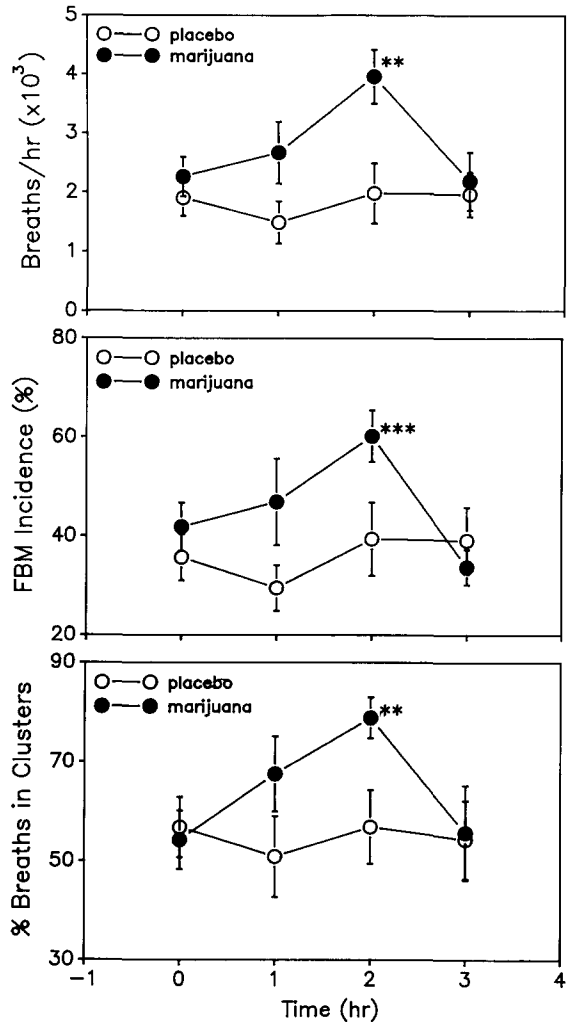

FIG. 2. Respiratory parameters before and at hourly intervals after maternal inhalation of either placebo or marijuana smoke. A cigarette containing either 0 or 1.84% tetrahydrocannabinol (THC) was "smoked" over a 10-min interval starting at time 0. Data shown are mean ± SEM for eight animals. $^{**}p < 0.01$, $^{***}p < 0.001$ compared to presmoke values.

as the incidence of FBMs in the second hour after smoke inhalation ($p < 0.001$) ($n = 8$) (Fig. 2). Breathing activity returned to control presmoke level by the third hour. Duration of the longest epoch was significantly increased from 16.8 ± 3.3 min to 31.9 ± 5.2 min ($p < 0.005$), and this was observed during the second hour after smoke inhalation. Instantaneous breathing rate was much more stable after marijuana exposure, and the percent of breaths that occurred in stable clusters increased from 54.3 ± 5.9% to 81.9 ± 3.5% ($p < 0.01$) (Fig. 2). There was a significant increase in mean cluster duration, from 2.2 ± 0.2 s to 3.2 ± 0.3 s ($p < 0.05$), and the average number of breaths per stable cluster increased from 5.5 ± 0.2 to 7.0 ± 0.4 ($p < 0.005$).

Inhalation of placebo smoke under the same experimental conditions did not result in any significant change in either overall breathing activity or the stability of the breathing rate (Fig. 2) ($n = 8$). The duration of the longest epoch after placebo smoke (22.7 ± 3.5 min) was also unchanged from presmoke values (22.3 ± 4.7 min).

The effects of marijuana smoke on fetal breathing were not observed following repeated drug exposure. Figure 3 illustrates the peak effect of single and repeated marijuana smoke on fetal breathing activity. The first exposure to marijuana (MJ1) resulted in a significantly higher number of breaths/h and incidence of FBMs ($p < 0.001$). Exposure to a second marijuana cigarette 3 days later (MJ2) did not alter either parameter of breathing activity and was not different from placebo smoke inhalation. Likewise, a third marijuana cigarette 3 days later (MJ3) was also without effect. Repeated marijuana exposure also did not alter the continuity or stability (Fig. 3) of the breathing pattern. The higher percentage of breaths occurring in stable clusters in the repeated-exposure group were partly due to a gestational age-related increase in stability even in the presmoke period (25).

DISCUSSION

This simple smoking system has been used to systematically investigate the effects of marijuana smoking on various maternal and fetal physiological parameters in sheep. Introduction of marijuana smoke to pregnant ewes using this method was associated with a number of neurobehavioral effects in the ewe. These included sedation, relaxation of neck muscles, ptosis, mild ataxia, and startle reflexes that lasted 2–4 h (20). The plasma THC profile achieved in maternal plasma was similar to that found in nonpregnant human subjects under similar smoking conditions (1,22). Peak plasma levels occurred at the end of the 10-min smoking period and were found to be comparable to those reported in human volunteers. THC was detected in fetal plasma by 10–15 min after onset of smoke inhalation, but peak levels were not reached until 1.5–2 h and were only 30% of corresponding maternal THC levels.

With cigarettes containing 1.84–2.64% THC, similar to those used in this study, Clapp and coworkers reported a 55–70% reduction in maternal respiratory rate and a significant decrease in maternal heart rate and mean arterial pressure (7). These effects were short lived, with peak effect occurring by 10–20 min, and the total duration of action was only 1–2 h. However, despite the reduction in mean arterial pressure there was no evidence of any change in uterine or umbilical blood flow (6). In the fetus, this level of exposure resulted in a moderate reduction in arterial pO_2 with no change in pCO_2 or pH (6,7). Unlike the mother, fetal pO_2 remained significantly depressed at 2 h after smoke inhalation.

We recently reported that this level of marijuana exposure also significantly altered fetal EEG activity in the first hour after smoke inhalation (27). Power spectral analysis revealed that marijuana exposure resulted in an activation of fetal EEG, as demonstrated by a decrease in total power and acquisition of faster frequencies. This increase in low-voltage, fast-activity (LVFA) EEG activity appeared to be a direct drug effect and was not secondary to the reduction in fetal pO_2 because mild to moderate hypoxia has been reported to either result in a decrease (5,8) or no change (15) in the incidence of LVFA EEG.

In the fetal lamb, spontaneous breathing activity is known to be closely associated with EEG activity, with breathing movements observed only during LVFA and apnea during high-voltage, slow-activity (HVSA) EEG (9). The results of this study show that this level of marijuana exposure also significantly increased fetal breathing activity and enhanced the continuity and stability of the breathing pattern. This was

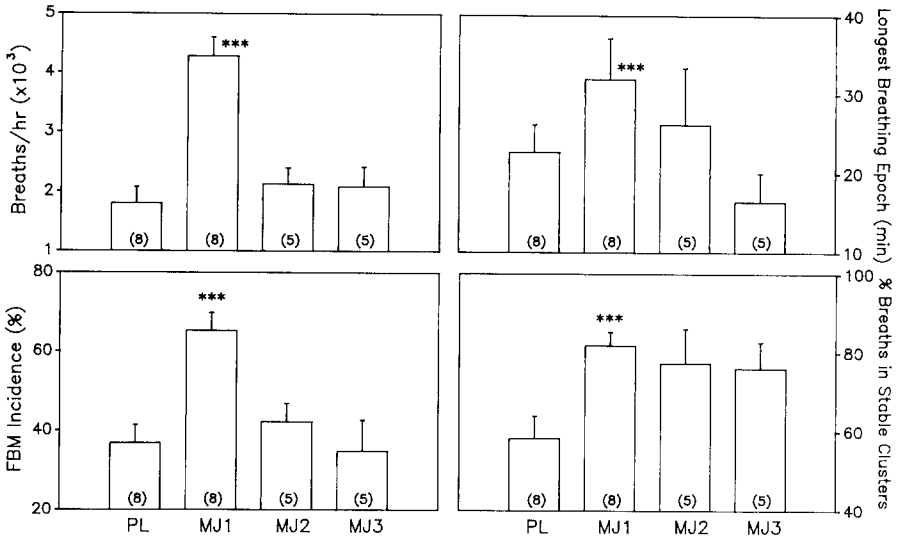

FIG. 3. Respiratory parameters after maternal inhalation of placebo (PL), first (MJ1), second (MJ2), and third (MJ3) marijuana cigarette. Repeated exposures were separated by 3 days. Number of animals in each group are denoted in parentheses. ***$p < 0.005$ compared to presmoke value in the same group.

a direct drug effect and not due to the stress of smoke inhalation alone or increased carboxyhemoglobin because the changes were not observed after inhalation of placebo smoke. However, the effect on breathing cannot be explained simply by the increase in LVFA EEG because the effect on EEG was observed in the first hour after smoke inhalation while the effect on breathing was not evident until the second hour. This difference in time course suggest that cannabinoids may have an independent action on fetal respiratory control. The time course of breathing effect is consistent with the plasma THC profile in fetal plasma, which peaks between 1.5–2 h after smoke inhalation (1).

This stimulation of fetal breathing activity by marijuana smoke was surprising in view of the reduction in fetal pO_2 demonstrated in earlier publications (6,7). Moderate hypoxia has been demonstrated to decrease the number of breaths/h and the incidence of FBMs (5,8,15). In addition, this finding was unexpected based upon the mild respiratory depression reported following marijuana or cannabinoid administration in the human adult (4,13,17). More pronounced respiratory depression has been reported in animals, but these were in general following high doses of intravenous cannabinoids in anesthetized animals (10,19,21). Cannabinoid use is also known to decrease respiratory cycle duration. Marked slowing of respiratory frequency was found in anesthetized cats following IV cannabinoids, and it was thought to be due to a direct depressant action on the respiratory rhythm generator (10). A significant and prolonged decrease in respiratory rate was also reported with THC and marijuana cigarettes in adult nonpregnant and pregnant sheep (7,20). This reduction in respiratory rate was associated with a significant decrease in pO_2 but only a small increase in pCO_2 (7,20). This lack of a significant hypercapnia suggested that hypoventilation was not the sole cause of hypoxia and that there is probably some diffusion impairment or ventilation : perfusion inequality (20).

The increase in breathing activity in the fetal lamb may be due to the lower level of cannabinoid exposure in the fetus because plasma THC levels were threefold lower than in the mother (1). It is possible that higher cannabinoid levels may also result in respiratory depression in the fetus. It is not clear whether low doses of cannabinoids may stimulate respiratory activity in conscious adults. However, there are reports of no change in respiratory function with marijuana smoking in experienced marijuana users (3,28). The THC content of the cigarettes used in these studies was lower than that used by Bellville et al. (4) and probably lower than the IV THC doses reported to produce respiratory depression (13,17). In addition, Zwillich et al. (30) actually reported a significant increase in resting respiratory rate and minute ventilation and increased hypercapneic ventilatory response in experienced marijuana users after smoking a marijuana cigarette containing 2.2% THC.

The inconsistencies in these human studies may be due to the fact that they were carried out in experienced marijuana users. Our present data show that the fetus adapts rapidly to the respiratory stimulant action of cannabinoids. The response is greatly attenuated by the second exposure so that no significant changes can be detected in any of the breathing parameters. Comparable data are not available in adult humans or animals. Such rapid adaptation was also found to the marijuana-induced EEG effects in the fetal lamb (27). The EEG activation was completely abolished with as few as three prior exposures given once every 3 days. Tolerance has been observed to develop to many, but not all, of the effects of marijuana and THC in adult animals (18), and the lack of EEG (11,14) or respiratory changes (3,28) in chronic marijuana users may represent tolerance in these subjects.

The results of this present study add to our understanding of the global effects of marijuana smoking on maternal and fetal physiology (2,6,7,20,27). It has been possible to integrate all these findings because they were carried out with a common experimental design, using the same animal model, route and dose of cannabinoid administration, and experimental protocol. Most interestingly, these studies have shown that effects on the fetus can be very different from those in the mother. In the mother, marijuana smoking has a sedative

effect with muscle relaxation and respiratory depression (1,6,20). On the other hand, the fetus responds with cortical activation (27) and respiratory stimulation (this study). This dramatic difference is most likely due to the threefold lower THC level in the fetus that was demonstrated in the pharmacokinetic studies (1). The reason for the restricted delivery of such a lipophilic compound across the placenta is not apparent but may be due to the extensive binding of THC to maternal plasma proteins. It is not due to a decrease in placental perfusion because uterine blood flow is unchanged and there is actually a decrease in both uterine and umbilical placental vascular resistance (6). The effects of marijuana smoking on fetal cortical and respiratory activity appear to be direct drug actions and are observed even in the presence of a moderate fetal hypoxia (7). Their different time courses also suggest that they are unrelated and due to different mechanisms.

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