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Sensitivity of EEG in Young Rats to Toluene Exposure

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GHOSH, T. K., R. L. COPELAND, JR. AND S. N. PRADHAN *Sensitivity of EEG in young rats to toluene exposure*. PHARMACOL BIOCHEM BEHAV 36(4) 779–785, 1990.—Effects of toluene on the electroencephalogram (EEG) and its power spectra were measured during a 2-hr exposure in a dynamic inhalational chamber in young rats (30–53 days old) and compared to those in adult rats (63–77 days old). Rats were exposed to one of the three concentrations [low (108–111 ppm), medium (160–163 ppm), and high (407–432 ppm)] of toluene on different days. In tests on sleep-wake cycle, in the young animals the duration of the wake stage (W) was increased with decreases of rapid eye movement (REM) and non-REM (NREM) sleep during hr 1 and hr 2 of exposure to the low concentration. These effects were marked at the medium and the high concentrations. In adult rats, at the low concentration the increase of W and the decrease of REM were observed only at hr 1; however, at medium and high concentrations these changes of W and REM sleep were marked along with a decrease of NREM. Comparison of the changes of duration of different states in rats of two age groups showed that there was a significant difference in the increase of W and the decrease of NREM sleep in young rats at hr 2 of exposure to low concentrations only compared to those in adult rats. Tested on power spectrum in young rats during REM sleep recorded from the visual cortex, the power of δ waves increased at the medium and high concentrations and that of θ wave decreased at the high concentration during hr 2 of exposure compared to the controls. In adult animals the power of θ wave recorded from the visual cortex during REM sleep was also decreased at hr 2 of exposure to the high concentration. In both groups no significant change in power spectrum was observed during W and NREM sleep. However, from the effects on sleep-wake cycle at low concentration the young rats appear to be more sensitive to toluene exposure compared to adult rats.

Toluene EEG Power spectrum analysis Inhalation Young vs. adult rats

AS a lipophilic substance, toluene is accumulated in the brain and can affect the central nervous system (CNS) easily. Inhalation of toluene at a very low concentration produces effects on learned behavior in laboratory animals (9, 15, 17, 23, 24). Behavior as a function of the brain was found to be a good measure to delineate the effects of an organic solvent at a minimal concentration (15). To measure the effects of toluene on the brain, in addition to behavior, an electroencephalographic (EEG) study has been conducted in laboratory animals (12, 21, 35, 36).

It has been reported that the early postnatal brain is highly sensitive to industrial solvents which might influence the development of the normal growing brain and the later behavior (19–21, 31). Thus, exposure of neonatal rats to lacquer thinner or toluene inhalation causes increased locomotor activity (10,20) and delayed maturation of swimming behavior and physical development (19, 20, 31), indicating some interference with the development of those cortical and brainstem structures underlying swimming and locomotor activities (20). Learning abilities during operant behavior have shown long-lasting impairment following neonatal exposure of rats to the industrial solvents (9, 10, 15). Chronic toluene exposure also produced a significant prolongation in the mean peak latencies of cortical evoked potentials in neonatal rats (21). Weanling rats have also been shown to be more sensitive to the irreversible high-frequency hearing loss due to toluene inhalation compared to adult rats (29,30). Thus, it appears that younger rats are more sensitive to toluene exposure compared to adults. In a recent study (16) from our laboratory, exposure of adult rats to different concentrations of toluene was shown to alter the durations of various stages of their sleep-wake cycle and the EEG power spectrum. The present study was therefore undertaken to test whether toluene inhalation would have more sensitive effects on the sleep-wake behavior and the EEG spectral power in young rats (30–53 days old) compared to those in adult rats (63–77 days old).

METHOD

Animal

Seven male F344 weanling rats (21 days old) and 6 male F344 adult rats (50 days old) were obtained from Charles River Breeding Lab. Weanling rats weighed 50–90 g (25–30 days) and adult rats weighed 210–230 g at the time of surgical operation. Rats were housed individually in stainless steel cages in the animal room with a 12-hr light-darkness cycle (light 7 a.m. to 7 p.m.). The animal care room was maintained at a temperature of 24 ± 1°C and relative humidity of 55 ± 5%.

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Surgical Procedure

Implantation of electrodes (consisting of 0-80 × ⅛ inch stainless steel screws) was carried out under sodium pentobarbital anesthesia (40 mg/kg, IP). Two electrodes were implanted over the visual cortex and other two were placed over the somatosensory cortex (parietal region) [(16,21), modified]. The coordinates of the visual cortex for weanling rats were 4.5 mm posterior to the bregma and 2.5 lateral to the midline on both sides, and for the adults rats were 6 mm posterior to the bregma and 3.5 mm lateral to the midline. The coordinates for the somatosensory area were 1 mm posterior to the bregma and 2 mm lateral to the midline on both sides in weanling animals, and 1.5 mm posterior to the bregma and 3 mm lateral in adult animals. Another electrode placed 7.7 mm anterior in weanling rats and 11 mm anterior in adult animals served as the ground. For EMG recording pairs of stainless steel wires were inserted into the neck muscle. All electrodes were soldered to a miniature socket (March Electronics MMS22-7) which was attached to the skull with dental cement.

Polygraphic Recording and Classification of Sleep-Wake Stages

Two days after the surgery, each rat was placed in the inhalational chamber (see later) for 3 days of habituation, while EEG and EMG were recorded via a Grass Model 7 Polygraph for 6 hr daily (9:30 a.m. to 3:30 p.m.). EEG frequencies from 0.3 to 30 Hz and EMG frequencies from 5 to 75 Hz were allowed to pass through the filter. The EEG was recorded via electrodes placed on the two sides of the visual cortex and also via electrodes on the two sides of the somatosensory cortex. The EMG was recorded from the neck muscles. Even after initial habituation, when the animal was placed inside the inhalational chamber, it took some time for the sleep cycles to be stabilized. For this reason, only the last 4-hr recordings (11:30 a.m. to 3:30 p.m.) were used for calculating the durations of sleep-waking stages per hour. When these values from the last two consecutive days were consistent, rats were exposed to toluene for 2 hr (12:30 p.m. to 2:30 p.m.). One-hour recording preceding the exposure was considered as the preexposure control, and the postexposure effect was recorded during the last hour. Data from the day preceding the exposure were considered as the previous day control.

Polygraphic recordings of the rat were grouped into three stages, as already described (4,8): 1) wake (W) stage characterized by the low amplitude EEG from both the somatosensory and visual cortices and the high amplitude EMG; 2) nonrapid eye movement (NREM) sleep characterized by the high amplitude irregular EEG from both the cortices and the low amplitude EMG; 3) rapid eye movement (REM) or paradoxical sleep (PS) characterized by the low amplitude EEG from the somatosensory cortex, continuous waves from the visual cortex and the low amplitude EMG. The activity originating from the visual cortex during REM sleep was confirmed with spectral analysis.

Power Spectrum Analysis

EEG and EMG activities were also recorded on an FM magnetic tape recorder (A.R. Vetter Co., Model C4). Power spectral analysis of EEG was performed off-line using a Nicolet MED-80 minicomputer system which uses Fast Fourier Transformation for computation. EEG power spectra were derived from 10-sec samples of EEG that were digitized at a sampling rate of 50/sec and power spectral densities were estimated from 0 to 25 Hz and plotted on a X-Y plotter. The digital values of power spectra of the four major frequency bands: δ (0–3 Hz), θ (4–7 Hz), α (8–13 Hz) and β (14–20 Hz) from six to twelve 10-sec EEG samples (for details see the Statistical analysis section) during each of W, NREM and REM sleep stages were obtained from the printout.

Exposure to Toluene

Rats were exposed to toluene (laboratory grade, Fisher Scientific Company) in a dynamic inhalational chamber described in detail by Pradhan and Copeland (27). Briefly, the chamber consisted of an inverted cylindrical glass chromatography jar suitable for exposure of a single rat. The chamber was infused with a flow of air derived from the house air supply. After filtering the air, it was passed through a pressure regulator and a gas flowmeter. Toluene was injected into an evaporating flask by an infusion pump. The filtered house air was mixed with toluene vapor in the flask and passed through a condenser to lower the temperature of the mixture before entering into the exposure chamber. To obtain a homogeneous distribution of vapor into the chamber the mixture was introduced through a cross-shaped copper tubing system suspended from the ceiling of the chamber.

While the exposure was continued, the concentration of toluene in the chamber was monitored by collecting gas samples in a sampling bulb from inside the chamber at 15-min intervals and then injecting 1 ml of the sample into a Shimadzu dual-column gas chromatograph (GC) equipped with flame ionization detectors (Model GC Mini 2). The concentration was measured with the help of a digital integrator connected to the GC. The average concentration of toluene during a session based on the samples was calculated as the mean, and variation of session means for a concentration was expressed as the grand mean ± S.E. Silanized glass columns (3.5 meter, 3 mm i.d.) were packed with GP 5% SP-1200/5% Bentone 34 on 100/120 Supelcoport. Gas flow for the GC was maintained at N_2 500 ml/min, air 450 ml/min, and H_2 40 ml/min. Column temperature was maintained at 80°C and the injector and detector temperatures were 110°C.

Rats were exposed to 3 levels of concentrations of toluene, e.g., low (107.7 ± 5.3 ppm in the young and 110.6 ± 5.0 ppm in the adult), medium (159.5 ± 4.2 ppm in the young and 162.5 ± 15.4 ppm in the adult), and high (406.8 ± 8.1 ppm in the young and 432.0 ± 17.0 ppm in the adult) for 2 hr in a random order on different days. The same rat was not exposed to the next concentration for at least 5 days. Thus, last exposure to young adult was given within 53 days of age and in adult animal it was given within 77 days of age.

Statistical Analysis

Sleep-wake stage analysis. The behavioral stage duration variables (wake, REM sleep, NREM sleep) were analyzed for young and adult animals separately, to identify significant changes from the previous day control in any hour. For each animal, the difference between the exposure day value and the control day value, during each hour, was obtained. These differences were analyzed with a cell means model in the general linear models procedures for one-way analysis of variance (ANOVA) followed by the Dunnett's post hoc test, so that the exposure/control comparison is modeled directly, yielding single degree-of-freedom tests of significance ($p<0.05$) for each exposure by time cell.

Power spectrum analysis. The spectral power variables were also analyzed for young and adult animals separately, to identify significant changes from control in any hour. The control value for each animal was determined for each stage and exposure level by taking the mean of twelve 10-second EEG samples during the preexposure control period (one hour before exposure) and twelve 10-second EEG samples during various times on the previous day. Power spectra of six 10-second of each stage during the last halves of the first and second hour of the exposure period, and the last

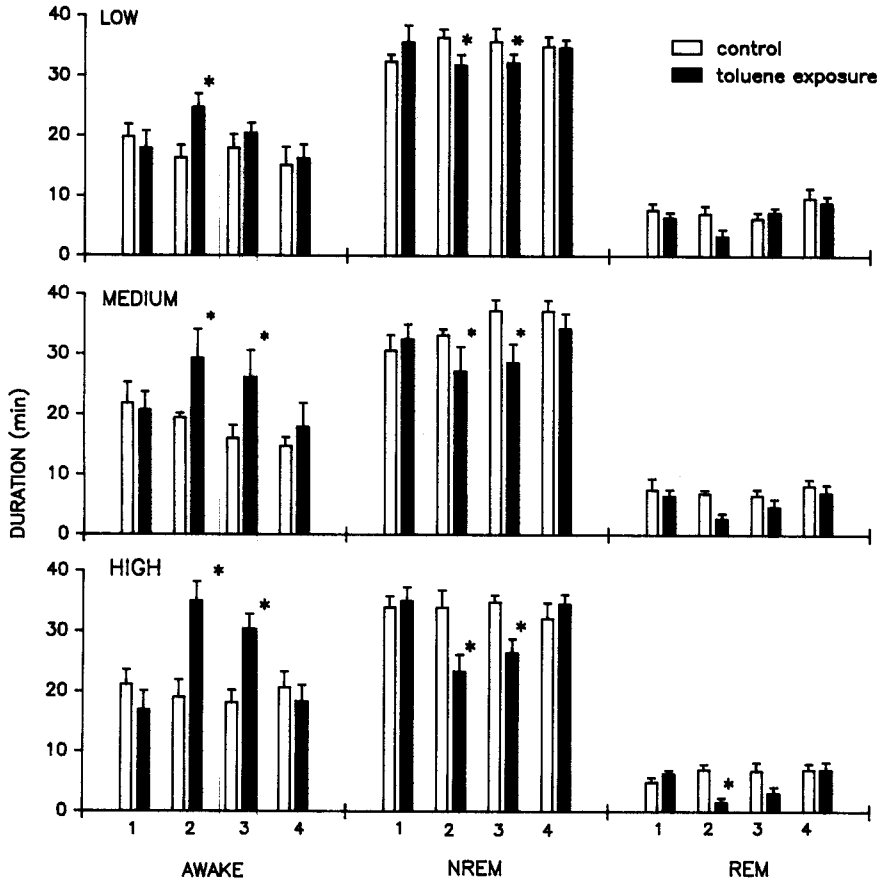

FIG. 1. Changes in the hourly durations of awake, NREM and REM sleep in adult rats during exposure to 3 concentrations of toluene. The 3 concentrations are: low, 110.6 ± 5 ppm; medium, 162.5 ± 15.4 ppm; high, 432.0 ± 17.0 ppm. The numbers on the x-axis represent: 1) preexposure control; 2) HR 1 exposure; 3) HR 2 exposure; 4) postexposure. The data presented are the mean ± S.E. for 6 rats. *$p<0.05$.

half of the first postexposure hour, were calculated for each of the spectral power variables, at each exposure level and stage. Separate, independent analyses were then performed for each variable (i.e., each frequency band from a particular area of the cortex) in each behavioral stage and at each exposure level. In each analysis, one-way ANOVA followed by Dunnett's post hoc test was used to compare the control value to the data for the first exposure, second exposure, and postexposure hours. These comparisons were considered significant at $p<0.05$.

Comparison of data for young and adult animals. The young and adult groups were compared for each of the four (control and experimental) hours. One-way ANOVA followed by Dunnett's test was used for each of the three behavioral stages to compare the mean treatment/control differences of the eight power spectral variables (i.e., each frequency band from a particular area of the cortex), and of the time duration of a stage, between the two groups.

RESULTS

Duration of Sleep-Wake Stage

Measurement of hourly durations of W, NREM and REM sleep stages during control sessions showed that sleep dominated during the 4-hr recording session (Fig. 1 and 2). During exposure to toluene this baseline pattern changed, and the W stage increased with decreases of NREM and REM sleep stages (Figs. 1 and 2). In adult rats, at low concentration, there were significant increase in W at hr 1 and decreases in NREM sleep in hr 1 and 2; at medium and high concentrations, there were significant increases in W and decreases in NREM sleep at hr 1 and 2; no significant change in REM sleep was observed except at high concentration at hr 1 (Fig. 1).

In young rats, at low concentration, there were significant increases in W and decreases in NREM sleep at hr 1 and 2 and decrease in REM sleep at hr 1; at medium and high concentrations, there were increases in W and decreases in REM sleep at hr 1 and 2, and also decreases in NREM sleep (at hr 2 in medium concentration and at hr 1 in high concentration); some postexposure changes (e.g., increase in W at high concentration and decreases in REM at medium and high concentrations) were also observed (Fig. 2).

From Figs. 1 and 2 percent changes for the posttreatment data over the controls were calculated. Although a rough dose-effect relationship was observed in adult animals, young animals were found to be most sensitive at low concentration and least at the medium concentration.

Differences between durations (min) of various sleep-wake stages from the toluene exposure day and those from the respective

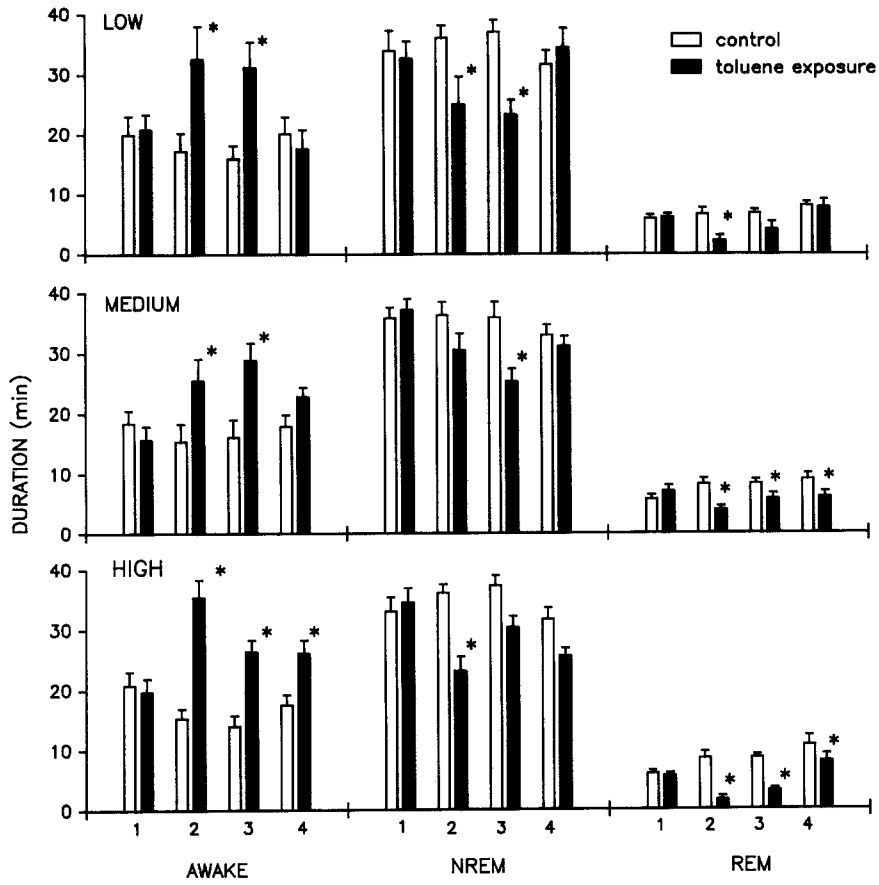

FIG. 2. Changes in the hourly durations of awake, NREM and REM sleep in young rats during exposure to 3 concentrations of toluene. The 3 concentrations are: low, 107.7 ± 5.3 ppm; medium, 159.5 ± 9.2 ppm; high, 406.8 ± 8.1 ppm. Other details are same as in Fig. 1; N = 7.

previous day controls were calculated in both young and adult rats. Statistical comparison between these differences in young and adult groups showed that in young animals there were significant increases in the W stage during hr 2 of exposure at the low concentration and during the postexposure period at the high concentration.

Power Spectrum Analysis

Power spectra of EEG samples recorded from the somatosensory and visual cortices during sleep-wake stages indicate some qualitative and quantitative differences during W, NREM and REM sleep. But those differences between the two age groups in their control values were not significant. Power spectra for EEG recorded from the visual cortex during REM sleep showed some changes in both age groups. In young rats during hr 2 exposure an increase of power of δ wave with exposure to the medium concentration and an increase of δ power of wave and decrease of power of θ wave with exposure to the high concentration were noted, although not significantly (Fig. 3). In the adult group a significant decrease of θ power was noted during hr 2 of exposure at high concentration (Fig. 4). From these figures, differences in the power spectra of various EEG waves from the toluene exposure day and those from the respective previous day controls were calculated in young and old rats. Statistical evaluation of these differences in the two age groups failed to show any significant change.

Power spectrum analysis of EEG recorded during W and NREM sleep from the visual cortex as well as during W, REM and NREM sleep from the somatosensory cortex in both groups of rats exposed to toluene did not show any significant change (data not presented).

DISCUSSION

The present study showed that the duration of W was increased with decreases of NREM and REM sleep after exposure of rats to 100 and 450 ppm of toluene. Similar changes were reported in rats at 2000 and 4000 ppm of toluene by Takeuchi and Hisanaga (35). While the latter investigators considered time duration of each stage during a 6-hr session, in the present study durations of the stages in each hour were measured. Changes observed at lower concentrations in the present study may be due to the different methods of calculating the percent change of an individual stage. Increase in waking immediately after toluene injection (200, 400, 600 mg/kg, IP) was also reported in the bihourly data in rats (5). Behavioral excitation and EEG arousal were also reported after toluene exposure in cats (1, 12, 34) and in rabbits (2).

Reviewing the electrographic effects of various psychoactive

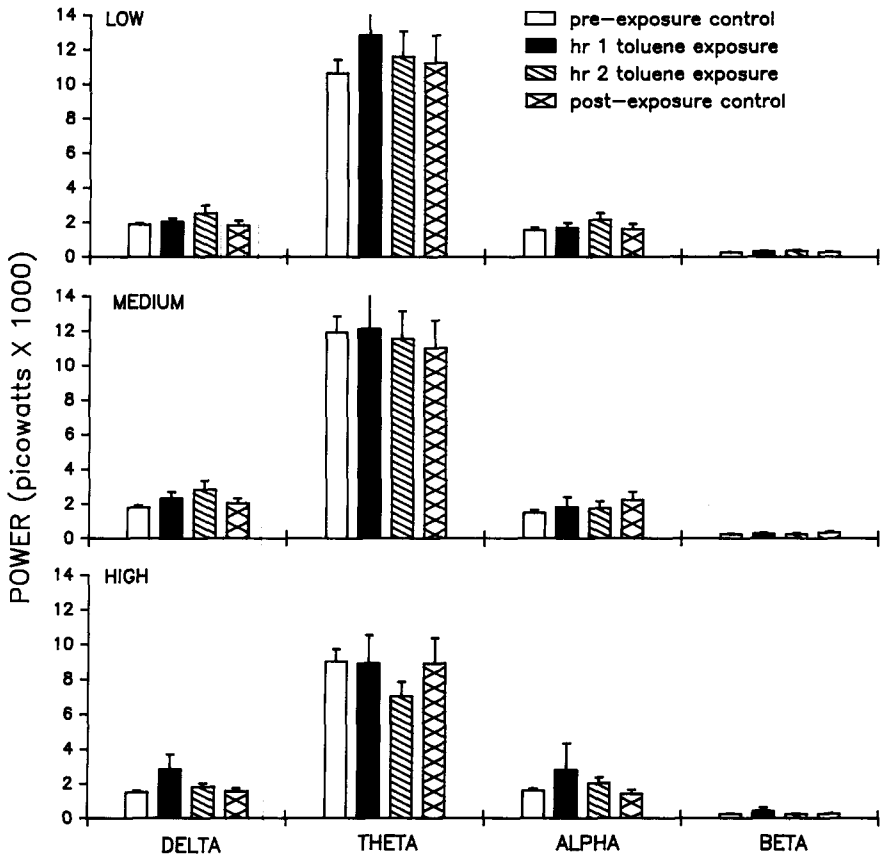

FIG. 3. Effect of toluene exposure on the power spectrum analysis of EEG recorded from the visual cortex during REM sleep in young rats. The toluene concentrations are: low, 107.7 ± 5.3 ppm; medium, 159.5 ± 9.2 ppm; and high, 406.8 ± 8.1 ppm. Other details are same as in Fig. 1; N = 7.

drugs based on EEG power spectral analysis, Young *et al.* (37) concluded that different classes of these drugs would produce very characteristic power spectral profiles. In the present study, toluene exposure did not produce any change in the powers of different frequency bands during NREM sleep and wake stages in both the age groups. Powers of δ and θ frequency bands were changed during toluene exposure only in REM sleep recorded from the visual cortex. In young rats the increase of δ power was noted even at 150 ppm and at 400 ppm; this increase of δ power was observed with a decrease of θ power during hr 2 of exposure. In adult rats only a decrease of θ power was noted during hr 2 of exposure to 400 ppm. Takeuchi and Hisanaga (35) recorded EEG activities from the hippocampus during 4 hr exposure to toluene; they observed an increased β frequency during exposure to 2,000 and 4,000 ppm levels of toluene and a decrease in the θ frequency during exposure to 4000 ppm level. Significant reduction of hippocampal θ wave frequency was also reported during chronic exposure to 500 ppm of toluene in rats (25).

Thus, a decrease of θ power indicative of an excitatory effect was noted on exposure to 400 ppm and higher levels, although increase of δ power indicative of depression was noted initially or at lower levels. Such biphasic effects of toluene are also corroborated by its principle health effects in man, according to which toluene at low levels produces depressant effects including reduced performance, fatigue and dizziness, whereas at higher levels it causes "hilarity" in man and excitatory effects in some species (7).

The changes observed in the power of different frequency bands during toluene exposure did not show any statistically significant difference between the two age groups. This suggests that the sensitivity to toluene in the two age groups are similar in respect to their power spectra. However, the increase in duration of W and the decrease in NREM sleep during hr 2 of exposure to the low concentration (108–111 ppm) of toluene in young rats were significantly different from that of the adult rats. This probably indicates a higher sensitivity of young rat brain to toluene compared to that in the adult.

Effect of toluene exposure on waking behavior could be due to arousal in the CNS or local irritant effects on eye and upper respiratory tract. Although the latter effects cannot be ruled out, they appear to be less likely, since no observable signs of irritation of eye or nose were noted during or after the exposure. Moreover, such effects would increase with dose and duration of exposure, with a possibility of developing habituation, which were not evident in these experiments. On the other hand, the CNS effects which could also be produced by IP injection, would produce biphasic or even triphasic effects (6,7).

In a study involving car painters exposed for 1–40 years to an average of 30 ppm toluene daily, the subjects were reported to have lower intelligence test scores and lower emotional reactivity (18), but showed no difference in EEG or nerve conduction velocities compared to unexposed controls (33). Workers exposed to 60–100 ppm toluene for 3–4 months had increased incidence of tendon reflex abnormality and muscular weakness (22). Medical

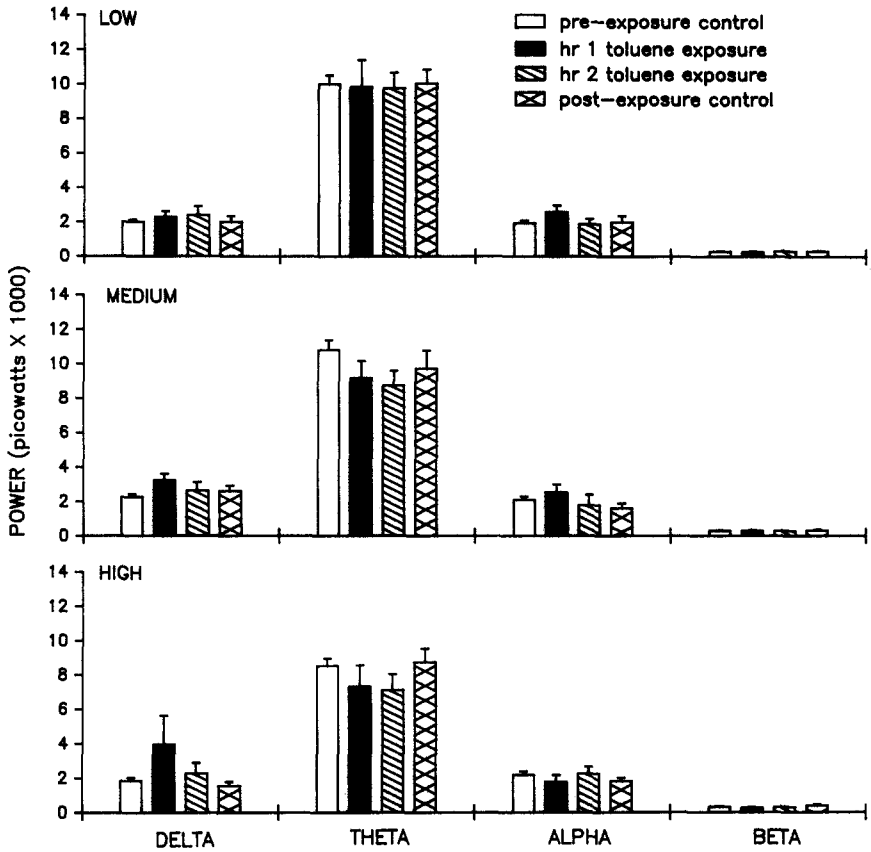

FIG. 4. Effect of toluene exposure on the power spectrum of EEG recorded from the visual cortex during REM sleep in adult rats. The toluene concentrations are: low, 110.6 ± 5.0 ppm; medium, 162.5 ± 15.4 ppm; high, 432.0 ± 17.0 ppm. Other details are same as in Fig. 1; N = 6.

examination of 100 factory workers exposed to toluene for 1–3 weeks showed that effects ranged from dizziness at 0–200 ppm to mild incoordination at 500–1,500 ppm. Reviewing these and many other effects of toluene exposure in humans and animals, Benignus (7) concluded that the minimum thresholds for inducing effects after toluene exposure were in the 100–300 ppm range in man and as low as 150 ppm in rats. The threshold from our experiments in rats appears to be lower compared to these values. However, our threshold for exposure to toluene appears to tally with those set up by OSHA (Occupational Safety and Health Administration). The following are the limits set up by OSHA (26): 100 ppm as the time weighted average (i.e., the employee's average airborne exposure in any 9-hr work shift of a 40-hr work week); and 150 ppm as the short-term exposure limit (i.e., the employee's 15-minute time weighted average exposure which shall not be ordinarily exceeded at any time during a work day).

During the early postnatal period a newborn is highly sensitive to the effects of various chemical agents including the industrial solvents which might influence the normal brain ontogeny and neurobehavioral development (19–21, 39). Electrocorticogram (ECoG) and evoked potentials are commonly used as indicators of brain maturation (3, 28, 32, 38). Chronic toluene exposure has also been reported to produce in neonatal rats a significant prolongation in the mean peak latencies of cortical evoked responses (21).

Toluene, like some other industrial solvents, is able to dissolve and be stored in the CNS fatty tissue (14), probably causing disruption in the process of myelination in the central neurons (21). Toluene has also been reported to cause fragmentation or loss of axons and dendrites in both the peripheral and central neural structures (11,13). These effects of toluene may be responsible for the neurobehavioral anomalies observed in the neonatal rats following their chronic exposure to the solvent which might have caused delays or disruption in the CNS maturation. In the present experiment, the rats were only exposed to 3 levels of toluene for 2 hr each in different sessions at the intervals of at least 5 days. Effects of toluene on the sleep cycle observed in this experiment may be due to the sensitivity of the young rats. It is difficult to state whether such exposures affected their brain maturation process, since these rats were not further monitored for their behavior beyond three exposure periods.

ACKNOWLEDGEMENTS

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