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Multimodal Effects of Acute Exposure to Toluene Evidenced by Sensory-Evoked Potentials From Fischer-344 Rats

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REBERT, C. S., M. J. MATTEUCCI AND G. T. PRYOR. *Multimodal effects of acute exposure to toluene evidenced by sensory-evoked potentials from Fischer-344 rats*. PHARMACOL BIOCHEM BEHAV **32**(3) 757–768, 1989.—Male Fischer-344 rats were exposed by inhalation to 500, 2000, 5000, 8000 and 16000 ppm toluene for 30 min in two experiments. Exposures up to 8000 ppm in Experiment 1 caused concentration-related changes in the click-elicited brainstem auditory-evoked response (CBAER), flash-evoked potential (FEP) and somatosensory-evoked potential (SEP). Latencies of CBAER components were prolonged and amplitudes of late components were increased by toluene. Toluene did not detectably alter the latencies of FEP or SEP components. Early FEP component-amplitudes were increased and late component-amplitudes were decreased; toluene also induced a poststimulus oscillation in the FEP. Most component-amplitudes of the SEP were substantially increased, but N2P2 amplitude appeared to be more sensitive than other components to depressant effects of the solvent. The same effects on the CBAER were observed in Experiment 2, but a more substantial increase in the amplitudes of late components elicited by tone pips suggested that frequency-dependent cochlear irritation might underlie previously observed subchronic ototoxicity. These effects were increased by exposure to 16000 ppm toluene. Effects like those observed in Experiment 1 were noted on the FEP, but the oscillations were less with exposure to 16000 than 8000 ppm. Changes in the SEP were evident within 2 minutes of exposure onset, and amplitudes increased over the course of about 15 min, leveling off or decreasing thereafter. The amplitude of the N2P2 component was again less influenced than other components during exposure to 8000 ppm and was reduced to less than baseline amplitude by 16000 ppm. Effects of concentration and rates of development and recovery were systematically related to SEP component latency. Toluene appears to have both enhancing and inhibiting effects on neural pathways serving sensory systems, depending on the modality and the site of generation of the components within modalities. A particular balance between these properties might relate to the hedonic characteristics of this abused solvent.

Toluene Solvent abuse Sensory-evoked potentials BAER FEP SEP Rats

BECAUSE toluene is a major component of abused solvents and a common industrial and household substance, exposure to it varies from large, intermittent, and variable concentrations during solvent abuse to low continuous exposures during the workday in some industries. Of the possible toxic consequences of toluene exposure, its lipid solubility, the high lipid content of brain, and toluene's psychoactive effects suggest concern about damage to the nervous system. In general, moderate concentration × time exposures to toluene are relatively innocuous (2, 3, 25), with the exception of ototoxic sequelae (26, 27, 31), but long-term abuse of solvents, implicating toluene, has been reported to cause a variety of neurologic abnormalities (7, 13, 16, 17, 20, 22). Understanding the characteristics of toluene that underlie its abuse might have implications for preventative or treatment programs.

Those who abuse volatile solvents appear to experience a state of euphoria associated with "light-headedness" and dissociation from the environment, but sedation and unconsciousness may also occur with prolonged exposure to high concentrations (5). Whereas the acute effects of toluene on a variety of behavioral functions have been studied (3), there is relatively little information about the acute effects of this solvent on brain electrophysiology. Electroencephalographic changes include enhancement of theta activity in cats (1) and rats (35), and the induction of 20- to 30-Hz oscillations in visual cortex of cats (23). Because the measurement of sensory-evoked potentials (EPs) can characterize the effects of chemicals on several aspects of sensory functioning—both within and among sensory modalities—(28) we examined the acute effects of inhaled toluene on brain potentials elicited by auditory, visual, and somatosensory stimulation.

Our goals for this research were several. We wanted to determine: 1) if toluene would affect EPs, and if so, if the several sensory modalities, and EP components within modalities, were in any ways differentially sensitive to toluene; 2) the concentrations at which any effects of toluene might occur and the time courses of any such effects; 3) if EPs would reflect an excitatory/sedative dimension as suggested by behavioral studies; and 4) if EP

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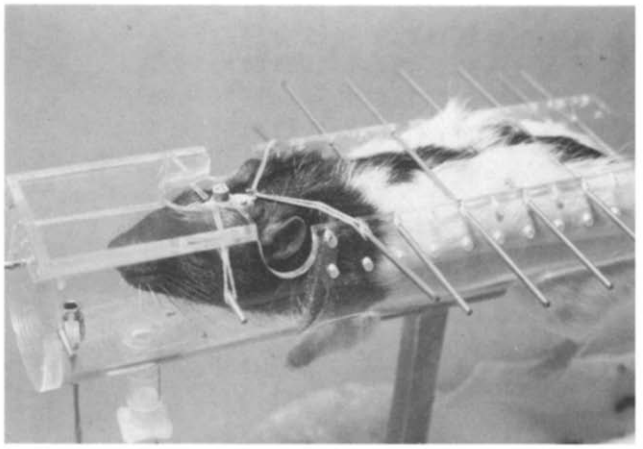

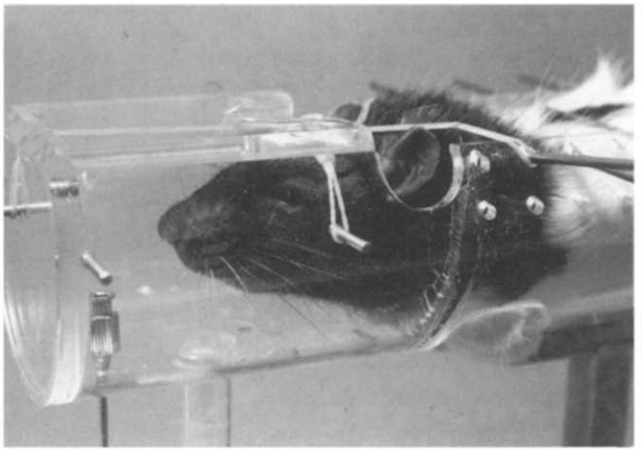

FIG. 1. Rat restrainer and head-only exposure system for electrophysiologic recording during exposure to volatile solvents. Rubber bands connected to hooks on the electrode plug help maintain consistent orientation of the rat's head to sources of stimulation and prevent the head from being pulled back against the neck stock, which can block the meatus. Gas flow is directed anteriorally on entry from the bottom of the chamber. Chamber atmosphere is sampled via the needle shown. [Reprinted with permission from (32).]

changes were a consequence of changes in blood gases rather than to direct neural effects of toluene.

Since subchronic exposure of rats to toluene causes a permanent frequency-dependent hearing loss (26) that is evident in the brainstem auditory-evoked response (BAER) (31), BAER intensity amplitude functions were also obtained to determine if there were acute effects that might be predictive of subsequent ototoxicity.

Our findings from this study are also relevant to a report by Dyer *et al.* (9) that appeared subsequent to our initiation of this investigation. Those authors indicated that orally administered toluene reduced the amplitude of a late negative component (N3) of the flash EP (FEP). We determined if such an effect would occur with inhalation exposure and if this route of exposure would also affect other components. Similarly, Mattsson *et al.* (21)

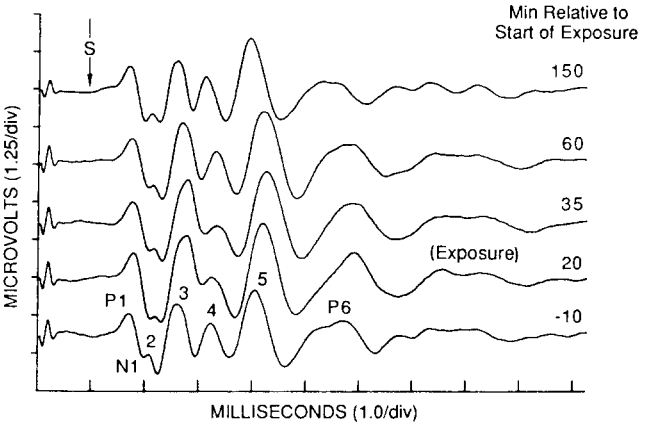

FIG. 2. Group-averaged CBAER waveforms at various times relative to the start of a 30-min exposure to 8000 ppm toluene. During exposure, latency increases are evident for all components, as is ampltiude enhancement of wave 5.

recently reported that toluene enhances a specific positive component of the somatosensory EP (SEP). However, the inhalation exposure level was not specified in that report nor were the effects of various concentrations examined. We additionally determined effective concentrations, examined the temporal course of changes in the SEP, and found a less specific enhancement of SEP amplitude. Because the reports by Dyer *et al.* (9) and Mattsson *et al.* (21) employed different rat strains, different exposure routes, and focused on different EPs, the reliability and generality of toluene's effects on EPs have not been clearly established, warranting additional study of such effects. By studying several modalities in the same rats exposed in the same manner, differential effects on the several senses were more readily discernible. In addition we examined blood gases, the electroretinogram, and peripheral nerve action potentials to clarify the loci of toluene's effects.

METHOD

Subjects and Surgical Preparation

Male Fischer-344 rats weighing about 250 g were used in two experiments. They were obtained from Simonsen Laboratories in Gilroy, CA. Upon arrival at SRI they were kept in $23 \times 14 \times 45$ cm plastic cages (3/cage) housed in laminar flow racks. Food and water were available ad lib. Lights were on from 7 a.m. to 7 p.m. Nine rats were used in Experiment 1 and six in Experiment 2. Surgical procedures were like those described before (29). Epidural stainless steel screws were placed in the cranium over visual and somatosensory cortices and in the nasal bone (reference electrode). Wires were soldered to the screws prior to implant to preclude heat damage to the cortex (10). Hooks embedded in the acrylic headplug were used during testing to hold the head to a frame with rubber bands to maintain proper orientation of the rat to the stimulus sources (Fig. 1).

Exposure to Toluene

Mallinckrodt reagent grade toluene (99.8% pure) was used, and two channels of a mass-flow controlled gas blending system were adjusted to deliver the desired concentrations of toluene. One channel gated compressed air through a 4-l container of toluene, the outflow of which was mixed with air from the other channel in

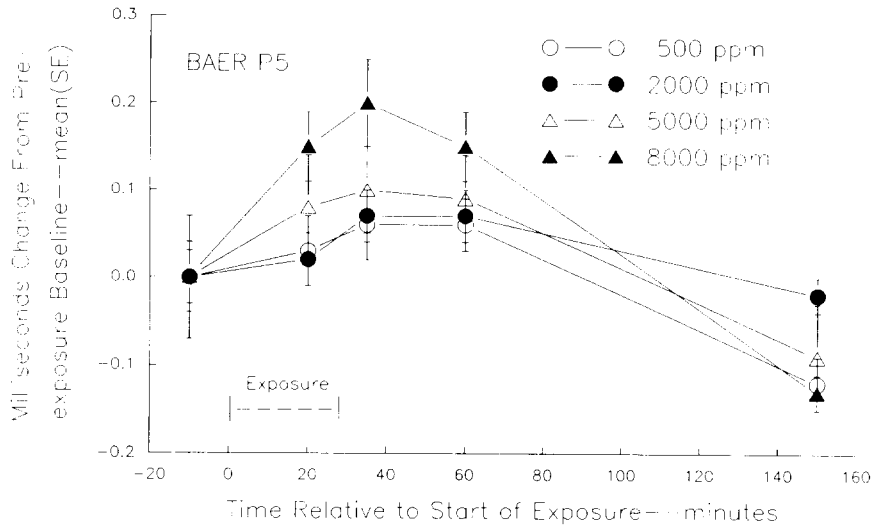

FIG. 3. Changes in latency of BAER peak P5 as a function of toluene concentration and time relative to the exposures. Latency increased only with exposures to 5000 and 8000 ppm—the effect was most pronounced 5 min postexposure.

a 500-ml flask. Outflow from the flask was routed through a 190-ml sampling bulb in the line just before entry into the rat exposure chamber. The sampling bulb helped stabilize concentrations and provided a source of gas samples just before exit to the rat. The rat was restrained in the plastic restrainer described by Rebert (29) that was modified as shown in Fig. 1 to provide a head-only exposure to gases during electrophysiological recording. Presence of the plastic did not alter flash or pattern reversal visual EPs examined in other investigations (32). Total gas flow was 2500 ml/min; flow rates higher than 3000 ml/min generated sufficient noise to partially mask auditory stimuli. Gas concentrations were sampled from the sampling bulb and through the needle in front of the rat's nose (Fig. 1). Exposures were calibrated against standards by gas chromatography. Extensive preexperimental tests demonstrated a high degree of consistency of concentrations with flow-rate selection on the mass-flow controller. However, because movement and respiratory activity of the rats could modify the exposure to some extent, samples were periodically obtained during the several phases of the exposures.

Electrophysiologic Tests

Three kinds of electrophysiologic responses, making up a test battery program called NIDTST, were routinely obtained. These were the BAER, FEP, and SEP tested in that order. Two consecutive acquisitions of each EP were obtained to insure reliable averages. If these were comparable, the two waveforms were averaged, otherwise the test was repeated.

The *click-evoked brainstem auditory-evoked response* (CBAER), recorded from the visual cortex, was elicited by 100-μsec-duration clicks, with alternating polarity. The clicks were delivered through a tweeter (1.5 to 20 kHz) suspended 24 cm directly above the rat's head (adding 0.8 msec to component latencies). Intensity was about 70 dB above the level at which BAERs are just discernible in rats (30,31). BAERs were also elicited by 16-kHz tone pips (PBAERs) of 0.2-msec risetimes and 1-msec plateau at various intensities. BAER averages were based on 600 (CBAER) or 1000 (PBAER) stimuli presented at 18.8/sec, using a bandpass of 400 Hz to 6 kHz. We have previously found this bandpass to provide the clearest definition of transient peaks, although it eliminates the slow component of this response (25, 27, 29–32).

Flash-evoked potentials were recorded from visual cortex and were elicited by a strobe lamp placed behind a diffusing plate of glass 20 cm directly in front of the rat. Intensity of the flashes (Grass PS-2 intensity setting = 16), measured at a rate of 50/sec, was 109 ft Lamberts. During testing, 50 flashes were presented at 0.37/sec and averaged using a bandpass of 1 to 50 Hz. Prior to the first of two consecutive FEP tests the chamber was illuminated (14.0 ft Lamberts). The chamber light was extinguished 15 to 30 sec before obtaining the FEP and then turned on again following FEP acquisition (which took about 3 min to complete for each test). This procedure appeared to improve the P2N2P3 complex of the FEP.

Somatosensory-evoked potentials, recorded from somatosensory cortex, were elicited by 50-μsec-duration, 3-mA, constant-current shocks applied via needles inserted into the mid-ventral aspect of the tail (cathode proximal). The bandpass used for SEPs was 1 to 250 Hz. Fifty shocks were presented at a rate of 1.3/sec.

In separate tests, four rats were anaesthetized with 65 mg/kg sodium pentobarbital and the *electroretinogram* (ERG) was recorded using a Burian-Allen contact lens electrode. The corneal contact was used with reference to the electrode in nasal bone. ERGs were recorded with a bandpass of 0.5 to 50 Hz. A caudal nerve *compound action potential* (AP) was also recorded (1 Hz to 1 kHz bandpass) in three awake, restrained rats using the tail-restraining device described before (29); this device consisted of a slotted piece of Plexiglas with stimulating and recording needles in the base that protruded into the ventral aspect of the tail. Stimuli were constant-current shocks (the same as for the SEP) presented at 18.8/sec.

Data Quantification and Analysis

Evoked potentials were quantified in three ways: 1) by measuring peak amplitudes and latencies; 2) integrating the waveforms or portions thereof; and 3) spectral analysis. Amplitude of the first component was measured with respect to the prestimulus baseline and subsequent components were measured peak-to-peak. We routinely quantified nine parameters of the SEP and 14 each from

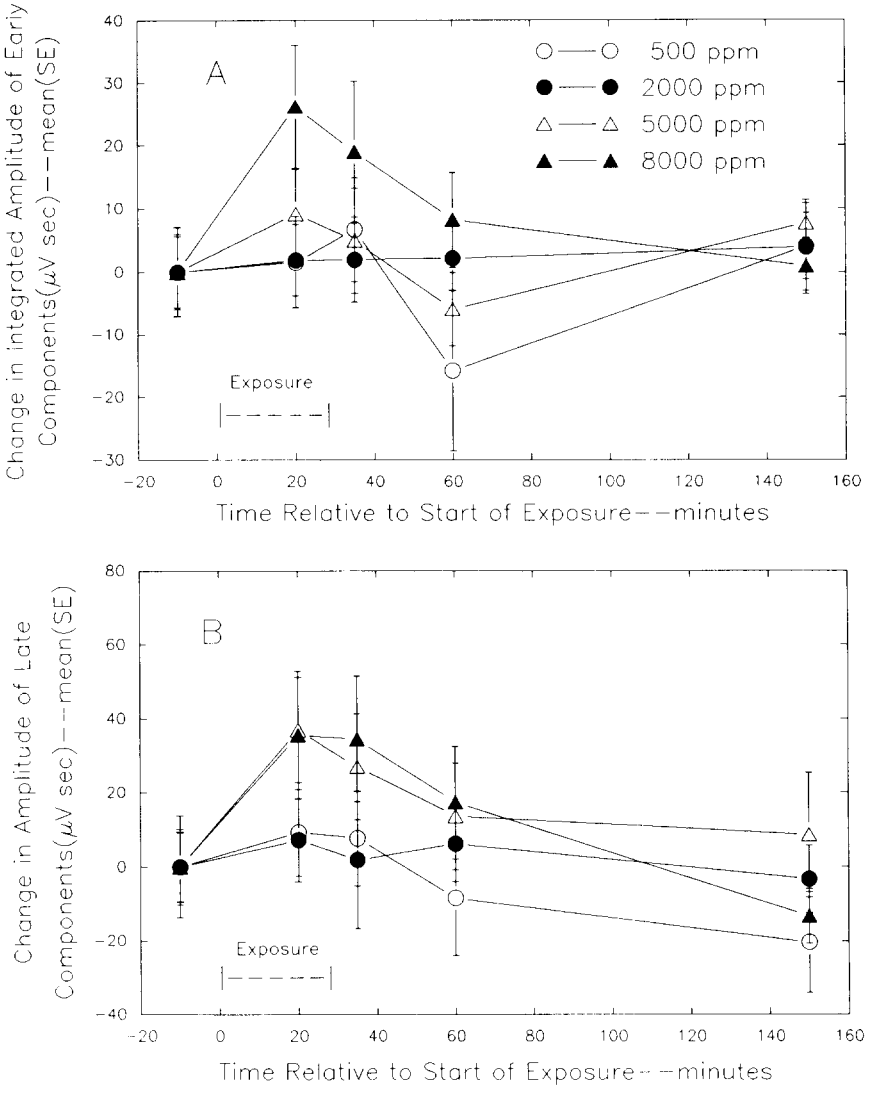

FIG. 4. Changes in integrated amplitudes of early (A) and late (B) portions of CBAERs as a function of toluene concentration and time relative to the exposures. These amplitudes increased only during exposure to 5000 and 8000 ppm.

the FEP and BAER; to clarify any ambiguous results from peak measurement, integrated scores were obtained as indicated in the Results section. Statistical comparisons were made with repeated measures ANOVAs and/or *t*-tests, and linear regression was employed descriptively. Because of lost head plugs and other technical difficulties in Experiment 1, the number of rats for which data were available for the several parameters and conditions varied from seven to nine. Repeated-measures ANOVAs included the baseline, exposure, and 30-min recovery tests as the within-subjects variable. In order to utilize data from all the rats in the several conditions, ANOVAs were carried out for each exposure level separately. Because of the large number of statistical comparisons required, actual probability values for type I errors are given for results where $p \approx 0.05$. We considered probabilities of type I errors <0.05 to reflect real effects. The experimental replication of most results supports the general reliability of the reported observations.

Experiment 1: 500 to 8000 ppm Toluene

Rats were exposed to nominal concentrations of 500, 2000, 5000, or 8000 ppm toluene for 30 min. They were tested just before exposure, 20 min after the beginning of exposure, and 5, 30, and (for most of the rats) 120 min after the end of exposure (during the last interim they were removed from the restrainer). Each rat served as its own control; consecutive exposures were separated, on the average, by 2 days, ranging from 1 to 3 days, and the sequence of exposure concentrations was balanced across rats. Baseline tests were done to confirm that responses had returned to normal before the next exposure. After the main experiment, tests of the ERG were carried out in four rats, and APs were examined in three rats; these tests were done to determine if effects noted on EPs were associated with retinal or peripheral nerve alterations.

Experiment 2: 8000 and 16000 ppm Toluene

The purposes of this experiment were to: 1) examine the time-course of changes in the SEP caused by exposure to toluene; 2) determine the effects of a higher concentration of toluene than used in Experiment 1; and 3) study toluene's effects on PBAERs.

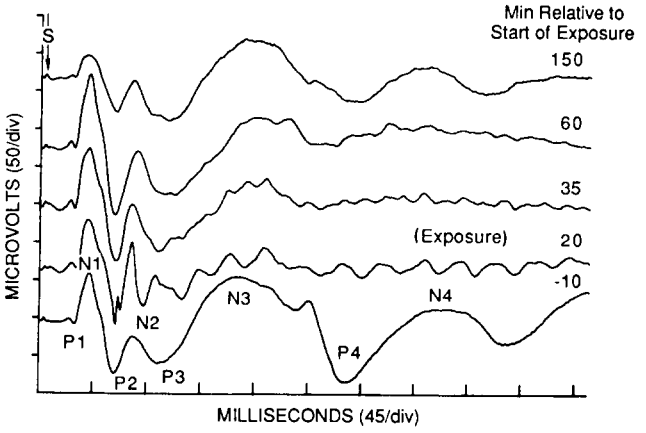

FIG. 5. Group-averaged FEP waveforms at various times relative to the start of a 30-min exposure to 8000 ppm toluene. Toluene increased the ampltiude of the P2N2P3 complex, flattened components beyond P3, and induced oscillations in the waveform.

Six rats were tested before exposure and during exposures to 8000 and 16000 ppm toluene. Following collection of baseline data with the routine test battery (NIDTST), PBAERs elicited by 20 to 95 dB (machine setting), 16-kHz tone pips (in 25-dB steps) were acquired. Nine SEPs were then recorded at 2-min intervals—the first before 8000 ppm toluene was introduced, and eight afterward. After 20 min of exposure, the PBAER sequence was repeated. On completion of the PBAERs, NIDTST was repeated, then the concentration of toluene was increased to 16000 ppm; after 20 min of exposure, NIDTST was run again.

Several weeks after this experiment was completed, four of the rats were prepared with a chronic femoral artery cannula and exposed sequentially to 8000 and 16000 ppm toluene (30 min each) two days later. On the day of the experiment, the rats were placed in the inhalation restrainer with their cannulas connected by a 15-in. piece of PE 60 tubing to a stopcock outside of the recording chamber for blood sampling. The stopcock was connected to a pressure transducer and chart recorder for blood-pressure recording. The procedure for blood sampling was to withdraw and discard 0.75 ml of fluid from the cannula's dead space, then withdraw the 0.25 ml needed for the blood gas analysis. A portion of each blood sample was injected into an Instrumentation Laboratories 1301 Blood-Gas analyzer for measurement of pH, PCO_2, PO_2, and HCO_3^-. Then, 1.0 ml of heparinized saline was infused to keep the cannula patent between samples and maintain blood volume.

RESULTS

Experiment 1: 500 to 8000 ppm Toluene

Exposure levels and colonic temperatures. Means of 5 to 8 determinations of exposure concentrations were 571, 1792, 4800, and 7875 ppm, respectively, for the intended concentrations noted above. Colonic temperatures were maintained within 0.7° of the baseline temperature, but decreases of 0.4° or greater were statistically significant. This magnitude of change is consequential only for latencies of the BAER, components of which increase by about 0.07 msec per °C decrease in body temperature at near-normal temperatures (33,34).

Brainstem auditory-evoked response.

Latency. Figure 2 shows group-averaged CBAERs (8000 ppm exposure) with peak designations. Exposure to 500 and 2000 ppm toluene had little, if any, effect on the CBAER. Small increases in the latencies of the P3 and P5 components occurred primarily during the recovery period (Fig. 3) when temperature dropped by 0.3 (500 ppm) and 0.4°C (2000 ppm). About half of the increased latencies at those exposure concentrations could be attributed to the temperature changes. The higher exposures caused significant increases in the latencies of all but one component [the least significant increase was for P5 (5000): $F(2,12)=9.99$, $p=2.8\times10^{-3}$]; these changes were not attributable to declines in temperature (see the Discussion section). These latency shifts are clear in the group-averaged CBAERs associated with exposure to 8000 ppm toluene (Fig. 2). Figure 3 shows quantitative changes in P5 latency over the course of the test sessions (expressed as differences from the baseline value). For each exposure the toluene-induced increase in latency was greatest at the test 5 min after cessation of exposure and declined thereafter. Results were similar for the P1, P3, and P6 components although the increases from preexposure latencies were greater the later the component; these were 70, 170, 200, and 260 μsec for the P1, P3, P5, and P6 components, respectively, 5 min after the end of exposure to 8000 ppm. The increase in the latency of component 1 indicates a peripheral effect, but 8000 ppm toluene also induced a significant increase, during exposure, of 90 μsec in the P1–P5 interwave time, $F(2,16)=23.98$, $p=1.5\times10^{-5}$. The relative decreases in latency at the last test were associated with elevated temperature (+0.7°C in the 8000-ppm condition) consequent to removing and replacing the rat between the 60- and 150-min tests.

Amplitude. The lower concentrations of toluene had minimal effects on the amplitudes of CBAER components. There was a tendency for early (P1 to N3) and late (N4 to P6) components to increase in amplitude during exposure to 5000 and 8000 ppm toluene compared to baseline. In the 5000-ppm condition these changes were significant for individual components from P1 to P3 and P5 to P6, e.g., F(2,12) P1N2 = 4.49, $p=3.50\times10^{-2}$, but in the 8000 ppm condition only the N4P5 component was significantly enhanced ($p=4.46\times10^{-2}$). To further examine these trends the BAERs were integrated across early (onset of P1 to the midpoint of P3N3), middle (midpoint of P3N3 to the midpoint of N4P5) and late (midpoint of N4P5 to P6) portions of the waveforms. These analyses confirmed the increases in early and late component amplitudes in both the 5000- and 8000-ppm exposures (e.g., for early components in the 5000 ppm condition, comparing baseline and exposure, $t=3.97$, $p7.37\times10^{-3}$; for the late components at 8000 ppm, $t=3.11$, $p=1.44\times10^{-2}$). There were no significant differences between baseline and exposure for the integrated amplitude of the middle components. Changes in the integrated early and late component scores for the various experimental conditions are shown in Fig. 4. The effect of toluene on the intgrated amplitude of the late components (Fig. 4B) was the same for both concentrations during exposure (it was 125% of baseline), but there was a tendency for the response to return toward normal sooner following exposure to 5000 than 8000 ppm toluene. Although the effect of 5000 ppm on the amplitude of early components was statistically significant, a substantial increase was produced only by the 8000 ppm concentration.

Flash-evoked potential.

Latency and amplitude. Toluene did not appear to affect the latencies of FEP components. However, the FEP was increasingly deformed as the concentration of toluene was increased, making identification of the later components questionable. For example, Fig. 5 shows the group-averaged changes associated with exposure to 8000 ppm toluene. There were three main effects: 1) a small increase in the amplitudes of early and intermediate components, N1 to P3 (the P1 component was too small to reliably quantify and so was not evaluated); 2) a substantial decrease in the amplitudes of later components, P3 to N4; and 3) the induction of oscillations in the post-N2 part of the waveform.

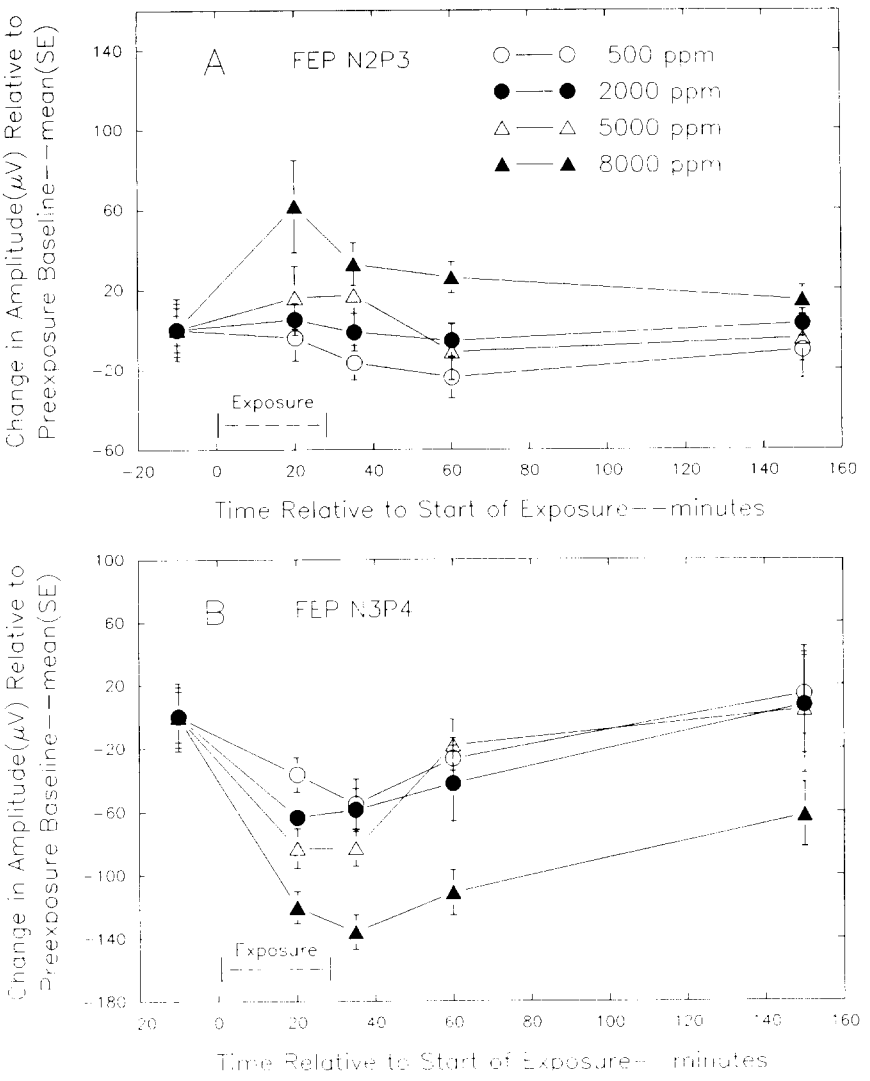

FIG. 6. Changes in peak-to-peak amplitudes of N2P3 and N3P4 components of the FEP as a function of toluene concentration and time relative to the exposures. The earlier component (N2P3) increased in amplitude, whereas the later one (N3P4) decreased in amplitude during exposure to toluene—the later component was also affected at lower concentrations than the earlier one.

Exposure to 8000 ppm caused significant increases in amplitude of the early components through P3; for the least significant of these (P2N2), $F(2,16)=3.95$; $p=4.03\times10^{-2}$ and for the most significant (N1P2), $F(2,16)=10.65$, $p=1.5\times10^{-3}$. The N2P3 component exhibited the most systematic relationship to toluene concentration; its changes across conditions are shown in Fig. 6A.

The amplitudes of the late components N3P4 and P4N4 were decreased by toluene. As shown in Fig. 6B, N3P4 was reduced in amplitude in relation to toluene concentration; during exposure to 2000 ppm, $F(2,12)=5.29$, $p=2.25\times10^{-2}$, and to 8000 ppm, $F(2,16)=41.04$, $p=5.02\times10^{-7}$. N3P4 amplitude had not returned to normal by two hr postexposure. Because these components were not precisely identifiable in all cases, an integrated value from the midpoint of P3N3 to N4 was calculated. This analysis confirmed the peak-to-peak scoring, e.g., comparing baseline to exposure at 5000 ppm, $t(6)=6.28$, $p=7.58\times10^{-4}$. There was a substantial relationship between integrated amplitude deviations from baseline and toluene concentration; the linear correlation between these variables was 0.98.

Spectral composition. During baseline tests, spectral energy of the FEP was confined primarily to frequencies below 13 Hz, but during exposure, peaks appeared in the 20 to 40 Hz range. To quantify these, power at or near the frequency observed during exposure was measured during the other conditions. The average frequency of the peak tended to increase with increasing toluene concentration; mean frequencies were 23.1, 23.3, 27.5, and 34.8 Hz for the low-to-high exposures, respectively, $t(6)=2.29$, $p=6.19\times10^{-2}$ for 500 vs. 8000 ppm. Power of the third peak was significantly increased only by 8000 ppm toluene during exposure, $t(8)=2.67$, $p=2.84\times10^{-2}$, and it decreased rapidly after exposure.

Electroretinogram. The ERG evidenced no shifts in latency, but its integrated amplitude decreased on the average by 32% after 20 min of exposure in the four rats so examined. There was no evidence of oscillations as seen in the FEP, but it is possible that they may have been eliminated by the anesthetic.

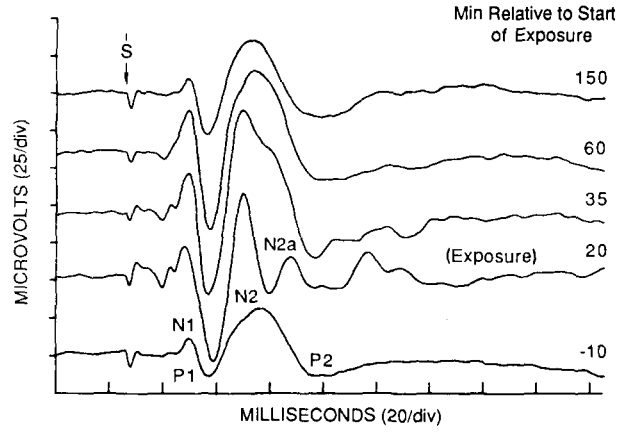

FIG. 7. Group-averaged SEP waveforms at various times relative to the start of a 30-min exposure to 8000 ppm toluene. Toluene substantially increased the ampltiude of all components and dissociated elements of the N2 wave.

Somatosensory-evoked potential. As shown in Fig. 7 toluene caused a dramatic change in the shape and size of the SEP, although there were no systematic effects on latencies of the routinely scored components. However, at 8000 ppm, the single N2 component seen before exposure appeared as two components after 20 min of exposure, suggesting that the latency of an imbedded component (N2a) had increased. This was associated with a steepening of the rising phase of N2 and an increase in the size of all components. By 5 min after exposure the N2a component was apparent only as a shoulder in the group-averaged waveform shown in Fig. 7. During exposure to 2000 and 5000 ppm, this effect was evident only as a widening and flattening of N2, with a slight shoulder evident 5 min after exposure to 5000 ppm. At or above 2000 ppm the repeated-measures ANOVAs including the preexposure, exposure, and 30-min postexposure conditions were statistically significant for every component except N1 at 5000 ppm [e.g., for N1P1 at 2000 ppm, $F(2,12)=30.72$, $p=1.9\times10^{-5}$; for N1P1 at 8000 ppm, $F(2,16)=30.82$, $p=3.25\times10^{-6}$].

Changes in the amplitudes of these components in the several experimental conditions are shown in Fig. 8. Except for component N2P2, amplitudes were generally largest in the 8000 ppm condition. They did not always decrease immediately after the termination of the exposure. For example, the amplitude of N1 continued to increase for 5 and 30 min after exposure to 5000- and 8000-ppm toluene, respectively, whereas it declined at the 5-min recovery test after exposure to the lower concentrations. Although substantially enhanced by 5000 ppm toluene, N2P2 amplitude was only slightly increased during exposure to 8000 ppm, but it became much larger following that exposure.

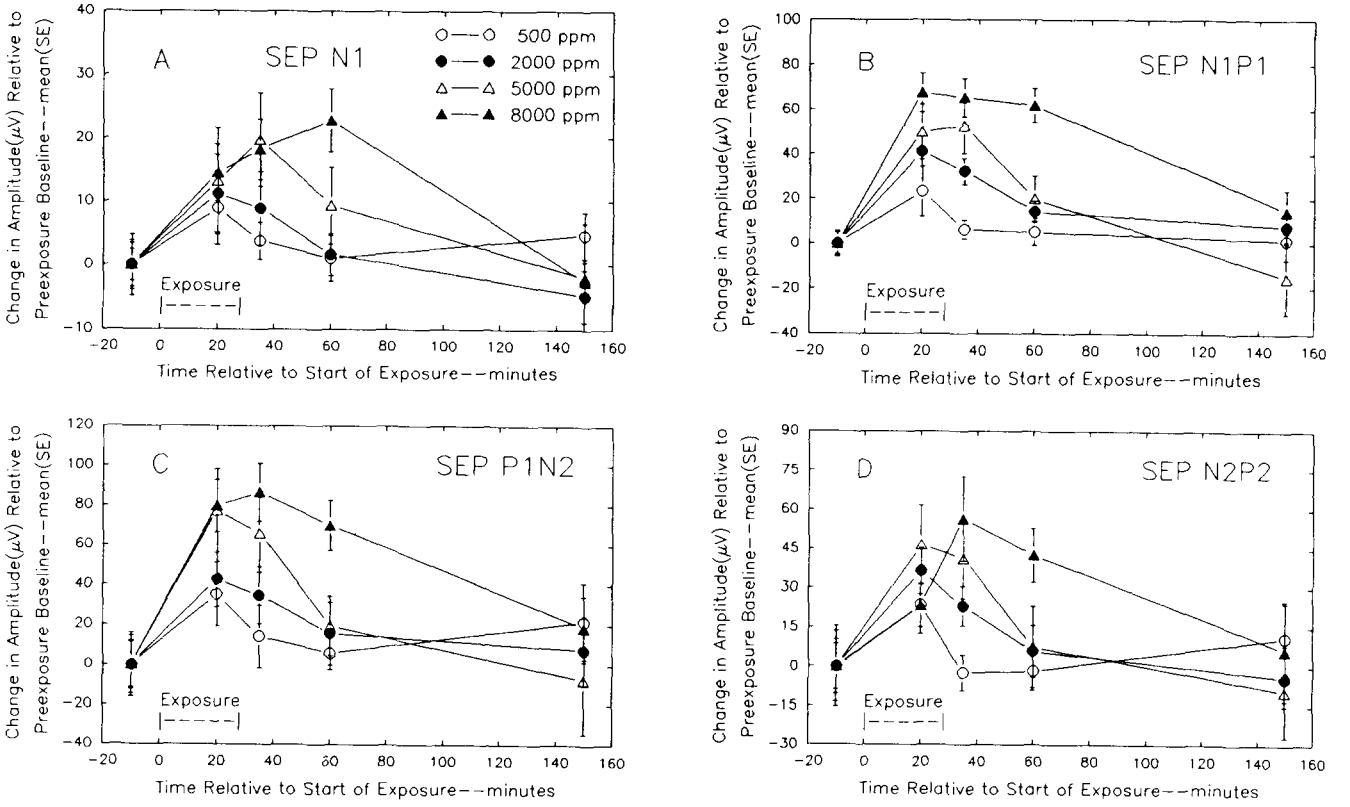

FIG. 8. Changes in peak-to-peak amplitudes of several SEP components as a function of toluene concentration and time relative to the exposures. Increased amplitudes were most systematically related to concentration 5 min after the exposure ended. Suppressant effects of 8000 ppm toluene appeared to differentially affect the N2P2 component.

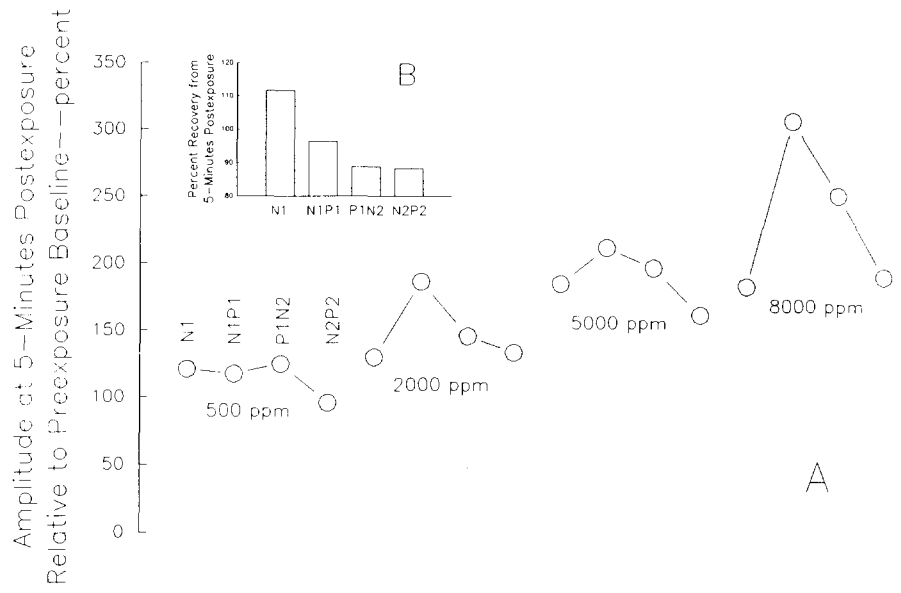

FIG. 9. (A) Changes in SEP component amplitudes as a function of exposure concentration five minutes after the end of exposure, expressed as a percent of the baseline amptliude, calculated from group means. (B) Recovery after the five-minute postexposure test; SEP component amplitudes measured 30 minutes after exposure expressed as a percentage of the five-minute postexposure test, calculated from group means.

Because of the different rates of recovery after the different exposures were terminated, concentration-related functions were generally more systematic in the recovery phase than during exposure. Amplitudes at the 5-min postexposure test, expressed as a percentage of the preexposure amplitudes, are shown in Fig. 9A. Linear correlations computed between amplitude and exposure concentrations of toluene at the 5-min postexposure test were .93, .98, .99, and .88 for the N1, N1P1, P1N2, and N2P2 components, respectively. In contrast, during exposure, the correlations were .75, .91, .93, and .42, respectively. At the 5-min postexposure test the effect of toluene on the N1P1 to N2P2 components was a decreasing function of component latency (Fig. 9A). Recovery from exposure to 8000 ppm after five min was also systematically related to component latency; recovery at 30 min, expressed as a percentage of the 5-min postexposure amplitude, is shown in Fig. 9B. The later the component the more complete the recovery.

Caudal nerve action potential. To determine if changes in the SEP were mediated peripherally, the compound action potential of the ventral caudal (tail) nerve was recorded from three rats exposed for 30 min to 8000 ppm toluene. There were no effects on parameters of this response.

Experiment 2: 8000 and 16000 ppm Toluene

Exposure levels and colonic temperature. Mean toluene concentrations for the intended exposures of 8000 and 16000 ppm were 8083 and 16733 ppm with standard deviations of about 6%. Throughout the tests involving exposure to 8000 ppm, average colonic temperature ranged from 37.4 to 37.6°C. During exposure to 16000 ppm toluene, average colonic temperature decreased to 36.8°C (baseline was 37.6°C), but this difference of 0.8°C was not statistically significant, $t(5) = 1.71$, $p = 0.15$.

Brainstem auditory-evoked response.

CBAER latency. The effects of toluene on CBAER component latencies were like those in Experiment 1. In this experiment, however, the increase in component 1 latency was only marginally significant [means were 1.56, 1.84, and 1.91 msec in the baseline, 8000 and 16000 ppm conditions, respectively; $F(2,10) = 3.09$, $p = 5.6 \times 10^{-2}$]. For the other components, $Fs(2,10) = 13$ to 22. Latencies increased with increasing toluene concentration. As in Experiment 1, the effect was greatest for the later components; average deviations from baseline for the P1 to P6 components in the 16000 ppm condition were 35 (P1), 46 (P3), 75 (P5), and 103 (P6) μsec, respectively. The P1 to P5 interval was significantly increased by both exposure concentrations [e.g., $t(5)$ for 8000 ppm = 11.15, $p = 1.01 \times 10^{-4}$].

CBAER amplitude. The amplitudes of the P4N4 and N4P5 components were, as in Experiment 1, increased by toluene ($ps = 3.19 \times 10^{-2}$ and 4.37×10^{-2}, respectively), but the increase in N5P6 was not significant. However, the integrated value for all late components was significantly increased ($p = 2.5 \times 10^{-2}$), as a function of toluene concentration (98.3, 119.8, and 129.5 μV·sec for the baseline, 8000 and 16000 ppm toluene conditions, respectively). During exposure to 8000 ppm, integrated amplitude of the late components was 122% of the baseline value.

PBAER intensity function. Group-averaged waveforms of PBAERs elicited by 16-kHz tone pips of different intensities before and during exposure to 8000 ppm toluene are shown in Fig. 10. Latencies, which could be reliably measured only at the 70 and 95 dB levels, were increased by toluene [e.g., $t(5)$ for component 1 at 95 dB = 5.9, $p = 2.3 \times 10^{-3}$; $t(5)$ for component 5 at 95 dB = 9.5, $p = 2.2 \times 10^{-4}$]. At 45 dB the response was clearer before than during exposure, but at 20 dB no response was discernible in either condition (Fig. 10).

PBAER integrated amplitudes for early, middle, and late integrated areas increased as a function of stimulus intensity, but only the late component function was altered by toluene; exposure caused significant enhancement of late-component amplitudes at the 70 and 95 dB intensities, $t(5)70 = 2.61$, $p = 4.88 \times 10^{-2}$; $t(5)95 = 6.34$, $p = 1.4 \times 10^{-3}$. At 95 dB during exposure to 8000 ppm the integrated amplitude of late components was 179% of the baseline value.

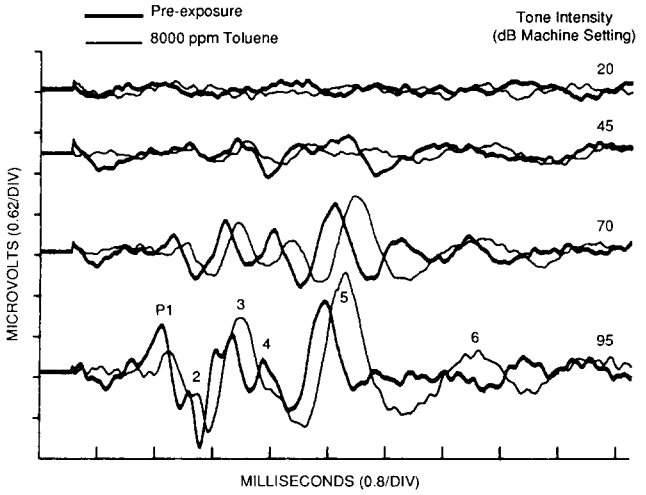

FIG. 10. Group-averaged PBAER waveforms elicited by the 16-kHz tone pips of various intensities before and during exposure to 8000 ppm toluene. Amplitudes increased and latencies decreased as tone intensity increased; toluene exaggerated these functions for late components (e.g., P5).

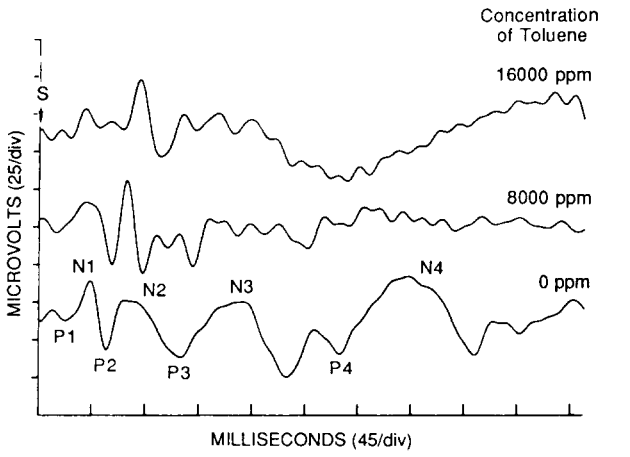

FIG. 11. Group-averaged FEP waveforms before and during acute exposure to 8000 and 16000 ppm toluene. Abnormal baseline responses in these rats could not be reliably quantified but the group averaged waveform exhibited changes like those observed in Experiment 1.

Flash-evoked potential. Normal individual FEPs were not obtained in this group of rats. Although the typical complement of components could be identified in the group average (Fig. 11), the waveform was distorted in a number of ways, and it was not possible to quantify the responses in individual rats. From the group averages, effects similar to those observed in Experiment 1 were suggested. When the FEPs were spectrally analyzed, high-frequency peaks with an average frequency of 33 Hz were evident; average power of the peaks was significantly larger during exposure (38.8 μV^2) to 8000 ppm toluene than during baseline (12.0 μV^2), $t(5) = 3.69$, $p = 1.41 \times 10^{-2}$. During exposure to 16000 ppm peak power was only 17.7 $t(5)$ μV^2.

Somatosensory-evoked potential. Toluene's effects on the SEP in this experiment were similar to those observed in Experiment 1. As before, toluene had no significant effect on component latencies, but exposure to 8000 ppm toluene increased most of their amplitudes (Fig. 12). F-ratios were significant for all components [e.g., for P1N2, $F(2,10) = 9.25$, $p = 5.3 \times 10^{-3}$], but for component N2P2 the significant effect was due primarily to its decline from the 8000 to the 16000 ppm condition, $t(5)8\text{–}16 = 7.38$, $p = 7.18 \times 10^{-4}$. As shown by the shaded bars in Fig. 12 (amplitude during exposure to 16000 ppm expressed as a percentage of the value during exposure to 8000 ppm), the decrease in amplitude with the higher exposure was greater, the later the component.

When the SEP was recorded at 2-min intervals after the beginning of exposure, increases in the amplitudes of some components were evident at 2 min, and the changes were substantial at 6 min (Fig. 13). The last point plotted is the amplitude obtained during NIDTST, begun at about 25 min into the exposure (following the PBAER tests). The N1 component increased very gradually over the 16 min, whereas the other components increased more rapidly. Amplitudes of components N1P1 and P1N2 differed significantly from baseline at 16 min, $t(5)\text{N1P1} = 5.3$, $p = 3.2 \times 10^{-3}$; $t(5)\text{P1N2} = 5.8$, $p = 2.1 \times 10^{-3}$. As before, the N2P2 component exhibited less change from baseline to exposure than N1P1 and P1N2, but the 16-min test did differ significantly from baseline, $t(5) = 3.6$, $p = 1.5 \times 10^{-2}$. N1 amplitude during NIDTST was larger than previously.

After 12 to 14 min of exposure, the curves for N1P1 and P1N2 flattened, and the responses obtained during NIDTST for N1P1, P1N2, and N2P2 were smaller than earlier. It appeared that for the later components the facilitative effects of toluene were diminishing with continued exposure, and that suppressant effects came into play. These changes were systematically related to component latency—amplitudes of the several components measured during NIDST, expressed as a percentage of the last repeated SEP, were as follows: N1 = 125, N1P1 = 100, P1N2 = 83, N2P2 = 76.

Parameters of arterial blood. None of the blood parameters obtained from the four rats exposed a second time were altered significantly by toluene. For example, pH decreased on the average by only 0.03 units during the exposures, and PaO_2 increased by about 10 mmHg. Blood pressure remained above 96 mmHg throughout the individual experiments.

DISCUSSION

BAERS

Acute exposure of rats to toluene caused a variety of effects on sensory-evoked potentials. Because arterial pH and blood gases remained normal in four rats so examined, it is unlikely that the effects on EPs were caused by acidosis or hypoxia. The latencies of BAER components were prolonged, and the increase in Component 1 (reflecting activity in the eighth nerve) suggested an effect on the cochlea or eighth nerve. Although this effect on the CBAER in Experiment 2 was only marginally significant, it was concentration-related and was consistent with the more robust effect observed in Experiment 1. In addition, the N1 component of PBAERs was prolonged. In both experiments the latency deviation from baseline during exposure or at the 5-min postexposure test was larger the later in time a component appeared. This seems consistent with a cumulative slowing along the brainstem auditory pathway and was reflected by significant increases in the P1–P5 interwave time.

That these latency shifts were not secondary to changes in body temperature is supported by several considerations. First, latencies during exposure were prolonged by 5000 ppm in Experiment 1, but the temperature change was not statistically significant (−0.2°C). Second, there was the same temperature change from baseline to exposure in the 2000 and 5000 ppm conditions of Experiment 1, but there was a greater change in latency with the higher exposure; similar relationships existed for the 5000 and 8000 ppm conditions 5 min after exposure (−0.6°C temperature change in both, but a much larger latency shift with the higher

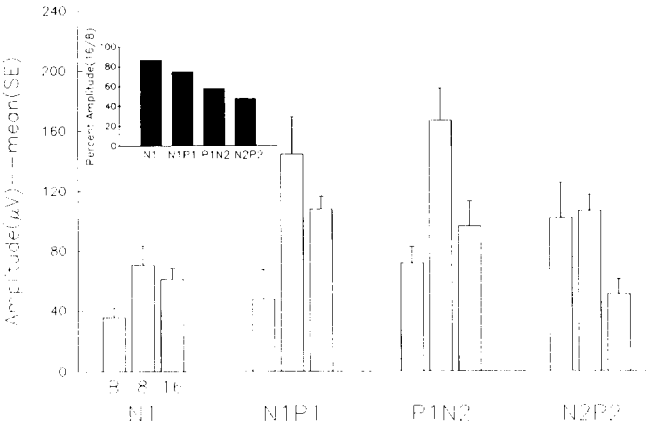

FIG. 12. Effects of 8000 and 16000 ppm toluene on SEP component amplitudes. The toluene-induced increase in amplitudes was less for 16000 than 8000 ppm, and 16000 ppm suppressed the N2P2 component below its baseline level. Apparent suppressant effects of the higher concentration were greater the later the component, as shown in the shaded insert, i.e., ampltiude during exposure to 16000 ppm was a smaller proportion of the response during exposure to 8000 ppm the later the component.

exposure). Third, significant increases in latency occurred during exposure to 8000 ppm toluene in Experiment 2 with but a minor and nonsignificant decrease (0.15°C) in temperature from baseline to exposure, and this was also true for the PBAER tests.

In contrast to the SEP, BAER components that were enhanced by 8000 ppm toluene were further augmented by 16000 ppm. Also, there was not the same relationship at the lower concentrations as existed for the SEP and FEP, i.e., for these EPs, changes at the lower concentrations were part of a linear concentration-response relationship, but for the BAER, there was a more abrupt change from low to high levels. This suggests that the range of effective concentrations is higher for the BAER than the other EPs. The augmentation of effects at 16000 ppm is also compatible with this notion.

Toluene's enhancement of late components was more pronounced for BAERs elicited by tone pips (PBAERs) than those elicited by clicks (CBAERs). Integrated amplitudes of CBAERs consequent to exposures were 125 and 122% of baseline with 8000 ppm in Experiments 1 and 2, respectively, whereas PBAER late wave integrations were 179% of baseline with exposure to 8000 ppm toluene. Since the frequency of the speaker output activated by the click was about 5 kHz, toluene appears to have a frequency specificity in its acute effects. Subchronic exposure to toluene causes a mid- to high-frequency hearing loss in rats (27,31), and the question arises concerning the relationship of the acute and chronic effects. Since only the late waves were enhanced, it is not certain that the effect was mediated peripherally. However, because of divergence of fibers in the auditory pathway, it is conceivable that selective changes in the late components could occur. This would be analogous to the selective survival of the P5 component at low intensities of stimulation.

These effects on the BAER are somewhat unusual in their multiplicity and patterning. Increased latency of the eighth nerve component suggests a peripheral effect. In addition, the increased P1–P5 interwave time indicates a central conduction delay as well. However, such a neurologic deficit would be expected to be associated with a reduction in amplitude rather than an increase. However, a selective increase in late wave amplitudes could be mediated peripherally in the following way: because of the fast travelling wave in the basal cochlea and great synchrony of firing, the basal cochlea contributes most to the eighth nerve component (P1), but P5 receives approximately equal contributions from all parts of the cochlea. Tumors affecting the basal cochlea may induce sufficient change to decrease P5 but, because of the degree of synchrony, wave 1 may be little affected [(8); and E. Don, House Ear Research Institute, Los Angeles, CA; personal communication]. Thus, conversely, it would seem possible that P1 is normally "saturated" such that increased activity in the basal region would have little effect, but could be reflected by P5. Thus, given a selective peripheral activation and the fact that the basal cochlea may have a higher metabolic rate than other parts of the cochlea (4,19), it is possible that "irritative" effects of toluene could eventually lead to selective metabolic overload and cellular death. An examination of acute toluene effects at several tone frequencies should clarify this possibility. The increasing enhancement of PBAER late waves as a function of increasing tone frequency would make it likely that this acute effect is related to frank ototoxicity following semichronic exposure.

FEPs

Although the FEPs obtained in Experiment 2 were not quantifiable in all respects, changes in the group-averaged waveform were like those observed in Experiment 1, and the quantitative spectral analysis indicated a similar change in the frequency composition of the FEPs. In contrast to the BAERs, no changes in component latencies were observed in FEPs. However, this difference may be due to the greater precision with which the latency of BAER components are measured. BAER P5 latency changed by about 4% and this would be difficult to detect in the FEP with our sampling rate and the standard errors obtained for FEP components. Effects on amplitudes were mixed; early components were slightly enlarged, whereas late components were reduced in relation to concentration. These results were similar to those reported by Dyer *et al.* (9). They observed a decrease in amplitude of the N3 component and an increase in P2 amplitude. Thus, the results from the two laboratories are quite comparable, although we observed enhancement of other early components as well, and depression of P4 and N4 components in addition to that of N3. Because of the enhancement of early components, it is unlikely that depression of the later components was caused by the change in retinal activity suggested by the decrease in ERG amplitude. As in the study by Dyer *et al.* (9) toluene's effects on the FEP were long-lasting—at the 8000 ppm concentration they persisted for at least two hours postexposure. However, the oscillations did not persist beyond the period of exposure. Changes in the BAER and SEP were not as long-lasting as those in the FEP, being almost normal two hours postexposure.

There is only the slightest suggestion of oscillations in the group average FEPs after oral doses of 500 and 1000 mg/kg toluene in the report by Dyer *et al.* (9), but we have observed the phenomenon in other Fischer-344 rats given toluene orally, and in Long-Evans rats exposed by inhalation or dosed orally (unpublished observations). From preliminary observations of spontaneous EEG spectra with and without light flashes, it appeared originally that the FEP oscillations were time-locked to the flash and dissipated over a period of about two seconds, but they may, in fact, be unrelated to the flashes. Formal examination of these observations is in progress. We have also observed tremor of the extremities of the rats similar to that described by Pérez *et al.* (23) in cats, but have not determined if the tremor and FEP oscillations are related. They would seem not to be since the tremor persists beyond the period of exposure.

SEPs

The most striking effects of toluene were on the SEP. As with

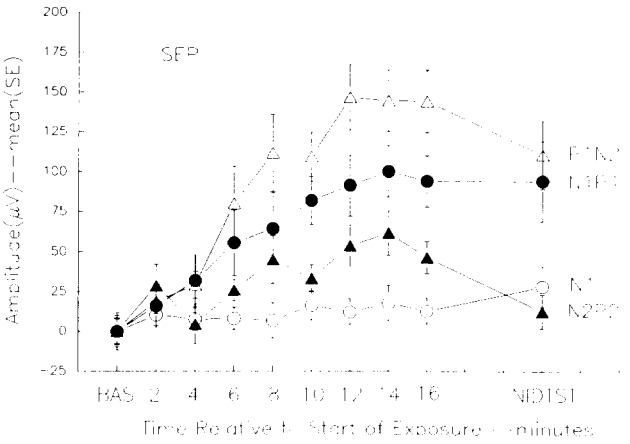

FIG. 13. Differential changes in several SEP component amplitudes as a function of time during exposure to 8000 ppm toluene.

the FEP, toluene did not affect the latencies of SEP components, but in contrast to the FEP, late as well as some early components were markedly increased. However, since reduction of FEP late components may reflect nonspecific arousal (9), it is possible that the seemingly disparate effects on FEPs and SEPs (decrease and increase of late components, respectively) actually reflect a common mechanism.

SEP components varied with respect to their responses to different concentrations of toluene and in their temporal patterns of change in relation to exposures. In Experiment 1 the P1N1 and N1P2 amplitudes were increased more by changing concentration than were N1 and N2P2 amplitudes. Also, the rate of recovery from the 5- to the 30-min test was a function of component latency; N1 continued to increase in amplitude and the other components decreased. In Experiment 2 the components changed at different rates over the course of the exposure period, and N1P1 and P1N2 were again augmented more than N1 and N2P2. The N1 component changed little until very late in the exposure period. As exposures were continued beyond the repeated SEP tests, component amplitudes changed in relation to their latencies—N1 became larger, whereas the others became smaller; the extent of change was greater the later the component. When exposure concentration was increased from 8000 to 16000 ppm amplitudes decreased, also as a function of their latencies, N1 decreasing the least. These changes suggest differential sensitivities of the several components to "facilitatory" and "sedative" effects of toluene.

The N1 component of the SEP appears to be relatively insensitive to either effect—it took a long time to exhibit an increase in amplitude, the increase was relatively small, and it exhibited little decrease in the 16000 ppm condition. The other components appear to be more sensitive to inhibitory effects the greater their latency. This is suggested by their relative changes as a function of exposure to 16000 ppm and, especially, by the concentration and time effects on component N2P2. That component was substantially augmented by exposure to 5000 ppm toluene and following exposure to 8000 ppm, but it increased in amplitude relatively little during 8000 ppm exposures.

So called "giant" SEPs have been reported in several clinical conditions, predominantly in myoclonic epilepsy (11). The locus of effect appears to be cortical as enhancement of subcortically generated SEPs is not observed, but the mechanisms of the effect are not known (18). Whereas acute exposure to toluene has been reported to produce seizures in animals (6), such effects were evident only after multiple exposures to very high concentrations. And, since toluene has anticonvulsant properties (37), it is unlikely that the mechanisms of SEP augmentation by toluene are the same as those in myoclonic or photosensitive epilepsy. However, it is likely that the effects are similarly focused in the cortex. The later and more limited effects of toluene on the N1 component suggest that cortical mechanisms reactive to the initial sensory volley is the focus of toluene's actions, with limited effects on subcortical pathways of the somatosensory system; this is in contrast to evident effects on auditory brainstem structures.

There are a variety of mechanisms by which EPs could be enhanced. For example, Garsik *et al.* (15) reported that hypertension reduces dorsal column-medial lemniscus field potentials, and conversely that hypotension augments transmission through dorsal column nuclei (14). However, we observed no reduction in blood pressure when rats were exposed to 8000 or 16000 ppm toluene. Perhaps of greatest relevance to our results, because of the magnitude of effect and differential sensitivity of early and late SEP components, is the report by Ebner and Deuschl (12) showing that the hypnotic anesthetic etomidate causes giant SEPs in nonepileptic patients.

General

With respect to the research goals presented before, we can conclude, in general, that 1) toluene does, indeed, exert effects on EPs, 2) the effects (at least on the SEP) are evident only a few minutes after the beginning of exposure, increasing and then (dependent on component) decreasing with continued exposure, 3) a toluene concentration of 500 ppm is near threshold for most responses, but some components of the FEP and SEP, but not the BAER, were altered at this level, 4) differential sensitivites are evident both among modalities and among components within modalities, 5) both facilitative and suppressant effects were observed, and 6) changes in blood gases, the retina, or peripheral nerve could not account for the effects.

It is difficult to know what aspects of the complex neural effects of solvents on the brain account for their hedonic potency; it is clear that solvents are not indiscriminantly abused and that toluene-containing substances are particularly popular (36). Perhaps the titration of exposures by abusers (24) may be an attempt to balance the excitatory and sedative effects of toluene, and that a particular balance is individually achieved. Mattsson *et al.* (21) have suggested that the excitatory effects of toluene are mediated by the metabolite orthocresol, whereas the solvent directly induces sedation. Eventually it may be possible to relate electrophysiologic profiles of solvents to their propensity for abuse.

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