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Contribution of Hypothermia to Effects of Chloral Hydrate on Flash Evoked Potentials of Hooded Rats[1]

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HETZLER, B. E. AND R. S. DYER. *Contribution of hypothermia to effects of chloral hydrate on flash evoked potentials of hooded rats.* PHARMACOL BIOCHEM BEHAV 21(4) 599–607, 1984.—This study examined the contribution of hypothermia to the effects of chloral hydrate on the flash evoked potential (FEP) of hooded rats. Three experiments were performed, all employing intraperitoneal injections of saline, and of 75, 150 and 300 mg chloral hydrate/kg body weight. In the first experiment, body temperature was measured in a standard (23°C) environment for 6 hr following injection. Rats were hypothermic following administration of the 150 and 300 mg/kg dosages for up to 1 and 2 hr, respectively. In the second experiment, FEPs were recorded from the visual cortex of chronically implanted rats 30 min after injection (22°C environment). P1N1, N1P2 and P2N2 amplitudes and P1, N1, P2, N2 and P3 peak latencies were significantly increased by the 300 mg/kg dosage. Increased latencies were also noted for the primary components with the 150 mg/kg dosage. The final experiment replicated the second experiment, but at an ambient temperature of 30°C, which prevented hypothermia. Amplitudes were unaffected by chloral hydrate. Significantly increased peak latencies were observed, even with the 75 mg/kg dose for some components. However, the magnitude of the latency increases of the primary components was less than half of that found with a standard environment. These results indicate that depending upon ambient temperature, hypothermia may contribute to chloral hydrate-induced alterations in FEPs.

Chloral hydrate Hypothermia VER VEP Evoked potentials Hooded rats
Flash evoked potentials FEP Anesthesia

CHLORAL hydrate is one of the oldest reliable sedatives, introduced into medicine in 1869 by Liebreich [22]. Although it has been replaced as a general anesthetic for humans because of a low margin of safety, it is still used as an hypnotic [16]. In animal research, chloral hydrate is used as a background anesthetic for microelectrode cellular recordings [23, 26, 33]. Chloral hydrate is also a component of the animal anesthetics, Chloropent (Fort Dodge Labs) and Equithesin (Jensen Salsbury).

Sensory evoked potentials have frequently been utilized to characterize the effects of drugs and toxic substances on the functioning of the nervous system [3, 10, 12]. In this regard, numerous studies have examined the acute effects of pentobarbital on the amplitudes and latencies of flash evoked potentials (FEPs) recorded from the primary visual cortex of the rat [9, 18, 29, 31, 35]. By comparison, no studies have yet investigated the effects of chloral hydrate on FEPs.

Chemical agents which alter evoked potentials may also alter other physiological parameters, such as body temperature [7]. Body temperature changes may, in turn, lead to secondary changes in evoked potentials [3,13]. Interpretation of the agent-induced changes in electrophysiological measures may therefore be compromised, if the observed alterations result from a combination of specific and nonspecific (e.g., body temperature) consequences of agent administration.

The present study contains three experiments designed to address these issues. The first experiment documents the normal time course of hypothermia produced by a range of dosages of chloral hydrate. Chloral hydrate-induced changes in FEPs recorded from hooded rats were noted in the second experiment. A third experiment duplicated the procedures employed to collect FEPs, with the exception that the ambient temperature was maintained at 30°C instead of the standard 22°C. The elevated ambient temperature prevented the contribution of hypothermia to any observed changes in the FEPs.

EXPERIMENT 1: CHLORAL HYDRATE-INDUCED HYPOTHERMIA

The purpose of this study was to determine the relationship between the dosage of chloral hydrate administered and both the magnitude and time-course of its effect on body

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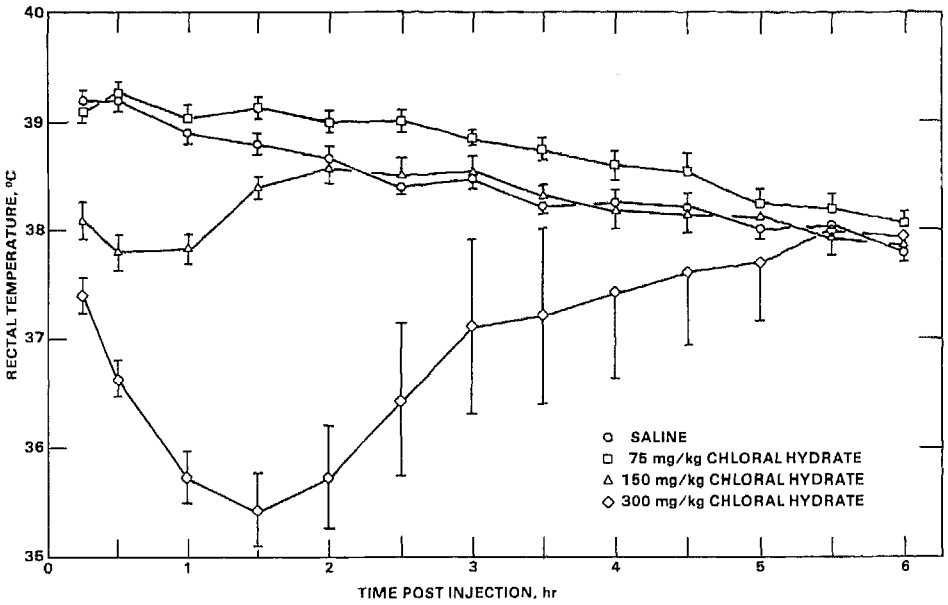

FIG. 1. Averaged rectal temperature at different times following injection of saline and 3 doses of chloral hydrate. Data were obtained from 9 rats in each group. Ambient room temperature was maintained at 23.0°C. Vertical bars in this and succeeding figures represent ±1 SEM.

temperature. The animals were tested at a standard ambient temperature of 23°C.

METHOD

Animals

Thirty-six adult male Long-Evans hooded rats were used. They were obtained from Charles River Breeding Company, and had previously served as control subjects during a single day of testing in prior experiments. The rats were individually housed with free access to food and water, and weighed 235–344 g on the day of testing.

Procedure

Animals were injected IP with either saline (n=9), 75 (n=9), 150 (n=9), or 300 (n=9) mg/kg chloral hydrate (Fisher) in saline vehicle. The injection volume for all doses was 1 ml per 100 g body weight. All rats were immediately placed in restraining tubes, and rectal thermistor probes (YSI No. 402) were inserted 8 cm into the rectum. Temperature readings (YSI 44TA Tele-Thermometer) were taken 15 and 30 min after injection, and then at 30 min intervals until 6 hours had elapsed. The rats were restrained continuously during the 6-hr sessions and the probes remained in place. Ambient room temperature was maintained at 23.0°C±0.35 (SD).

Data collected at the 0.25, 0.5, 1, 2, 4 and 6 hr intervals were subjected to a 4 (dose) × 6 (time) repeated measures ANOVA, with the α level set at 0.05. The resulting significant dose × time interaction was followed by a series of *t*-tests, in which the data collected at each chloral hydrate dose were compared to the saline value at a particular time interval. Since there were 18 comparisons, the criterion for significance was set at 0.05/18=0.0028 for each test. Time-dependent changes were not examined.

RESULTS

Administration of chloral hydrate produced hypothermia in a dose-dependent fashion (Fig. 1). The ANOVA for body temperature demonstrated significant effects of both dose, $F(3,32)=39.84, p<0.0001$, and time, $F(5,160)=5.74, p<0.0001$, as well as a significant dose × time interaction, $F(15,160)=12.50$, $p<0.0001$. *t*-Test comparisons revealed significant hypothermia at 0.25, 0.5 and 1 hr following administration of the 150 mg/kg dose of chloral hydrate, and at the 0.25, 0.5, 1 hr and 2 hr intervals when the highest dose was given. Body temperatures of animals in all groups were virtually identical at the end of the 6 hour test (Fig. 1).

EXPERIMENT 2: EFFECTS OF CHLORAL HYDRATE ON FLASH EVOKED POTENTIALS: 22°–23°C ENVIRONMENT

The foregoing experiment demonstrated that chloral hydrate induces a dosage-dependent hypothermia when animals are maintained at conventional room temperatures. The present study sought to characterize the effects of the same dosages of chloral hydrate on FEPs when animals were tested at the same ambient temperature.

METHOD

Animals

Seventy adult male Long-Evans hooded rats were obtained from Charles River Breeding Company. The rats weighed 245–328 g at the time of surgery, and were individually housed with free access to food and water. At least one week before testing, recording electrodes (00–90 × 1/16" stainless steel screws) were implanted under Chloropent anesthesia (0.37 ml/100 g b.w., IP). The ground and reference screw electrodes were placed 2 mm anterior and 2 mm left and right of bregma, respectively. Visual cortex electrodes were placed over both the left and right visual areas, 6

mm posterior to bregma and 3 mm lateral to the midline. All electrodes were led to an Amphenol connector, and the whole assembly was secured to the skull with additional screws and dental acrylic. Following the procedure, each animal was administered 100,000 units penicillin G IM and returned to its home cage.

Recording Procedure

Recordings were obtained while animals were placed in a box with mirrors on 3 walls and a Grass PS22C strobe on the 4th. This box, in turn, was enclosed within a large shielded cage. At the time of recording, the receptacle on the skull was connected to the amplifiers via Microdot low noise cable. High and low filter settings were 1 kHz and 0.8 Hz, respectively. Amplified waveforms were averaged (n=128) by a PDP 11/70 computer (2500 Hz sample rate, 0.4096 sec epoch). The averaged waveforms were displayed on a Tektronix 4054 terminal, where peak latencies and peak-to-peak amplitudes were measured. Hard copies of the averaged waveforms were obtained on a Tektronix 4631 hard copy unit. All averaged waveforms were also stored on disk. Stimuli (10 μ sec flashes) were presented by the Grass strobe at 0.3 Hz and an intensity of 16 (approximately 4.53×10^7 lux, peak power). Overhead fluorescent lights provided background illumination of about 115 lux. To ensure constant pupillary dilation, 1% atropine was instilled in the eyes 30 min prior to all recording sessions. Ambient temperature was maintained at a 21.6°C±0.34.

FEPs were recorded 30 min following IP injection of either saline (n=18), 75 (n=17), 150 (n=18) or 300 (n=17) mg chloral hydrate/kg b.w. The injection volume for all doses was 1 ml per 100 g b.w. Animals were placed in the recording chamber just prior to data collection. FEPs were analyzed in only the right visual cortex, although data from both cortices were simultaneously collected. Immediately following data collection, rectal temperature was measured while the animal was restrained by a gloved hand.

Data Analysis

The FEP data were analyzed using multivariate statistical techniques (MANOVA). The five peak-to-peak amplitudes (P1N1, N1P2, P2N2, N2P3, and P3N3) and six latencies (P1, N1, P2, N2, P3 and N3) obtained under each drug treatment were the dependent variables (see Fig. 2). Separate MANOVAs were performed for amplitude and latency using the General Linear Models procedures provided under SAS [17]. A Bonferroni correction was used to adjust the required significance level for each MANOVA to compensate for the fact that two MANOVAs were done (0.05/2=0.025). If the overall MANOVAs were significant, univariate ANOVAs were performed. To ensure an overall α level of 0.05, the Bonferroni correction was also applied to ANOVAs. Since five amplitudes were measured, any given univariate ANOVA was required to have a $p<0.025/5=0.005$ in order to be considered statistically significant. Similarly, the latency ANOVAs required a probability value of 0.025/6=0.0042 or less to be considered significant. A significant ANOVA was followed by a series of t-tests comparing values collected at each chloral hydrate dosage with saline levels. Since three such comparisons were performed for each amplitude or latency, the criterion for significance was set at $p\leq 0.025/3=0.0083$. However, for descriptive purposes, probability levels of 0.05 or less are also noted for these latter t-tests.

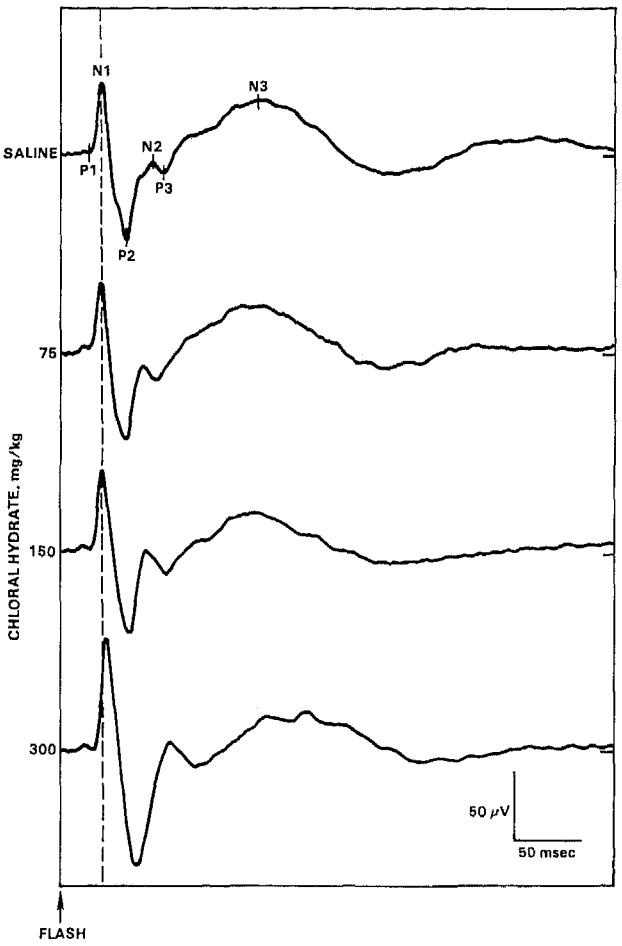

FIG. 2. Averaged FEP waveforms from all animals recorded at different levels of chloral hydrate anesthesia. Ambient temperature was maintained at 21.6°C.

RESULTS

Amplitude

The influence of chloral hydrate upon FEPs is illustrated in Fig. 2. Figure 3 presents peak-to-peak amplitudes as a function of chloral hydrate dosage. The MANOVA including all peak-to-peak amplitudes was significant, $F(15,182)=2.78$, $p=0.0007$. The ANOVAs for individual peak-to-peak amplitudes indicated that chloral hydrate significantly increased the amplitudes of the early components: P1N1, $F(3,66)=7.97$, $p=0.0002$; N1P2, $F(3,66)=7.38$, $p=0.0003$; P2N2, $F(3,66)=5.11$, $p=0.0032$. Amplitudes of the later components were not significantly altered by chloral hydrate: N2P3, $F(3,66)=3.56$, $p=0.0187$; P3N3, $F(3,66)=1.75$, $p=0.1640$. The t-test comparisons revealed significant augmentation following administration of only the 300 mg/kg dosage of chloral hydrate for components P1N1, N1P2 and P2N2.

Latency

The latency data are displayed in Fig. 4. The MANOVA for peak latencies was statistically significant, $F(18,179)=4.45$, $p<0.0001$. Subsequent ANOVAs indicated that all

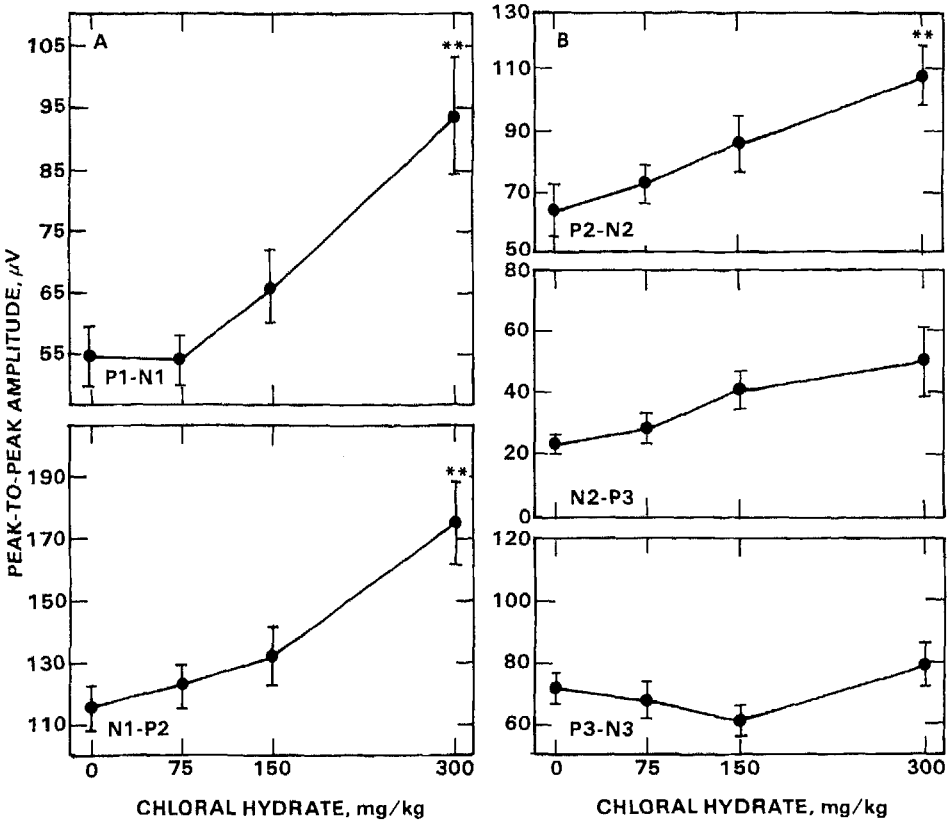

FIG. 3. Effects of chloral hydrate anesthesia upon peak-to-peak amplitudes of FEPs. A, P1N1 and N1P2 amplitudes; B, P2N2, N2P3 and P3N3 amplitudes. Component notation as in Fig. 2. Ambient temperature was maintained at 21.6°C. *=$p<0.05$, **=$p<0.0083$.

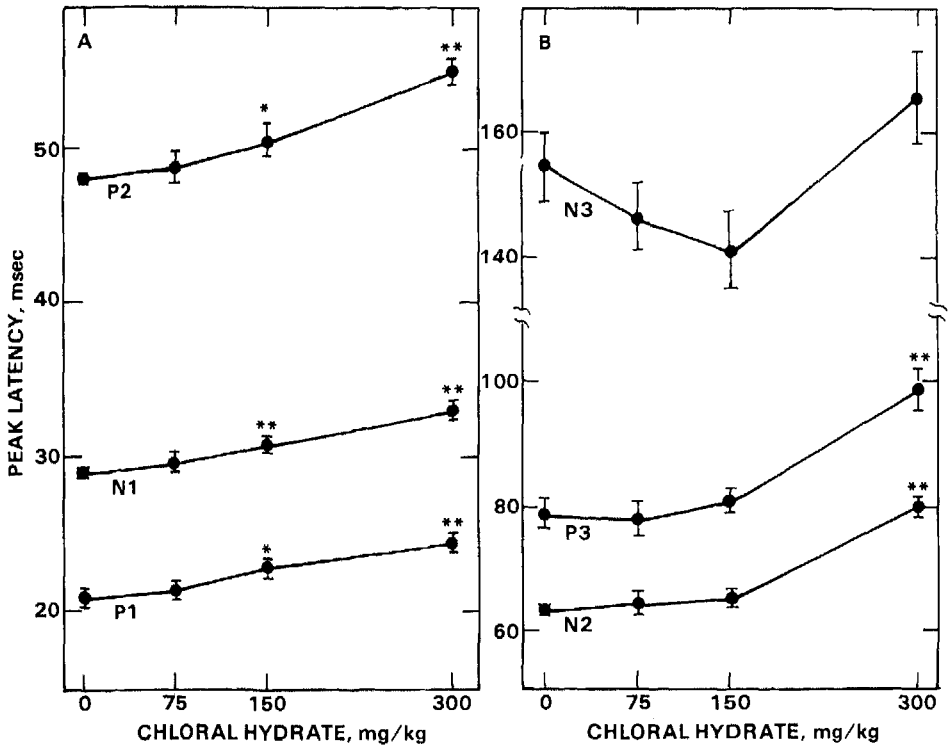

FIG. 4. Effects of chloral hydrate anesthesia upon FEP latencies. A, P1, N1 and P2 latencies; B, N2, P3 and N3 latencies. Component notation as in Fig. 2. Ambient temperature was maintained at 21.6°C. *=$p<0.05$, **=$p<0.0083$.

peaks, with the exception of N3, were significantly increased in latency by chloral hydrate, all F's(3,66)>8.80, all p's<0.0001. The ANOVA for component N3 did not reach statistical significance, F(3,66)=3.07, p=0.0334 since the required p value after Bonferroni correction was 0.0042. Using the probability criterion of 0.0083 for the t-tests, increased latencies of components P1, N1, P2, N2, and P3 were observed with the 300 mg/kg dosage of chloral hydrate. In addition, the peak latency of component N1 was augmented by the 150 mg/kg dosage.

Body Temperature

Measurements of body temperature performed immediately after testing demonstrated a progressive hypothermia with increasing dosage of chloral hydrate: saline, 38.37°C±0.10 (SEM); 75 mg/kg, 37.63°C±0.17; 150 mg/kg, 36.77°C±0.25; and 300 mg/kg, 35.77°C±0.18.

EXPERIMENT 3: EFFECTS OF CHLORAL HYDRATE ON FLASH EVOKED POTENTIALS: WARM ENVIRONMENT

The results of the previous experiments demonstrated that chloral hydrate will produce both alterations in evoked potential parameters and hypothermia when animals are tested in a normal (22°C–23°C) laboratory environment. In an effort to determine the contribution of hypothermia to any observed electrophysiological changes following chloral hydrate administration, a third experiment was conducted in a relatively warm environment. A warm temperature of 30°C was chosen in order to produce thermoneutrality in the rats [27].

METHOD

Sixty-eight adult male Long-Evans hooded rats, weighing 246–290 g at the time of surgery, were used. The general procedures for electrode implantation, electrophysiological recording and data analysis were the same as those described in Experiment 2. The main difference involved ambient temperature, which was maintained at 30.3°C±0.36. FEPs were recorded 30 min following IP injection of either saline (n=16), 75 (n=17), 150 (n=18) or 300 (n=17) mg chloral hydrate/kg b.w. FEPs were analyzed in the right visual cortex with the exception of 1 animal from the 75 mg/kg group and 3 animals from the 150 mg/kg group. FEPs from the right visual cortex of these latter animals were atypically small and irregular, corresponding neither to the "classical" waveform [8] nor the response recorded from the left hemisphere. Potentials recorded from the left hemisphere of these animals were therefore utilized in the analyses.

RESULTS

Amplitude

Figure 5 illustrates the influence of chloral hydrate upon FEPs when animals were tested at 30°C. Peak-to-peak amplitudes as a function of chloral hydrate dosage are presented in Fig. 6. Although the MANOVA for FEP peak-to-peak amplitudes was statistically significant, F(15,176)=2.34, p=0.0046, none of the five individual amplitude ANOVAs reached significance after Bonferroni correction (required p=0.025/5=0.005). The P2N2 amplitude was closest to achieving significance, F(3,64)=3.07, p=0.0334. The conservative interpretation of these data is that a linear combination of the individual FEP peak-to-peak amplitudes significantly discriminates among the dosage groups.

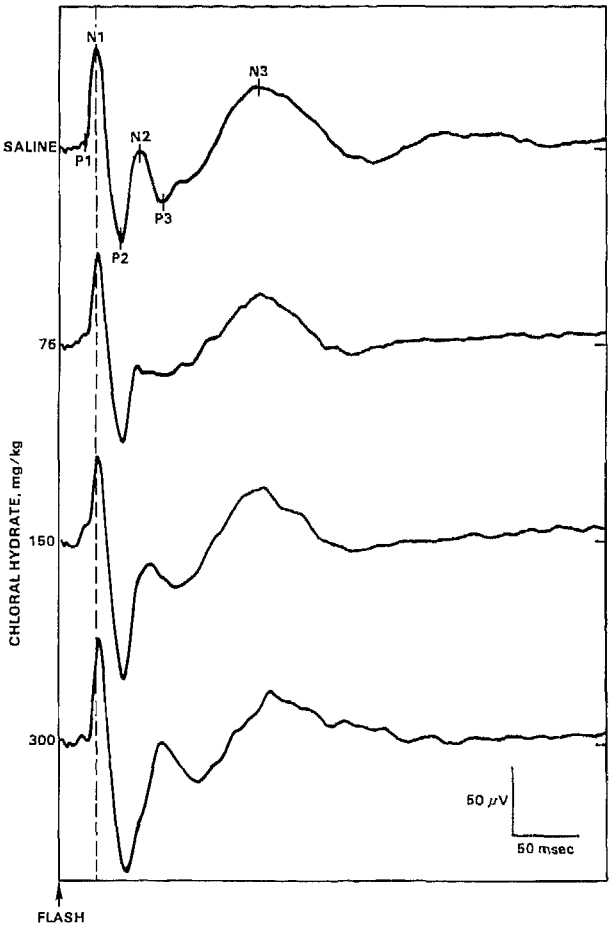

FIG. 5. Group average FEP waveforms recorded at different levels of chloral hydrate anesthesia with an ambient temperature of 30.3°C.

Latency

The latency data are presented in Fig. 7. The MANOVA for peak latencies was statistically significant, F(18,173)=6.08, p<0.0001. Subsequent ANOVAs indicated that chloral hydrate significantly increased the peak latencies of components P1, P2, N2 and P3, all F's(3,64)>6.30, all p's<0.001. The ANOVAs for components N1, F(3,64)=3.04, p=0.0349, and N3, F(3,64)=4.07, p=0.0105 did not reach significance, since the required p value after Bonferroni correction was 0.0042. Bonferroni corrected t-test comparisons demonstrated that components P1, P2, N2 and P3 were reliably increased in latency by both the 150 and the 300 mg/kg doses of chloral hydrate. Component P2 was also increased in latency by the 75 mg/kg dosage.

Body Temperature

The following mean body temperatures were obtained immediately after testing: saline, 38.64°C±0.06; 75 mg/kg, 38.36°C±0.08; 150 mg/kg, 38.19°C±0.07; and 300 mg/kg, 37.96°C±0.09.

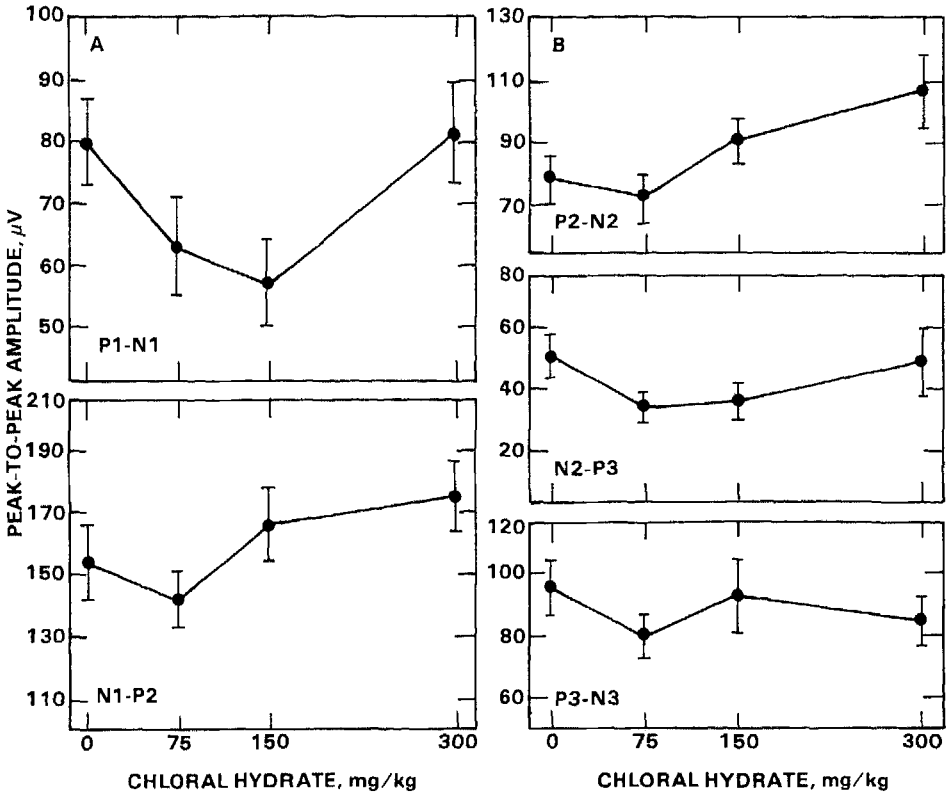

FIG. 6. Effects of chloral hydrate anesthesia upon peak-to-peak amplitudes of FEPs with an ambient temperature of 30.3°C. A, P1N1 and N1P2 amplitudes; B, P2N2, N2P3 and P3N3 amplitudes. Component notation as in Fig. 5.

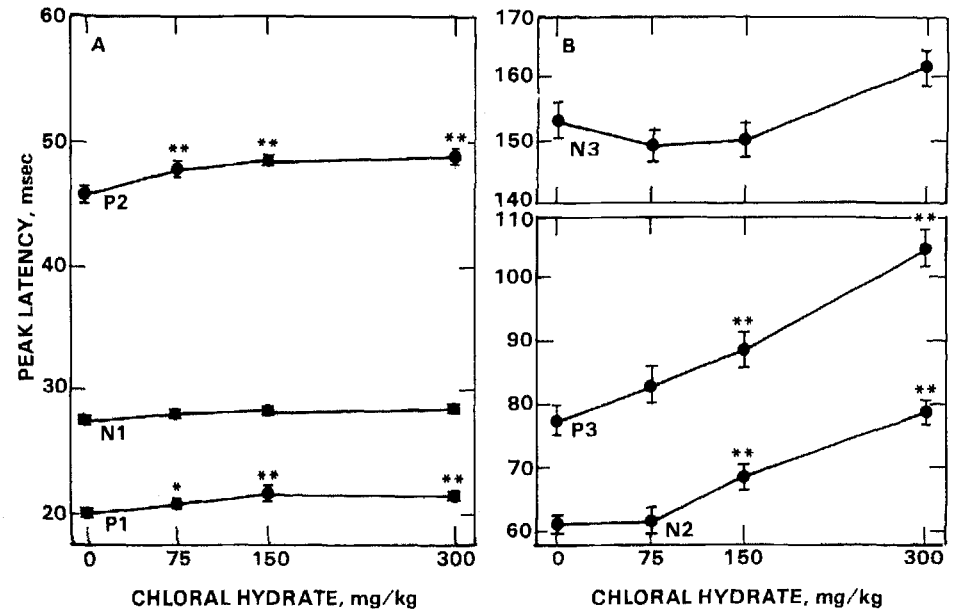

FIG. 7. Effects of chloral hydrate anesthesia upon FEP latencies with an ambient temperature of 30.3°C. A, P1, N1 and P2 latencies; B, N2, P3 and N3 latencies. Component notation as in Fig. 5. *=$p<0.05$, **=$p<0.0083$.

GENERAL DISCUSSION

Chloral hydrate-induced anesthesia produces EEG recordings similar to those obtained with barbiturates [5,21]. Thus, slow delta waves dominate the EEG of a chloral hydrate anesthetized rat [26]. The behavioral manifestations of the dosages of chloral hydrate employed in the present study have also previously been delineated in the rat [5]. Sedation is produced by the 75 mg/kg dosage of chloral hydrate, while severe ataxia results from the 150 mg/kg dosage. Loss of the righting reflex occurs when 300 mg/kg chloral hydrate is administered.

The results of the present series of experiments indicate that both hypothermia and changes in FEPs result from chloral hydrate administration in a standard laboratory environment (22°C). Hypothermia produced by chloral hydrate has been noted previously in mice, rats and rabbits [7]. However, to the best of our knowledge this is the first study to demonstrate changes in FEPs resulting from chloral hydrate.

At standard room temperatures, a 300 mg/kg dosage of chloral hydrate significantly increased the amplitude of components P1N1, N1P2, P2N2 and N2P3. The P3N3 portion of the waveform was not affected by any dosage of chloral hydrate utilized. The general finding of increases in amplitude of the early components is in line with other studies involving pentobarbital's effects on FEPs recorded from the rat cortex [9, 18, 29, 35].

The finding that P3N3 amplitude is unchanged by chloral hydrate is in contrast with other studies involving the effects of pentobarbital, which have noted a marked depression in the P3N3 portion of the waveform, even with subanesthetic doses [9, 18, 29, 31, 35]. These conflicting observations probably result from differences in testing techniques. Other studies have typically involved an adaptation period prior to recording, thereby allowing increased development of these later waves [1,31]. It may be that in the absence of such adaptation-induced enhancement of the later waves, anesthetics do not produce significant amplitude reductions. However, it is also possible that there are agent differences, such that barbiturates more readily depress these later components.

Peak latencies were also affected by a 300 mg/kg dosage of chloral hydrate. All components other than N3 were increased in latency. These findings are in accordance with previous reports of increases in the latency of FEPs following pentobarbital treatment in rats, cats and rabbits [9, 18, 29, 30, 34].

To what extent does hypothermia contribute to the electrophysiological changes observed following chloral hydrate administration? The final experiment in the present study examined this issue by administering chloral hydrate to animals who were in a thermoneutral temperature environment. In that experiment, increases in amplitude were no longer observed when the chloral hydrate dosage of 300 mg/kg was given. Significant increases in peak latency, on the other hand, were present for most components following administration of both the 150 and 300 mg/kg dosages of chloral hydrate. At first glance, these results suggest that hypothermia is involved in the amplitude enhancements, but not the increased latencies, resulting from chloral hydrate administration. However, a 300 mg/kg dosage of chloral hydrate given at an ambient temperature of 30°C resulted in latency increases for the primary components (P1, N1, P2) which were less than half of those found when the drug was given at 21.5°C. Hypothermia may therefore be a contributing factor to both amplitude and latency alterations observed during chloral hydrate-induced anesthesia.

In a previous study, Dyer and Boyes [13] examined the effects of Chloropent (an anesthetic mixture of chloral hydrate and pentobarbital) on FEPs collected from rats at an ambient temperature of 30°C. They observed that a dosage of 0.20 ml/100 g produced significant increases in the peak latencies of all components in the absence of significant alterations in peak-to-peak amplitudes. These results, in close agreement with those obtained in Experiment 3 of the present series, suggest that in the absence of hypothermia the only reliable effect of a moderate dosage of anesthetic is an increase in peak latencies. However, these findings do not preclude the possibility that higher dosages of an anesthetic such as chloral hydrate could produce increased component amplitudes in a normothermic animal.

Dyer and Boyes [13] also manipulated body temperature in Chloropent-anesthetized rats (0.35 ml Chloropent/100 g b.w.). Hypothermia of 6°C below normal body temperature resulted in increases in all peak latencies. The amplitude of P1N1 was also increased by the hypothermia, while P2N2 was decreased in amplitude. Peak-to-peak amplitudes of the other components were not significantly altered by the hypothermia. In other work on anesthetized rats [2], a reduction in body temperature to 30–31°C likewise produced increased peak latencies accompanied by the greatest increase in amplitude for the shortest latency FEP components. Short latency somatosensory potentials evoked by forepaw stimulation are also increased in latency by progressive cooling in anesthetized rats. The cortical surface potential I is increased in amplitude with hypothermia, while all other components are decreased in amplitude [6]. It would therefore appear that while hypothermia contributes to increased latencies for nearly all evoked potential components, there are differential amplitude effects: earlier components are augmented by hypothermia, while later ones may either be depressed or remain relatively unaffected.

The same general pattern of cortical evoked potential changes (i.e., increased latencies, augmented amplitude of primary components, depressed late components) has often been described in barbiturate-anesthetized animals [4, 15, 18, 34]. On the one hand, it is possible that in such studies, where body temperature was neither monitored nor controlled, hypothermia *per se* was a major factor in the alteration of evoked potentials. On the other hand, however, the earlier mentioned hypothermia studies were all conducted on anesthetized animals. As such, these studies have not been able to determine whether there is a specific effect of hypothermia which is superimposed on the effects of the anesthetic, or if hypothermia alters the action of the anesthetic in some way, perhaps thereby enhancing the anesthetic's effects. Indeed, hypothermia and anesthesia are known to interact [24,32].

Anesthetics such as chloral hydrate and barbiturates produce their central nervous system effects by a variety of pre-, post- and nonsynaptic mechanisms. Physiological data indicate that most anesthetics depress excitatory synaptic transmission, while inhibitory transmission may be enhanced by some agents, including chloral hydrate. The reduced effectiveness of excitatory transmission involves a combination of reduced presynaptic transmitter release and decreased postsynaptic functioning [20,28]. Reduction in transmitter release may result from interference with presynaptic calcium influx [19], while postsynaptic actions

presumably involve interactions between the drugs and the receptors themselves [28]. Finally, a number of anesthetics (including chloral hydrate) have been shown to hyperpolarize at least some central nervous system neurons, probably by increasing potassium conductance [25]. This latter effect would contribute to a decreased responsiveness in central nervous system neurons.

For a drug such as chloral hydrate to produce these effects on neuronal populations, it (or its active metabolite) must arrive at the appropriate biological receptors in sufficient concentration. Electrophysiological changes resulting from an IP injection of the drug therefore depend on a number of biological processes: absorption, distribution, metabolism and elimination, as well as receptor sensitivity. All of these factors are in some regard temperature-dependent [11]. Thus, when a drug alters body temperature, the resulting change in body temperature may in turn alter the response of the organism to the drug. The resulting interrelationships between body temperature and drug-induced alterations can thereby be quite complex. It seems clear that the contribution of body temperature cannot be ignored. To restate a directive made over 20 years ago, "it is . . . essential to control environmental temperature, and to measure body temperature" [14] when investigating the effects of drugs and toxic substances on brain function.

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