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Effects of Ketamine, Naloxone, and Physostigmine on Flash Evoked Potentials in Rat Superior Colliculus

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HETZLER, B. E. AND A.-M. MELK. *Effects of ketamine, naloxone, and physostigmine on flash evoked potentials in rat superior colliculus.* PHARMACOL BIOCHEM BEHAV 32(2) 511–518, 1989.—Flash evoked potentials were recorded from the superior colliculus of chronically implanted hooded rats at 5 and 20 min following IP injections of saline, ketamine (75 mg/kg), naloxone (10 mg/kg), or physostigmine (0.4 mg/kg) on separate days. Components in an early positive complex were unaffected by ketamine and naloxone, but were reduced in amplitude by physostigmine. A positive spike emerged from the middle of a later negative wave following ketamine administration, but the amplitude of the negative wave was unaltered by naloxone or physostigmine. A succeeding positive component was enhanced by both ketamine and physostigmine. Physostigmine produced the most consistent alterations in latency, with most components increasing in latency. Naloxone pretreatment did not alter ketamine's influence on evoked potential amplitudes. Pretreatment with physostigmine briefly decreased the amplitude of the ketamine-induced positive spike, augmented the amplitude of the succeeding positive component, and also increased most peak latencies. Ketamine, naloxone and physostigmine all produced approximately equivalent hypothermia. Physostigmine, but not naloxone, pretreatment augmented the ketamine-induced hypothermia. The body temperature data suggest that some of the observed latency alterations are secondary to hypothermia. The amplitude data indicate that ketamine and physostigmine produce a combination of similar, distinct, and antagonistic effects on evoked potentials.

Ketamine Naloxone Physostigmine Flash evoked potentials Superior colliculus Hypothermia Hooded rats

THE evoked potential technique is a sensitive method for assessing the functional integrity of the brain, and it has often been utilized to characterize the effects of drugs and toxic substances on the nervous system [e.g., (10,17)]. However, despite the large number of such studies which have examined the flash evoked potential (FEP) recorded from the rat visual cortex [VC; see reviews (7, 17, 53)], relatively few studies have examined FEPs recorded from the rat superior colliculus [SC; e.g., (18, 31, 57, 58)], a structure involved in the control of visual orientation and eye movements (25).

We recently described the effects of ketamine hydrochloride on FEPs recorded from the rat SC (29). Ketamine hydrochloride is an arylcyclohexylamine which produces a rapidly acting analgesia and anesthesia in both humans and animals. The clinical use of this drug is nonetheless limited by emergence reactions, including unpleasant disorienting effects, visual illusions and transient blindness (23,62). An understanding of the pharmacological basis of ketamine-induced changes in visual system electrophysiology may suggest means whereby such emergence reactions can be reduced in clinical practice.

Among the suggested antagonists to at least some of ketamine's effects are the acetylcholinesterase inhibitor, physostigmine, and the opiate antagonist, naloxone. With respect to physostigmine, it has been reported that ketamine interacts with cholinergic mechanisms (12,45) and it has also been shown that a number of phencyclidine derivatives (structural homologues of ketamine) interact with muscarinic cholinergic receptors (61). Still, clinical pretreatment with physostigmine has produced mixed results (16,60). Similar discrepancies involving the interaction of ketamine and physostigmine on the duration of anesthesia have been found in laboratory animal studies (28,37). Phencyclidines and ketamine also interact with opiate receptors (54,61). Naloxone is an opiate antagonist which is effective against many classes of opiate pharmacological actions (kappa, mu, sigma), although it is most effective against mu effects (56). A number of reports indicate that the analgesic effects of ketamine are inhibited by naloxone (34,54), although there is also conflicting evidence (24,63).

Electrophysiological evidence involving physostigmine or naloxone in combination with ketamine is sparse. One report involving cats indicated that ketamine-induced EEG hypersynchrony is blocked by physostigmine pretreatment (64). Past studies of the effects of physostigmine and naloxone on the rat FEP have involved recordings from only the VC (8, 32, 52). None of these studies employed ketamine as well. Thus, the influence of physostigmine and naloxone, either alone or in combination with ketamine, on the FEP recorded from the rat SC remains unexplored.

Finally, drugs which produce alterations in evoked po-

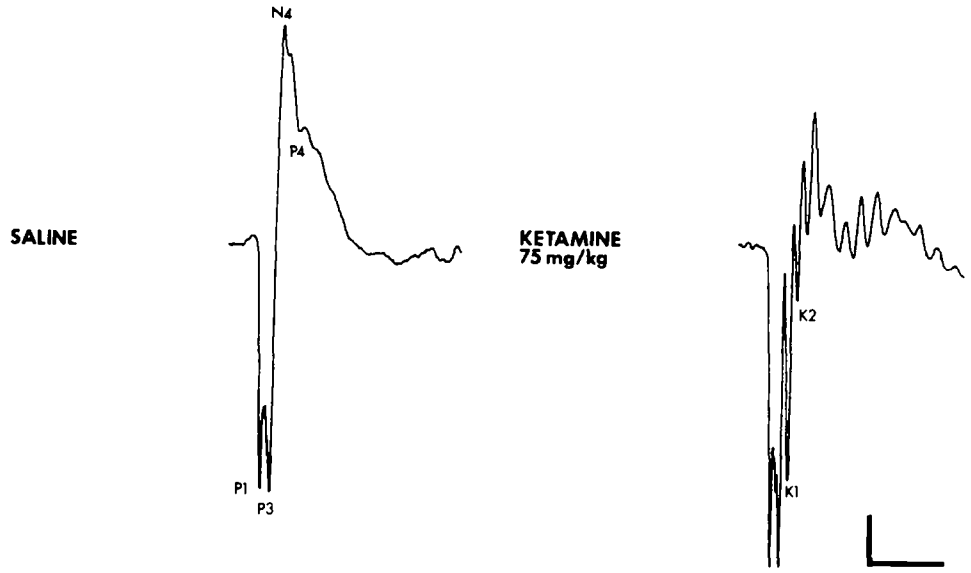

FIG. 1. Averaged flash evoked potentials recorded from the superior colliculus of one rat 5 min after drug administration. Each trace represents an average of 100 responses. Component K1 emerged from near the middle of component N4 following the administration of ketamine, either alone or in combination with naloxone or physostigmine. Component K2 was either an elaboration of, or superimposed on, component P4. Calibration: 100 μV and 100 msec.

tentials may also alter body temperature. Such changes in body temperature may then result in secondary changes in evoked potential parameters (10,30). In particular, there is an increase in peak latencies following a decrease in body temperature (19). It is therefore important to determine to what extent the tested drugs produce alterations in body temperature.

The present investigation was undertaken to address these issues by examining: 1) the influence of ketamine, physostigmine and naloxone on FEPs recorded from the SC of chronically implanted hooded rats, 2) the extent to which physostigmine and naloxone alter the effects of ketamine on FEPs recorded from the SC, and 3) the effects of ketamine, physostigmine and naloxone, alone and in combination, on body temperature.

EXPERIMENT 1: ELECTROPHYSIOLOGICAL EFFECTS

METHOD

Animals

Sixteen male Long-Evans hooded rats, weighing 320–446 g at the time of surgery, were tested. At least two weeks before testing, they were implanted with recording electrodes under pentobarbital anesthesia. Superior colliculus recording electrodes consisted of a twisted pair of nichrome wires (each 250 μm in dia.), insulated to the tip, with a 1 mm intertip distance. With the skull surface located in a horizontal plane, the coordinates for the superior colliculus electrodes (which were placed in both left and right superior colliculi) were 6.5–7.0 mm posterior to bregma, 1.5 mm lateral to the midline, and 4.3 mm ventral to the skull surface. A ground screw electrode was placed 3 mm anterior and 2 mm left of bregma. All electrodes were led to an Amphenol connector, and the whole assembly was secured to the skull with additional screws and dental acrylic. At the conclusion of the experiments, placements of the superior colliculus electrodes were histologically verified with the photographic histologic technique (27). Results are reported for 1 site from each animal, and include only those sites in which the lower member of the electrode pair penetrated the superficial layer of the superior colliculus (18).

Recording Procedure

Electrophysiological recording utilized Microdot cables. Evoked potentials were amplified with Tektronix 122 preamplifiers with high and low filter settings of 1.0 kHz and 0.8 Hz, respectively. Amplified waveforms were averaged (n=100) by a laboratory computer (1,000 Hz sample rate, 300 msec epoch). Seventeen msec of the epoch occurred prior to the application of the evoking stimulus. Stimuli were presented by a Grass Model PS22C photostimulator, with an interstimulus interval of 2.4 sec, and an intensity setting of 8. Computer-averaged evoked potentials were plotted on an X-Y plotter and also listed in numeric form on a printer.

The animals were given at least 2 days of familiarization to the testing procedures, followed by at least 1 day of rest, prior to actual data collection. Testing was conducted with the animal inside a Plexiglas chamber. Three of the walls, as well as the top and bottom, were white, while the fourth wall was clear. This chamber was enclosed within a larger shielded recording chamber, with dim background illumination, and a fan providing both ventilation and white noise. The flash lamp of the photostimulator was placed in a small sound-attenuating chamber (to eliminate the auditory click present with each flash) and positioned outside the shielded recording chamber against a window panel that was centered with respect to the clear side of the Plexiglas testing chamber. A mercury swivel provided freedom of movement.

During testing, animals were given intraperitoneal injections on separate days of physiological saline, 75 mg ketamine hydrochloride/kg body wt., 10 mg/kg naloxone hy-

drochloride followed by saline, 10 mg/kg naloxone followed by 75 mg/kg ketamine, 0.4 mg/kg physostigmine salicylate followed by saline, and 0.4 mg/kg physostigmine followed by 75 mg/kg ketamine. Testing was conducted every third day according to a counterbalanced design. Three to six days after the last of these injections, all animals received a final saline injection (the 7th testing session). The 75 mg/kg dosage of ketamine was selected on the basis of our prior study (29) as a moderate dose which would selectively induce components K1 and K2 in the FEP recorded from the SC, without altering the amplitudes of components P1 and P3 (see Fig. 1). The 10 mg/kg dosage of naloxone and the 0.4 mg/kg dosage of physostigmine were selected in view of earlier work indicating that these dosages produce significant alterations in the FEPs recorded from the VC of rats (8,52).

An injection volume of 1 ml/kg was observed throughout. Naloxone and physostigmine were dissolved in saline and were injected 5 min prior to the saline or ketamine injections. The ketamine was prepared from a standard concentration of 100 mg/ml (Ketaset, Bristol Labs.) by dilution with saline. Animals were placed in the recording chamber immediately after the saline or ketamine injections. FEPs were then recorded 5 and 20 min later. To insure constant pupillary dilations, 1% atropine sulfate was instilled in the eyes 20 min prior to recording.

Measurement and Statistical Analysis

FEPs recorded from the superior colliculus displayed the general wave form described in other work (18,29). There was an early positive complex, in which the first and last spikes were labelled P1 and P3, respectively (see left side of Fig. 1). A small negative wave may precede this P1-P3 complex, but it was not studied in the present experiment. The positive complex was followed by a prominent negative component (N4), and then a variable, small positive component (P4). As reported previously (29), ketamine administration dramatically alters the N4-P4 portion of the waveform. A large positive spike (labelled K1, see right side of Fig. 1) emerges from near the middle of the N4 component, producing an N4a-K1-N4b complex, while a second positive spike (K2) becomes prominent at the approximate location of component P4. A series of late oscillatory potentials may also become more prominent following high doses of ketamine.

Separate analyses were performed on components P1, P3, N4(K1) and P4(K2). For the statistical analysis of N4(K1), an a priori decision was made based on our earlier results (29) to examine the most prominent peak occurring at the latency of about 50–55 msec. For the saline, naloxone and physostigmine conditions, the peak was negative (N4), while for those conditions involving ketamine, the peak was positive (K1). Thus, when ketamine was given (either alone or in combination with other drugs), peaks N4a and N4b were ignored in the analysis. The amplitude of each component was expressed as the difference between peak amplitude and a mean amplitude of the first 20 msec of EEG activity collected. Peak latency was measured in msec from the presentation of the light flash. Data were subjected to two-factor analyses of variance, involving repeated measures on both factors (i.e., drug and time). When a significant main effect was found, individual means were compared with Dunnett's test. In all of the analyses, statistical significance was assumed when $p<0.05$ for two-tailed comparisons. Changes in evoked potential amplitudes and latencies resulting from time-related factors are not included. Likewise, significant drug × time interactions are described only in relation to the main drug effects.

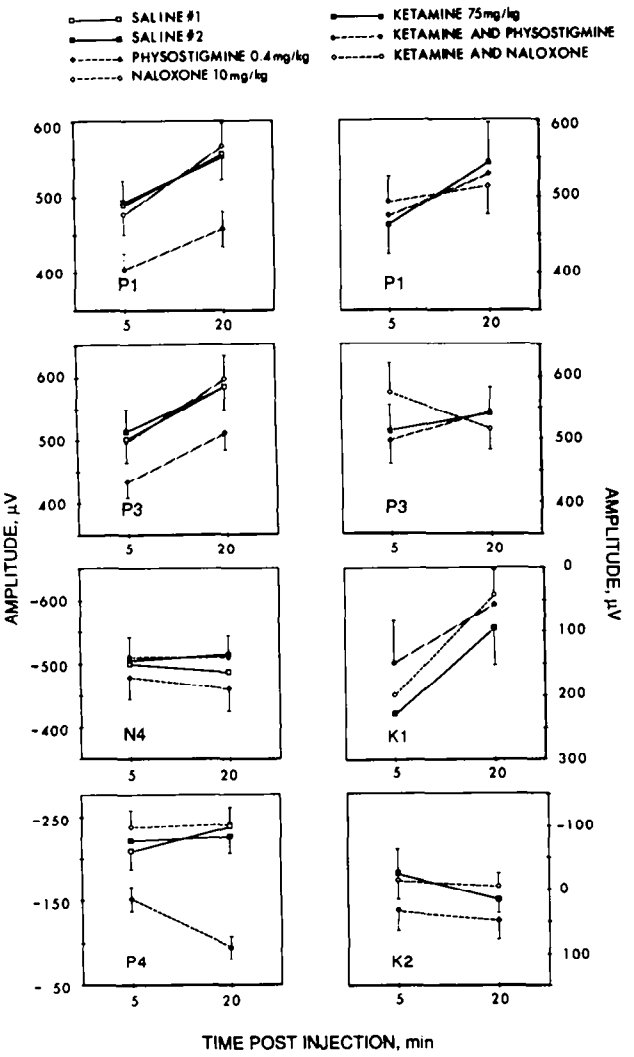

FIG. 2. Mean amplitudes (±SEM) of flash evoked potential components recorded from the superior colliculus at 2 time intervals following drug administration. Component amplitudes located in the "negative" direction relative to the prestimulus baseline are indicated with minus signs. Data were obtained from 16 rats. Component notation as in Fig. 1.

RESULTS

Amplitude

The data are presented in Fig. 2 and are partially displayed for one animal in Fig. 1. There were significant main drug treatment effects for most components: P1, $F(6,90)=3.04$, $p<0.025$; P3, $F(6,90)=1.68$, $p>0.1$; N4(K1), $F(6,90)=90.74$, $p<0.001$; P4(K2), $F(6,90)=57.69$, $p<0.001$. Most components also displayed a significant drug × time interaction: P1, $F(6,90)=1.42$, $p>0.1$; P3, $F(6,90)=4.90$, $p<0.001$; N4(K1), $F(6,90)=7.34$, $p<0.001$; P4(K2), $F(6,90)=3.72$, $p<0.005$. No significant differences in component amplitudes were observed between the two saline trials. In comparison to the first saline trial, a ketamine dose of 75 mg/kg had no influence on the amplitude of components P1 and P3. However, this same dose of ketamine dramatically altered the N4 portion of the waveform, producing a positive spike (labelled K1, see Fig. 1) near the middle of the N4 component. The peak amplitude of this K1 component was greatest

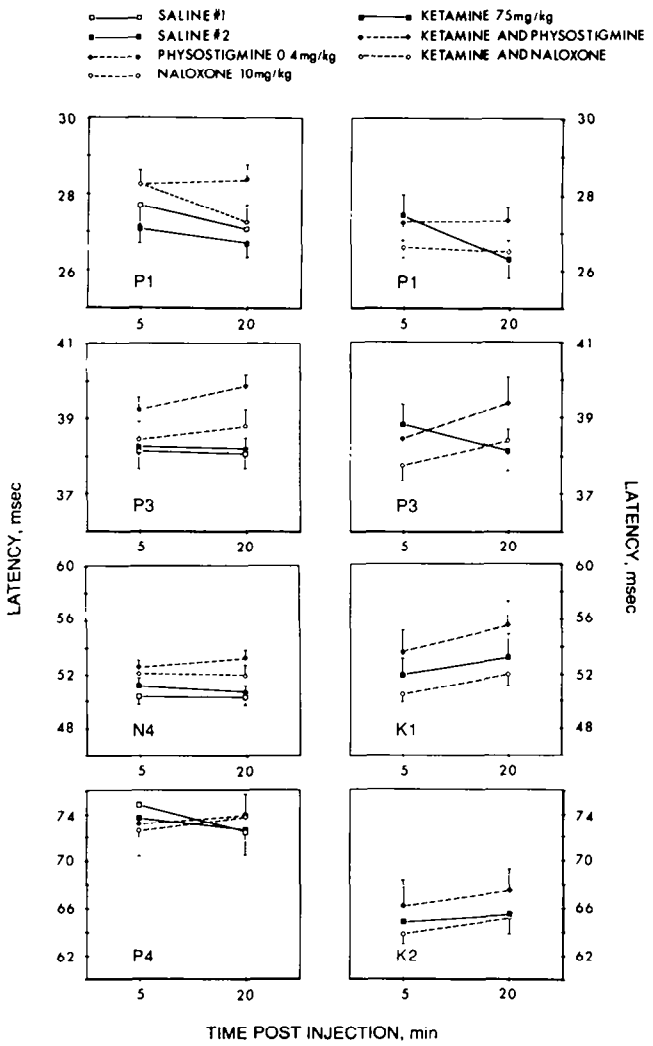

FIG. 3. Mean latencies (±SEM) of flash evoked potential components recorded from the superior colliculus at 2 time intervals following drug administration. Data were obtained from 16 rats. Component notation as in Fig. 1.

at the 5 min recording interval, showing a significant reduction at the 20 min interval. Component P4 was modified in a similar manner, with the resulting positive spike labelled K2 (see Fig. 1). Component K2 appeared to be either superimposed on, or an elaboration of, component P4. However, unlike component K1, component K2 was significantly greater in amplitude at the 20 min recording interval than at the 5 min interval.

In contrast to the marked effects of ketamine, administration of naloxone did not significantly alter the amplitude of any of the components examined in this study. Physostigmine, however, significantly depressed the amplitudes of components P1 and P3, while enhancing the amplitude of component P4. (Since component P4 is normally located in the "negative" direction relative to the prestimulus baseline, the physostigmine-induced decrease in baseline-to-peak amplitude of this component can be viewed as an enhancement. See Fig. 1.) Of interest also, the amplitude of the physostigmine-related change in component P4 was significantly greater at the 20 min interval than at the 5 min interval.

Naloxone pretreatment did not significantly alter the effects of ketamine on the amplitudes of components P1, P3, K1 or K2 (see right side of Fig. 2). Pretreatment with physostigmine likewise did not produce any significant effects on the amplitudes of components P1 and P3 relative to the amplitudes observed with ketamine alone. However, physostigmine pretreatment interacted differentially with the amplitudes of ketamine-induced components K1 and K2 at the 5 min recording interval. The amplitude of K1 was significantly reduced while the amplitude of K2 was significantly enhanced.

Latency

Latency data are displayed in Fig. 3. The latency of all components was altered by at least one of the drug treatments: P1, $F(6,90)=4.37, p<0.001$; P3, $F(6,90)=2.96, p<0.025$; N4(K1), $F(6,90)=4.65$, $p<0.001$; P4(K2), $F(6,90)=13.97$, $p<0.001$, but such latency effects were often not uniform across time, as indicated by significant drug × time interactions for most components: P1, $F(6,90)=3.17, p<0.01$; P3, $F(6,90)=3.21$, $p<0.01$; N4(K1), $F(6,90)=2.75$, $p<0.025$; P4(K2), $F(6,90)=2.01, p>0.05$. No significant differences in component latencies were observed between the two saline trials. The latency of component P1 was decreased by ketamine at the 20 min interval only, while the latency of component P3 was unaffected. The latency of K1 was significantly greater than the latency of the N4 (saline) component, while the latency of K2 was significantly less than that of the P4 (saline) component. Naloxone significantly increased the latency of only component N4, while physostigmine significantly increased the latency of component P1 at the 20 min interval, and components P3 and N4 at both recording intervals.

Pretreatment with naloxone and physostigmine had differential effects on component latencies in comparison to the effects of ketamine alone. Thus, pretreatment with naloxone significantly reduced the latencies of components P1 and P3 at the 5 min recording interval, while physostigmine significantly increased the latencies of both components at the 20 min interval, and also increased the latency of component K1 at both recording intervals (see the right side of Fig. 3).

EXPERIMENT 2: DRUG-INDUCED HYPOTHERMIA

The purpose of this study was to determine the influence of ketamine, naloxone and physostigmine, alone and in combination, on body temperature. The animals were tested at an ambient temperature of 20.25°C.

METHOD

Animals

Fourteen adult male Long-Evans hooded rats, weighing 345–454 g, were tested. These animals had not been used in any prior study.

Procedure

The animals were given 1 day of familiarization to the testing procedures prior to actual data collection. During testing, animals were given intraperitoneal injections on separate days of physiological saline, 75 mg ketamine hydrochloride/kg body wt., 10 mg/kg naloxone hydrochloride followed by saline, 10 mg/kg naloxone followed by 75 mg/kg ketamine, 0.4 mg/kg physostigmine salicylate followed by saline, and 0.4 mg/kg physostigmine followed by 75 mg/kg

ketamine. Testing was conducted every third or fourth day according to a counterbalanced design. An injection volume of 1 ml/kg was observed throughout. Naloxone and physostigmine were dissolved in saline and were injected 5 min prior to the saline or ketamine injections. The ketamine was prepared from a standard concentration of 100 mg/ml (Ketaset, Bristol Labs.) by dilution with saline. Animals were placed in restraining tubes after the saline or ketamine injections, and rectal thermistor probes (YSI No. 402) were inserted 10 cm into the rectum. Temperature readings (YSI 44TA Tele-Thermometer) were taken 5, 20, 40 and 60 min after the saline or ketamine injections. The rats were restrained continuously during the 1 hr sessions and the probes remained in place. Ambient room temperature was maintained at 20.25°C.

Body temperature data were subjected to two-factor analyses of variance, involving repeated measures on both factors (i.e., drug and time). The resulting drug × time interaction was followed by comparisons of individual means with Dunnett's test. In all of the analyses, statistical significance was assumed when $p<0.05$ for two-tailed comparisons.

RESULTS

Administration of ketamine, naloxone and physostigmine, alone and in combination, produced significant hypothermia (Fig. 4). There were significant main effects of both drug, $F(5,65)=4.93$, $p<0.001$, and time, $F(3,39)=63.97$, $p<0.001$, as well as a significant drug × time interaction, $F(15,195)=5.63$, $p<0.001$. In comparison to saline, naloxone produced significant hypothermia at all time intervals, while physostigmine and ketamine did so at the 20, 40 and 60 min intervals. Physostigmine in combination with ketamine produced a significantly greater hypothermia than ketamine alone at the 20, 40 and 60 min intervals, but naloxone pretreatment did not alter the ketamine-induced hypothermia. Body temperature did not change significantly over the 1 hr testing interval following saline or naloxone administration. In contrast, body temperature was significantly lower at the 40 and 60 min intervals than at the 5 min interval when physostigmine was employed. With ketamine, alone and in combination with either naloxone or physostigmine, body temperature was significantly reduced at 20, 40 and 60 min in comparison to the 5 min interval.

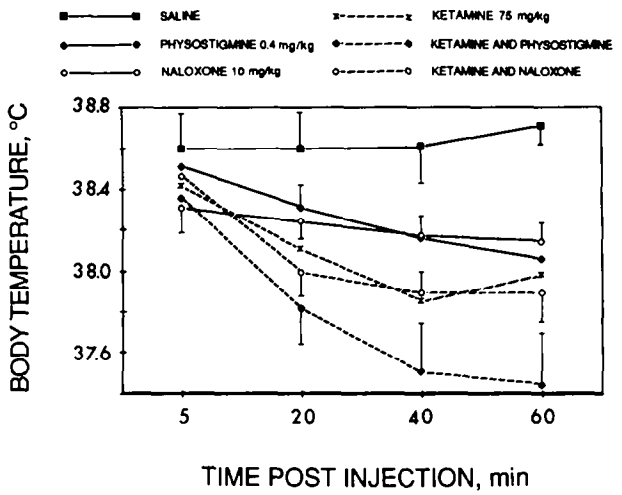

FIG. 4. Averaged rectal temperature (mean±SEM) at different times following drug administration. Data were obtained from 14 rats. Ambient room temperature was maintained at 20.25°C.

GENERAL DISCUSSION

Ketamine

A moderate (75 mg/kg) dose of ketamine resulted in selective alterations in the waveform of FEPs recorded from the SC of hooded rats. While the amplitudes of components P1 and P3 remained unchanged, a large positive peak (K1) emerged from the middle of the large negative component N4. A succeeding positive spike (K2) also became prominent. These results are in good agreement with past work on the dose effects of ketamine (29). In that study, the amplitude of components P1 and P3 were increased by a 100 mg/kg dose, but not by a 50 mg/kg dose. Components K1 and K2, on the other hand, were both reliably present following administration of both the 50 and 100 mg/kg doses of ketamine.

The early peaks P1 and P3 showed little or no change in latency following ketamine administration. Rather, ketamine produced its main latency effects on the later peaks examined in this study. Thus, following saline administration, components N4 and P4 had mean latencies of 50.4 and 73.6 msec, respectively, while ketamine produced the following sequence of late peaks: N4a (46.3 msec), K1 (52.6 msec), N4b (59.3 msec) and K2 (65.2 msec). Past work involving both flash and acoustic evoked potentials recorded from various portions of the rat brain found no influence of ketamine on the latency of early components, while a later component was increased in latency by large doses (>100 mg/kg) of ketamine (15).

Prior work has shown that ketamine produces a dose-dependent hypothermia in rats when they are tested in standard ambient temperatures (20,36). In the present study, there was a mean hypothermia of 0.66°C during the 20–60 min intervals following ketamine administration. It has been suggested that serotonin plays a role in the ketamine-induced hypothermia, since pretreatment with either p-chlorophenylalanine (PCPA) or reserpine antagonizes the hypothermia, while pretreatment with sodium diethyldithiocarbamate has no effect (20). However, it has also been reported that pretreatment with thyrotropin releasing hormone will antagonize ketamine-induced hypothermia (5).

The development of component K1 in the SC appears to be relatively specific to ketamine's influence on that structure. Similar effects have not been observed on FEPs recorded from other areas of the rat brain, although each structure examined apparently reacts differently to ketamine administration (15). Also, other anesthetics do not exert similar influences on FEPs recorded from the SC (18,31). The mechanism(s) by which ketamine produces its actions on the SC are uncertain. In fact, using the 2-deoxyglucose functional mapping method, no metabolic changes were found in the SC following injection of ketamine [25–75 mg/kg, IM, (44)]. It was in part to address this issue that we have examined the effects of naloxone and physostigmine on the FEP recorded from the SC.

Naloxone

A 10 mg/kg dose of naloxone had virtually no effect on the FEP recorded from the SC of the hooded rat. The only significant alteration was a mild (1.7 msec) increase in latency of component N4. These results thus suggest that endogenous opiates do not play a role in the elaboration of the SC FEP.

In earlier work, naloxone (5–15 mg/kg) has been shown to reliably increase flash evoked afterdischarges in rat primary visual cortex (52). The authors suggest that these results indicate that the evoked afterdischarge is sensitive to naloxone-induced changes in GABA levels. However, naloxone has also been shown to decrease locomotor activity (1, 3, 63). Since low levels of activity are often associated with well-elaborated flash evoked afterdischarges (50,51), it is possible that naloxone-induced changes in the afterdischarge are secondary to mild changes in movement.

In the present experiment, naloxone did produce a mild hypothermia of about 0.4°C throughout the hour-long testing interval. These results are in agreement with past reports showing small but significant hypothermic responses to naloxone or naltrexone when rats are tested at 18–23°C (4, 9, 26). There is some evidence that the hypothermic response is dose-dependent (4,59), and two studies employing low doses of naloxone (2–5 mg/kg) failed to find hypothermia (14,35).

Naloxone pretreatment did very little to alter ketamine's effects on either the evoked potential waveform or body temperature. In particular, the two ketamine-induced components (K1 and K2) were unaltered in either their amplitude or latency by naloxone pretreatment. The hypothermia produced by the combination of naloxone and ketamine was virtually identical to that produced by either drug alone. A minor influence of naloxone was that the latencies of components P1 and P3 were decreased by about 1 msec at the 5 min interval following the combination of naloxone and ketamine in comparison to ketamine alone. The source of this effect is uncertain.

In previous work, a 10 mg/kg dose of naloxone has been effective in reducing or preventing ketamine's analgesic action (34, 49, 54) and also reducing the duration of anesthesia (42). On the other hand, naloxone doses ranging from 10–20 mg/kg have also been reported to have no influence on ketamine-induced locomotor activity and analgesia (42,63). Lower dosages have likewise yielded conflicting results. Pekoe and Smith (47) observed that naloxone in the range of 0.06–2.0 mg/kg reduced the analgesic effects of ketamine in a dose-dependent fashion, while other laboratories have reported that doses of 4–5 mg/kg were uneffective (24,49).

Recently, phencyclidine receptors (to which ketamine will also bind) have been identified, and they appear to be distinct from opiate sigma receptors (48,68). Naloxone is an opiate antagonist which has been viewed as effective against many classes of opiate pharmacological actions (kappa, mu, sigma), although it is most potent against mu effects (56). However, it has also been suggested that both the phencyclidine receptor site and the sigma receptor site are naloxone-insensitive (48). The results of the present investigation appear to be consistent with this latter view.

Physostigmine

Modification of the cholinergic brain systems via administration of physostigmine clearly altered the SC evoked potential waveform. The amplitudes of components P1 and P3 were depressed, while the amplitude of component P4 was enhanced (i.e., became more positive). Similar, but more profound effects were reported by Woolley (66) following administration of 3 mg/kg parathion SC. Parathion is an organophosphate insecticide which produces essentially irreversible inhibition of acetylcholinesterase activity. In her study, the amplitudes of the main FEP components recorded from the rat SC at 2 and 4 hours after parathion administration were reduced by at least $^2/_3$, while component latencies were increased at least 40% in relation to control responses. FEPs did not return to normal until about 8 hours after parathion administration.

In other work, the amplitudes of evoked potentials recorded from the VC of rats have also generally been depressed by physostigmine [0.4–0.6 mg/kg (8,32)] and parathion (66). The present results are also consistent with the finding of a physostigmine-induced increase in SC activity, as shown by the 2-deoxyglucose functional mapping technique (43). In this regard, the SC has a large cholinergic innervation, though not from primary visual pathways (6). The dorsal tegmental pathway provides cholinergic innervation to the deep layers of the SC, but the origin of the cholinergic input to the superficial layers of the SC remains unknown (21).

In combination with ketamine, the amplitudes of components P1 and P3 were unaffected, suggesting that ketamine antagonized the depressant effect of physostigmine on these components. On the other hand, the effects of ketamine and physostigmine on the amplitude of component K2 appeared to be almost additive at the 5 min recording interval, since the positivity of this component was greater with the combination of these 2 drugs than with either alone. Finally, however, physostigmine produced a brief reduction in amplitude of the ketamine-induced component K1 at the 5 min recording interval.

Changes in component latencies were also noted following physostigmine administration. The latencies of components P1, P3 and N4 were all increased, although for component P1 the increase was significant at only the 20 min recording interval. The combination of ketamine and physostigmine produced a greater increase in peak latency for components P1, P3 and K1 than was evident following administration of ketamine alone. The resulting increase in peak latency at the 20 min recording interval compared to ketamine alone was 1.0 msec for P1, 1.25 msec for P3 and 2.37 msec for K1. These latency alterations following the combined administration of ketamine and physostigmine may well reflect drug-induced changes in body temperature.

Physostigmine and other cholinesterase inhibitors have previously been reported to produce hypothermia (13,41), which is apparently dose-dependent (38). In the present study, physostigmine produced a mean hypothermia of 0.46°C over the 20–60 min portion of the testing session, while the combination of ketamine and physostigmine produced hypothermia which was on the average 0.39°C greater than that produced by ketamine alone. The combined hypothermia was therefore close to 1.0°C. In anesthetized rats, hypothermia increases the latency of component N1 recorded from the VC at the rate of about 2.1 msec/°C, while component P2 is increased at the rate of about 2.9 msec/°C (19). In general, hypothermia alters the latency of earlier components less than later components (11), which is in line with the latency data noted above.

As shown by the results of the present study, the interactions between ketamine and physostigmine are quite complex, and not simply a presence or absence of antagonism. It is therefore perhaps not surprising that there have been mixed reports of physostigmine's effectiveness in conteracting ketamine. Using cats, Winters and Kott (64) showed that ketamine-induced catalepsy and EEG hypersynchrony could be blocked by physostigmine. Shortened recovery time from ketamine anesthesia has also been demonstrated in rats (37). However, using rats and cats, others have reported no ef-

fects of physostigmine on the duration of ketamine anesthesia (28,46), while one report noted an increase in sleeping time (22). Two studies employing human subjects have likewise yielded contradictory results (16,60). In fact, in one study there was a significantly poorer level of consciousness and orientation, as well as a longer time for recovery room discharge, for those patients receiving physostigmine immediately following the operative procedure (16). These authors therefore suggested the possibility of a synergistic action between physostigmine and ketamine. The latency, body temperature, and K2 amplitude data from the present study are in line with this suggestion.

CONCLUSIONS

Ketamine and physostigmine reliably alter the waveform of the FEP recorded from the rat SC, while naloxone has virtually no effect. However, the origin(s) of the ketamine-induced components K1 and K2 in the rat SC remain unclear. It would appear from the results of the present study that internal opiate brain systems do not play a major role in their production. Component K2 may be related to cholinergic functions, but the electrophysiological interaction between physostigmine and ketamine is complex. Ketamine interacts with numerous neurotransmitter systems, including GABA (65), serotonin (39), epinephrine (33), norepinephrine (33,67), dopamine (33,67) and the N-methyl-D-aspartate subclass of receptors of the excitatory amino acid glutamate (2,55). The observed ketamine-induced changes in SC electrophysiology may therefore result from the complex involvement of many neurotransmitters. Further studies will be required to assess the participation of these other neurotransmitter systems.

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