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Effects of Dizocilpine (MK-801) on Flash-Evoked Potentials, Body Temperature, and Locomotor Activity of Hooded Rats

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HETZLER, B. E. AND H. K. BURKARD. *Effects of Dizocilpine (MK-801) on flash-evoked potentials, body temperature, and locomotor activity of hooded rats.* PHARMACOL BIOCHEM BEHAV **62**(3) 559–573, 1999.—The present study examined the effects of Dizocilpine (MK-801; a noncompetitive *N*-methyl-D-aspartate receptor antagonist) on flash-evoked potentials recorded from both the visual cortex (VC) and superior colliculus (SC) of chronically implanted hooded rats. The potentials were recorded at 5, 20, and 35 min following IP injections of saline, and of 0.1, 0.3, and 1.0 mg/kg MK-801 on separate days. The amplitude of VC component P1 was unaltered following drug treatment. N1 was increased in amplitude by the 0.1-, 0.3-, and 1.0-mg/kg doses, while two other negative peaks in the VC emerged, beginning with the 0.1-mg/kg dose, to complicate the waveform. One negative peak developed between N1 and P2, while the other effectively split peak P2 (forming P2A and P2B). P2A was depressed at all doses, while P2B was depressed at 0.1 mg/kg but augmented at the 1.0-mg/kg dose. N2 was elevated by the 0.3- and 1.0-mg/kg doses, while P3 was increased in amplitude by all doses. N3 was transiently enhanced by the 0.3-mg/kg dose. SC amplitudes were less affected, with P3 and N4 reduced in amplitude by the 0.3- and 1.0-mg/kg doses. The latencies of most components in both structures were decreased, often with all doses, but generally at the later recording times. A second experiment demonstrated significant MK-801-induced hyperthermia at all of the above doses, although a higher dose of 3.0 mg/kg MK-801 caused hypothermia. The reduction in component latencies may, therefore, result at least in part from a drug-induced hyperthermia. A third experiment demonstrated MK-801–induced changes in locomotor activity in rats in an open field. The effects were both dose and time dependent. The 0.3-mg/kg dose of MK-801 produced significant increases in the number of line crossings from 20–60 min in comparison to the saline condition. Increases in the number of line crossings with the 1.0-mg/kg dose peaked at 15 min, and then gradually declined. It is unlikely, however, that these changes in movement can account for the effects of MK-801 on evoked potentials. In conclusion, the results show that blockade of the ion channel associated with the NMDA receptor produces profound changes in the activity of the neural pathways that are reflected in the middle components of the flash-evoked potential recorded from the VC. © 1999 Elsevier Science Inc.

MK-801 Glutamate NMDA Hyperthermia Visual cortex Superior colliculus
Flash-evoked potentials Visual evoked potentials Behavior Rats

THE flash-evoked potential (FEP), which can be easily recorded from both cortical and subcortical sites in laboratory animals, is a complex electrical response that occurs immediately following the presentation of a brief flash of light. Such FEPs are often used to assess the functional integrity of the brain (10), because they provide an integrated view of neural activity and sensory processing (46). Because the individual components of FEPs are representations of neural pathways that are activated during the photic stimulation (18), increased knowledge of the role of neurotransmitters and their receptor subtypes in component production will not only enhance the utility of FEPs, but also give us a better understanding of information transmission and processing in the visual system.

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In this regard, excitatory amino acids (EAAs; *l*-glutamate and/or *l*-aspartate) are major excitatory neurotransmitters in the mammalian central nervous system (33,48) and appear to be present at many levels of the visual system: retinogeniculate and retinotectal pathways (8,40), geniculocortical pathway (26,29), corticogeniculate and corticotectal pathways (16,27,48), and intracortical circuits (26,30). Drugs that interact with receptors for such neurotransmitters may, therefore, result in altered visual functioning, and such alterations should be reflected in changes in FEPs.

EAAs exert their effects via several distinct receptor subtypes. The ionotropic receptors are distinguished in terms of their sensitivity to activation by different agonists: *N*-methyl-D-aspartate (NMDA), Quisqualate/alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA), kainate, and 2-amino-4-phosphonobutanoate (L-AP-4). There are also more recently described metabotropic receptors, where receptor activation is coupled to an intracellular biochemical cascade (43,49).

A number of past studies have sought to explore the contribution of NMDA vs. non-NMDA receptors to the production of the primary components of evoked responses recorded from both the visual cortex (VC) and the superior colliculus (SC). Using a cortical cup allowing perfusion over the cortical surface, Siegel and Sisson (45) recorded FEPs during superperfusion with kynurenic acid, a nonselective blocker of EAA receptor sites. Components N1 and N2 were abolished in a dose-dependent manner, while P1 and P2 were unaffected. 6-Cyano-7-nitroquinoxaline-2,3-dione (CNQX; an antagonist for non-NMDA receptors) produced effects similar to kynurenic acid, while D-2-amino-5-phosphonopentanoic acid (AP5; a specific NMDA receptor antagonist) had no significant effects. They concluded that NMDA receptors are not involved in the production of primary geniculocortical postsynaptic potentials, or the subsequent secondary potentials, in the rat VC in response to flashes of light.

Crunelli et al. (8) demonstrated that an excitatory amino acid mediates the optic nerve epsp recorded in the dorsal and ventral LGN of in vitro slice preparations of the rat. However, AP5 had no effect on the optic nerve epsp, indicating that NMDA receptors are not involved. More recently, Schwarz and Block (44) examined NMDA and non-NMDA receptor involvement in FEPs recorded from the primary VC in pentobarbital-anesthetized rats. Microapplication of both the specific non-NMDA antagonist 6,7-dinitroquinoxaline-2,3-dione (DNQX) and the specific NMDA antagonist 2-amino-7-phosphonoheptanoate (AP7) into the dorsal lateral geniculate nucleus resulted in dose-dependent decreases in amplitude and increases in latency of FEP components P1–N1, although the effects of AP7 were less potent (and less specific at higher doses) than DNQX. Their results, therefore, demonstrated the main contribution of non-NMDA receptors to retinogeniculate transmission in the rat, with a lesser involvement of NMDA receptors.

In regard to the SC, Roberts et al. (40) iontophoretically applied the NMDA receptor antagonist 3-((±)-2-carboxypiperazin-4-yl)-propyl-l-phosphonic acid (CPP) and CNQX in the vicinity of single visually responsive cells in the rat SC. Flash-evoked responses were antagonized by non-NMDA receptor selective currents of CNQX in most cells studied, while of 18 cells studied with NMDA receptor selective currents of CPP, the flash-evoked responses were antagonized only twice, indicating little involvement of the NMDA receptors.

However, while the NMDA receptor can be competitively antagonized by substituted five-carbon and seven-carbon chain glutamate analogues such as AP5 and CPP, it can also be antagonized in a noncompetitive manner by phencyclidine (PCP) and the related dissociative anesthetic ketamine hydrochloride (43). Noncompetitive NMDA antagonists such as PCP block the receptor at a different site than the competitive antagonists. Thus, PCP binds at a site within the ion channel linked to the NMDA receptor, while a competitive antagonist competes with the normal endogenous ligand at the agonist recognition site. By antagonizing the effects of the NMDA receptor through different sites, the noncompetitive and competitive compounds sometimes produce qualitatively different behavioral, physiological, and neurochemical consequences (4,9,13,19,34). It would be expected that noncompetitive antagonists would produce changes in FEPs, given the prominence of visual disturbances produced by PCP-type drugs [e.g., (14,50)].

One of the most potent noncompetitive NMDA antagonists is MK-801 (Dizocilpine; (+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5,10-imine maleate). Although MK-801 acts at the PCP site inside the ion channel associated with the NMDA receptor, MK-801 has a higher affinity for the PCP site than does PCP itself, and a much lower affinity than PCP for other sites to which PCP also binds, such as the sigma opiate receptor (17). Also unlike PCP, MK-801 is not a dopamine reuptake blocker (47). MK-801, therefore, provides greater specificity in investigating the physiological consequences of blocking the NMDA receptor ion channel (36). In fact, MK-801 and PCP produce qualitatively dissimilar patterns of locomotion in rats, but pretreatment with haloperidol (a dopamine and sigma opiate receptor antagonist) in PCP-treated animals results in MK-801-type behavior (32).

This study examined the role of the NMDA receptor in FEP component production through the use of the noncompetitive NMDA receptor antagonist MK-801. There have been relatively few past studies of the effects of MK-801 on EEG and evoked potential activity in the rat, and none of these have involved the visual system (12,42). We examined the effects of MK-801 on flash-evoked potentials (FEPs) recorded from the visual cortex (VC) and superior colliculus (SC) of hooded rats. In addition, because drugs that produce alterations in FEPs may also alter body temperature, and such changes in body temperature may then result in secondary changes in evoked potential parameters (21,22), a second experiment was conducted that examined the effects of MK-801 on body temperature. Finally, given the prominence of alterations in behavior produced by MK-801 in laboratory animals (9,31,41,52), we also investigated the influence of MK-801 on open-field behavior in rats.

EXPERIMENT 1: EVOKED POTENTIALS

Method

Subjects and surgical preparation. Twenty-one adult male Long–Evans hooded rats, weighing 370–540 g at the time of surgery, were tested. At least 2 weeks before testing, recording electrodes in the VC and/or SC were implanted under pentobarbital anesthesia. The visual cortex electrode (0–80 × 1/8" stainless steel screw) was placed 7 mm posterior to bregma and 3 mm lateral to the right of the midline. Similar screw electrodes placed over the ipsilateral and contralateral frontal cortex provided for a recording reference and grounding, respectively. That is, the VC electrode and the ipsilateral frontal cortex electrode were connected to the differential inputs of a Tektronix 122 preamplifier, thereby allowing for a "differential" recording. SC recordings were made from a

twisted pair of nichrome wires (each 250 micra in diameter), insulated to the tip, with a vertical intertip distance of 1 mm. With the head in a horizontal position, the bipolar SC electrode was implanted 6.5 mm posterior to bregma, 1.5 mm lateral to the left of the midline, and lowered 4.7 mm below the surface of the skull. At this depth, the lower member of the electrode pair would be considered the "active" lead. 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 experiment, placements of the SC electrodes were histologically verified (23). Results for the SC are reported for those 14 animals in which the lower member of the electrode pair penetrated the superficial layer of the superior colliculus (11). VC recordings from three of the animals were unusable, due to broken wires or other problems with the cap.

Recording procedure. Evoked potentials were amplified with Tektronix 122 preamplifiers with high and low filter settings of 1.0 kHz and 0.8 Hz for the SC, and 250 and 0.8 Hz for the VC, respectively. Amplified waveforms were averaged ($n = 100$) by a laboratory computer (2,000 Hz sample rate, 400 ms epoch). Fifty milliseconds of the epoch occurred prior to the application of the evoking stimulus. Evoking stimuli were presented with an interstimulus interval of 2 s. Data collection was controlled with a Modular Instruments, Inc., Signal Averaging Program. Ambient temperature was maintained at 22.9–25°C.

Recordings were obtained while animals were located inside a shielded recording chamber with dim background illumination of about 3 lx. The testing box located inside the shielded chamber measured 10 × 10 × 10 inches, and was constructed of white Plexiglas on three sides, the top, and bottom, while the front panel was clear. Shielded Microdot cables, which are designed to reduce artifacts associated with cable movements (18), were attached to the top of the chamber with a mercury swivel, allowing freedom of movement. Flash stimuli were presented by a Grass Model PS22C photostimulator with an intensity setting of 8. The flash lamp of the photostimulator was placed in a small sound-attenuating chamber to eliminate the auditory click present with each flash. The flash lamp was positioned outside of the shielded recording chamber, and was visible to the rat through a clear Plexiglas window.

The animals were given 2 successive days of familiarization to the testing procedures in which the evoking stimuli were presented. This adaptation was followed by at least 1 day of rest, prior to actual data collection. On each testing day, 30 min prior to testing animals received one drop of 1% opthalmic atropine in each eye to maintain constant pupil dilation. Five minutes prior to testing, the animals were injected intraperitoneally every third or fourth day with physiological saline (0.9% sodium chloride, 1 ml/kg), 0.1, 0.3, or 1.0-mg MK-801/kg body weight. The sequence of injections was randomized. Evoked potentials were collected simultaneously from the VC and SC at 5, 20, and 35 min following injection.

Measurement and statistical analysis. For the VC FEP data, baseline-to-peak amplitudes and peak latencies were obtained for nine components (P1, N1, K1, P2A, K2, P2B, N2, P3, and N3; see Fig. 1). Component K1 was a small inflection occurring between the N1 and P2 peaks, during baseline conditions (see Fig. 1). K2 was a peak that effectively split the traditional P2 component into two portions, which we have labeled P2A and P2B. Selection of locations of peaks K1, P2A, K2, and P2B was based on pilot observations in other animals utilizing ketamine and MK-801. In control situations where such peaks were not obvious, latency windows were used to select the "peaks."

Components P1, P3, and N4 were similarly analyzed in the SC waveforms. However, the N4 component was subdivided into N4A, N4B, and N4C (see Fig. 4), on the basis of previous work indicating the possible emergence of a pronounced positive deflection in the middle of N4 following some drug treatments [e.g., (20,24)]. The baseline-to-peak amplitudes consisted of the difference between the mean voltage of 50 ms of prestimulus activity and the peak voltage. Peak latencies were measured from the onset of the evoking stimulus.

Data were subjected to two factor (i.e., MK-801 dose and time) repeated-measures analyses of variance. When a significant main effect, or drug × time interaction, was found, individual means were compared with Dunnett's test. The saline treatment and 5-min recording interval data served as the bases for comparisons in the Dunnett's tests. In all of the analyses, statistical significance was assumed when $p \leqslant 0.05$ 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 effects of the drug.

Results

Visual cortex: Amplitude. Group mean evoked potentials are displayed in Fig. 1, while the amplitude data are presented in Fig. 2. In addition to the traditional peaks, beginning with the 0.1-mg/kg dose of MK-801, two additional peaks emerged to complicate the VC waveform. K1 was a negative peak appearing between N1 and P2, while K2 split P2, forming P2A and P2B. MK-801 increased the amplitude of components N1, K1, K2, P3, and N3, decreased the amplitude of components P2A and N2, produced a biphasic effect on P2B, but had no significant effect on component P1: P1, $F(3, 51) = 1.24$, $p > 0.1$; N1, $F(3, 51) = 25.43$, $p < 0.001$; K1, $F(3, 51) = 38.263$, $p < 0.001$; P2A, $F(3, 51) = 40.670$, $p < 0.001$; K2, $F(3, 51) = 40.62$, $p < 0.001$; P2B, $F(3, 51) = 17.220$, $p < 0.001$; N2, $F(3, 51) = 23.104$, $p < 0.001$; P3, $F(3, 51) = 49.366$, $p < 0.001$; N3, $F(3, 51) = 4.665$, $p < 0.01$. Significant drug × time interactions were also present for most components (the only exception was P1): N1, $F(6, 102) = 9.06$, $p < 0.001$; K1, $F(6, 102) = 7.381$, $p < 0.001$; P2A, $F(6, 102) = 7.826$, $p < 0.001$; K2, $F(6, 102) = 5.21$, $p < 0.001$; P2B, $F(6, 102) = 7.156$, $p < 0.001$; N2, $F(6, 102) = 7.383$, $p < 0.001$; P3, $F(6, 102) = 11.768$, $p < 0.001$; N3, $F(6, 102) = 2.835$, $p < 0.025$.

In comparison to saline, no dose of MK-801 significantly altered the amplitude of component P1. However, N1 was significantly increased in amplitude at both the 20- and 35-min recording intervals by all three doses of MK-801, and at the 5-min interval by the 1.0-mg/kg dose. Similarly, component K1 (which may or may not be present in the saline condition, but if it is, consists of a small inflection between N1 and P2) was also increased. Both the 0.1 and 0.3 mg/kg doses of MK-801 increased the amplitude of this peak at the 20-min recording interval, while the peak was enhanced at all time intervals by the 1.0-mg/kg dose.

In contrast, the amplitude of component P2A was decreased by all doses of MK-801 at all time intervals, the only exception being the 5-min interval for the lowest dose. K2 (a negative deflection riding on a larger positive component) was increased in amplitude (i.e., became less positive) following administration of all three doses of MK-801 at both the 20- and 35-min intervals, and also at the 5-min interval after ad-

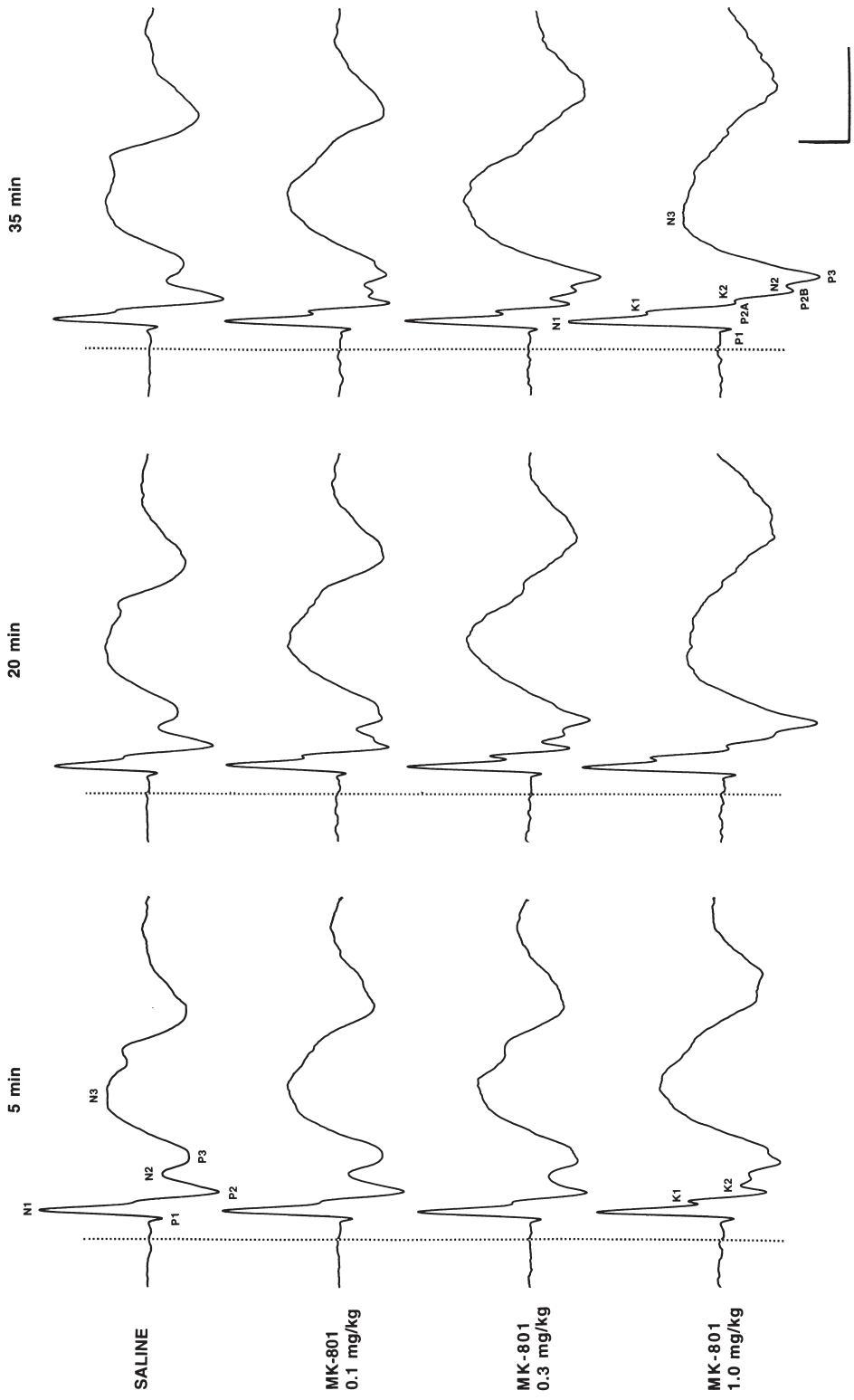

FIG. 1. Group average VC FEP waveforms (n = 18) for each dose of MK-801 and each time interval. Vertical dotted lines represent onset of the evoking stimulus. Calibration: 50 μvolts and 100 ms.

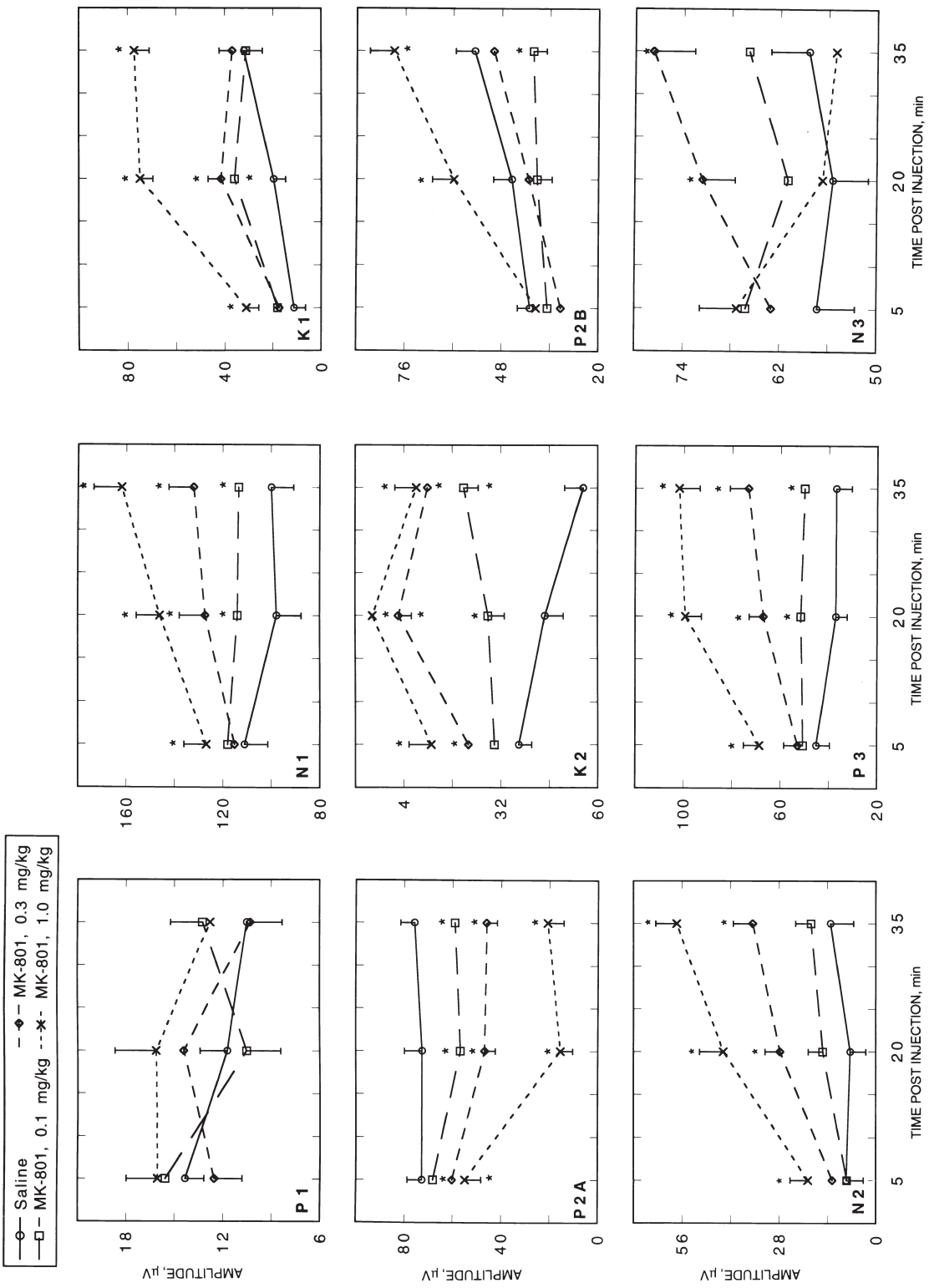

FIG. 2. Peak amplitudes of VC FEP components as a function of MK-801 dosage and time interval. Component notation as in Fig. 1. Vertical bars represent + or − 1 SEM. *$p < 0.05$ in comparison to saline.

ministration of the 0.3 and 1.0 mg/kg doses. Component P2B displayed a biphasic effect, in which the amplitude was diminished at the 35-min interval by the 0.1-mg/kg dose, but increased in amplitude at the 20- and 35-min intervals by the 1.0-mg/kg dose. N2 was elevated (i.e., became less of a negative deflection) at the 20- and 35-min intervals by the 0.3-mg/kg dose, and at all time intervals by the 1.0-mg/kg dose. Component P3 was increased in amplitude at the 20- and 35-min intervals by all three doses of MK-801, and at the 5-min interval by the 1.0-mg/kg dose. Finally, N3 was increased in amplitude by only the 0.3-mg/kg dose at the 20- and 35-min recording intervals.

Latency. The VC latency data are displayed in Fig. 3. MK-801 significantly decreased the latency of most of the components (P2B and N3 were the only exceptions): P1, $F(3, 51) = 11.829$, $p < 0.001$; N1, $F(3, 51) = 19.647$, $p < 0.001$; K1, $F(3, 51) = 3.841$, $p < 0.025$; P2A, $F(3, 51) = 10.602$, $p < 0.001$; K2, $F(3, 51) = 14.044$, $p < 0.001$; P2B, $F(3, 51) = 9.958$, $p < 0.001$; N2, $F(3, 51) = 7.350$, $p < 0.001$; P3, $F(3, 51) = 11.674$, $p < 0.001$; N3, $F(3, 51) = 1.152$, $p > 0.1$. For most components, there were also significant drug × time interactions, typically reflecting the absence of latency changes at the 5-min recording interval: P1, $F(6, 102) = 11.991$, $p < 0.001$; N1, $F(6, 102) = 16.286$, $p < 0.001$; K1, $F(6, 102) = 11.241$, $p < 0.001$; P2A, $F(6, 102) = 12.094$, $p < 0.001$; K2, $F(6, 102) = 11.649$, $p < 0.001$; P2B, $F(6, 102) = 1.107$, $p > 0.1$; N2, $F(6, 102) = 6.584$, $p < 0.001$; P3, $F(6, 102) = 1.867$, $p > 0.1$; N3, $F(6, 102) = 1.388$, $p > 0.1$).

All three doses of MK-801 significantly decreased the latency of components P1 and N1 at both the 20- and 35-min recording intervals. The latency of K1 was decreased at the 20-min interval by the 1.0 mg/kg dose, and at the 35-min interval by both the 0.3- and 1.0-mg/kg doses. P2A, K2, and N2 were all decreased in latency by both the 0.3- and 1.0-mg/kg doses at the 20- and 35-min intervals. In addition, the 0.1-mg/kg dose decreased the latency of P2A and N2 at the 35-min recording interval. In marked contrast, the latency of P2B was significantly increased following administration of all three doses of MK-801. However, this may merely reflect the development of the preceding component K2 rather than a unique drug-induced change in the latency of component P2B. The latency of component P3 was significantly decreased at all time intervals by both the 0.3- and 1.0-m/kg doses of MK-801. Finally, component N3 was not significantly altered by any dose of MK-801 in comparison to the saline latencies.

Superior colliculus: Amplitude. Figure 4 contains group average potentials for the SC, while the amplitude data are shown in Fig. 5. Compared to MK-801–induced changes in the VC, the results in the SC are not as prominent. Nonetheless, all components examined except P1 were significantly reduced in amplitude by MK-801: P1, $F(3, 39) = 4.009$, $p < 0.025$; P3, $F(3, 39) = 9.39$, $p < 0.001$; N4A, $F(3, 39) = 1.022$, $p > 0.1$; N4B, $F(3, 39) = 5.581$, $p < 0.005$; N4C, $F(3, 39) = 13.313$, $p < 0.001$. Significant drug × time interactions were present for these components as well: P3, $F(6, 78) = 5.37$, $p < 0.001$; N4A, $F(6, 78) = 2.873$, $p < 0.025$; N4B, $F(6, 78) = 3.543$, $p < 0.005$; N4C, $F(6, 78) = 2.637$, $p < 0.025$.

Although the main effect of drug dose on component P1 was significant, Dunnett tests did not reveal any significant amplitude change in comparison to the saline treatment. However, component P3 was significantly reduced in amplitude at the 20- and 35-min recording intervals by both the 0.3- and 1.0-mg/kg doses of MK-801. N4A and N4B were likewise reduced in amplitude at the 20- and 35-min recording intervals, although for these two components the effects were restricted to the 1.0-mg/kg dose. The amplitude of N4C was reduced by both the 0.3- and 1.0-mg/kg doses of MK-801 at the 20- and 35-min intervals, and also at the 5-min recording interval following administration of the 1.0-mg/kg dose.

Although not obvious in the group average potentials (Fig. 4), a positive peak did emerge from the middle of the N4 component (i.e., N4B location) following administration of the 1.0-mg/kg dose in four of the animals. It reached its maximum height at the 35-min recording interval, and was followed by a small series of oscillatory potentials. Perhaps with higher dosages of MK-801, more animals would display this alteration as well.

Latency. The latencies of all SC components were decreased to some extent by MK-801, as shown in Fig. 6: P1, $F(3, 39) = 9.950$, $p < 0.001$; P3, $F(3, 39) = 6.962$, $p < 0.001$; N4A, $F(3, 39) = 8.885$, $p < 0.001$; N4B, $F(3, 39) = 3.036$, $p < 0.05$, N4C, $F(3, 39) = 6.541$, $p < 0.005$, though different components were influenced in part by different doses at the 5- and 20-min time intervals, as indicated by significant drug × time interactions: P1, $F(6, 78) = 4.047$, $p < 0.005$; P3, $F(6, 78) = 7.376$, $p < 0.001$; N4A, $F(6, 78) = 9.154$, $p < 0.001$; N4B, $F(6, 78) = 4.285$, $p < 0.005$; N4C, $F(6, 78) = 2.676$, $p < 0.025$.

The latency of both components P1 and P3 was decreased at the 5-min interval by only the 1.0-mg/kg dose, at the 20-min interval by both the 0.3- and 1.0-mg/kg doses, and at the 35-min interval by all three doses of MK-801. The latency of components N4A, N4B, and N4C was not altered by any dose of MK-801 at the 5-min recording interval. However, at the 20-min interval, N4A was reduced in latency by the 0.3- and 1.0-mg/kg doses, N4B by the 1.0-mg/kg dose, and N4C by all three doses of MK-801. Finally, as was true of the early components, N4A, N4B, and N4C were all decreased in latency at the 35-min interval by all three doses of MK-801.

EXPERIMENT 2: BODY TEMPERATURE

The decreased latency changes observed in Experiment 1 could be the result of drug-induced changes in body temperature. Therefore, a second experiment was conducted to determine the relationship between the dosage of MK-801 administered and both the magnitude and time course of its effect on body temperature. The animals were tested at a standard ambient temperature of 23–24°C.

Method

Animals. Ten naive adult male Long–Evans hooded rats were employed, weighing 395–440 g on the first day of testing.

Procedure. Prior to testing, the animals were given 1 day of adaptation to the testing procedures, followed by 1 day of rest. During testing, animals were injected intraperitoneally every third or fourth day with physiological saline (0.9% sodium chloride, 1 ml/kg), 0.1, 0.3, 1.0, or 3.0 mg MK-801/kg body weight. The sequence of injections was randomized with the exception of the 3.0-mg/kg dose of MK-801, which was always administered last. Animals were placed in restraining tubes after the injection, and rectal thermistor probes (YSI No. 402) were inserted 10 cm into the rectum. Temperature readings (YSI 44TA Tele-Thermometer) were taken 5, 20, 35, and 60 min after the injections. The rats were restrained continuously during the 1-h sessions and the probes remained in place.

Body temperature data were subjected to two-factor analyses of variance, involving repeated measures on both factors (i.e., drug dose 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 $p \leq 0.05$ for two-tailed comparisons.

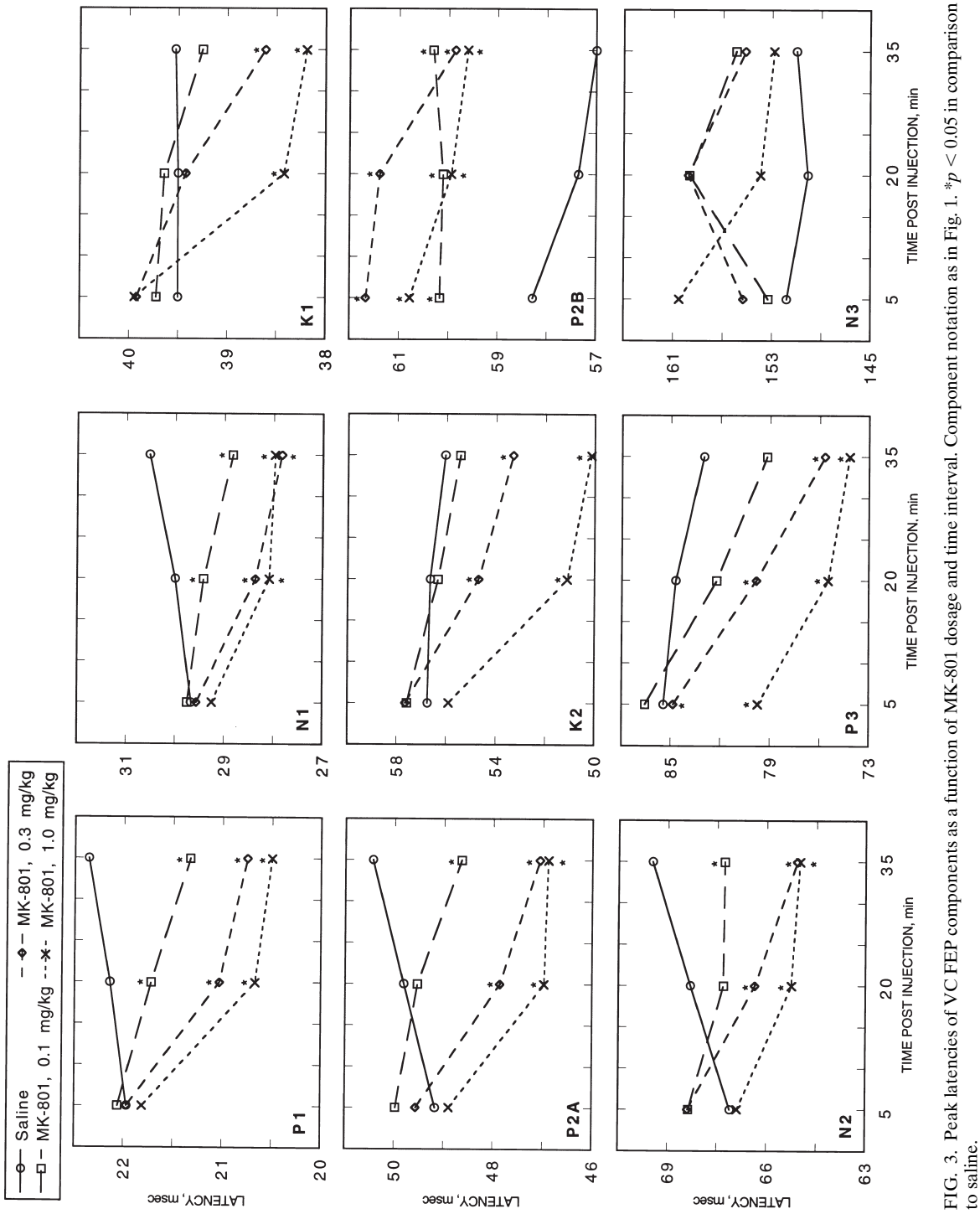

FIG. 3. Peak latencies of VC FEP components as a function of MK-801 dosage and time interval. Component notation as in Fig. 1. *$p < 0.05$ in comparison to saline.

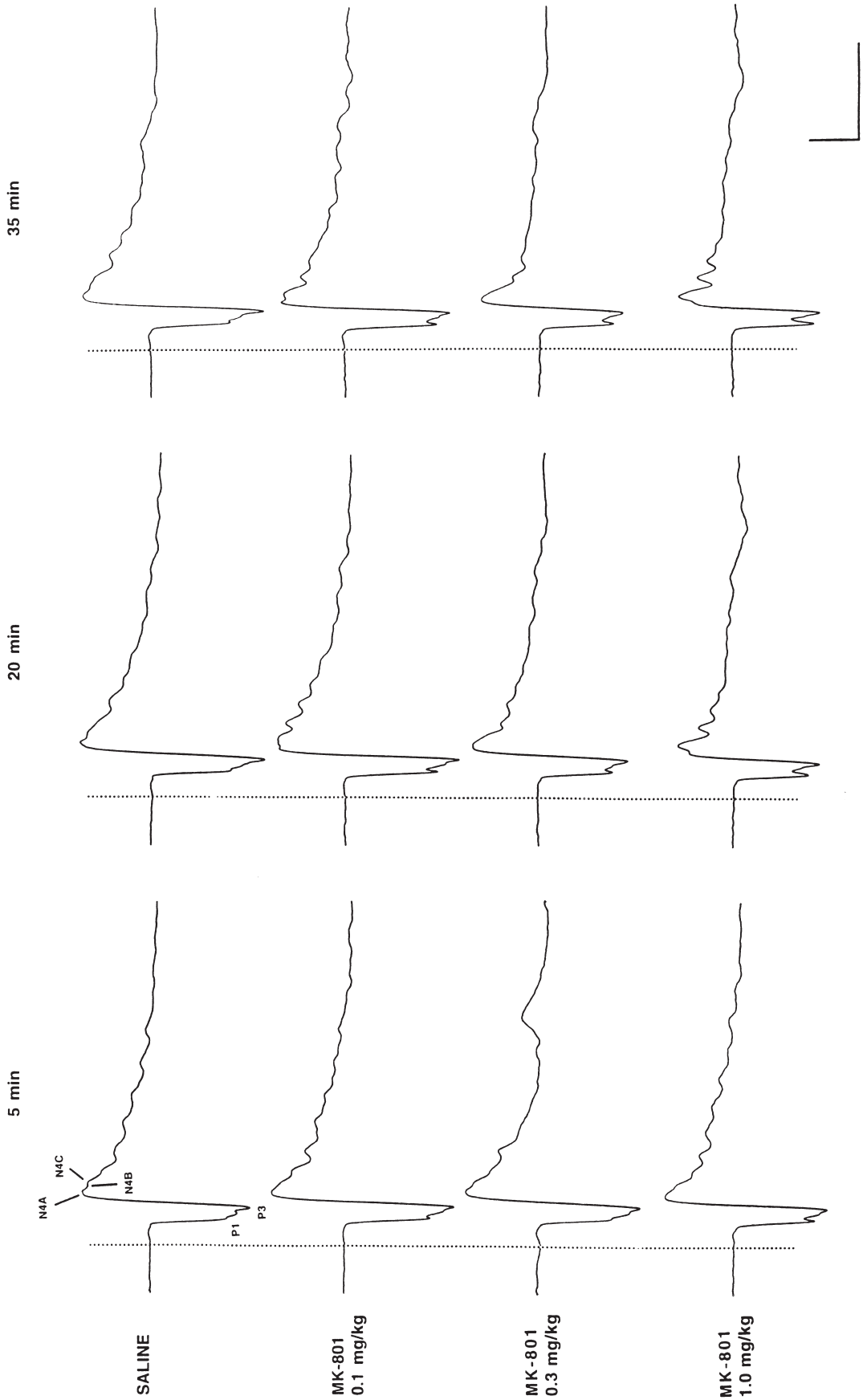

FIG. 4. Group average SC FEP waveforms ($n = 14$) for each dose of MK-801 and each time interval. Vertical dotted lines represent onset of the evoking stimulus. Calibration: 200 μvolts and 100 ms.

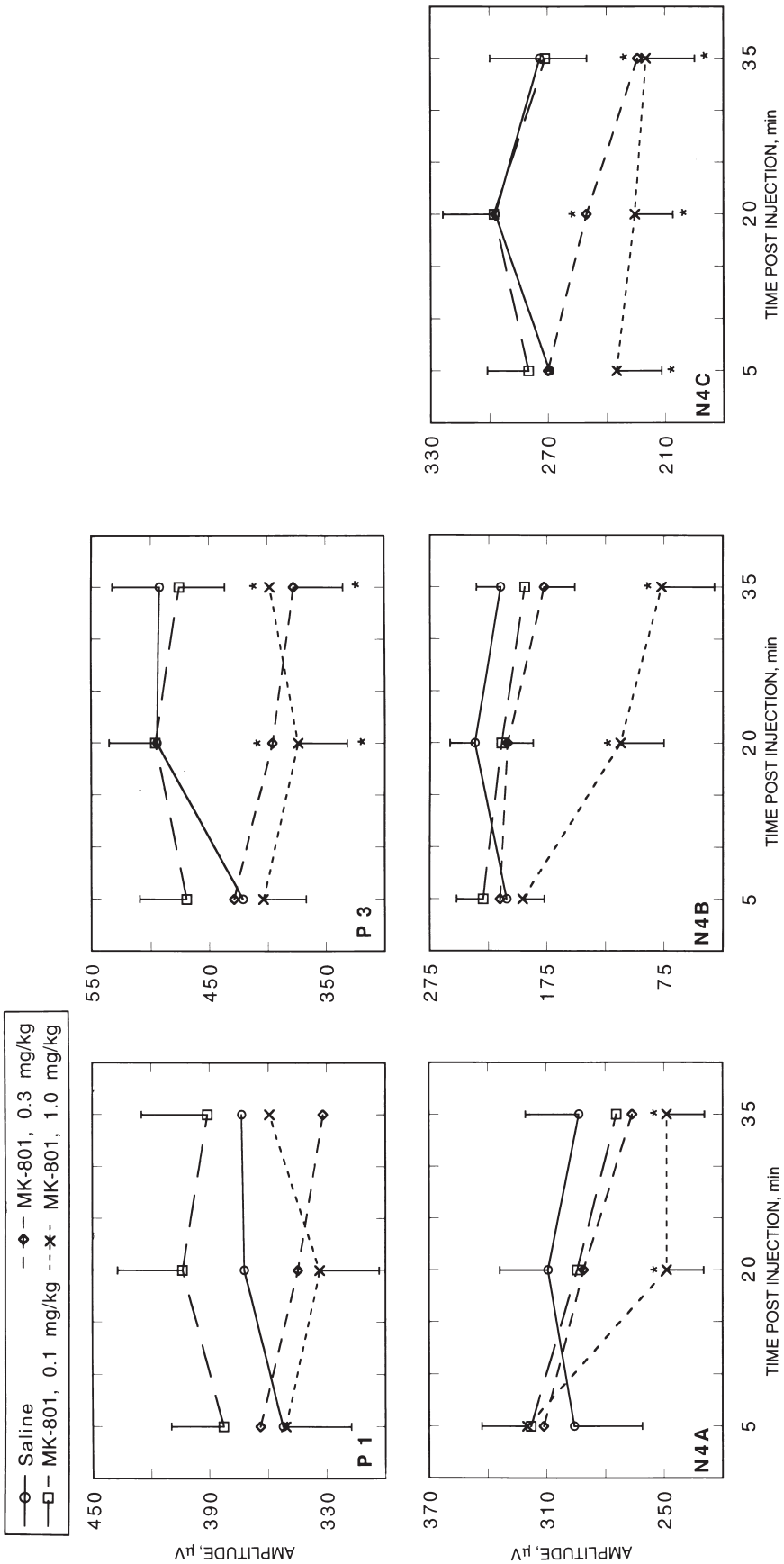

FIG. 5. Peak amplitudes of SC FEP components as a function of MK-801 dosage and time interval. Component notation as in Fig. 4. Vertical bars represent + or − 1 SEM. *$p < 0.05$ in comparison to saline.

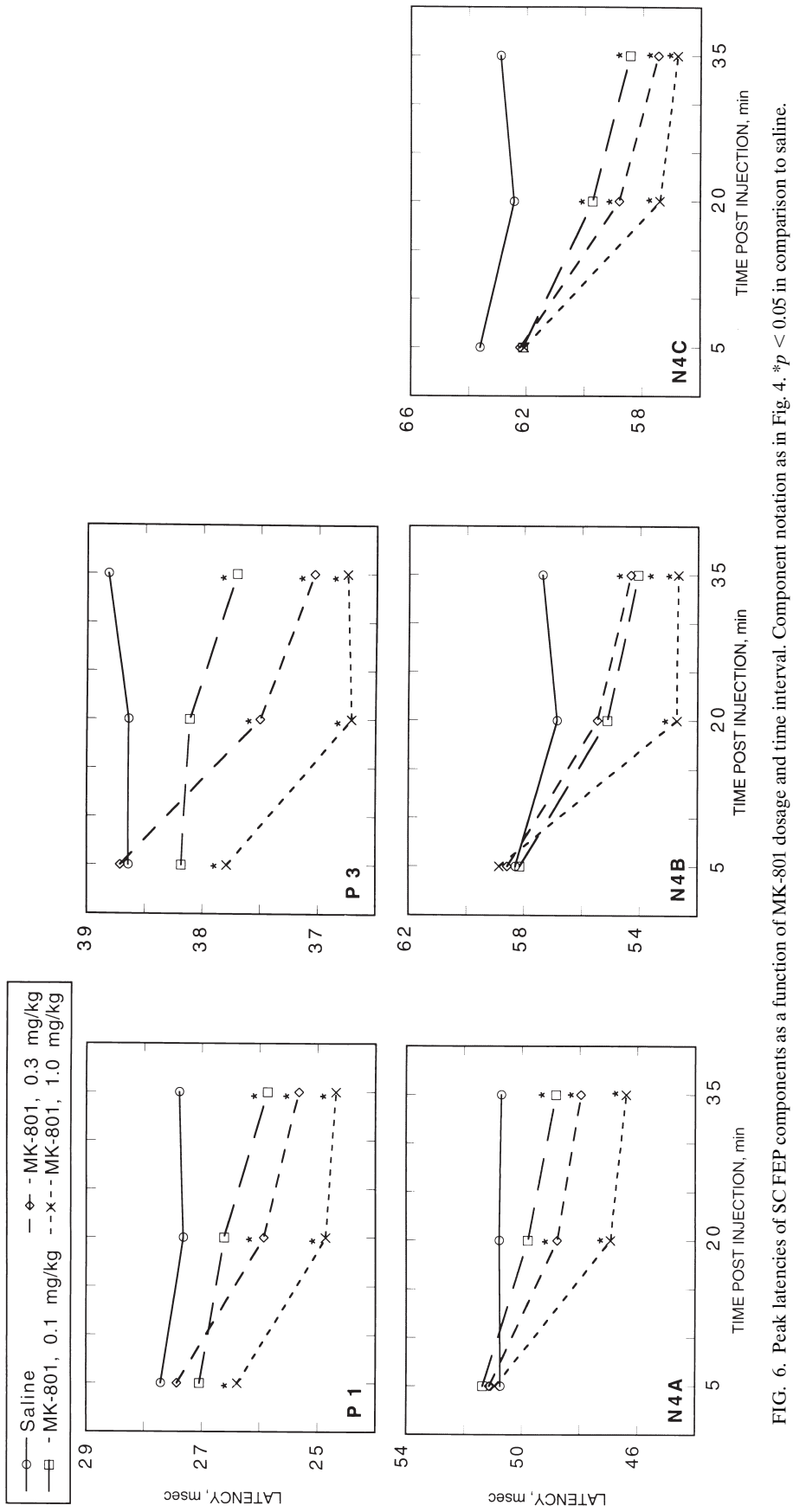

FIG. 6. Peak latencies of SC FEP components as a function of MK-801 dosage and time interval. Component notation as in Fig. 4. *$p < 0.05$ in comparison to saline.

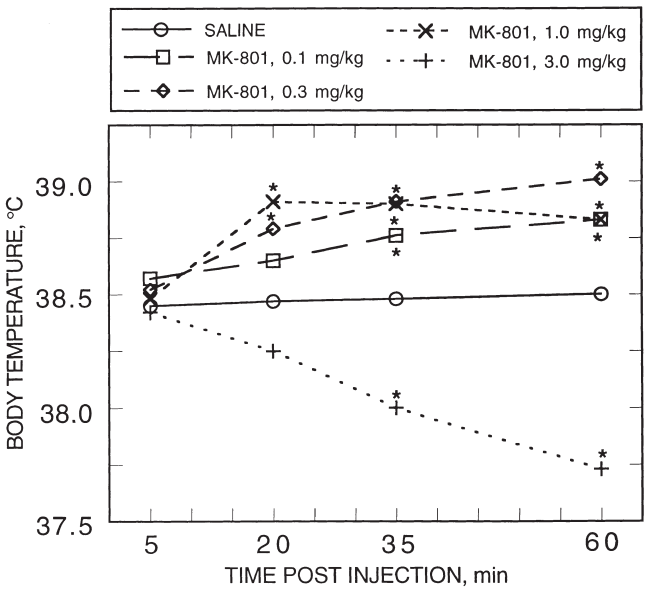

FIG. 7. Body temperature ($n = 10$) as a function of MK-801 dosage and time interval. *$p < 0.05$ in comparison to saline.

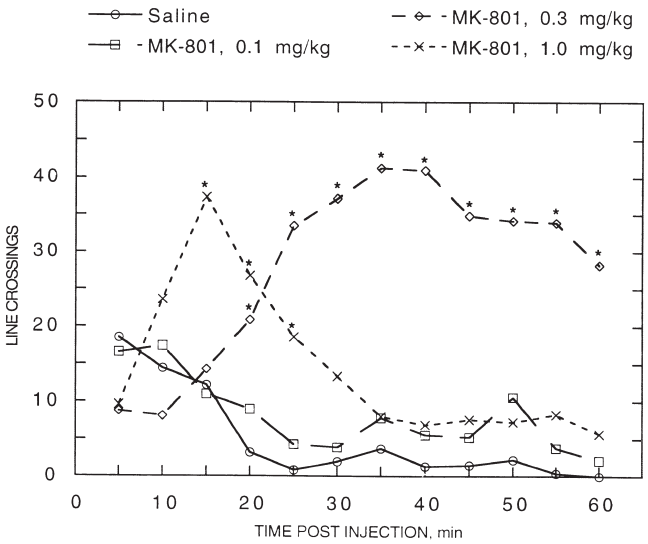

FIG. 8. Mean line crossings (per min) during a 60-min open-field test session. Data are presented for successive 5-min periods following administration of saline and three doses of MK-801. Data were obtained from 10 rats. *$p < 0.05$ in comparison to saline.

Results

Administration of MK-801 produced dose-dependent effects on body temperature (Fig. 7). The main effect of drug dose was significant, $F(4, 36) = 10.140$, $p < 0.001$, as was the drug × time interaction, $F(12, 108) = 7.851$, $p < 0.001$. The 0.1-mg/kg dose of MK-801 produced a significant hyperthermia at the 35- and 60-min intervals, while both the 0.3- and 1.0-mg/kg doses produced hyperthermia at the 20-, 35-, and 60-min intervals. In contrast, the 3.0-mg/kg dose of MK-801 produced significant hypothermia at the 35- and 60-min intervals.

EXPERIMENT 3: OPEN-FIELD BEHAVIOR

Pharmacological agents capable of modifying FEPs may also produce changes in behavior. In this study we sought to examine the behavioral effects of MK-801 at the dosages and time intervals employed in our first (electrophysiological) experiment. An open-field was employed as the testing environment, thereby allowing for both quantitative and qualitative evaluations of behavior.

Method

Animals. Ten naive adult male Long–Evans hooded rats, weighing 384–490 g on the first day of testing, were used.

Procedure. Prior to testing, the animals were handled briefly on 4 days, and were placed in the apparatus once during this time to acclimate them to the field. The animals were tested in a 0.92 meter-square open field, with walls 46 cm high. The field was constructed of standard plywood, and was painted gray. The Plexiglas floor of the apparatus was divided into 36 equal squares, 15 cm on each side. Overhead fluorescent lights provided illumination of approximately 635 lx.

During testing, animals were injected intraperitoneally every third or fourth day with physiological saline (0.9% sodium chloride, 1 ml/kg), 0.1, 0.3, or 1.0 mg MK-801/kg body weight. The sequence of injections was randomized, and each animal was tested at approximately the same time on each testing day.

One minute after injection, each animal was placed in the same middle square of the open field, and allowed to explore for 59 min. Line crossings (movement of all four limbs of the rat across a line) were recorded per 30-s interval. Also, general qualitative observations were made of each animal's behavior.

Statistical analyses were performed on the line crossing data. Data were first averaged within successive 5-min intervals (with the exception of the first interval, which included data from only 4 min). The line-crossing data were then subjected to two-factor analyses of variance, involving repeated measures on both factors (i.e., MK-801 dose and time). When a significant main effect was found, individual means were compared with Dunnett's test. The saline treatment and the first time interval served as the basis for comparisons in the Dunnett's tests. In all of the analyses, statistical significance was assumed when $p < 0.05$ for two-tailed comparisons.

Results

Figure 8 presents the mean number of line crossings per minute, for each 5-min interval during the testing session. There was a significant main effect of MK-801 dose, $F(3, 27) = 5.767$, $p < 0.005$, but not time, $F(11, 99) = 1.480$, $p > 0.10$, on line crossings. In addition, the MK-801 × time interaction was significant, $F(33, 297) = 5.591$, $p < 0.001$.

Dunnett test comparisons revealed that following saline administration, the number of line crossings gradually decreased over time, showing significant decreases (in comparison to the 5-min interval) at 25, 40, 45, 55, and 60 min. Administration of the 0.1-mg/kg dose of MK-801 produced relatively constant, low-level line crossings, with no significant changes over time. There were also no significant differences in comparison to saline with this dose. In contrast, the 0.3-mg/kg dose of MK-801 produced significant increases in the number of line crossings from 20–60 min in comparison to the saline condition. The total number of line crossings remained relatively constant from 25–60 min, during which time the number

was significantly greater than that observed when the animal was first put in the open field (i.e., the 5-min data). Increases in the number of line crossings were also observed with the 1.0 mg/kg dose both over time and in comparison to saline. However, the increase peaked at 15 min and then gradually declined. The 15–25 min data were significantly increased in comparison to saline, while only the 15- and 20-min data were significantly increased in comparison to the 5-min data at this dose.

Behavioral observations. For the first 10–20 min following saline injection, the animals tended to walk along the walls, with some grooming, sniffing, and standing in the corners, and brief walks to the middle for three of the animals. This was followed mostly by sitting or laying in a corner, interrupted by occasional brief walks along the walls. At the end of the hour, all of the animals were resting in a corner. A dose of 0.1 mg/kg MK-801 resulted in similar behaviors, with early walking along walls, accompanied by grooming, sniffing, and standing in corners. Sniffing did seem more prominent than in the saline condition, however. Increasing time was again spent in a corner, sitting, or grooming, interrupted by brief walks along the walls. With the 0.3-mg/kg dose of MK-801, behavior gradually changed over the course of the hour. The first 2–5 min mainly involved walking along walls and grooming. This was followed by sitting in a corner grooming and sniffing for about 10–15 min. Beginning around 15–20 min, there was then increased movement. This was mainly along the walls, often with sniffing everywhere, but there was also some tight circling. There was brief sitting in corners between bouts of running along the walls. The movement along the walls was a combination of back and forth, counterclockwise, and clockwise. There was also gradually increasing body and head swaying, as well as ataxia (with the animal occasionally falling on its side). At the end of the hour, three of the animals were sitting in a corner, but the rest were mainly running along the walls or in tight circles.

The most pronounced change in behavior occurred with the 1.0-mg/kg dose of MK-801. The first 5 min or so appeared fairly normal, with the animal grooming/sitting in a corner or walking along the walls. Beginning around 6–10 min, there was increased running along the walls, with some tight circling, many changes in direction, and head swaying when stopped. Ataxia in the hind legs became apparent, with the animal occasionally falling on its side. "Swimming" movements in the hind legs became prominent around 20–25 min. The amount of running movement declined as the animals then displayed mostly head and body swaying, "swimming" in large circles, and some tight circling accompanied by falling on one side to the end of the hour.

GENERAL DISCUSSION

Evoked potentials

In the present study, MK-801 produced significant dose-dependent effects on FEPs recorded in both the VC and SC, with the 1.0-mg/kg dose affecting most components. In the VC, components N1 and P3 were increased in amplitude by this dose, while N2 was elevated (i.e., made more positive) along with P3. Also at this dose, two novel peaks (K1 and K2) were quite prominent, complicating the VC waveform. Only components P1 and N3 were unchanged in amplitude by the 1.0-mg/kg dose of MK-801. From these results, it is clear that blockade of the ion currents associated with the NMDA receptor causes profound changes in the middle components of the VC FEP.

The role of excitatory amino acids (EAAs) in the production of the rat VC FEP was recently investigated by Siegel and Sisson (45). Using a cortical cup allowing perfusion over the cortical surface, they recorded FEPs during perfusion with kynurenic acid, a nonselective blocker of EAA receptor sites. Components N1 and N2 were abolished in a dose-dependent manner, while P1 and P2 were unaffected (P3 and N3 were not examined). Superfusion with CNQX produced effects similar to kynurenic acid, while superfusion with AP5 (a specific NMDA receptor antagonist) had no significant effects. The authors interpreted their data as follows: P1 is the correlate of the presynaptic geniculate volley, N1 represents a geniculocortical synaptic process produced by EAA release, P2 represents a nongeniculate, non-EAA–mediated postsynaptic potential, while N2 reflects an EAA-mediated intracortical or subcortical (but not direct dorsal lateral geniculate) input to the VC. Their data, therefore, argue that NMDA receptors are not involved in the production of primary geniculocortical postsynaptic potentials, or the subsequent secondary potentials, in the VC in response to flashes of light.

The role of NMDA receptors in the transmission of information within the visual system has been the subject of a number of studies. Crunelli et al. (8) demonstrated that an excitatory amino acid mediates the optic nerve epsp recorded in the dorsal and ventral LGN of in vitro slice preparations of the rat. However, 2-amino-5-phosphonovaleric acid had no effect on the optic nerve epsp, in the presence or in the absence of Mg^{+2}, indicating that NMDA receptors are not involved. More recently, Schwarz and Block (44) examined NMDA and non-NMDA receptor involvement in FEPs recorded from primary VC in pentobarbital-anesthetized rats. Microapplication of both the specific non-NMDA antagonist 6,7-dinitroquinoxaline-2,3-dione (DNQX) and the specific NMDA antagonist 2-amino-7-phosphonoheptanoate (AP7) into the dorsal lateral geniculate nucleus resulted in dose-dependent decreases in amplitude and increases in latency of FEP components P1–N1, although the effects of AP7 were less potent (and less specific at higher doses) than DNQX. Their results, therefore, demonstrate the main contribution of non-NMDA receptors to retinogeniculate transmission in the rat, with a lesser involvement of NMDA receptors. The finding in the present study that MK-801 did not alter the amplitude of FEP VC component P1 is in accord with the aforementioned studies in demonstrating that NMDA receptors probably contribute little to the retinogeniculate projections in the rat.

However, our data implicate NMDA receptor contributions to the middle components of rat VC FEPs. This is in line with the results of a study (35), which found that NMDA receptors participate in transmission at second-order synapses in the rat VC. Using a slice preparation of the rat's VC, these authors recorded extracellular and intracellular responses from layer II/III cells in response to electrical stimulation of the underlying white matter. Extracellular responses of nearly all cells were suppressed by CNQX. In contrast, about half of the long-latency response cells were suppressed by APV, while most of the short-latency response cells were not. In addition, most polysynaptically elicited excitatory postsynaptic potentials (EPSPs) evoked by white-matter stimulation were sensitive to APV, but most monosynaptic EPSPs were not. These authors, therefore, concluded that while non-NMDA receptors are mainly involved in first-order transmission in the rat VC, NMDA receptors participate in second-order transmission, but it is clear that further work will be required to elucidate the involvement of both NMDA and non-NMDA receptors in the production of FEPs in the rat VC.

The results of the present investigation also found significant, though modest, MK-801–induced reductions in the amplitude of components P3, N4A, N4B, and N4C in the SC, although there was some indication that higher doses may more dramatically alter the waveform, somewhat like ketamine (20). However, the amplitude of SC component P1 was unaffected, arguing that NMDA receptors play little or no role in the initial retinocollicular response. These data are in line with the results of a study by Roberts et al. (40). In their work, the NMDA receptor antagonist CPP and 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX; an antagonist for non-NMDA receptors) were applied iontophoretically in the vicinity of single visually responsive cells in the rat SC. Flash-evoked responses were antagonized by non-NMDA receptor selective currents of CNQX in most cells studied, while of 18 cells studied with NMDA receptor selective currents of CPP, the flash-evoked responses were antagonized only twice. Somewhat similar results have been reported in the cat (2). Iontophoretic application of CNQX consistently reduces visual responses in the superficial layers of the cat SC; CPP and AP5 also reduce visual responses of most SC neurons, although the effects of these NMDA antagonists varies with recording depth, suggesting a more limited role for NMDA than non-NMDA receptors in the SC (2).

On a more general note, MK-801 is similar in action to PCP and ketamine hydrochloride, in that it acts at the PCP site inside the ion channel associated with the NMDA receptor (17). Both PCP and ketamine hydrochloride produce rapidly acting analgesia and anesthesia in humans and animals. PCP also causes a schizophrenia-like psychosis (1,25), while the clinical use of ketamine (PCP is not available for clinical use) is limited by emergence reactions, including unpleasant disorienting effects, visual illusions, and transient blindness (14,50). In initial clinical trials, MK-801 also produces psychotomimetic activity in humans (38). The cortical effects of MK-801 on the FEP could well be the physiological correlates of some of the psychotomimetic/visual disturbance properties of PCP-type compounds.

Past research has examined the influence of ketamine hydrochloride on FEPs recorded from the VC and SC. Rigdon and Dyer (39) examined the effects of ketamine on FEPs recorded from the VC of rats. P1 amplitude was increased, while N1 was decreased in a dose-dependent manner. P3 amplitude was decreased by 37- and 75-mg/kg doses of ketamine, while N3 amplitude was depressed by 75- and 150-mg/kg doses. Effects of ketamine on components P2 and N2 were more complex. Finally, the latencies of most components were increased in a dose-dependent manner. In our earlier work on the SC (20), P1 and P3 amplitudes were significantly increased by a 100-mg/kg dose of ketamine, while a positive spike emerged from the middle of N4 within 5 min following administration of both 50- and 100-mg/kg doses. These results are obviously quite different from those observed in the present study.

It is possible, however, that the ketamine-induced changes observed in prior FEP studies (20,39) may relate to pharmacological actions of ketamine other than the blockade of the PCP receptor site. In this regard, Kelland et al. (28) directly compared the behavioral and electrophysiological effects of ketamine and MK-801 in rats. There were some similarities between the drugs. Thus, under appropriate testing conditions (including IV administration of ketamine and either IP or IV administration of MK-801), both drugs significantly altered and/or overrode apomorphine-induced stereotypy and apomorphine-induced excitation of type II globus pallidus neurons. However, there was a pronounced difference in terms of the ability to induce anesthesia. Ketamine (75 mg/kg IV or 150 mg/kg IP) induced anesthesia in all animals tested. While IP administration of high doses of MK-801 produced ataxia, surprisingly, MK-801 did not produce anesthesia. When administered IV, high-dose MK-801 produced respiratory distress. They concluded that MK-801 does not induce dissociative anesthesia in rats, and that NMDA receptor blockade was, therefore, not the underlying cause of dissociative anesthesia in rats. In line with that conclusion, it is possible that the electrophysiological changes found in prior ketamine studies on FEPs in the visual system (20,39) reflect the actions of systems altered in the course of production of dissociative anesthesia.

Body Temperature

Administration of MK-801 produced significant changes in body temperature. For the doses employed in the first experiment (i.e., 0.1, 0.3, and 1.0 mg/kg) significant hyperthermic effects resulted. Only with a very high dose of 3.0 mg/kg did hypothermia result. These results are in line with a previous study (37), which also found that MK-801 produced hyperthermia in rats.

It is well known that drugs can alter body temperature [e.g., (5–7)], although the secondary effects on evoked potentials are often not considered (22). Those few studies that have examined hyperthermic effects on cortical FEPs have found that peak latencies decrease as body temperature increases (3,21), while for the range of hyperthermic temperatures observed, amplitudes of components in the VC should remain unaffected (21). Similar data are not available for the SC.

Decreases in component latency were found in both the VC and SC in the present study. It seems likely that at least part of these latency changes in the present research are the secondary result of MK-801–induced hyperthermia. For example, past research has demonstrated that for VC component P1, the estimated latency decrease from a 1.0°C increase in body temperature is about 1.4–1.7 ms, while for component N1 the expected decrease in latency is 1.6–2.2 ms (21). In the present study, the average hyperthermia at the 20- and 35-min testing intervals following administration of the 1.0-mg/kg dose of MK-801 was 0.43°C, so this could account for about a 0.7-ms decrease in latency for VC component P1 and a 1.0-ms decrease for N1. The average decrease in latency for these two components at these two testing intervals was 1.67 ms for P1 and 2.24 ms for N1. Thus, about half of the decrease in latency can be explained by MK-801–induced hyperthermia. The remaining portion of the latency decrements may result from the direct action of the drug itself.

Behavioral Effects

Behavioral changes in rats are apparent following administration of MK-801. We observed significant increases in the number of line crossings (as a result of running along the walls with some intermittent tight circling and sniffing) from 20–60 min following administration of the 0.3-mg/kg dose of MK-801. This was accompanied by some ataxia and head and body swaying. Increases in the number of line crossings were also observed with the 1.0-mg/kg dose. However, the increase peaked at 15 min and then gradually declined, with only the 15–25 min data significantly increased in comparison to saline. With this high dose, following the period of rapid running there was increasingly pronounced ataxia, with "swimming"

movements in the hind legs, as well as prominent head and body swaying.

The present observations are in line with the results of past studies in other laboratories. When tested 30 min after a single IP injection, MK-801, at a dose of 0.1 mg/kg, produces no obvious effect on behavior in the rat. The minimal effective dose is 0.2 mg/kg for significant ataxia, stereotyped head waving, increased horizontal, and decreased vertical activity in an open field. Effects are dose dependent for the range of 0.2–0.6 mg/kg (9). Wozniak et al. (52) likewise found that performance on several sensorimotor tasks was impaired, and the animals appeared grossly intoxicated when given 0.2 mg/kg IP, but not when treated with lower doses of 0.05 or 0.1 mg/kg. When measured by photocell beam breaks, however, a dose of 0.1 mg/kg SC is effective in increasing the behavior of rats for 2 h after drug administration. Behavior is then significantly reduced starting at 2 h postdrug and lasting through 6 h postdrug (41).

Using a cumulative dosing procedure in which injections are given IP at 15-min intervals, with observations 13–15 min later, MK-801 produces significant locomotion, sniffing, swaying, and falling, beginning at a dose of 1 mg/kg (31). In contrast, IV injections of MK-801 into the lingual vein produce hyperactivity and impair acquisition of a new place response in a swimming pool at doses as low as 0.05–0.1 mg/kg (51). In that same study, higher doses (0.25–1.0 mg/kg IV) resulted in somnolence, akinesia, impaired food consumption, locomotion, and swimming, as well as impaired navigation to a hidden platform. The doses employed in the present study (0.1–1.0 mg/kg IP), therefore, allowed for an electrophysiological assessment within a behaviorally relevant range.

Danysz and colleagues (9) speculate that the inhibition of rearings (i.e., decreased vertical activity) caused by MK-801 (and other NMDA antagonists) could have resulted from a sensory deficit-induced loss of interest in the environment. Clearly, the changes in VC FEPs observed in the present study could be correlated with pronounced visual disturbances, resulting in loss of normal visual functioning.

To look at the data from a different perspective, however, it may instead be asked to what extent the observed changes in evoked potentials are secondary to MK-801–induced changes in movement. After all, it is apparent that at the 20- and 35-min testing intervals following administration of the 0.3 mg/kg dose, as well as the 20- and possibly 35-min intervals with the 1.0 mg/kg dose, there were significant changes in behavior in comparison to the saline condition.

It is unlikely that these MK-801–induced changes in behavior can explain the observed alterations in FEPs, because the 1.0 mg/kg dose produced significant amplitude changes in some VC components (e.g., N1, P2A, K2, P3) at the 5-min recording interval, prior to any observed change in movement. Also, most significant VC amplitude changes persisted throughout the 20- and 35-min recording intervals at both the 0.3- and 1.0-mg/kg doses, despite quite different behavioral effects at these same time intervals. Finally, if motor activity played a prominent role in the observed effects on VC FEPs, then it would be expected that the amplitude of component N3 would be reduced (15). This was not the case; in the present study, N3 was increased in amplitude by the 0.3-mg/kg dose at the 20- and 35-min recording intervals, but not significantly altered by the 1.0-mg/kg dose of MK-801.

In conclusion, it is clear that blockade of the ion currents associated with the NMDA receptor causes profound changes in the middle components of the VC FEP, accompanied by hyperthermia and alterations in locomotor activity. More modest changes were observed in the SC FEP, following administration of 0.3–1.0 mg/kg MK-801. However, the neurogenesis of both cortically and subcortically recorded FEPs involves complex circuits that presumably contain a variety of neurotransmitters. Additional studies will be necessary to determine the exact role that NMDA receptors play in FEP component production.

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