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Nicotine alters flash-evoked potentials in Long–Evans rats

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Abstract

This experiment examined the effects of nicotine on flash-evoked potentials (FEPs) recorded from both the visual cortex (VC) and the superior colliculus (SC) of chronically implanted male Long–Evans rats. FEPs were recorded at 5, 20, 40, and 60 min following subcutaneous injections of saline, and of 0.4, 0.7, and 1.0 mg/kg nicotine on separate days. In the VC, the amplitude of components N_{39}, N_{53}, N_{67}, and P_{88} increased, while the amplitude of components N_{30} and P_{235} decreased following nicotine administration. P_{22}, P_{47}, and N_{153} were unchanged. In the SC, components P_{27}, N_{48}, and N_{53} were reduced in amplitude, while P_{37} and N_{57} were unaffected by nicotine. Many peak latencies in the VC and SC were increased by nicotine, often at all three doses. However, effects of nicotine on FEPs were both dose- and time-dependent. When body temperature was recorded 65 min after drug administration, significant hypothermia was found with both the 0.7- and 1.0-mg/kg nicotine doses. The 1.0-mg/kg dose of nicotine resulted in a significant increase in movement during the recording sessions, but not in subsequent open-field observations. The results demonstrate that nicotinic acetylcholine receptors (nAChRs) play a differential role in the production/modulation of the various components of FEPs.

Keywords: Nicotine; Visual cortex; Superior colliculus; Flash-evoked potentials; Visual-evoked potentials; Rats; Hypothermia; Locomotion

1. Introduction

Nicotine is a powerful psychoactive drug that produces a variety of effects in the central and peripheral nervous system. Peripherally, both sympathetic and parasympathetic ganglia are stimulated, resulting in a complex mix of sympathetic nervous system arousal combined with some indications of physiological relaxation. Centrally, nicotine administration produces EEG activation and behavioral arousal or alerting, which may improve some cognitive performance (Levin, 1992; U.S. Department of Health and Human Services [USDHHS], 1988).

Nicotine works as a nicotinic acetylcholine receptor (nAChR) agonist. nAChRs are ligand-gated ion channels which have a wide distribution in the central nervous system (CNS), with locations not only on neuronal cell bodies and dendrites, but also on axon endings, where they can modulate the release of numerous transmitters, including dopamine, noradrenaline, serotonin, acetylcholine, glutamate, and GABA. There are also a variety of subtypes of nAChRs, composed of distinct combinations of at least 11 neuronal subunits ($\alpha2-\alpha9$ and $\beta2-\beta4$). Despite this distribution and diversity, the functional significance of nAChRs has remained elusive (Levin and Simon, 1998; MacDermott et al., 1999; Vizi and Lendvai, 1999; Wonnacott, 1997).

Sensory-evoked potentials have frequently been utilized to characterize the effects of drugs and toxic substances on the functioning of the nervous system (Borbély, 1973; Dyer, 1985). The flash-evoked potential (FEP) is a complex electrical response that occurs immediately following the presentation of a brief flash of light. In laboratory animals, it can be easily recorded from both cortical and subcortical sites. The individual components of FEPs are representations of neural pathways that are activated during the photic stimulation (Fox and Rosenfeld, 1972), and alterations in these components produced by exposure to pharmacological agents can indicate visual system dysfunction (Dyer, 1985). With respect to nicotine, nAChRs have been identified throughout the visual system, including the dorsal lateral geniculate nucleus (dLGN), the superficial layers of the superior colliculus

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(SC), and Layers III and IV of the primary visual cortex (VC; Clarke et al., 1984). It might therefore be expected that nicotine administration would result in reliable alterations in visual system functioning, as reflected in FEPs.

However, while there have been numerous previous human studies of the effects of cigarette smoking (and therefore, nicotine) on cortical FEPs, the results have not been consistent. Thus, there are reports of cigarette smoking producing amplitude increases (Friedman et al., 1974; Hall et al., 1973; Woodson et al., 1982), decreases (Knott and Venables, 1978; Vazquez and Toman, 1967), and no change (Brown, 1968; Golding, 1988). When measured, FEP component latencies typically have been unaltered by smoking (Golding, 1988; Hall et al., 1973; Woodson et al., 1982), although there are exceptions (Brown, 1968). Visual P_{300} amplitudes and latencies also have been recorded following nicotine administration/smoking in human studies, with divergent results (Ilan and Polich, 1999). For example, Knott et al. (1999) reported that nicotine induced increased P_{300} amplitudes with no change in P_{300} latency, while others have reported shorter P_{300} latencies but no amplitude changes following smoking (e.g., Houlihan et al., 1996).

Surprisingly, few animal studies have investigated the effects of nicotine on FEPs, again with no clear pattern of results emerging. Using female Long–Evans rats, Bringmann (1994) and Bringmann and Klingberg (1995) reported that nicotine tartrate (1 mg/kg ip) decreased the amplitude of the N_{41} component, without altering the amplitude or latency of any other component studied. In rabbits, nicotine (0.025–0.5 mg/kg iv) produced both dose- and time-dependent effects on amplitudes of red light FEPs (Sabelli and Giardini, 1972). Both an early fast positive complex (onset latency of 25–35 ms) and a slow negative wave (peak latency of about 200 ms) were depressed at 2 min following injection, but enhanced at 5 min. The late negative wave displayed a subsequent longer cycle of depression and augmentation following administration of some nicotine doses.

The present study sought to determine the role of nAChRs in visual system functioning by examining the effects of nicotine on FEPs recorded from both the VC and the SC of Long–Evans rats. With respect to the VC, we examined both a larger range of nicotine dosages, and a greater number of FEP components, than has heretofore been the case in rat FEP research. FEPs recorded from the SC, a structure involved in attention and orientation (Binns, 1999; Goldberg and Robinson, 1978), were also examined. To date, there have been no studies of the impact of nicotine on FEPs recorded from the SC, although there is a high density of ^{3}H-nicotine binding there (Clarke et al., 1984; London et al., 1985), and nicotine produces a marked increase in local cerebral glucose utilization in this structure (London et al., 1985).

In addition to recording FEPs, body temperature was also measured in the present study, because nicotine produces a dose-dependent hypothermia in rodents (de Fiebre et al., 1991; Luo et al., 1994; Rezvani and Levin, 2002), and such changes in body temperature may then result in secondary changes in evoked potential parameters (Hetzler and Dyer, 1984; Hetzler et al., 1988). Finally, because nicotine alters behavior in rats (e.g., Qiu et al., 1992), we monitored gross body movement during and after the evoked potential recording sessions.

2. Materials and methods

2.1. Animals

Twenty-two adult male Long–Evans hooded rats (Harlan, Indianapolis, IN), about 4 months old and weighing 354–404 g at the time of surgery, were used in the study. The rats were housed individually in standard cages in a room with a light/dark cycle (light from 0600 to 1800 h) and climate control (temperature about 22 °C and humidity about 50%). Purina Lab Chow (St. Louis, MO) and tap water were provided ad libitum.

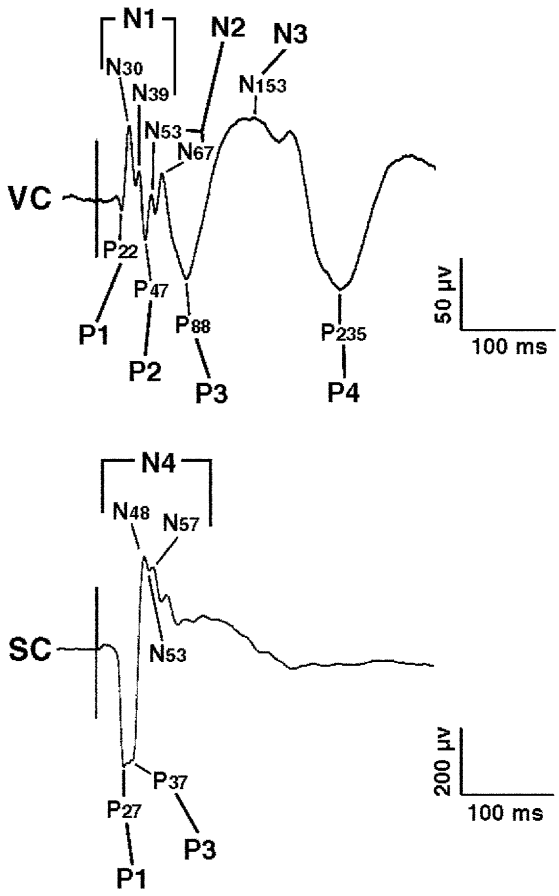

Fig. 1. Group average FEP waveforms for the 5-min saline condition. Upper trace: VC ($n = 19$). Lower trace: SC ($n = 17$). Vertical lines represent onset of the evoking stimulus. Individual FEP components traditionally include only the larger peaks, named by polarity and sequence (large font). The designation employed in the present study is based on polarity and latency from the onset of the evoking stimulus, and includes more components (smaller font).

2.2. Electrode implantation surgery

At least 1 week before adaptation, recording electrodes in the VC and the SC were implanted while the animals were under the effect of pentobarbital anesthesia. The rats first received an intraperitoneal injection of atropine sulfate (0.06 mg) to minimize respiratory distress during anesthesia. They were then anesthetized with an intraperitoneal injection of 50 mg sodium pentobarbital/kg body weight. The VC electrode (0−80 × 1/8 in. stainless steel screw) was placed 6 mm posterior to the bregma and 3 mm lateral to the right of the midline. Similar screw electrodes placed over the ipsilateral and the contralateral frontal cortex provided for a recording reference and grounding, respectively. SC recordings were made from a twisted pair of nichrome wires (250 μm in diameter each), insulated to the tip, with a vertical intertip distance of 1 mm. With the skull surface of the animal located in a horizontal plane (König and Klippel, 1963), the bipolar SC electrode was implanted 6.5 mm posterior to the bregma and 1.5 mm lateral to the left of the midline and then lowered 4.7 mm below the surface of the skull. All electrodes were led to an Amphenol connector, and the whole assembly was secured to the skull with additional screws and dental acrylic. After surgery, animals were handled briefly on a daily basis before testing.

At the conclusion of the experiment, placements of the SC electrodes were histologically verified (Hetzler et al., 1981). Results for the SC are reported for those 17 animals in which the lower member of the electrode pair penetrated the superficial layer of the SC (Dyer and Annau, 1977). VC recordings from three animals were unusable because of problems with the cap.

2.3. Chemicals

Nicotine as the (−)-nicotine tartrate salt (Sigma Product No. 5260, St. Louis, MO) was dissolved in 0.9% saline to obtain the different concentrations, which were injected subcutaneously in a volume of 1 ml/kg. Doses of 0.4, 0.7, and 1.0 mg nicotine/kg body weight were based on the salt form of the drug. Expressed as the base, the corresponding doses would be 0.13, 0.23, and 0.33 mg nicotine/kg, respectively. The goal was to utilize a range of dosages commonly found in rat studies (Levin, 1992).

2.4. Procedure

Evoked potentials were amplified with Tektronix 122 preamplifiers (Tektronix, Beaverton, OR) with high- and low-filter settings of 1.0 kHz and 0.8 Hz for both the VC

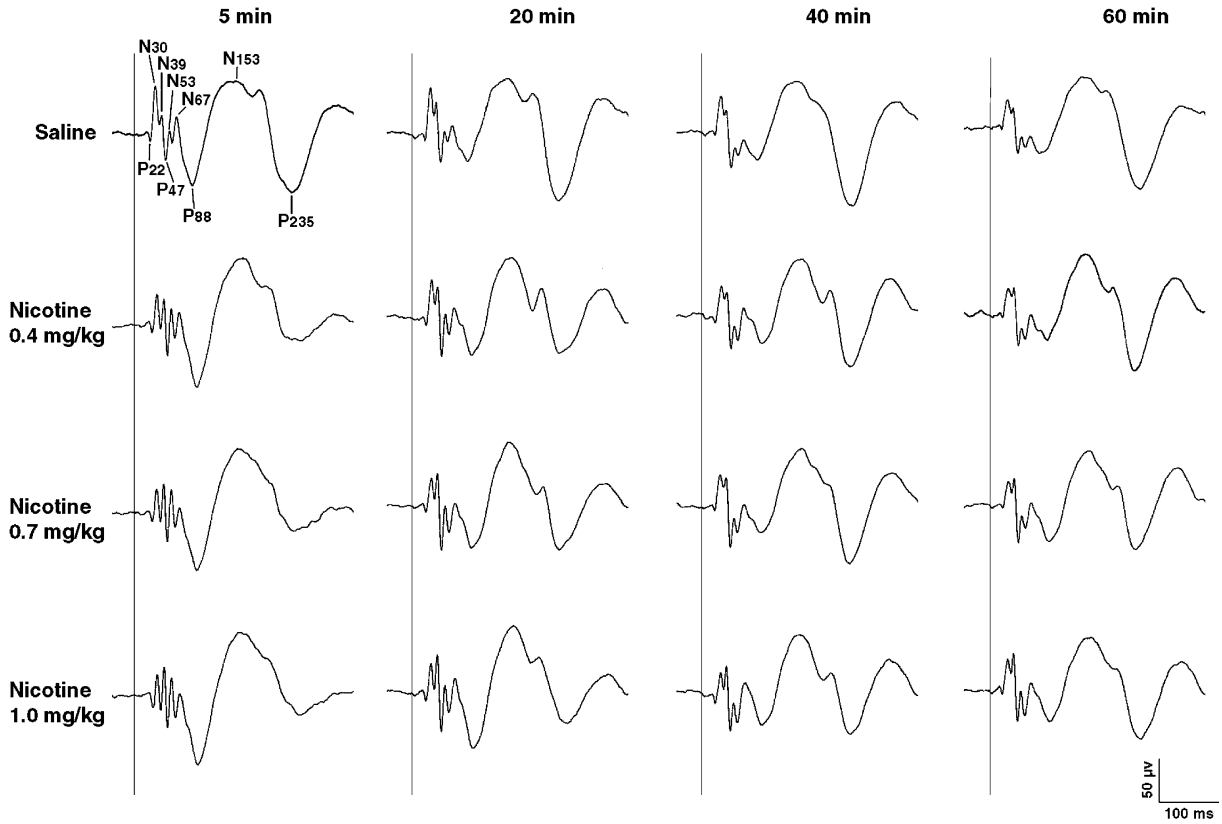

Fig. 2. Group average VC FEP waveforms ($n = 19$) for each dose of nicotine and each time interval. Vertical lines represent onset of the evoking stimulus. Individual FEP components are named by polarity and latency from the onset of the evoking stimulus. The effects of nicotine varied with the component and time interval. In general, the amplitudes of components N_{39}, N_{53}, N_{67}, and P_{88} were increased by nicotine, while the amplitudes of components N_{30} and P_{235} were decreased by nicotine. Amplitudes of the other components were unchanged.

and the SC. Amplified waveforms were averaged (2000 Hz sample rate, 400 ms epoch, $n=100$) by an IBM PS/ValuePoint computer connected to a Modular Instruments M100 Mainframe containing the following modules: M202 Fast A/D, M210 Memory, and M214 Data Acquisition Timer. Fifty milliseconds of the epoch occurred before the application of the evoking stimulus. Evoking stimuli were presented with an interstimulus interval of 2 s. Data collection was controlled with an S-215 Signal Averager program (Modular Instruments, West Chester, PA).

Recordings were obtained while animals were located inside a shielded recording chamber with dim background illumination of about 3 lx. The testing box, which was located inside the shielded chamber, measured 10 × 10 × 10 in. and was constructed of white Plexiglas on three sides, the top, and the bottom, whereas the front panel was clear. Shielded Microdot cables (Microdot Connectors, South Pasadena, CA), which are designed to reduce artifacts associated with cable movements (Fox and Rosenfeld, 1972), 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 (Grass-Telefactor, West Warwick, RI) 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 the shielded recording chamber and was visible to the rat through a clear Plexiglas window.

The animals were given two successive days of familiarization to the testing procedures, followed by 1–2 days of rest before actual data collection. On each testing day, 30 min prior to testing, the animal received one drop of 1% ophthalmic atropine in each eye to maintain constant pupil dilation (Gelatt, 1981). This was important because nicotine can decrease pupil dilation (Furuta and Miyao, 1992). Direct monitoring of the pupils was not conducted during the experiment itself, as it would require light anesthesia and/or stress-inducing restraint, which could compromise the results. However, pilot work demonstrated the effectiveness of the eye drops.

Five minutes prior to testing, the animal was injected subcutaneously in the dorsal surface of the neck on separate days with physiological saline (0.9% sodium chloride, 1 ml/

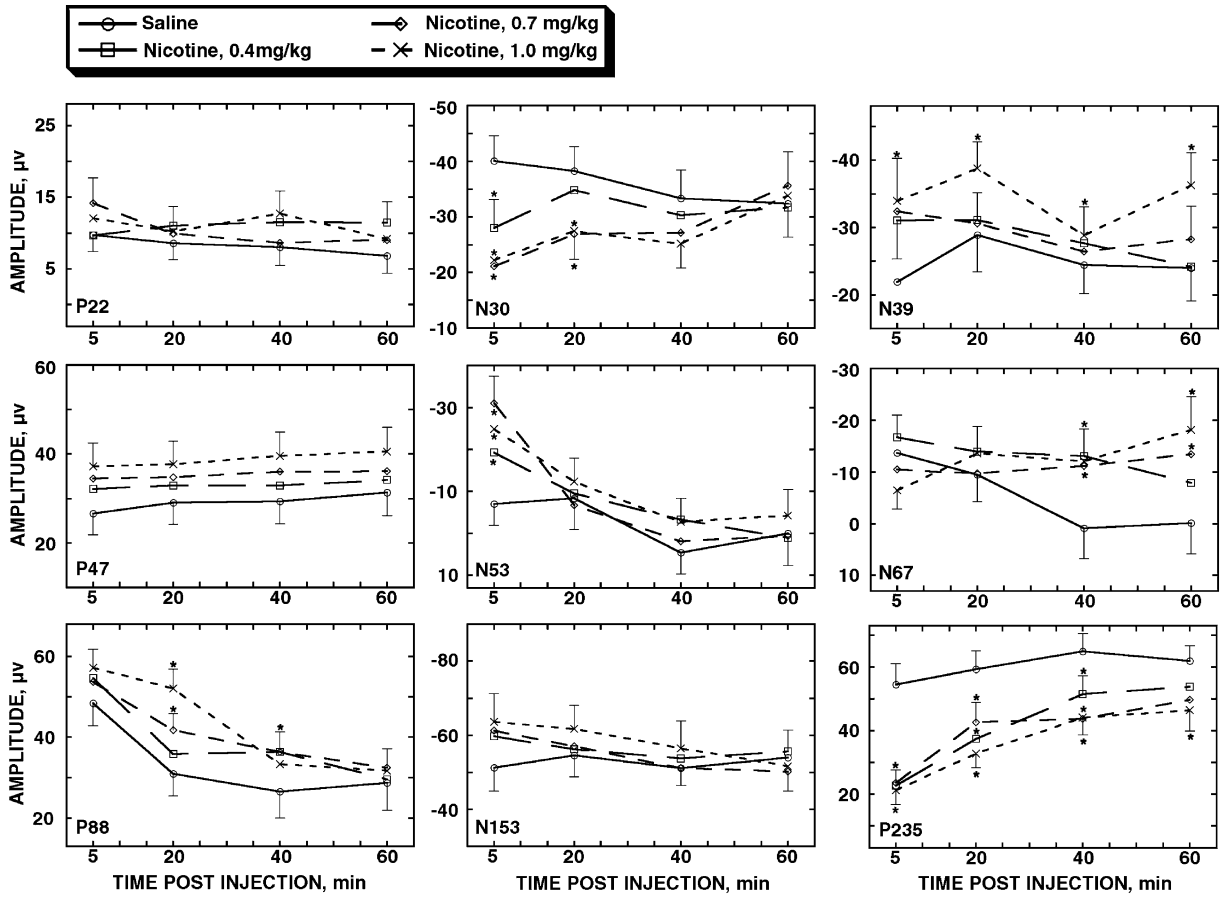

Fig. 3. Peak amplitudes of VC FEP components ($n=19$) as a function of nicotine dosage and time interval. Each panel illustrates the results for one FEP component, named by polarity and latency from the onset of the evoking stimulus. Vertical bars above or below the mean values represent ± 1 S.E.M. * $P<.05$ when compared to the saline value by a two-factor repeated-measures ANOVA followed by Dunnett test comparisons.

kg), 0.4, 0.7, or 1.0 mg of (−)-nicotine tartrate per kilogram of body weight (1 ml/kg). The sequence of injections was counterbalanced. Animals were given 2 days of rest between tests.

Evoked potentials were collected simultaneously from the VC and the SC at 5, 20, 40, and 60 min following injection. In addition, gross body movement was measured by a photocell sensor (H20-93; Coulbourn Instruments, Allentown, PA) that was positioned diagonally in the cage corners 3.5 cm above the floor of the cage. Electronic counters tallied the number of beam interruptions. Immediately after testing, the animal was placed in a restraining tube, and a rectal thermistor probe (YSI No. 402; Yellow Springs Instruments, Yellow Springs, OH) was inserted 10 cm into the rectum. A rectal temperature reading (YSI 49TA Tele-Thermometer; Yellow Springs Instruments) was then taken. Ambient temperature (20.89 °C ± 0.3 S.E.M.) was controlled by a wall thermostat, and was recorded (along with body temperature) at the conclusion of each test.

Following body temperature measurement, each animal was observed for 2 min in a 0.92-m^2 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. On each testing day, the animal was placed in the same middle square of the open field, and allowed to explore for 2 min. Line crossings (movement of all four limbs of the rat across a line) were recorded, and general qualitative observations were made of each animal's behavior. All procedures were approved by the Lawrence University Animal Care and Use Committee.

2.5. FEP component identification

Fig. 1 presents group average FEP waveforms for the 5-min saline condition, recorded from both the VC (upper trace) and the SC (lower trace). Traditional major components identified in early FEP studies (e.g., Creel et al., 1974; Dyer and Annau, 1977; Roig et al., 1961) included only the larger peaks, named by polarity and sequence (large font). However, in the present study, FEP components were designated by their polarity and by their latency from the onset of the light flash (smaller font). This was done because both pilot data for the present study and prior research (e.g.,

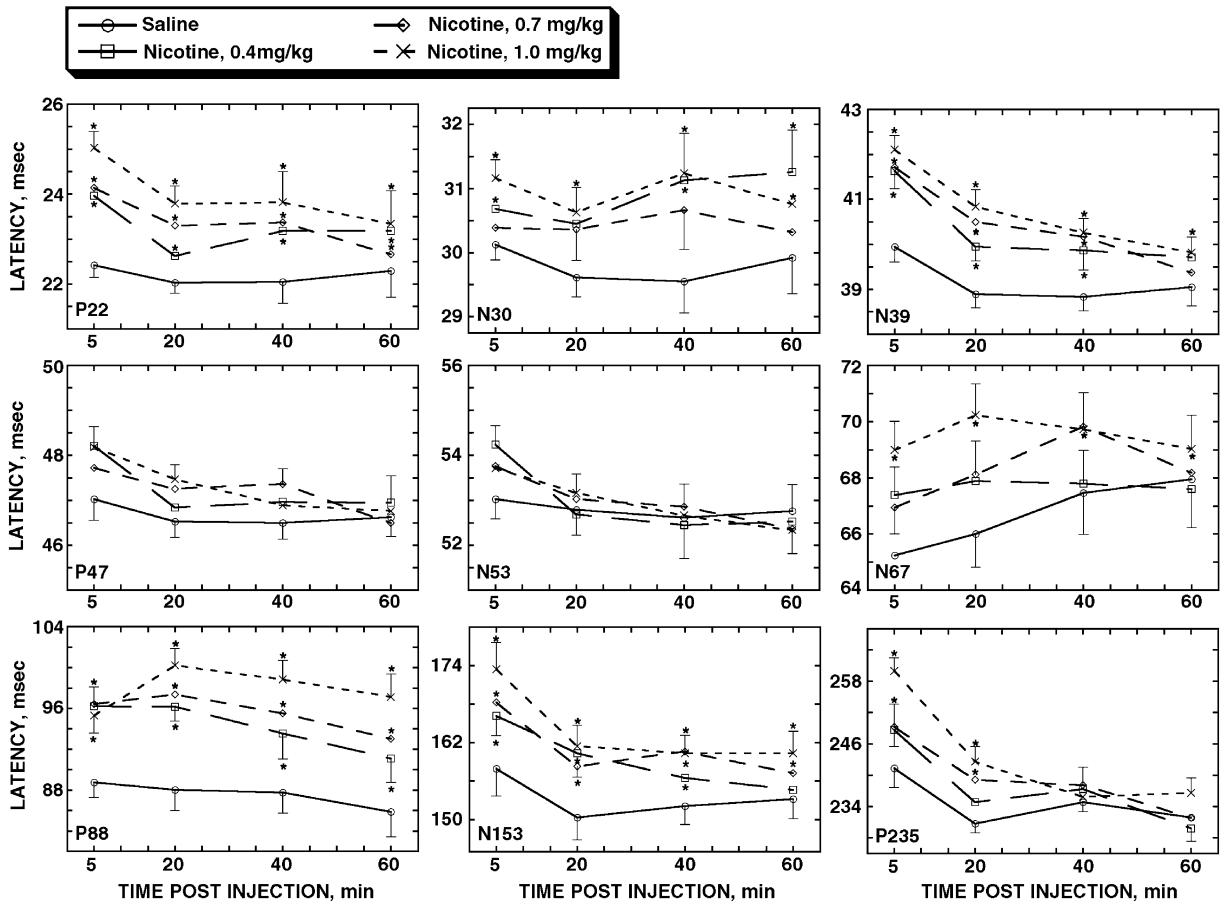

Fig. 4. Peak latencies of VC FEP components ($n = 19$) as a function of nicotine dosage and time interval. Each panel illustrates the results for one FEP component, named by polarity and latency from the onset of the evoking stimulus. Vertical bars above or below the mean values represent ± 1 S.E.M. * $P < .05$ when compared to the saline value by a two-factor repeated-measures ANOVA followed by Dunnett test comparisons.

Brankačk and Klingberg, 1982; Hetzler and Zeisset, 1997) had made clear that the traditional major components often consist of two or more separate components of similar latency.

In the VC, P_{22} corresponds to traditional component P1. While N_{30} corresponds to N1, a second portion (N_{39}) of this component may be prominent in cortical recordings (e.g., Bringmann, 1994; Coenen, 1995). P_{47} is the same as traditional component P2, while N2 has been divided into the two subcomponents, N_{53} and N_{67}. P_{88}, N_{153}, and P_{235} correspond to traditional components P3, N3, and P4, respectively.

In the SC, P_{27} corresponds to the P1 component described by Dyer and Annau (1977), while P_{37} represents the P3 component. N_{48}, N_{53}, and N_{57} collectively constitute the N4 wave.

Baseline-to-peak amplitudes and peak latencies were obtained for nine VC components (P_{22}, N_{30}, N_{39}, P_{47}, N_{53}, N_{67}, P_{88}, N_{153}, and P_{235}). Components P_{27}, P_{37}, N_{48}, N_{53}, and N_{57} were similarly analyzed in the SC waveforms. 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.

2.6. Data analysis

VC, SC, and photocell data were subjected to two-factor (i.e., nicotine dose and time) repeated-measures analyses of variance (ANOVAs). When a significant main effect, or Drug × Time interaction, was found, individual means were compared with the Dunnett test. The saline treatment and 5-min recording interval data served as the basis for comparisons in the Dunnett tests. Body temperature and open-field line crossings data were subjected to repeated-measures ANOVAs in which drug treatment was the repeated factor. A significant main effect was followed by the Dunnett test. In all analyses, statistical significance was assumed when $P<.05$ 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.

3. Results

3.1. VC: amplitude

Group mean evoked potentials are displayed in Fig. 2, where it is apparent that the effects of nicotine varied with the component. In general, nicotine reduced the amplitude of components N_{30} and P_{235}, but increased the amplitude of components N_{39}, N_{53}, N_{67}, and P_{88}. No significant effect of nicotine was observed on components P_{22}, P_{47}, or N_{153}. ANOVA results for the main effect of nicotine for each component were as follows:

P_{22}: $F(3,54)=0.65$, $P=.587$
N_{30}: $F(3,54)=4.53$, $P=.007$
N_{39}: $F(3,54)=3.01$, $P=.038$
P_{47}: $F(3,54)=1.68$, $P=.183$
N_{53}: $F(3,54)=2.62$, $P=.060$
N_{67}: $F(3,54)=3.07$, $P=.035$
P_{88}: $F(3,54)=2.81$, $P=.048$
N_{153}: $F(3,54)=0.87$, $P=.465$
P_{235}: $F(3,54)=24.05$, $P<.001$

Significant Drug × Time interactions were also present for components N_{30}, N_{53}, N_{67}, P_{88}, and P_{235}.

Baseline-to-peak amplitude data are presented for each component in Fig. 3. In comparison to saline, no dose of nicotine significantly altered the amplitude of components P_{22}, P_{47}, or N_{153}, although there was a trend toward increasing amplitude of component P_{47} with increasingly high-nicotine dosage. However, component N_{30} was reduced in amplitude at the 5-min interval by all doses of nicotine, and at the 20-min interval by the 0.7 and 1.0 mg/kg doses. In marked contrast, the subsequent negative component N_{39} was augmented by the 1.0 mg/kg dose of nicotine. N_{53} was briefly enhanced at the 5-min interval by all doses of nicotine, while N_{67} was enhanced by all doses at the 40-min recording interval and by the 0.7 and 1.0 doses at 60 min. P_{88} was augmented at the 20-min interval by the 0.7 and 1.0 doses, and at the 40-min interval by the 0.4 and 0.7 doses of nicotine. Finally, all three doses of nicotine reduced the amplitude of component P_{235} at 5, 20, and 40 min, while both the 0.7 and 1.0 mg/kg doses continued the depression at the 60-min recording interval.

3.2. VC: latency

The VC latency data are displayed in Fig. 4. Nicotine increased the latency of most VC components in comparison with findings for the saline condition, as revealed by the ANOVA test results for the main effects of nicotine:

P_{22}: $F(3,54)=9.02$, $P<.001$
N_{30}: $F(3,54)=4.77$, $P=.005$
N_{39}: $F(3,54)=10.84$, $P<.001$
P_{47}: $F(3,54)=1.28$, $P=.290$
N_{53}: $F(3,54)=0.13$, $P=.942$
N_{67}: $F(3,54)=3.87$, $P=.014$
P_{88}: $F(3,54)=21.83$, $P<.001$
N_{153}: $F(3,54)=11.22$, $P<.001$
P_{235}: $F(3,54)=3.90$, $P=.014$

Drug × Time interactions were significant only for components N_{39} and P_{235}.

As shown in Fig. 4, the 0.4-mg/kg dose of nicotine significantly increased the latency of components P_{22}, N_{30}, N_{39}, P_{88}, and N_{153}, although the increase did not last through

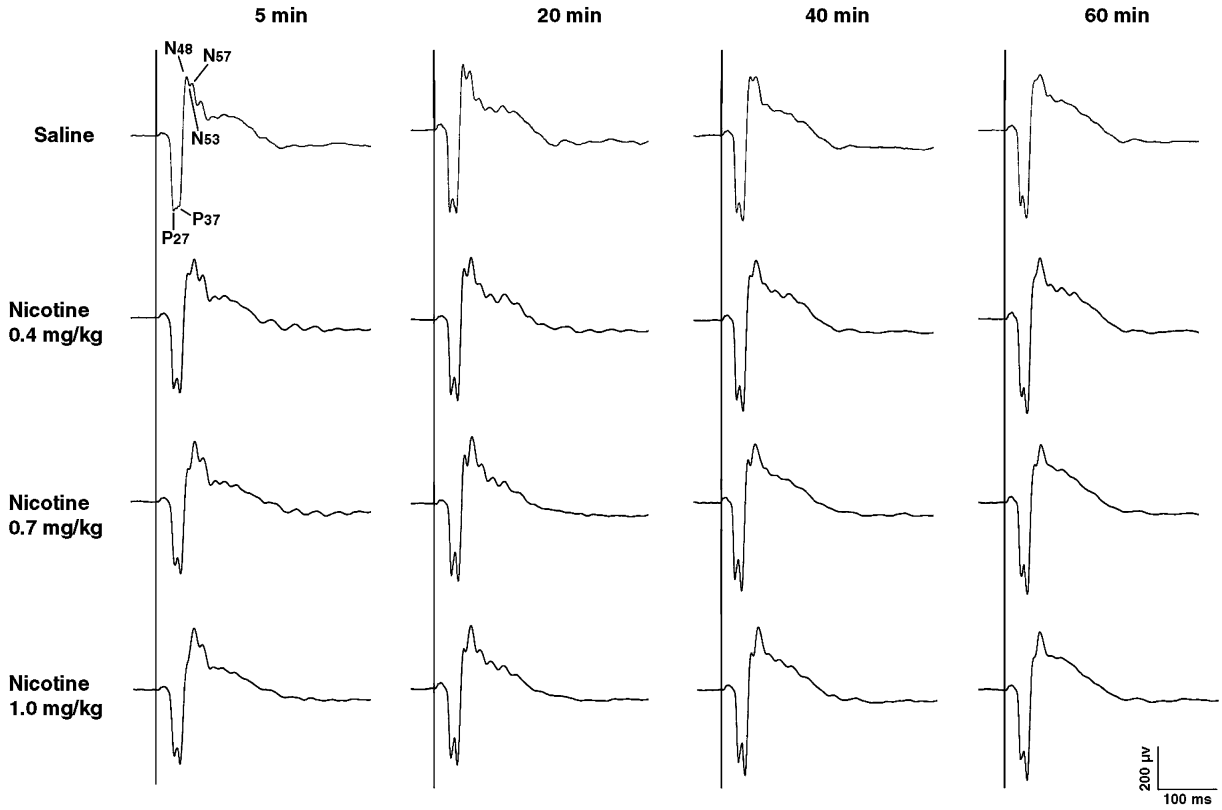

Fig. 5. Group average SC FEP waveforms ($n = 17$) for each dose of nicotine and each time interval. Vertical lines represent onset of the evoking stimulus. Individual FEP components are named by polarity and latency from the onset of the evoking stimulus. The effects of nicotine varied with the component and time interval. In general, the amplitudes of components P_{27}, N_{48}, and N_{53} were decreased by nicotine. Amplitudes of the other components were unchanged.

the 60-min recording interval for component N_{39}. Following administration of the 0.7 mg/kg dose of nicotine, components P_{22}, N_{39}, P_{88}, N_{153}, and P_{235} were all increased in latency. However, the latency for component P_{235} returned to saline values at the 40- and 60-min recording intervals, and the latency for component N_{39} was normal at the 60-min

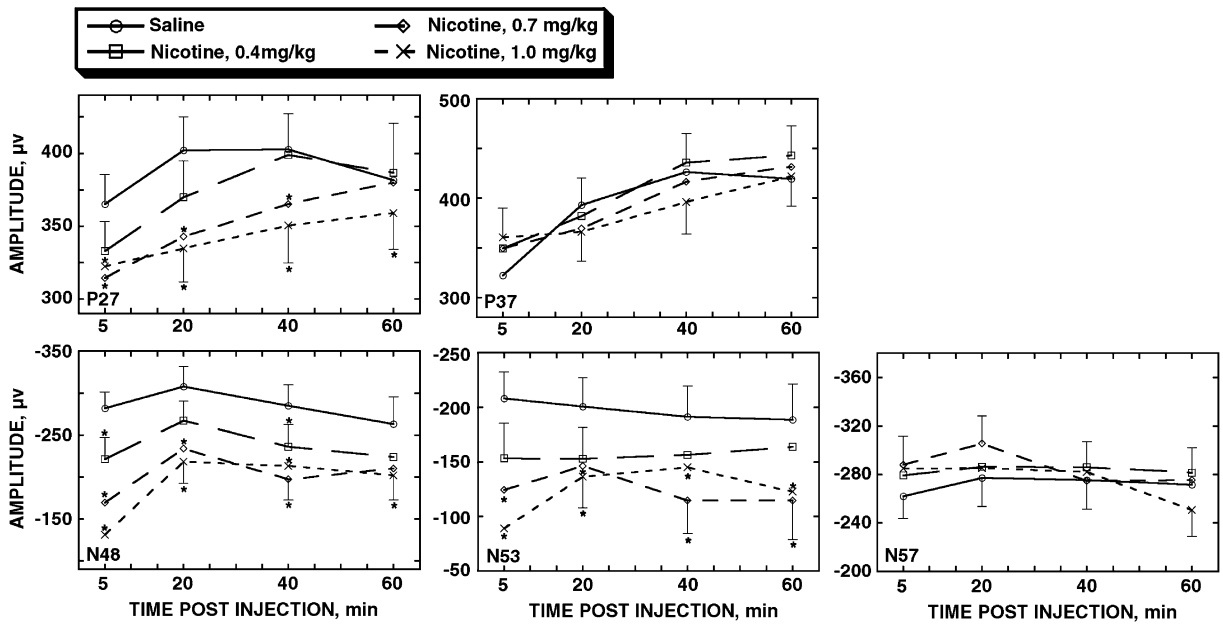

Fig. 6. Peak amplitudes of SC FEP components ($n = 17$) as a function of nicotine dosage and time interval. Each panel illustrates the results for one FEP component, named by polarity and latency from the onset of the evoking stimulus. Vertical bars above or below the mean values represent ± 1 S.E.M. * $P < .05$ when compared to the saline value by a two-factor repeated-measures ANOVA followed by Dunnett test comparisons.

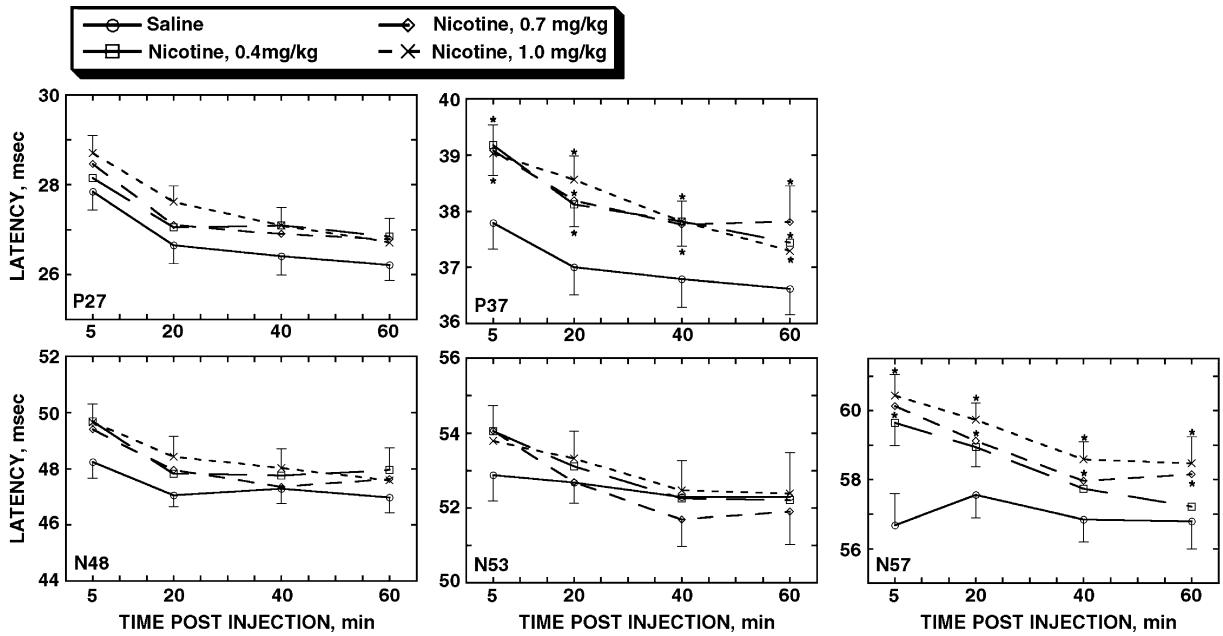

Fig. 7. Peak latencies of SC FEP components ($n = 17$) as a function of nicotine dosage and time interval. Each panel illustrates the results for one FEP component, named by polarity and latency from the onset of the evoking stimulus. Vertical bars above or below the mean values represent ± 1 S.E.M. * $P < .05$ when compared to the saline value by a two-factor repeated-measures ANOVA followed by Dunnett test comparisons.

interval. Finally, the 1.0-mg/kg dose of nicotine produced the most apparent increase in latency, with all components except P_{47} and N_{53} being affected. As was the case with the 0.7-mg/kg dose, for component P_{235}, the augmented latency occurred only at the 5- and 20-min intervals.

3.3. SC: amplitude

Group mean SC evoked potentials are displayed in Fig. 5. The components measured were P_{27} and P_{37} in the early positive complex, and N_{48}, N_{53}, and N_{57} on the subsequent negative portion of the waveform. Baseline-to-peak amplitude data for each of these components are presented in Fig. 6. Nicotine doses of 0.7 and 1.0 mg/kg decreased the amplitude of components P_{27}, N_{48}, and N_{53}:

P_{27}: $F(3,48) = 6.46$, $P = .001$
P_{37}: $F(3,48) = 0.70$, $P = .557$
N_{48}: $F(3,48) = 17.52$, $P < .001$
N_{53}: $F(3,48) = 5.13$, $P = .004$
N_{57}: $F(3,48) = 0.47$, $P = .702$

In addition, the 0.4-mg/kg dose decreased the amplitude of component N_{48} at the 5- and 40-min recording intervals, as reflected in a significant Drug × Time interaction.

3.4. SC: latency

SC latency data are presented in Fig. 7. Both the 0.7- and 1.0-mg/kg doses of nicotine increased the latency of components P_{37} and N_{57}, while the 0.4-mg/kg dose also augmented P_{37} latency and approached significance ($P = .06$) for component N_{57} as well:

P_{27}: $F(3,48) = 1.41$, $P = .253$
P_{37}: $F(3,48) = 3.26$, $P = .029$
N_{48}: $F(3,48) = 1.34$, $P = 2.72$
N_{53}: $F(3,48) = 0.29$, $P = .834$
N_{57}: $F(3,48) = 5.24$, $P = .003$

There were no significant Drug × Time interactions.

3.5. Body temperature

Body temperature data are presented in Fig. 8. Both the 0.7- and 1.0-mg/kg doses of nicotine produced significant hypothermia [$F(3,63) = 5.89$, $P = .001$], with a mean drop of 0.30 °C.

3.6. Body movement

Fig. 9 (left panel) presents the mean number of photocell beam interruptions recorded during 3.5 min of evoked potential recording for each recording session. The 1.0-mg/kg dose of nicotine resulted in significantly more photocell beam interruptions than were observed following saline administration [$F(3,63) = 3.95$, $P = .012$]. The Drug × Time interaction was not significant. The mean number of line crossings during the 2-min observation period following evoked potential testing is shown in the right panel of Fig. 9. Although there was a tendency for nicotine to increase activity, the effect did not reach statistical significance: [$F(3,63) = 2.33$, $P = .083$].

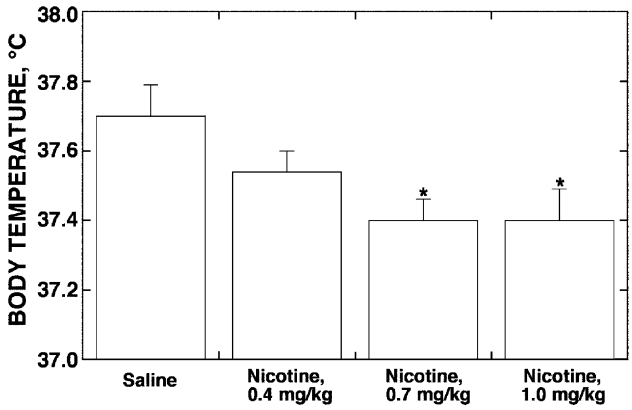

Fig. 8. Body temperature ($n=22$) as a function of nicotine dosage. Body temperature was measured immediately after FEP testing with a rectal thermistor probe. Vertical bars above the mean values represent +1 S.E.M. * $P<.05$ when compared to the saline value by a repeated-measures ANOVA followed by Dunnett test comparisons.

Behavioral observations were also made during this 2-min observational time. Following saline administration, all rats tended to walk around the periphery, and only occasionally walked into the center of the maze. They also spent much of the time in the corners—sniffing, sitting, standing, turning in circles, or just gazing. By the end of 2 min, nearly all of the rats were sitting in a corner. Following nicotine administration, the rats' behavior in the open field differed from the saline control in several ways: First, motion in general seemed to increase (e.g., turning in circles, grooming, sniffing), especially at the 0.7- and 1.0-mg/kg doses. Second, rearing behavior increased, mainly at the 1.0-mg/kg dose. Third, the rats were more likely to venture into the center of the maze in the nicotine trials, although this behavior was not uniformly present. Nonetheless, by the end of 2 min, they were commonly located in a corner.

4. Discussion

The results of the present study made it clear that nAChRs play a differential role in the production/modulation of the various components of both the VC and SC FEP. Because cortically recorded FEPs are generated in the cortex (Herr and Boyes, 1995), and high densities of ^{3}H-nicotine binding have been found in Layers III and IV in the VC (Clarke et al., 1984), the effects of nicotine on VC FEPs could originate within the cortex itself. However, it is possible that the actions of nicotine in other brain areas could be reflected in the cortical recordings (Herr and Boyes, 1995).

Of interest in this regard, Lavine et al. (1997) reported that unilateral excitotoxic lesions in the dLGN of rats produced a partial loss (less than 50%) of ^{3}H-nicotine binding in the ipsilateral VC, mainly in Layer IV, suggesting that some nAChRs are located on thalamocortical terminals in the rat VC. However, other cortical ^{3}H-nicotinic binding sites must therefore be located on other cortical afferents and/or intrinsic cortical neurons. These authors suggest that cholinergic input from the basal forebrain probably plays at most a minor role, because lesions of the basal forebrain produce little or no reduction in ^{3}H-nicotine binding in the cerebral cortex (e.g., Rossner et al., 1995; Wenk and Rökåeus, 1988).

Indeed, it remains to be demonstrated that the basal forebrain cholinergic pathway to the VC (Carey and Rieck, 1987) has any modulatory role on cortical FEPs. Bringmann (1995) recorded VC FEPs from male Long–Evans rats after

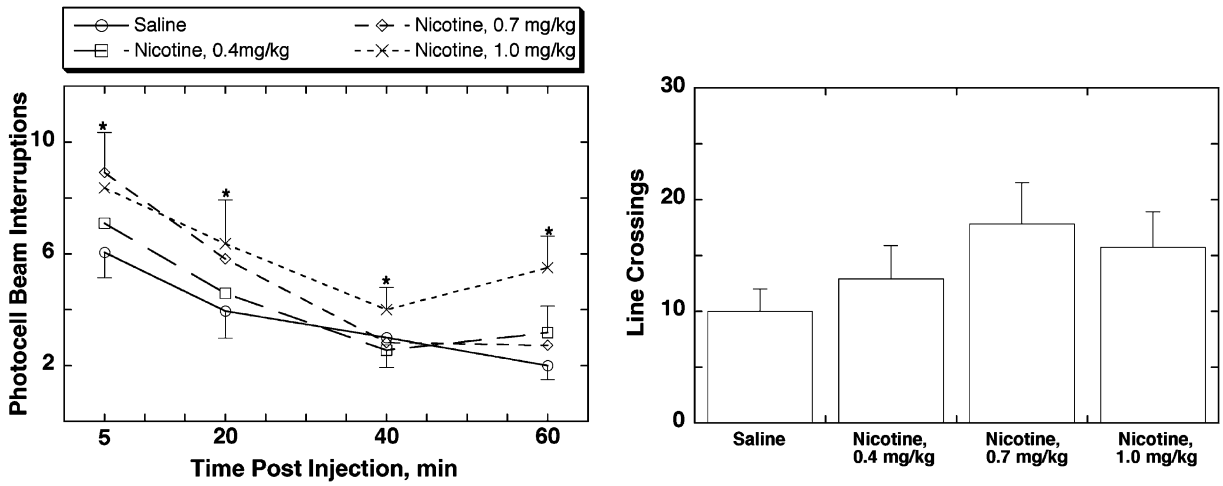

Fig. 9. This figure illustrates the effects of nicotine on body movement. Left panel: Body movement ($n=22$) as measured by photocell beam interruptions during the 3.5-min evoked potential test sessions. Data are presented as a function of nicotine dosage and time interval. Vertical bars above or below the mean values represent ± 1 S.E.M. * $P<.05$ when compared to the saline value by two-factor repeated-measures ANOVA followed by Dunnett test comparisons. Right panel: Mean line crossings ($n=22$) during a 2-min open-field test session which followed evoked potential collection. Data are presented as a function of nicotine dosage. Vertical bars above the mean values represent +1 S.E.M. No significant effects of nicotine were observed in a repeated-measures ANOVA.

unilateral ibotenic acid lesion of the nucleus basalis magnocellularis or the pedunculopontine tegmental nucleus. The nucleus basalis lesion did not alter N_{31} peak latency or the amplitude of any component examined (up to a latency of 200 ms). Although the pedunculopontine tegmental lesion shortened the latency of N_{31} in the lesioned hemisphere, it also did not alter peak amplitudes (up to 200 ms).

Nonetheless, nicotine did produce a series of changes in the VC FEP in the present study. However, interpretation of these nicotine-induced changes is difficult because little is known about the neuronal processes responsible for peak generation. The first component, P_{22}, is typically viewed as the correlate of the presynaptic geniculate volley (Siegel and Sisson, 1993), and is often unaffected by pharmacological manipulations (e.g., Hetzler and Burkard, 1999; Hetzler and Zeisset, 1997), as was the case in the present study.

N_{30} represents a geniculocortical synaptic process produced by excitatory amino acid (EAA) release in Layer IV of the VC (Meeren et al., 1998; Siegel and Sisson, 1993), while N_{39} has not often been studied. Nicotine had differential effects on N_{30} and N_{39}, with N_{30} decreased in amplitude (at only the 5- and 20-min time intervals), while N_{39} was enhanced by nicotine. These results stand in sharp contrast to those previously reported by Bringmann (1994) and Bringmann and Klingberg (1995), in which their N_{31} component amplitude was unaltered by nicotine, while N_{41} amplitude was decreased by nicotine. A variety of factors may have contributed to these discrepancies. First, Bringmann and Bringmann and Klingberg recorded FEPs starting at 15 min postinjection, and then at 30 and 45 min, averaging all of the recordings together. It is quite possible that the delay until 15 min, combined with the averaging of all time intervals, prevented the observation of any effects on their component N_{31}. The discrepancy in the findings for the second negative component is more difficult to explain, but may be related to sex differences in the effects of nicotine (Faraday et al., 2003), because they employed female Long–Evans rats, while we used male rats (Dyer and Swartzwelder, 1978; Shearer et al., 1984). Finally, it is conceivable that pupillary changes were reflected in their results, because nicotine decreases pupil dilation (Furuta and Miyao, 1992), which they did not control for.

P_{47} represents a nongeniculate, non-EAA-mediated inhibitory postsynaptic potential on the pyramidal cells of cortical Layers V and VI (Meeren et al., 1998; Siegel and Sisson, 1993). Although there was a trend toward nicotine-induced enhancement of this component, the results were not statistically significant.

N_{53} and N_{67} were both augmented by nicotine, although at different time intervals. While Siegel and Sisson (1993) feel that these components reflect EAA-mediated intracortical or subcortical (but not direct dLGN) input to the VC, Bringmann (1994) speculates that this broad negative portion of the waveform is cholinergically generated because physostigmine enhanced its amplitude, a finding that we noted in prior research (Hetzler and Smith, 1984). In that early work, we also found that atropine decreased the amplitude of this portion of the waveform, demonstrating a muscarinic involvement. In this regard, although nicotine is a direct agonist for nAChRs, it can produce secondary effects mediated by muscarinic AChRs because nicotine stimulates ACh release (Levin and Simon, 1998). Perhaps, this is the mechanism by which nicotine augments components N_{53} and N_{67}.

Component P_{88} was significantly enhanced by nicotine. This is the last of the so-called secondary components (in addition to P_{47}, N_{53}, and N_{67}), which are thought to result from connections between the SC, brain stem, and diffuse thalamic projections (see Creel et al., 1974). In contrast, nicotine had no effect on the amplitude of component N_{153}. This component reflects secondary (or rebound) activation of cortical pyramidal cells (Meeren et al., 1998), and is generally viewed as the first component of the flash-evoked after-discharge (Bigler, 1977; Creel et al., 1974; Rhodes and Fleming, 1970). Of particular interest in the present context are the findings that nicotine suppressed the amplitude of the succeeding component P_{235}, while having no effect on N_{153}. This suggests that these two components are more independent than has heretofore thought to be the case.

An increase in amplitude of component P3 (i.e., P_{88}), along with no effect on N3 (N_{153}) and a reduction in P4 (P_{235}) can also be seen in VC FEPs reported in a prior study from this laboratory examining the effects of the $GABA_A$ agonist THIP (Hetzler and Zeisset, 1997). The effects of nicotine noted in the present study on these components may therefore relate to secondary effects of nicotine on GABA release (Lena and Changeux, 1997). This is especially likely because the after-discharge (beginning with components N_{153} and P_{235}) is produced by a thalamic recurrent inhibitory system involving both the dLGN and the thalamic reticular nucleus (see review by Bigler, 1977), and nAChRs are located on the somatodendritic area of dLGN relay neurons, on GABAergic terminals which make contact with the relay neurons, and on cells in the thalamic reticular nucleus (Lena and Changeux, 1997).

In the SC, components P_{27} and P_{37} are part of the early positive complex, and they were differentially affected by nicotine. Thus, P_{27} was reduced in amplitude by both the 0.7- and 1.0-mg/kg doses, while P_{37} was unaffected. A selective reduction of P_{27} was somewhat surprising, because P_{37} has been more labile in past pharmacological studies (e.g., Hetzler and Bednarek, 2001; Hetzler and Burkard, 1999).

Both N_{48} and N_{53} were reduced in amplitude by nicotine, with N_{48} being the most sensitive, because even the 0.4-mg/kg dose produced a significant effect on this component. In contrast, N_{57} was unaffected by nicotine administration. The differential effects of nicotine on these portions of the traditional N4 component support the proposal made elsewhere (Arakawa et al., 1993; Brankačk and Klingberg, 1982) that traditional evoked potential peaks are often

composed of several distinct subpeaks which may overlap temporally, but which can be separated experimentally (e.g., by pharmacological manipulations).

Components of the SC FEP show a polarity reversal in the stratum griseum superficiale (Dyer and Annau, 1977). The main cholinergic input to the superficial visual layers of the SC originates in the contralateral parabigeminal nucleus, which, in turn, receives visual input from the ipsilateral SC (Binns, 1999; Sefton and Martin, 1984). Acetylcholine released in the SC from this pathway appears to act on nicotinic receptors which modulate the release of GABA from inhibitory neurons. This is done via an apparent combination of nicotinic receptors located presynaptically on retinal axon terminals (which increase the release of glutamate onto the inhibitory neurons) and receptors located postsynaptically on the inhibitory neurons (which directly increase the release of GABA; Binns, 1999). This explains why the visual responses of neurons located in the stratum griseum superficiale of rats are inhibited by iontophoretic administration of lobeline (a nicotinic agonist) and augmented by hexamethonium (a nicotinic antagonist; Binns, 1999).

With respect to GABA involvement in the results of the present study, a high dose of THIP reduced the amplitudes of components N4a (N_{48}) and N4b (N_{53}) without altering N4c (N_{57}; Hetzler and Zeisset, 1997), a pattern similar to that observed here. However, in contrast to the findings in the present study, THIP enhanced the amplitude of P1 (P_{27}) and reduced P3 (P_{37}) amplitude. Secondary GABA release may therefore underlie some, but not all, of the SC amplitude effects observed in the present study.

Many FEP peak latencies in the VC and SC were increased by nicotine, often at all three doses. Those few past animal studies which have examined the effects of nicotine on FEPs have not reported changes in peak latencies (Bringmann, 1994; Bringmann and Klingberg, 1995; Sabelli and Giardini, 1972). Human studies often failed to measure FEP latencies. When measured, FEP component latencies have typically been unaltered by smoking (Golding, 1988; Hall et al., 1973; Woodson et al., 1982).

It is surprising that past animal studies have not reported augmented latencies, given the dose-dependent hypothermia induced by nicotine (de Fiebre et al., 1991; Rezvani and Levin, 2002). For example, de Fiebre et al. (1991) reported that a 0.8-mg/kg dose of nicotine produced a 1.5 °C drop in body temperature 15 min after injection. We also found significant hypothermia when body temperature was measured approximately 65 min after administration of both the 0.7- and 1.0-mg/kg nicotine doses. The relationship between reduced body temperature and increased FEP peak latency (but not peak amplitude) is clear (Hetzler et al., 1988), and would be expected to influence the results of any nicotine study involving rats.

In our study, the 1.0-mg/kg dose of nicotine resulted in a significant increase in photocell beam interruptions during the recording sessions. Photo beam interruptions detected any movement that broke the beam, such as general ambulation. However, the equipment was not able to discriminate between various types of movements. Following electrophysiological testing, there was a tendency for nicotine to increase the mean number of line crossings in an open field, but the effect did not reach statistical significance.

Enhancement of locomotion following nicotine administration is felt to occur because nicotine stimulates dopaminergic transmission (O'Neill et al., 1991). However, effects of nicotine on locomotor behavior in rats are complex, with many variables involved (see Jerome and Sanberg, 1987). Thus, in regard to ambulation, increases (Benwell and Balfour, 1992; Pradhan, 1970), decreases (Erickson, 1971), and no overall effect (Paulus and Geyer, 1991) have all been reported, as well as biphasic effects (Clarke and Kumar, 1983; Gasior et al., 2000), and increases in some aspects of ambulation (number of movements) but not others (horizontal activity; Jerome and Sanberg, 1987). It is clear that more work will be required to understand the significance of any observed changes in rodent behavior following nicotine administration.

In conclusion, the present study demonstrates the unique sensitivity of individual components of the VC and SC FEPs to the effects of nicotine administration. However, nAChRs in the CNS modulate the release of a variety of neurotransmitters, including acetylcholine, dopamine, norepinephrine, serotonin, glutamate, and GABA (Levin and Simon, 1998; McGehee et al., 1995; Role and Berg, 1996; Zhu and Chiappinelli, 1999). Thus, nicotine can simultaneously affect the activity of many types of neurons (USDHHS, 1988), making it difficult to localize the origin of the effects reported here.

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