Pharmacology Biochemistry and Behavior, Vol. 58, No. 3, pp. 713–720, 1997

0091-3057/97 $17.00 + .00

ELSEVIER

PII S0091-3057(97)00011-7

Effects of Neonatal Exposure to Nicotine on Electrophysiological Parameters in Adult Rats

CINDY L. EHLERS,*[1] CHRISTINE SOMES,* JENNIFER THOMAS*† AND EDWARD P. RILEY†

*Department of Neuropharmacology, CVN-14, The Scripps Research Institute, La Jolla, California 92037
†Department of Psychology, San Diego State University, San Diego, CA 92182-0350

Received 4 August 1996; Revised 17 December 1996; Accepted 24 January 1997

EHLERS, C. L., C. SOMES, J. THOMAS AND E. P. RILEY. *Effects of neonatal exposure to nicotine on electrophysiological parameters in adult rats.* PHARMACOL BIOCHEM BEHAV **58**(3) 713–720, 1997.—In clinical studies and animal models, there is evidence that nicotine exposure during gestation can result in deficits in cognitive performance. The present study examined the effects of two doses of neonatal nicotine exposure on adult brain activity as assessed by the N1 and P3 components of the event-related potential (ERP) and background electroencephalography (EEG). Nicotine (0 mg, 1 mg/kg/day, 4 mg/kg/day) was administered to neonatal rat pups from postnatal day 4 (PN4) through PN12 with an artificial rearing paradigm; suckled rats served as additional control subjects. Nicotine exposure was specifically found to alter responses of the P3 component of the ERP, recorded in dorsal hippocampus, to changes in stimulus parameters. A significant reduction in the response of the P3A component to the noise tone as compared with the level of the frequently presented tone was found. A significant reduction in the response to the noise tone as compared with the level of the infrequently presented tone also was seen in the P3B component. No effects of drug exposure were found on the N1 component in any lead, although artificial rearing produced specific effects on the latency of the N1 component in cortex. No significant differences among treatment groups were found on any of the EEG-dependent variables. Female rats overall were found to have significantly higher EEG amplitudes than the males, a finding previously reported in our laboratory. However, no overall effects of gender were found on any ERP component. These studies suggest that neonatal nicotine exposure specifically reduces the electrophysiological response of the hippocampus to changes in auditory stimuli. Additional studies will be necessary to link these P3 amplitude changes to the effects of nicotine on the developing brain in human and animal subjects. © 1997 Elsevier Science Inc.

Artificial rearing EEG Event-related potential P3 Pup-in-the-cup Nicotine Neonatal drug exposure

FROM the turn of the century, there have been reports that exposure to tobacco and cigarette smoke might be detrimental to fetal development [see (20)]. Since that time, numerous epidemiological studies have been conducted [see reviews in (32,35,41,58)], and there appears to be a consensus on many of the effects of prenatal nicotine exposure, although the interpretation of these data as to causality is still controversial. In general, most studies have reported that smoking during pregnancy results in intrauterine growth retardation, an increased frequency of spontaneous abortion, an increased incidence of still births and neonatal deaths and infants of smaller size and birth weight.

More recently, there has been a specific focus on identifying possible effects of smoking on the developing brain. Although congenital anomalies can only be demonstrated in very large population samples (40), more subtle effects of maternal smoking on brain function have been demonstrated in smaller clinical studies (53). Maternal smoking may increase the incidence of hyperkinesis (7) and minimal cerebral dysfunction (12). However, other well-controlled studies have failed to detect any significant difference in intellectual functioning in offspring of maternal smokers vs. offspring of maternal nonsmokers (22).

Although these studies in humans suggest that maternal smoking may have adverse developmental effects on the central nervous system in some populations, it is difficult to control for a myriad of potential causal factors in human studies. However, many of the characteristics associated with fetal tobacco exposure in humans, such as reduced birth weight and perinatal mortality, also occurs in animal models [see (3,4,31, 45,56,57,59)]. For instance, prenatal nicotine or tobacco exposure in rodents produces increased spontaneous motor activity (45,47); poor performance on fixed-ratio, variable interval discrimination and discrimination reversal (36); an accelerated rate of the acquisition of avoidance (5); impairments of performance in the radial-arm maze (61); and reduced sponta-

[1]To whom requests for reprints should be addressed.

neous alternation, neophobia and deficiencies on brightness discrimination (27) and swimming development (44).

Brain impairment produced by prenatal nicotine exposure also may have a regional selectivity that reflects the timetable of cellular development of specific brain regions. For instance, in one study, the most profound effects were seen in late-developing brain regions, and intermediate effects were found in earlier developing areas (59). Unfortunately, few studies have focused on nicotine exposure during the early neonatal period in the rat, the time period equivalent to the third trimester of pregnancy in humans [see (8,9)].

The present study utilized electrophysiological techniques [electroencephalography (EEG) and event-related potentials (ERPs)] to assess brain function in adult rats exposed to nicotine during the early neonatal period. We previously demonstrated that ERP paradigms are particularly sensitive to the effects of perinatal drug exposure in both humans and animal models [see (28,29)]. However, to date few investigators have obtained electrophysiological recordings in either humans or animals exposed to nicotine perinatally.

MATERIAL AND METHODS

Subjects

Ninety-nine male and female Sprague–Dawley rats served as subjects for electrophysiological experiments. These animals had either been artificially reared from postnatal day 4 (PN4) through PN12 or suckled normally. The rats were approximately 175 days old (range = 164–213 days) at the time of electrode implantation and weighed 450–630 g. Rats were housed in pairs in a temperature-controlled room and maintained on a 12-h light–dark cycle with lights on at 0600 and lights off at 1800. Unlimited food and water were available throughout the entire study.

Mating Procedures

The general procedure for artificial rearing has been described in detail elsewhere (21,37,38,39). Briefly, parent animals were Sprague–Dawley rats obtained from Charles River, Inc. Upon arrival, females were group housed and maintained on a 12-h light–dark cycle in a humidity- and temperature-controlled colony room. Following a 1-week acclimation period, female rats (approximately 240 g) were individually placed with males for mating in the late afternoon and were examined the next morning for the presence of a seminal plug, an indication that copulation had occurred. Pregnant females were then individually housed in a temperature- (70°C) and humidity- (40–60%) controlled room maintained exclusively as a nursery.

Perinatal Treatments

Twenty-four hours after the Sprague–Dawley females gave birth, the litters were weighed, examined for any obvious physical anomalies and culled to the five largest intact males and the five largest intact females. On PN4, pups were randomly assigned to one of four groups: artificially reared (0 nicotine), nicotine 1 mg/kg/day, nicotine 4 mg/kg/day and the suckle control group. For nicotine exposure, nicotine hydrogen-tartrate (Sigma) was dissolved in distilled water and added to the milk diet. Pups were exposed to nicotine for four consecutive feedings each day from PN4 to PN9. An equal volume of distilled water was added to the diet of the 0-mg-nicotine controls.

To accomplish the artificial rearing, anesthetized pups (50% halothane and 50% oxygen) were surgically implanted with a miniature intragastric feeding tube. This procedure has been described in detail elsewhere (1,2,38,39). Following gastrostomy, each artificially reared pup was housed individually with a small piece of artificial fur in a plastic cup filled with wood chips and covered with a perforated plastic lid. This cup was then placed in a ballasted cup floating in a tank filled with heated, aerated water (38°C). Intragastric feeding tubes were connected to syringes containing special rat milk formula [see (39)]. The feeding syringes were housed in infusion pumps controlled by a programmable timer to infuse the formula for 20 min every 2 h. Thus, artificially reared animals received liquid diet during 12 feeding periods every day. The volume of diet infused per day was calculated to be 33% of the animal's mean body weight. This regimen has been used in several other studies (2,65). The syringes and feeding tubes were cleaned daily while each animal had its anal/genital region lightly stroked with a cotton swab to stimulate urination and defecation twice a day. Gastrostomized animals were maintained under these conditions from PN4 to PN11 (or gestational days 26 to 34).

Following the artificial rearing period, the pups were bathed in a slurry of feces and water before being placed with surrogate dams. This procedure virtually eliminated rejection by the dam, and the pups were seen to nurse soon after their return to the dam. Animals assigned to the suckle control group underwent a sham gastrostomy procedure (also on PN4) in which the pups were anesthetized and a feeding tube was passed down the esophagus and then withdrawn. Following the sham operation, the pups were also placed with surrogate dams. All rats were weaned at PN21 and housed in pairs. Thirty-one suckle controls (17 males, 14 females), 23 artificially reared rats (14 males, 9 females), 22 1 mg/kg/day rats (12 males, 10 females), and 23 4 mg/kg/day animals (16 males, 7 females) were used in this study.

Surgical Procedures for Electrophysiological Recordings

Two to three weeks prior to the electrophysiological recordings, the rats were surgically implanted with recording electrodes. Screw electrodes were placed in the calvarium overlying the right frontal and left frontal cortex. A grounded "reference" screw electrode also was placed in the thick bony area of the calvarium 3 mm posterior to lambda, which lies parallel to the cerebellum. Rats were anesthetized (Nembutal, 50 mg/kg interperitoneally) and placed in a stereotaxic apparatus with the toothbar set at +5.0, and stainless steel bipolar electrodes were aimed at the dorsal hippocampus (AP −3.0, ML ±3.0, DV −3.0) and amygdala (AP −1.0, ML ±5.3., DV −8.5 (46). In all animals, electrode connections were made to a multipin (Amphenol) connector, and the entire assembly was anchored to the skull with dental acrylic.

Electrophysiological Measures

All recordings were obtained at least 2 weeks after surgery to allow for recovery. These data were collected from 0900 to 1400 in their own housing cage, which was placed in an electrically shielded light-, sound- and temperature-controlled BRS/LVE recording chamber. Female rats were run only during diestrous as verified by vaginal smears. Prior to the test day, each rat was habituated to the cable connection and chamber for 0.5 h on 2 nonconsecutive days and again for 1 h immediately prior to recording on the test day. At both habituation and recording periods, neither food nor water was available.

For recordings, pairs of cagemates were hooked to separate recording cables in their home cage such that they were able to move freely but not interact with each other. This procedure was used to maintain the recording environment as similar as possible to the housing environment to obtain a representative recording of the EEG.

EEG. On test days, rats in their housing cage were placed in the recording chamber, and a connector attached to a microdot cable was used to transfer the monopolar (referred to the lambda ground screw) EEG signals to a polygraph. Forty minutes of EEG were obtained from the frontal cortex and dorsal hippocampus. EEG signals were recorded on a Grass polygraph, amplified with a bandpass of 1–75 Hz and then transferred to a Vetter Model D recorder for off-line analysis. For quantification of the EEG, the 40 min of EEG were digitized (128 Hz). The power spectra of continuous 4-s epochs were determined for a 1–50-Hz range. The Fourier-transformed data were then further compressed into 8 frequency bands (1–2, 2–4, 4–6, 6–8, 8–16, 16–32, 32–64, 1–64 Hz). Mean power density was calculated for each band.

ERPs. ERPs were recorded immediately following the EEG recording. Free field auditory stimuli were presented through a small speaker centered approximately 20 cm above the rat's head. EEG signals were recorded on a Grass polygraph, amplified with a bandpass of 0.3–35 Hz and then transferred to a Macintosh computer. ERPs were elicited by an acoustic oddball paradigm. The tones utilized were generated by a programmable multiple-tone generator, the characteristics of which have been described previously (51). The acoustic parameters were three tones (rise and fall times < 1 ms): a frequently presented tone (20 ms, 1 kHz, 70 dB SPL) presented on 84% of the trials, a rare tone (20 ms, 2 kHz, 85 dB SPL) presented on 10% of the trials and a noise tone presented on 6% of the trials (20 ms, noise, 100 dB SPL). Rare tones were interspersed with standards so that no two rare tones occurred successively. The noise tone occurred every 16th trial. The digitizing epoch for each trial was 1 s, and a variable 0.5–1-s intertrial interval was used to reduce habituation. There was a total of 312 trials in a recording session.

ERP trials were digitized at a rate of 256 Hz and analyzed. The ERP components were quantified by computer by identifying a peak amplitude (baseline to peak) within a standard latency range. The baseline was determined by averaging the 100 ms of prestimulus activity obtained for each trial. Latencies and amplitudes were calculated for each of the ERP components of each brain site recorded. The latency from a component was defined as the time of occurrence of the peak amplitude after the stimulus within a latency window. The latency windows were: frontal cortex, N1: 50–1502; dorsal hippocampus, N1: 25–75, P3A, 220–285, P3B, 290–400; amygdala, N1, 50–100, P3A, 220–290; P3B, 290–400. Components were initially identified by visual inspection of the data and then standardized to allow for computer-automated peak determinations. Components were labeled solely by their polarities and latency positions relative to each other. Trials containing excessive movement artifact were eliminated ($<$10% of the trials) prior to averaging. To eliminate individual trials in which the EEG exceeded $\pm$250 V, an artifact-rejection program was utilized. These ERP analyses have been described previously (14–16,18).

An analysis of variance (ANOVA), with gender and perinatal treatment (artificial rearing vs. suckle controls and 1 vs. 4 mg/kg/day nicotine) as the between-subjects variables were used to evaluate body weight, EEG mean power and ERP latency. Amplitudes of the ERP components were evaluated by ANOVA by comparing the amplitude differences obtained between the three tones. Tukey HSD post hoc analyses were used to identify group differences.

RESULTS

Body Weight Gain

All groups gained weight over the study period. A repeated measures ANOVA with group and sex as between-subject variables and day as the repeated measure was conducted on the data from animals that completed the artificial rearing period. A significant group $\times$ day interaction [$F(21, 910) = 31.1$, $p < 0.001$] and a main effect of group [$F(3, 130) = 6.5$, $p < 0.001$] and day [$F(7, 910) = 2350$, $p < 0.001$] were found. In addition, males were significantly heavier than females, producing a main effect of sex [$F(1, 130) = 4.9$, $p < 0.001$]. No group differences were found until PN8, when all the artificially reared groups (0 mg, 1 mg/kg/day, 4 mg/kg/day) began to lag in growth as compared with the suckled control rats (Tukey HSD, $p < 0.05$). However, no significant differences in body weight were found between the artificially reared groups. Evaluation of the body weights at the time of implant surgery and the electrophysiology experiments revealed that, although the males were still heavier than the females, there was no significant main effect for group throughout the entire period of the adult study across the artificially reared and suckle control animals and any of the nicotine treatments (Fig. 1).

ERP Findings

The presentation of auditory stimuli in the form of infrequently and frequently presented tones produced a series of waves that could be averaged from the EEG. In response to the tones, the anterior cortex displayed a negative wave (N1) that had a mean latency of 70–90 ms. A negative wave with a mean latency of 50–70 ms in the dorsal hippocampus and a negative wave at 60–90 ms in amygdala also were present. Both dorsal hippocampus and amygdala also showed a late positive component complex with two peaks designated as P3A (220–290 ms) and P3B (290–390 ms). The ERP components recorded in this study were substantially similar to those reported previously [see (18)].

No overall effects of gender were found on any ERP component. Artificial rearing produced specific effects on the latency of the N1 component in cortex. Artificially reared (AR) rats had significantly longer N1 latencies in cortex [sham = 74.21 $\pm$ 1.62 ms, AR = 85.93 $\pm$ 3.25 ms; ANOVA, $F(3, 98) = 3.86$, $p < 0.01$; Tukey HSD, $p < 0.01$] in response to the infrequently presented tone and shorter N1 latencies in Dorsal Hippocampus (DHPC) to the frequently presented tone [sham = 50.9 $\pm$ 2.18, AR = 41.27 $\pm$ 2.15; ANOVA, $F(3, 95) = 4.123$, $p < 0.009$; Tukey HSD, $p < 0.01$]. No effects of drug exposure were found on the N1 component in any lead.

Nicotine exposure more specifically altered responses of the P3 component, recorded in DHPC, to changes in stimulus parameters (Fig. 2). Because no effect of rearing condition was found for P3, post hoc analyses were collapsed over rearing condition. A significant reduction in the response of the P3A component to the noise tone as compared with the level of the frequently presented tone was seen in nicotine-exposed rats (Fig. 3) [ANOVA, $F(3, 95) = 4.6$, $p < 0.01$; Tukey HSD, control vs. 4 mg nicotine $p < 0.009$]. A trend toward significance was found in the response of the P3A component difference between the infrequently presented tone and the

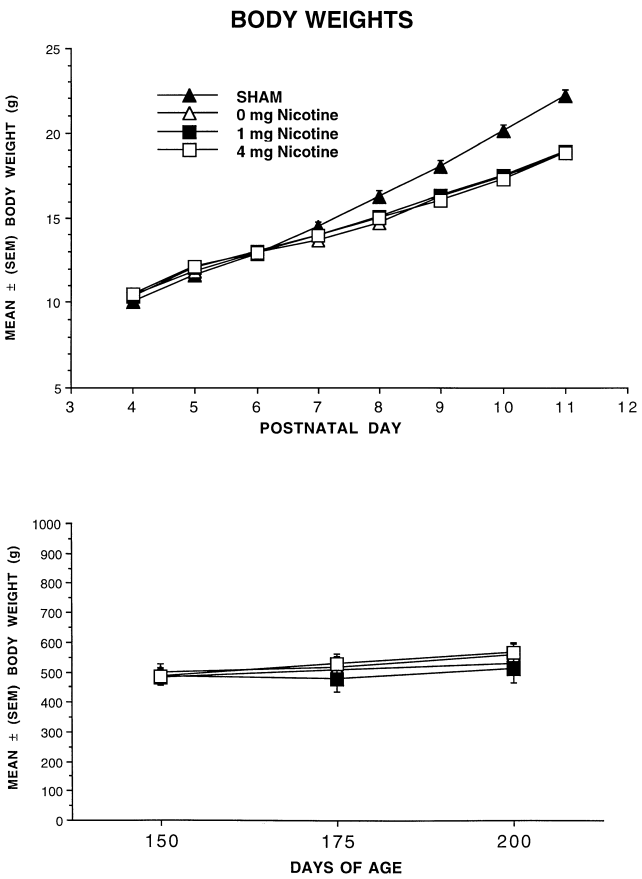

FIG. 1. Effects of rearing condition [suckled control vs. artificially reared (0 mg nicotine)] and nicotine exposure (1 vs. 4 mg/kg/day) on the body weights of the animals over the time of perinatal exposure and as adults. Suckled control rats had significant differences in body weight from the artificially reared rats (0 mg, 1 mg/kg/day, 4 mg/kg/day) from PN8 to PN11; no differences were found between artificially reared groups (Tukey HSD, $p < 0.05$). No significant differences in body weight were found across groups in the adult animals.

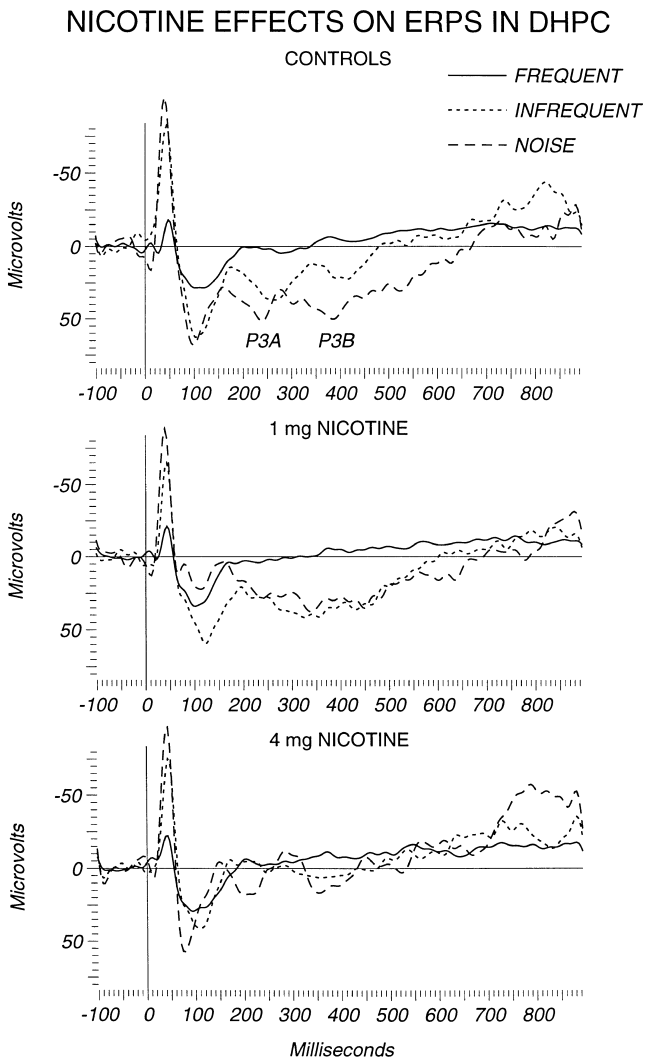

FIG. 2. Effects of nicotine exposure on grouped ERP responses (grand averages) to changes in stimulus parameters in control animals (top) and those that ingested 1 (middle) or 4 (bottom) mg/kg/day nicotine. Location of the P3A and P3B components are indicated.

noise tone [ANOVA, $F(3, 95) = 2.2$, $p < 0.09$; Tukey HSD, control vs. 4 mg nicotine $p < 0.1$; control vs. 1 mg nicotine $p < 0.2$]. A reduction in response to the P3B component in DHPC in response to nicotine exposure also was seen (Fig. 3). A significant reduction in the response of the noise tone as compared with the level of the infrequently presented tone was seen [ANOVA, $F(3, 95) = 3.1$, $p < 0.05$; Tukey HSD, control vs. 1 mg nicotine $p < 0.05$].

EEG Findings

Female rats overall were found to have higher EEG amplitudes than the males and significantly higher amplitudes in the DHPC [1–64 Hz; males = 2706 ± 321 μV^2/octave, females = 4230 ± 498 μV^2/octave; $F(1, 99) = 7.23$, $p < 0.008$], a finding previously reported in our laboratory (17). However, there were no significant differences found between treatment groups on any EEG-dependent variable (i.e., mean power density for any of the frequency bands) evaluated in any recording site (Fig. 4).

DISCUSSION

The ERPs have been utilized to assess neuronal circuitry, sensory integrity and information processing (33,34,50). The recording of ERPs represents a potentially valuable assessment tool for evaluating the consequences of perinatal experience on brain and behavior. Studies in rats have demonstrated that several ERP components can be identified that resemble those observed in human subjects using passive auditory stimulus paradigms (15,16,18,19,66). Studies evaluating the response of P3 to differences in stimuli have suggested that at least two "types" or components of the P3 can be recorded from the cortical surface. P3s that are generated by stimuli that are task relevant and correctly detected by the subject appear to be of maximal voltage over parietal cortex and have been designated the "target P3" or P3b, whereas nontarget stimuli that are "unexpected" or "novel" but re-

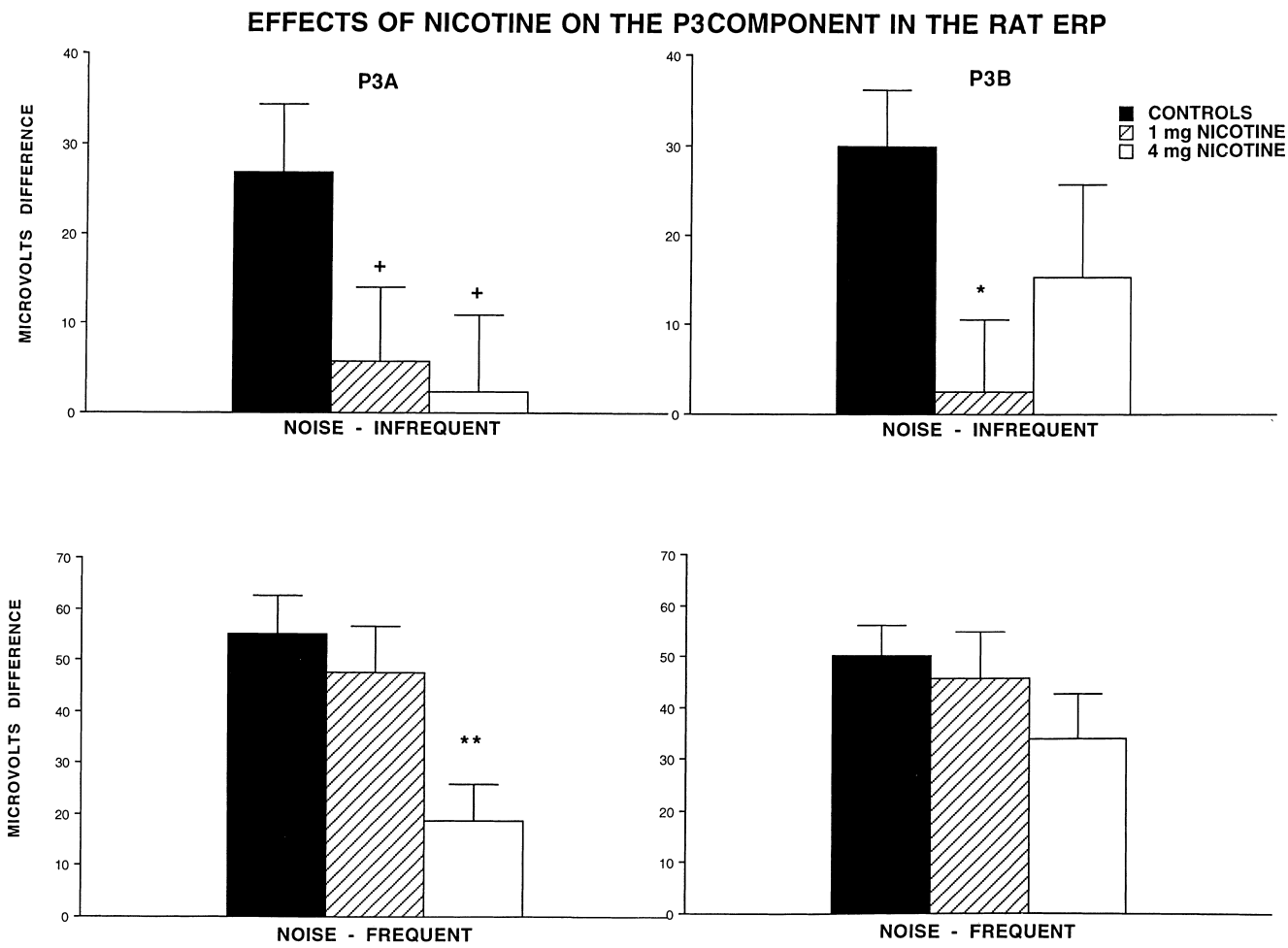

FIG. 3. Effects of nicotine exposure (1 vs. 4 mg/kg/day) on response of the P3A and P3B components to differences in stimulus parameters (e.g., noise tone vs. infrequently presented tone and noise tone vs. frequently presented tone). *A significant reduction in the response of the P3A component to the noise tone as compared with the level of the frequently presented tone was seen in nicotine-exposed rats [ANOVA, $F(3, 95) = 4.6$, $p < 0.01$; Tukey HSD, control vs. 4 mg nicotine $p < 0.009$]. +A trend toward significance was found in the response of the P3A component difference between the infrequently presented tone and the noise tone [ANOVA, $F(3, 95) = 2.2$, $p < 0.09$; Tukey HSD, control vs. 4 mg nicotine $p < 0.1$, control vs. 1 mg nicotine $p < 0.2$]. *A significant reduction in the response of the noise tone as compared with the level of the infrequently presented tone was seen in the P3B component [ANOVA, $F(3, 95) = 3.1$, $p < 0.05$; Tukey HSD, control vs. 1 mg nicotine $p < 0.05$].

quire no behavioral response appear to generate an earlier latency potential that may be more frontocentral in origin, designated the "novelty P3" or P3a [see (48,50)].

Nicotine exposure during the neonatal period specifically affected the P3 component of the ERP in the dorsal hippocampus of adult rats. Significant reductions in overall response of the rat P3A and P3B components to changes in stimulus parameters were noted in nicotine-exposed rats, although the reduction was not necessarily dose related. In humans, the P3 component may reflect stimulus evaluation and memory function [see (10,64)]. Stimulus probability also alters ERP components in humans (48,49,54) and rats (16,18). For instance, a decrease in the probability of a stimulus increases P3 amplitude (11,63). In the present study, the noise burst stimuli are presented less frequently and are louder than the infrequent tone or frequently presented tone. We hypothesized that ERP components in response to the noise burst would have higher amplitudes than those in response to the infrequent or frequent tone. For control rats, a significant increase in P300 amplitude in response to the noise burst was found when compared with responses to the infrequent tone. However, in nicotine-exposed rats, only slight increases in P300 amplitude were seen.

The N1 ERP component is a negative peak occurring approximately 100 ms after the onset of the stimulus. In humans, it has been called an "attention-related component," as suggested by the fact that its amplitude increases when the subject "attends" to a tone (23,24). An auditory oddball passive ERP paradigm was used in the present study to evaluate the effects of neonatal nicotine exposure on ERP components recorded in adult rats. Artificially reared rats displayed longer N1 latencies to infrequently presented tones than the suckle

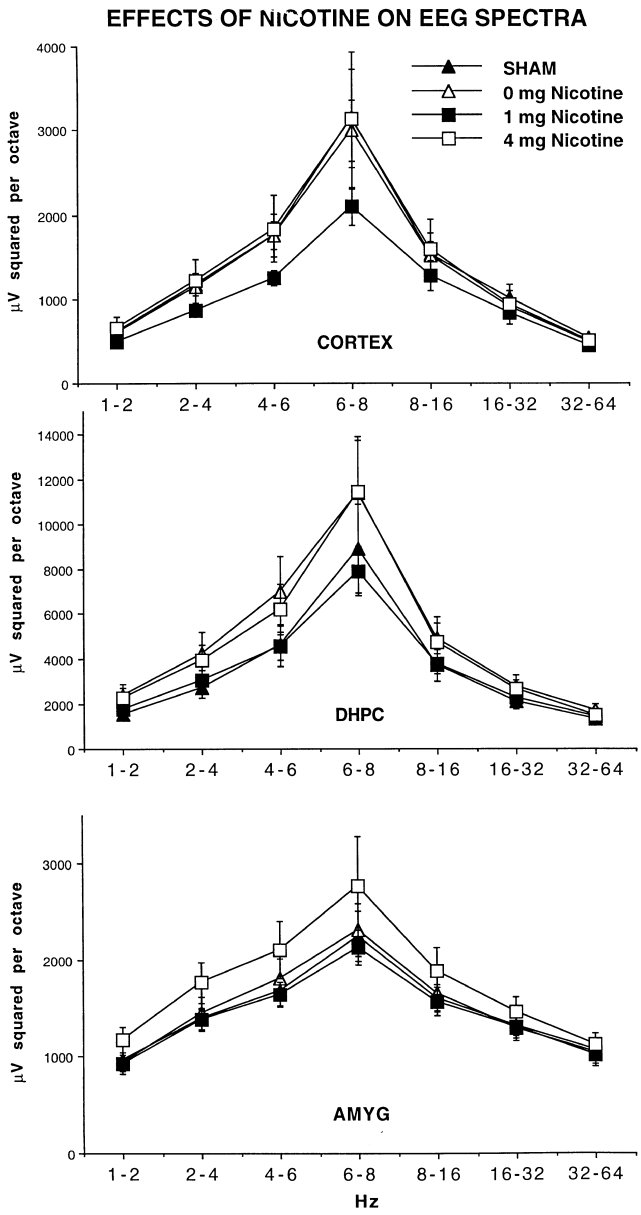

FIG. 4. Effects of rearing condition [suckled control vs. artificially reared (0 mg nicotine)] and nicotine exposure (1 vs. 4 mg/kg/day) on EEG spectral parameters. There were no significant differences across treatment groups on any EEG-dependent variable (i.e., mean power density for any of the frequency bands) evaluated in any recording site.

control rats in the cortex and shorter latencies to frequently presented tones in hippocampus. Increases in the latency of the N1 component has been described in artificial-rearing paradigms [see (29)]. Altered latencies of the N1 ERP component suggest that attentional processing may be an important variable associated with early rearing conditions.

The ERPs have not been recorded previously in humans or animals following perinatal nicotine exposure, making interpretation of the present data more difficult. A study evaluating nicotine effects on the neonatal auditory system demonstrated in a small sample of children that nicotine did not negatively affect maturation or the integrity of the neonatal auditory brainstem tract responses, and it was not associated with hearing loss in the neonate (62). ERPs have been recorded in children diagnosed with fetal alcohol syndrome (FAS) [see (29)]. In that study, children with FAS, like the subjects in the present study, also showed reduced P3 response to a noise tone with the identical passive ERP paradigm. Whether the children with FAS evaluated by Kaneko et al. (29) also were exposed to nicotine perinatally is not known, but alcoholics in general high comorbid rates of nicotine dependence (26). Further studies will be necessary to link P3 amplitude changes to the effects of nicotine on the developing brain in human and animal subjects.

In the present study, no differences in EEG spectral parameters were found as a function of rearing condition or when control animals were compared with animals exposed to neonatal nicotine. Previous findings have suggested that the normal sleep–wake cycle pattern of the rat pup is maintained by the rhythmicity and composition of the milk it receives, nest temperature and behavioral interaction with the mother (25). Although the present study did not specifically measure sleep–wake patterns, the present findings do confirm our previous studies, which demonstrated that artificial rearing does not affect EEG spectral parameters, and extends those findings to suggest that EEG spectral parameters are not affected by neonatal nicotine exposure in this dose range. Landesman-Dwyer et al. (30) noted that infants of mothers who smoke heavily were less visually alert and slept in an atypical left-oriented position, suggesting that these infants may have had some impairment of their sleep–wake cycle, although in that study no EEGs were obtained from the infants. In another study, a trend toward a greater incidence of abnormal or borderline EEGs was observed in the 6-year-old offspring of maternal smokers (13). What is not clear from these studies is whether the EEG abnormalities observed in some nicotine-exposed children reflects the presence of a general developmental disorder, exposure to possible multiple drugs of abuse or is a result of a toxic effect of nicotine on the systems that generate the cortical EEG. However, studies evaluating the effects of prenatal nicotine exposure on experimentally induced seizures in rats have revealed that nicotine exposure can increase susceptibility to electroconvulsive shock, suggesting that nicotine may specifically cause alterations in the systems that modulate brain excitability levels (6).

The mechanism whereby nicotine may specifically alter the brain substrates underlying the P3 response to stimuli is unknown. Prenatal exposure to relatively high doses of nicotine (6 mg/kg/day) causes growth retardation of the offspring, which does not spare the brain, and impairs nervous system development (42,43,52,53,59). Lower doses of nicotine also cause abnormalities of cellular development, without affecting growth, as assessed by measurements of ornithine decarboxylase activity and DNA (43,60) and morphology of somatosensory cortex (55). Further studies linking electrophysiology, anatomy and behavior should provide a better understanding of the potential harmful effects of perinatal nicotine exposure.

ACKNOWLEDGEMENTS

We thank Susan Lopez for her help in data analysis, Dr. James Havstad for the computer programs for EEG and ERP analysis and David Cloutier for statistical analyses. This study was supported by grant TRDRP 4RT-0285 from the state of California to C. L. E. and E. P. R. and by grants NIAAA 06059 and 00223 to C. L. E.

REFERENCES

1. Abel, E. L.: Smoking during pregnancy: A review of effects on growth and development of offspring. Hum. Biol. 52:593–625; 1980.
2. Barron, S.; Kelly, S. J.; Riley, E. P.: Neonatal alcohol exposure alters suckling behavior in neonatal rat pups. Pharmacol. Biochem. Behav. 39:423–427; 1991.
3. Becker, R. F.; Little, C. R. D.; King, J. E.: Experimental studies on nicotine absorption in rats during pregnancy. III. Effect of subcutaneous injection of small chronic doses upon mother, fetus, and neonate. Am. J. Obstet. Gynecol. 100:957–968; 1968.
4. Becker, R. F.; Martin, J. C.: Vital effects of chronic nicotine absorption and chronic hypoxic stress during pregnancy and the nursing period. Am. J. Obstet. Gynecol. 110:522–533; 1971.
5. Bertolini, A.; Bernardi, M.; Genedani, S.: Effects of prenatal exposure to cigarette smoke and nicotine on pregnancy, offspring development and avoidance behavior in rats. Neurobehav. Toxicol. Teratol. 4:545–548; 1982.
6. Britos, S. A.; Orsingher, O. A.: Prenatal nicotine exposure increased susceptibility to electroconvulsive shock (ECS) in adult rats. Neurotox. Teratol. 13:271–273; 1991.
7. Denson, R.; Nanson, J. L.; McWatters, M. A.: Hyperkinesis and maternal smoking. Can. Psychiatr. Assoc. J. 20:183–187; 1975.
8. Dobbing, J.: Undernutrition and the developing brain. In: Palettie, R.; Davison, A. N., eds. Chemistry and brain development. Advances in experimental medicine and biology, vol. 13. New York: Plenum Press; 1971:399–412.
9. Dobbing, J.; Sands, J.: Quantitative growth and development of the human brain. Arch. Dis. Child. 48:757–767; 1973.
10. Donchin, E.; Coles, M. G. H.: Is the P300 component a manifestation of context updating? Behav. Brain Sci. 11:357–374; 1988.
11. Duncan-Johnson, C. C.; Donchin, E.: On quantifying surprise: The variation in event-related potentials with subject probability. Psychophysiology 14:456–467; 1977.
12. Dunn, H. G.; McBurney, A. K.; Ingram, S.; Hunter, C. M.: Maternal cigarette smoking during pregnancy and the child's subsequent development. Neurological and intellectual maturation to the age of 6 1/2 years. Can. J. Publ. Health 67:499–505; 1976.
13. Dunn, H. G.; McBurney, A. K.; Sandraingram, N. A.; Hunter, C. M. Maternal cigarette smoking during pregnancy and the child's subsequent development: II. Neurological in intellectual maturation to the age of 6 1/2 years. Can. J. Publ. Health 68:43–50; 1977.
14. Ehlers, C. L.: ERP responses to ethanol and diazepam administration in squirrel monkeys. Alcohol 5:315–320; 1988.
15. Ehlers, C. L.; Chaplin, R. I.: EEG and ERP response to chronic ethanol exposure in rats. Psychopharmacology 104:67–74; 1992.
16. Ehlers, C. L.; Chaplin, R. I.: Long latency event-related potentials in rats: The effects of changes in stimulus parameters and neurochemical lesions. J. Neural Transm. 88:61–75; 1992.
17. Ehlers, C. L.; Kaneko, W. M.; Owens, M. J.; Nemeroff, C. B.: Effects of gender and social isolation on electroencephalogram and neuroendocrine parameters in rats. Biol. Psychiatr. 33:358–366; 1993.
18. Ehlers, C. L.; Kaneko, W. M.; Robledo, P.; Lopez, A. L.: Long latency event-related potentials in rats: Effects of task and stimulus parameters. Neuroscience 62:759–769; 1994.
19. Ehlers, C. L.; Wall, T. L.; Chaplin, R. I.: Long latency event-related potentials in rats: Effects of dopaminergic and serotonergic depletions. Pharmacol. Biochem. Behav. 38:789–793; 1991.
20. Guillain, G.; Gy, A.: Recherches experimentales sur l'influence de l'intoxication tabagique sur la gestation. Comp. Rend. Sci. Soc. Biol. 63:583–584; 1907.
21. Hall, W. G.: Weaning and growth of artificially reared rats. Science 190:1313–1315; 1975.
22. Hardy, J. B.; Mellits, E. D.: Does maternal smoking during pregnancy have a long-term effect on the child? Lancet 2:1332–1336; 1972
23. Hillyard, S. A.; Hansen, J. C.: Attention: electrophysiological approaches. In: Coles, M. G. H.; Hillyard, S. A.; Hink, R. F.; Schwent, V. L.; Picton, T. W., eds. Electrical signs of selective attention in the human brain. Science, vol. 182. New York: Science, 1973:177–180.
24. Hillyard, S. A.; Hansen, J. C.: Attention: Electrophysiological approaches. In: Coles, M. G. H.; Dohchin, R.; Porges, S. W., eds. Psychophysiology systems processes and application. New York: Guilford Press; 1986:227–243.
25. Hofer, M. A.; Shair, H.: Control of sleep–wake states in the infant rat by features of the mother–infant relationship. Dev. Psychobiol. 15:229–243; 1982.
26. Hurt, R. D.; Offord, K. P.; Crogham, I. T.; Gomez-Dahl, L.; Kottke, T. E.; Morse, R. M. Melton, L. J. III.: Mortality following inpatient addictions treatment. Role of tobacco use in a community based cohort. JAMA 275:1097–1103; 1996.
27. Johns, J. M.; Louis, T. M.; Becker, R. F.; Means, L. W.: Behavioral effects of prenatal exposure to nicotine in guinea pigs. Neurobehav. Toxicol. Teratol. 4:365–369; 1982.
28. Kaneko, W. M.; Riley, E. P.; Ehlers, C. L.: Electrophysiological and behavioral findings in rats prenatal exposed to alcohol. Alcohol 10:169–178; 1993.
29. Kaneko, W. M.; Ehlers, C. L.; Phillips, E. L.; Riley, E. P.: Auditory event-related potentials in fetal alcohol syndrome and Down's syndrome children. Alcohol Clin. Exp. Res. 20:35–42; 1996.
30. Landesman-Dwyer, S.; Killer, L. S.; Streissguth, A. P.: Naturalistic observations of newborns: Effects of maternal alcohol intake. Alcohol Clin. Exp. Res. 2:171–177; 1978.
31. Lichtensteiger, W.; Schlumph, M.: Prenatal nicotine affects fetal testosterone and sexual dimorphism of saccharine preference. Pharmacol. Biochem. Behav. 23:439–444; 1985.
32. Lowe, C. R.: Effects of mothers' smoking habits on birth weight of their children. Br. Med. J. 2:673–676; 1959.
33. Lukas, J. H.: Human auditory attention: The olivocochlear bundle may function as a peripheral filter. Psychophysiology 17:444–452; 1980.
34. Lukas, J. H.: The role of efferent inhibition in human auditory attention: An examination of the auditory brainstem potentials. Int. J. Neurosci. 12:137–145; 1981.
35. Martin, J. C.: An overview: Maternal nicotine and caffeine consumption and offspring outcome. Neurobehav. Toxicol. Teratol. 4:421–427; 1982.
36. Martin, J. C.; Becker, R. F.: The effects of maternal nicotine absorption or hypoxic episodes upon appetitive behavior of rat offspring. Dev. Psychobiol. 4:133–147; 1971.
37. Messer, M.; Thoman, E. B.; Terrasa, A. G.; Dallman, P. R.: Artificial feeding of infant rats by continuous gastric infusion. J. Nutrit. 98:404–410; 1969.
38. Meyer, L. S.; Kotch, L. E.; Riley, E. P.: Neonatal ethanol exposure: Functional alterations associated with cerebellar growth retardation. Neurotoxicol. Teratol. 12:15–22; 1990.
39. Meyer, L. S.; Kotch, L. E.; Riley, E. P.: Alterations in gait following ethanol exposure during the brain growth spurt in rats. Alcohol Clin. Exp. Res. 14:23–27 1990.
40. Naeye, R. L.: Relationship of cigarette smoke to congenital anomalies and perinatal death. Am. J. Pathol. 90:289–293; 1978.
41. Nash, J. E.; Persaud, T. V. N.: Embryopathic risks of cigarette smoking. Exp. Pathol. 33:65–73; 1988.
42. Navarro, H. A.; Seidler, F. J.; Schwartz, R. D.; Whitmore, W. L.; Slotkin, T. A.: Prenatal exposure to nicotine via maternal infusions: Effects on development of catecholamine systems. J. Pharmacol. Exp. Ther. 244:940–944; 1988.
43. Navarro, H. A.; Seidler, F. J.; Schwartz, R. D.; Baker, F. E.; Dobbins, S. S.; Slotkin, T. A.: Prenatal exposure to nicotine impairs nervous system development at a dose which does not affect viability or growth. Brain Res. Bull. 23:187–192; 1989.
44. Paulson, R. B.; Shanfeld, J.; Vorhees, C. V.; Sweazy, A.; Gagni, S.; Smith, A. R.; Paulson, J. O.: Behavioral effects of prenatally administered smokeless tobacco on rat offspring. Neurotoxicol. Teratol. 15:183–192; 1993.
45. Paulson, R. B.; Shanfeld, J.; Vorhees, C. V.; Cole, J.; Sweazy, A.; Paulson, J. O.: Behavioral effects of smokeless tobacco on the neonate and young Sprague–Dawley rat. Teratology 49:293–305; 1994.
46. Pellegrino, L. J.; Pellegrino, A. S.; Cushman, A. J.: A Sterotaxic atlas of the rat brain. New York: Plenum Press; 1979.
47. Peters, D. A. V.; Taub, H.; Tang, S.: Postnatal effects of maternal nicotine exposure. Neurobehav. Toxicol. 1:221–225; 1979.

48. Polich, J.: Attention, probability and task demands as determinants of P300 latency from auditory stimuli. Electroencephalogr. Clin. Neurophysiol. 63:251–259; 1986.
49. Polich, J.: Comparison of P300 from a passive tone sequence paradigm and an active discrimination task. Psychophysiology. 24:41–46; 1987.
50. Polich, J.: P300 in clinical applications: Meaning, method, and measurement. Am. J. EEG Technol. 31:201–231; 1991.
51. Polich, J.; Fischer, A.; Starr, A.: A programmable multi-tone generator. Behav. Res. Methods Instr. 15:30–41; 1983.
52. Rantakallio, P.: A follow-up study up to the age of 14 of children whose mothers smoked during pregnancy. Acta Paediatr. Scan. 72:747–753; 1983.
53. Ribary, U.; Lichtensteiger, W.: Effects of acute and chronic prenatal nicotine treatment on central catecholamine systems of male and female rat fetuses and offspring. J. Pharmacol. Exp. Ther. 248:786–792; 1989.
54. Roth, W. T.; Doyle, C. M.; Pfefferbaum, A.; Kopell, B. S.: Effects of stimulus intensity on P300. In: Kornhuber, H. H.; Deecke, L., eds. Motivation, motor and sensory processes of the brain: Electrical potentials, behavior, and clinical use, vol. 54. Amsterdam: Elsevier; 1980:296–300.
55. Roy, T. S.; Sabherwal, U.: Effects of prenatal nicotine exposure on the morphogenesis of somatosensory cortex. Neurotoxicol. Teratol. 16:411–421; 1994.
56. Schlumpf, M.; Gahwiler, M.; Ribary, U.; Lichtensteiger, W.: A new device for monitoring early motor development: Prenatal nicotine-induced changes. Pharmacol. Biochem. Behav. 30:199–203; 1988.
57. Segarra, A. C.; Strand, F. L.: Perinatal administration of nicotine alters subsequent sexual behavior and testosterone levels of male rats. Brain Res. 480:151–159; 1989.
58. Simpson, W. J.: A preliminary report of cigarette smoking and the incidence of prematurity. Am. J. Obstet. Gynecol. 73:808–815; 1957.
59. Slotkin, T. A.; Cho, H.; Whitmore, W. L.: Effects of prenatal nicotine exposure on neuronal development: Selective actions on central and peripheral catecholaminergic pathways. Brain Res. Bull. 18:601–614; 1987.
60. Slotkin, T. A.; Lappi, S. E.; Deidler, F. J.: Impact of fetal nicotine exposure on development of rat brain regions: Critical sensitive periods or effects of withdrawal? Brain Res. Bull. 31:319–328; 1993.
61. Sorenson, C. A.; Raskin, L. A.; Yongsook, S.: The effects of prenatal nicotine on radial-arm maze performance in rats. Pharmacol. Biochem. Behav. 40:991–993; 1991.
62. Trammer, R. M.; Aust, G.; Koster, K; Obladen, M.: Narcotic and nicotine effects on the neonatal auditory system. Acta Paediatr. 81:962–965; 1992.
63. Tueting, P.; Sutton, S.; Zubin, J.: Quantitative evoked potential correlates of the probability of events. Psychophysiology 7:385–394; 1971.
64. Verleger, R.: Event-related potentials and cognition: A critique of the context updating hypothesis and an alternative interpretation of P3. Behav. Brain Sci. 11:343–356; 1988.
65. West, J. R.: Use of pup in a cup model to study brain development. J. Nutr. 123(suppl. 2):382–385; 1993.
66. Yamaguchi, S.; Globus, H.; Knight, R. T.: P-3 like potentials in rats. Electroencephalogr. Clin. Neurophysiol. 88:151–154; 1993.