Brain Seizure Threshold of Prenatally Nicotine-Treated Offspring

Ghazi M. Al-Hachim, Ph.D.*
Faiza A. Mohmood, M. Sc.

DOI: http://dx.doi.org/10.5915/17-1-12718

The trimester of pregnancy through which nicotine may influence the postnatal development, has not been previously reported. Hence, 3 different doses of nicotine equivalent to 10 cigarettes (900 ug/kg), 20 cigarettes (1800 ug/kg) or 30 cigarettes (2700 ug/kg) were given daily subcutaneously (S.C.) during each trimester into 3 groups of pregnant mice. Their offspring were subjected to minimal electroshock seizure threshold (MEST) test. During the second trimester, the drug reduced the MEST of the offspring when they were 1 month old. However, during the third trimester, nicotine reduced their MEST when they were 1 and 2 months old. Thus, pregnant mothers are not recommended to be exposed to nicotine during the late stages of pregnancy.

Introduction

The minimal electroshock seizure threshold (MEST) is often employed to estimate brain excitability. Since brain excitability is related to the maturation and physiological function of the central nervous system (CNS)[1], it is widely used to study the prenatal effects of drugs on the postnatal development and maturation of the CNS[2].

It has been reported that prenatal exposure to nicotine, the major constituent of tobacco smoke, delayed the noraml maturation time of the postnatal development of the central nervous system excitatory and inhibitory functions[3]. However, the exact trimester during which nicotine or tobacco smoke may be most effective on the fetal maturation is not reported. Hence MEST is used to study the action of prenatal nicotine exposure during different trimesters on the brain seizure threshold of the offspring.

Procedure

Paired virgin adult female and male Swiss albino mice strain weighing between 25-30 gm were housed together in private microdone cages (27x21x14cm), with saw dust bedding. They were given food and water ad libitum. The day on which the vaginal plug was observed was designated as the first day of pregnancy. The room temperature was kept at 26 ± 4°C throughout the study period.

Three daily doses, small, intermediate or large dose of nicotine base, were used for 3 different groups of pregnant mice in each trimester. These doses were equivalent to 10 cigarettes (Cig.) (900 ug/kg), 20 cig. (1800 ug/kg) and 30 cig. (2700 ug/kg) respectively. The control groups for each trimester were given normal saline, 10 ml/kg, because each dose of the drug was dissolved in this amount of saline solution.

The drug and the normal saline were administered subcutaneously. The daily dose was divided into two equal parts. The first half of the dose was given in the morning and the second half was given late in the afternoon throughout the experiments. A similar dose was given to at least 10 pregnant mice in each trimester for 7 consecutive days. Each mother gave birth in its own cage. The offspring weaned when they were 1 month old.

MEST was measured for the 10 drug or saline-treated 1 and 2 months old offspring from each trimester. The method of Al-Hachim[2], was used. The results were reported and subjected to student t-test for statistical analysis[4].

Results

First Trimester

Table 1 shows the results of the MEST test of the offspring of mothers treated with nicotine during the first trimester.

Compared with the controls, all the offspring from mothers treated with nicotine during the first trimester showed no significant reduction of MEST when they were 1 and 2 months old.

Second Trimester

Table 2 shows the results of the MEST test of the offspring of mothers treated with nicotine at the second trimester.

Compared with the controls, all 3 doses of nicotine significantly (p .05) reduced the MEST of the offspring on postnatal day 31, while the large dose, in addition, significantly reduced it on postnatal day 61.

Third Trimester

Table 3 shows the results of the MEST test of the offspring from mothers treated with nicotine during the third trimester.

The small dose of nicotine administered to the mothers significantly (p .05) depressed the MEST of the offspring when they were 31 and 61 days old. The intermediate and large doses administered to the mothers showed highly significant (p .01) depression in the MEST of the offspring when they were 31 and 61 days old.

Discussion

It is well known that the mouse brain starts to develop

From the Department of Pharmacology
College of Medicine, Baghdad, Iraq
Address all correspondence to Dr. Ghazi M. Al-Hachim,
College of Medicine, King Abdul Aziz University,
P.O.Box 9029, Jeddah, Saudi Arabia 21413

Dose of Nicotine	Post Natal Day 31 (One Month Old)	Post Natal Day 61 (Two Months Old)
CONTROL	69.4 ± 5.07	72.0 ± 7.57
(450 mg/kg) X 2	64.4 ± 3.30	65.3 ± 3.72
(900 mg/kg) X 2	57.2 ± 4.04	63.0 ± 6.93
(1350 mg/kg) X 2	56.2 ± 4.80	59.7 ± 8.03

* 10 Animals Per Group.

Table 1. The mean ± SE of minimal electroshock seizure threshold (MEST) for mice progenies from mothers treated with nicotine base or normal saline (control) twice daily during the first trimester*.

MEAN ± S.E. OF MEST		
CONTROL	79.6 ± 15.80	87.6 ± 18.90
(450 mg/kg) X 2	38.5 ± 9.30**	52.0 ± 13.20
(900 mg/kg) X 2	40.2 ± 8.10**	48.0 ± 10.82
(1350 mg/kg) X 2	32.0 ± 8.60**	43.0 ± 10.20**

* 10 Animals Per Group

**Significantly Different From Corresponding Control
(P ⁵ Z 0.05)

Table 2. The mean ± SE of minimal electroshock seizure threshold (MEST) for mice progenies from mothers treated with nicotine base or normal saline (control) twice daily during the second trimester*.

CONTROL	76.0 ± 4.03	79.4 ± 4.24
(450 mg/kg) X 2	65.0 ± 1.63**	67.1 ± 3.83**
(900 mg/kg) X 2	62.2 ± 2.13***	50.2 ± 1.92***
(1450 mg/kg) X 2	45.4 ± 2.77***	44.8 ± 8.50***

* 10 Animals Per Group
** Significantly Differently For Corresponding Control (P= Z 0.05)
***Highly significantly different from corresponding control (P = Z 0.01)

Table 3. The mean ± SE of minimal electroshock seizure threshold (MEST) for mice progenies from mothers treated with nicotine base or normal saline (control) twice daily during the third trimester*.

during the second trimester[5] and nicotine is excreted from the body during the 24 hours after administration. Hence, there was no important effect of first trimester prenatal exposure to nicotine on the development and maturation of seizure activity. The second (Table 2) and third (Table 3) trimester prenatal exposure to nicotine on MEST is an indication that nicotine induces an action on the development of seizure activity, most likely involving subcortical inhibitory and excitatory pathways[6]. The decrease in brain seizure thresholds of the offspring from mothers treated with nicotine during the second and third trimesters is an indication of increased brain excitability[1,3]. It may also indicate immaturity of the CNS[3,7]. In addition, it may suggest that nicotine which was given during the late trimesters influences the normal maturational timetable for the excitatory and inhibitory systems, either by delaying the development of inhibition or accelerating the development of excitation.

Although the electroconvulsive responses normalize with increasing age (a phenomenon also observed in other parameters of CNS maturation)[3], because of the complexity of events taking place during the CNS development, even transient abnormalities occurring during maturational periods may have functional repercussions. Thus, the prenatal effect of small and intermediate doses of nicotine disappeared with the second trimester when the offspring were 2 months old, while the effect of the large dose continued (Tables 2 and 3).

Indeed, continuing studies of the effects of endogenous and exogenous factors on the CNS development consistently reveal that subtle alterations at critical periods of prenatal and postnatal brain maturation, although not always immediately observable, are frequently manifested at the onset of specific functions, or when a specialized demand is placed upon the organism. However, the prenatal effect of nicotine on the prenatal and/or postnatal brain maturation may be directly through its effect on the development and physiological functions of the CNS[3] AND/or indirectly through its effect on the uterine blood circulation and therefore maternal blood supply to the fetus[5]. In addition, nicotine may alter significantly the function of the placental cholinergic system by influencing levels of acetylcholine in the placental tissue, by releasing the bound acetylcholine or by acting competitively at the proposed nicotinic cholinergic receptor. The final result of these alterations would be disturbed fetal growth and development and the consequent production of poor quality life[8]. It may cause placental damage[9] and thereafter influence fetal growth. All the probable effects of prenatal nicotine on the reproductive system of the pregnant mice may reduce the nutritional requirements for the prenatal and/or postnatal development of the offspring in general and the CNS in particular. Thereafter, this might lead to delay in the development and maturation of the brain of the offspring during the second and third trimesters.

References

1. Al-Hachim GM, Al-Baker A: Effects of chlordane on conditioned avoidance response brain seizure threshold and open field performance of prenatally treated mice, Brit. J. Pharmac. 49: 311, 1973.
2. Al-Hachim GM: Effect of aldrin on the conditioned avoidance response and electroshock seizure threshold of offspring from aldrin-treated mothers, Psychopharmacologia (Berl) 21: 370, 1971.
3. Hudson, DB, Meisami E, et al: Brain development in offspring of rats treated with nicotine during pregnancy. Experi. 29: 286, 1973.
4. Lewis DG: Statistical methods in education, sampling theory: Means, properties and standard deviations, 110-116, 1975.
5. Rugh R: The mouse: Its reproduction and development, Burgess Publishing Co., 1968.
6. Toman JEP, Goodman LS: Anticonvulsants, Physiol Rev, 28: 409, 1948.
7. Al-Hachim GM. Fink GB: Effect of DDT or parathion on open-field behavior of offspring from DDT or parathion treated mothers, Psychological Reports 22: 1193, 1968.
8. Harbison RD, Olubadewo J, et al: Proposed role of the placental cholinergic system in the regulation of fetal growth and development, p. 107. In: basic and therapeutic aspectic of perinatal pharmacology, (eds) Morseli, P.L., Garahini, S. and Sereni, F.: Raven Press, NY. p. 107, 1975.
9. Mosier HD, Armstrong MK: Effects of maternal intake of nicotine on fetal and newborn rats. Proc Soc Exph Biol Med (NY), 116: 956, 1964.