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Toxicology 209 (2005) 245–261
TOXICOLOGY
www.elsevier.com/locate/toxicol

Maternal exposure of rats to nicotine via infusion during gestation produces neurobehavioral deficits and elevated expression of glial fibrillary acidic protein in the cerebellum and CA1 subfield in the offspring at puberty

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Received 1 July 2004; received in revised form 21 December 2004; accepted 30 December 2004
Available online 23 February 2005

Abstract

Maternal smoking during pregnancy is known to be a significant contributor to developmental neurological health problems in the offspring. In animal studies, nicotine treatment via injection during gestation has been shown to produce episodic hypoxia in the developing fetus. Nicotine delivery via mini osmotic pump, while avoiding effects due to hypoxia-ischemia, it also provides a steady level of nicotine in the plasma. In the present study timed-pregnant Sprague-Dawley rats (300–350 g) were treated with nicotine (3.3 mg/kg, in bacteriostatic water via s.c. implantation of mini osmotic pump) from gestational days (GD) 4–20. Control animals were treated with bacteriostatic water via s.c. implantation of mini osmotic pump. Offspring on postnatal day (PND) 30 and 60, were evaluated for changes in the ligand binding for various types of nicotinic acetylcholine receptors and neuropathological alterations. Neurobehavioral evaluations for sensorimotor functions, beam-walk score, beam-walk time, incline plane and grip time response were carried out on PND 60 offspring. Beam-walk time and forepaw grip time showed significant impairments in both male and female offspring. Ligand binding densities for [^{3}H]epibatidine, [^{3}H]cytisine and [^{3}H]α-bungarotoxin did not show any significant changes in nicotinic acetylcholine receptors subtypes in the cortex at PND 30 and 60. Histopathological evaluation using cresyl violet staining showed significant decrease in surviving Purkinje neurons in the cerebellum and a decrease in surviving neurons in the CA1 subfield of hippocampus on PND 30 and 60. An increase in glial fibrillary acidic protein (GFAP) immuno-staining was observed in cerebellum white matter as well as granular cell layer of cerebellum and the CA1 subfield of hippocampus on PND 30 and 60 of both male and female offspring. These results indicate that maternal exposure to nicotine produces significant neurobehavioral deficits, a decrease in the surviving neurons and an increased expression of GFAP in cerebellum and CA1 subfield of hippocampus of the offspring on PND 30 and 60. The results

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doi:10.1016/j.tox.2004.12.037

show that although 60-day-old male and female rat offspring of mothers exposed to nicotine during gestation did not differ from control in body weight gain or nicotinic acetylcholine receptors ligand binding, they exhibited significant sensorimotor deficits that were consistent with the neuropathological alterations seen in the brain. These neurobehavioral and pathological deficits indicate that maternal nicotine exposure may produce long-term adverse health effects in the offspring.
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Keywords: Cerebellum; Gestational; Glial fibrillary acidic protein; Hippocampus; Infusion; Maternal; Mini osmotic pump; Neurotoxicity; Nicotine; Nicotinic acetylcholine receptor; Offspring; Smoking

1. Introduction

Cigarette smoking during pregnancy has been suggested to cause neurobehavioral and cognitive deficit, and susceptibility to diseases in the offspring (Naeye, 1992; Johnson et al., 2000). These deficiencies may continue at all the developmental stages, including adulthood. Nicotine (3-(1-methyl-2-pyrrolidinyl) pyridine) is the main active constituent that has been associated with a variety of chronic diseases, including neurobehavioral toxicity following cigarette smoking (Hoffmann and Hoffmann, 1997; Law et al., 2003). Prenatal exposure to nicotine has been shown to produce cell loss in the brain throughout the developmental stage (Slotkin, 1998).

Nicotine is a direct cholinergic agonist at the nicotonic acetylcholine receptor (nAChR) site, resulting in behavioral (Martin and Becker, 1970; Benowitz, 1996) and cellular effects (Slotkin et al., 1986a). Exposure to nicotine early in life causes permanent changes in brain nicotinic receptors and consequently abnormal behavior in the adulthood (Nordberg et al., 1991; Slotkin, 1998). Nicotine is a suspected neuroteratogen, and gestational exposure leads to central nervous system neuronal cell loss and abnormalities of synaptic functions (Slotkin et al., 1999). Thus, exposure to nicotine during the fetal development could lead to long-lasting biochemical and pathological effects that may have detrimental health consequences during various stages of the growth and development, most notably during the adolescent stages. Indeed, our previous studies following s.c. injection of nicotine during the gestation days 5–20 have shown that nicotine treatment produced persistent pathological and neurochemical abnormalities in the brain of the offspring at adolescent period (Abdel-Rahman et al., 2003, 2004). However, it has been suggested that neurobehavioral and cellular and synaptic abnormalities observed in the offspring following repeated injection of nicotine to pregnant rats may also be due to fetal hypoxia–ischemia associated with episodic peak in the plasma nicotine concentration (Jonsson and Hallman, 1980; Slotkin et al., 1986b; Calos et al., 1994; Ulrich et al., 1997). Nicotine delivery via osmotic mini pump offers an alternate approach, whereby the episodic peak of plasma nicotine levels and resultant hypoxic episodes and stress of repeated injection can be avoided. Furthermore, mini osmotic pump delivers a steady-state plasma level of nicotine normally seen in smokers (Lichtenteiger et al., 1988; Ulrich et al., 1997; Slotkin, 1998). Therefore, the present studies were carried out in rat offspring on PND 30 and 60 born from mothers exposed to nicotine via mini osmotic pump during the gestation period (GD 4–20).

2. Materials and methods

Nicotine bitartrate was obtained from Sigma Chemical Co (St. Louis, MO). [^{3}H]cytisine (sp. activity, 15 Ci/mmol) and [^{3}H]epibatidine (sp. activity, 56.2 Ci/mmol) were obtained from NEN (Boston, MA). *N*-[*propionyl*-^{3}H]α-bungarotoxin (sp. activity 57 Ci/mmol) was obtained from Amersham Biosciences Corp., Piscataway, NJ. The polyclonal antibody against glial fibrillary acidic protein (GFAP) was obtained from Dako Laboratories, Carpinteria, CA. The avidin–biotin–peroxidase reagent kits were obtained from Vector Laboratories, Burlingame, CA. Mini osmotic pump (Type 2ML2) was obtained from Alzet Co., Cupertino, CA.

2.1. Methods

Timed pregnant Sprague-Dawley rats (300–350 g) were obtained from Zivic-Miller Laboratories (Allison

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