Physiology & Behavior 149 (2015) 131–141

Contents lists available at ScienceDirect

Physiology & Behavior

journal homepage: www.elsevier.com/locate/phb

Maternal nicotine exposure during lactation alters food preference, anxiety-like behavior and the brain dopaminergic reward system in the adult rat offspring

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HIGHLIGHTS

- Brain reward system in adult life is changed by exposure to nicotine during lactation.
- Early exposure to nicotine increases preference for sugar in adult life.
- Nicotine exposure decreases dopaminergic action in the nucleus accumbens.
- Nicotine exposure reduces dopaminergic action in the arcuate nucleus.
- Obese rats that were exposed to nicotine present higher anxiety levels at adulthood.

ARTICLE INFO

Article history:
Received 2 February 2015
Received in revised form 26 May 2015
Accepted 31 May 2015
Available online 3 June 2015

Keywords:
Behavior
Food preference
Lactation
Nicotine
Programming
Reward system

ABSTRACT

The mesolimbic reward pathway is activated by drugs of abuse and palatable food, causing a sense of pleasure, which promotes further consumption of these substances. Children whose parents smoke are more vulnerable to present addictive-like behavior to drugs and food. We evaluated the association between maternal nicotine exposure during lactation with changes in feeding, behavior and in the dopaminergic reward system. On postnatal day (PN) 2, Wistar rat dams were implanted with minipumps releasing nicotine (N; 6 mg/kg/day, s.c.) or saline (C) for 14 days. On PN150 and PN160, offspring were divided into 4 groups for a food challenge: N and C that received standard chow (SC); and N and C that could freely self-select (SSD) between high-fat and high-sugar diets (HFD and HSD, respectively). Offspring were tested in the elevated plus maze (EPM) and open field (OF) arena on PN152–153. On PN170, offspring were euthanized for central dopaminergic analysis. SSD animals showed an increased food intake compared to SC ones and a preference for HFD. However, N-SSD animals consumed relatively more HSD than C-SSD ones. Regarding behavior, N animals showed an increase in the time spent in the EPM center and a reduction in relative activity in the OF center. N offspring presented lower dopamine receptor (D2R) and transporter (DAT) contents in the nucleus accumbens, and lower D2R in the arcuate nucleus. Postnatal exposure to nicotine increases preference for sugar and anxiety levels in the adult progeny possibly due to a decrease in dopaminergic action in the nucleus accumbens and arcuate nucleus.

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1. Introduction

Smoking during critical periods of development, such as pregnancy and lactation, is associated with various health problems. During pregnancy, human studies show that smoking can lead to prematurity, low birth weight, impaired child growth, higher infant mortality [32,51] and behavioral changes [68,76]. In rats, it has also been demonstrated an association between smoking pregnancy and behavioral disorders [45]. Smoking after birth has been shown to cause changes in the neurological development of the child [73]. We have previously demonstrated in rats that exposure to either cigarette smoke or to nicotine alone during lactation affects the short- and long-term endocrine-metabolic development of the offspring. Lactating dam exposure to nicotine from the 2nd to 15th postnatal (PN) day causes, in the offspring, an increase in visceral fat mass, hyperleptinemia, primary hypothyroidism [77] and increased adrenal function at PN15 (end of maternal exposure to nicotine) [78]. In turn, 6 month-old (adult) offspring are overweight, have

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http://dx.doi.org/10.1016/j.physbeh.2015.05.040
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higher central adiposity, hyperleptinemia, central leptin and insulin resistance, secondary hypothyroidism [77,79] and adrenal gland dysfunction [86].

Studies using nicotine alone have been used to assess possible associations between smoking and neurobehavioral changes [28,42,100,110]. Since nicotine is considered the main psychoactive component of tobacco smoke that causes dependence [18,27], experimental models based on nicotine exposure during development should be useful to study the short- and long-term behavioral consequences of early tobacco smoke exposure ([4],; [3,69]).

Epidemiological studies show that children whose parents smoke are more vulnerable to drug use, such as cigarettes and alcohol, and comfort food, especially sugar [104]. In addition, studies have shown an association between gestational tobacco smoke exposure and increased consumption of palatable foods by the offspring both in humans [5] and rats [42]. Indeed, adult rats chronically exposed to nicotine eat greater amounts of sucrose [55].

It is known that the dopaminergic and opioid signaling pathways in the mesolimbic reward system play a role in motivation and reward [19,29,44]. The activation of this system creates a sense of pleasure and modulates the physiological satiety signals, which promotes further consumption of palatable foods or drugs of abuse [29]. Sugar intake stimulates neurons of the ventral tegmental area (VTA) to produce dopamine. Then, VTA axons that project to the nucleus accumbens (NAc) release dopamine that acts on receptors mediating sensations recognized as reward or pleasure [14,48,65,70,89]. Insulin and leptin may modulate the brain reward system [33,35]. These hormones have receptors on VTA dopaminergic neurons and are capable of stimulating reward in a way the causes animals to show less preference for sucrose intake or drug use [34,35]. Conversely, animals with resistance to insulin and/or leptin do not respond to the rewarding properties of these molecules and, consequently, tend to consume more sucrose or drugs [35]. It has also been shown in both humans [109] and in rats [56] that obese individuals with binge eating disorder exhibit dysfunctions in the brain reward system that lead to "food addiction".

In our laboratory, the programming model of maternal nicotine exposure leads the progeny to develop higher visceral adiposity and resistance to leptin and insulin at adulthood. So it is possible that these obese offspring become more susceptible to "food addiction". Human and animal studies have shown that not only metabolic alterations but also the behavioral profile can be programmed by changes in critical periods in life [38–40,57]. Our group has observed that being overweight, resistance to leptin and insulin is associated with behavioral disorders such as anxiety and high exploratory activity in two programming models: neonatal hyperleptinemia [38] and maternal prolactin inhibition at the end of lactation [40]. It is conceivable that early exposure to nicotine not only causes neurobehavioral alterations but also causes changes in the sensitivity of the reward system of the offspring's brain.

Since increased decision-making and risk assessment behaviors were related with the modulation of dopamine levels in the mesolimbic system, which leads to a higher vulnerability to drug addiction [15,43,62,81,111,118], in the present study we tested the hypothesis that maternal nicotine exposure during lactation is associated with changes in the dopaminergic and opioid signaling pathways in the brain reward system of the adult offspring, and that these alterations are associated with changes in the offspring's food preference and behavior.

2. Materials and methods

Wistar rats were kept in a temperature-controlled room (25 ± 1 °C) with artificial light–dark cycle (lights on 7:00 a.m., lights off 7:00 p.m.). Three month old, virgin female rats were caged with male rats at the ratio of 3:1. After mating, each female was placed in an individual cage with free access to water and food until delivery. The use of animals according to our experimental design was approved by the Animal Care and Use Committee of the Biology Institute of the State University of Rio de Janeiro (CEUA/066/2012; CEUA/019/2014), which based its decision on the principles promulgated by Brazilian Law no. 11.794/2008. Experiments were conducted to minimize the number of animals and the suffering caused by the procedures following the ethical doctrine of the three "Rs" — reduction, refinement and replacement [71].

2.1. Experimental model of maternal exposure to nicotine during lactation

Two days after birth, lactating rats were randomly assigned to one of the following groups:

1) Nicotine group (N) — 16 dams were lightly anesthetized with thiopental (Thiopentax, 30 mg/kg), a 3 × 6 cm area on the back was shaved; and an incision was made to permit subcutaneous (s.c.) insertion of osmotic minipumps (Alzet, 2ML2, California, USA). The pump implantation occurred on postnatal (PN) day 2 because, according to the manufacturer's recommendation, it must be filled with the solution of interest and immersed in saline for 24 h prior to implantation to release substances continuously and homogeneously. The activation of the minipump was done only after the pups' birth (PN1). Pumps were prepared with nicotine free-base diluted in a saline solution (NaCl 0.9%) to deliver an initial dose rate of 6 mg/kg of nicotine per day (during 14 days of lactation), as previously described [77]. Exposure to nicotine through subcutaneous osmotic minipump infusion was used to avoid the adverse effects of nicotine peaks [16,17]. Our model produces plasma nicotine concentrations of approximately 25 ng/ml, similar to those found in typical smokers [66]. The incision was closed and dams were permitted to recover in their home cages.

2) Control group (C) — 12 lactating rats were implanted with osmotic minipumps containing only saline solution, which was released for the same period indicated above.

At birth, litter adjustment was performed and 6 male pups were kept per nicotine or control dam to maximize the lactation performance. Weaning occurred at PN21. At weaning, two pups per litter were removed and used in a different study while the remaining four pups from the same litter were placed in the same cage. Body mass was monitored every day during lactation as well as after weaning (until PN170).

2.2. Food preference test

Sixty-four nicotine and 48 control offspring (4 animals per litter) were used. At PN150, two randomly selected animals per litter from both nicotine and control groups were submitted to the food challenge test, while the other two offspring remained in the standard diet. The food challenge was performed in PN150 because we have previously shown that nicotine offspring gain more weight than control ones [77] and because it is known that, at least in human studies, obese individuals eat a large amount of palatable food [108]. To evaluate if the pattern of food preference was stable, the same animals were again tested at PN160. Offspring were fasted from 9 a.m. until 9 p.m. After this period, the diets described below were offered for one continuous period of 12 h [6]. The offspring were fasted because food deprivation increases the compulsion to palatable foods and drugs [7]. The food challenge was offered at night, during the active period of the rodents as conducted by Avena et al. [8]. On the following day (9 a.m.), food and calorie intake was recorded by calculating the amount of chow that was consumed during the 12-h period. After the food challenge, all animals received standard chow. Regarding diet during the food challenge period, animals were divided into four subgroups, with two rats per cage in order to avoid the effects of social isolation: One subgroup of control (C-SC) animals and one of nicotine (N-SC) animals received only standard chow (SC) diet. One subgroup of control (C-SSD) animals and one of nicotine (N-SSD) animals could freely self-select (SSD) between two diets. In these subgroups, animals could select between a high-fat diet (20% higher content of saturated fat when compared to the standard chow — HFD) and a high-sugar diet (38% higher content of sucrose when compared to the standard chow — HSD). Therefore, the present study

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