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Research Report

Prenatal cocaine exposure accelerates morphological changes and transient expression of tyrosine hydroxylase in the cochlea of developing rats

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ARTICLE INFO

Article history:
Accepted 20 February 2006
Available online 13 April 2006

Keywords:
Prenatal cocaine exposure
Auditory system
Cochlea maturation
Tyrosine hydroxylase
Immunocytochemistry
Morphometry

ABSTRACT

Prenatal cocaine exposure causes alterations in auditory brainstem response in children and experimental animals and has adverse effects on auditory information processing and language skills in children. These effects may result from lesions in the cochlea since this organ is particularly sensitive to chemical insults during the development. We have thus studied here the effect of prenatal cocaine exposure on the maturation of the rat cochlea using the transient non-catecholaminergic expression of tyrosine hydroxylase in spiral ganglion neurons as an index of cochlear maturation and morphometry to evaluate the maturation of primary auditory neurons and the organ of Corti. We showed that prenatal cocaine exposure accelerated the cochlear maturation. In the basal coil of cochleas from PND8 cocaine-treated pups, the Kölliker's organ had disappeared, the tunnel of Corti was opened, and the stria vascularis no longer contained undifferentiated marginal cells. The maximum expression of tyrosine hydroxylase in type I primary auditory neurons occurred at PND8 instead of PND12 in pair-fed controls. On the other hand, the prenatal cocaine exposure had no effect on the width and height of the organ of Corti, spiral ganglion volume and number and size of primary auditory neurons. In conclusion, our data suggest that prenatal cocaine exposure, though not lethal to primary auditory neurons, accelerates aspects of the cochlear sensorineural maturation. This accelerated cochlear maturation in cocaine-treated rat pups could cause auditory dysfunctions by desynchronizing the development of the whole auditory pathway.

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doi:10.1016/j.brainres.2006.02.066

1. Introduction

Cocaine has become a very popular drug of addiction in Western countries. According to the SAMHSA 2003 National Survey on Drug Use and Health (National Survey on Drug Use and Health, 2003), 2.5% of the Americans aged 12 and older (circa 5.9 million) have used cocaine during the last 12 months, with 25.6% of them (circa 1.5 million) classified with dependence on or abuse of cocaine. In European Union countries, past year cocaine users account for 1 to 5% of young adults (15 to 34 years old) (European Monitoring Centre for Drugs and Drug Addiction Annual report, 2003a,b).

Cocaine abuse concerns mainly people in reproductive age, resulting in an increasing number of pregnant women consuming this drug and a high number of infants being exposed prenatally to cocaine. In the USA, although their number has decreased during the past decade, still 1% of the pregnant women are past month cocaine users (National Survey on Drug Use and Health, 2004).

In utero exposure to cocaine results in lower birth weight, reduced head circumference, and increased risk of seizures of newborns. Behaviorally, these newborns are more irritable and over-reactive to environmental stimuli. While most damages then recover close to normal, long-lasting deficits remain in processes related to attention and emotional expression, indicating that cocaine has interfered with the central nervous system development (Harvey, 2004; Keller and Snyder-Keller, 2000; Lidow, 2003; Mayes, 2002).

Indeed, in utero cocaine exposure has adverse effects on auditory information processing and language skills of exposed children (Lester et al., 1998; Potter et al., 2000; Singer et al., 2001). Auditory brainstem responses (ABR) show prolonged interpeak and absolute latencies during the first year of life in prenatally exposed infants (Salamy et al., 1990; Shih et al., 1988). The same electrophysiological alterations are retrieved in the rat, together with elevated ABR thresholds and latency–intensity curves consistent with sensorineural hearing loss with recruitment (Church and Overbeck, 1990a,b, 1991; Church et al., 1998).

These ABR alterations may be due to lesions in auditory receptor organs and spiral ganglion neurons since the developing cochlea is particularly sensitive to chemical insults (Du and Hamre, 2001; Henley and Rybak, 1995; Uziel et al., 1983). However, no studies concerning the effects of maternal cocaine abuse on the developing cochlea have been reported yet. In the present study, we have evaluated the effect of prenatal cocaine exposure on the maturation of the rat cochlea using the transient non-catecholaminergic expression of tyrosine hydroxylase (TH) in spiral ganglion neurons, as an index of cochlear maturation (Trigueiros-Cunha et al., 2003), light microscopy, and morphometry to evaluate the maturation of primary auditory neurons and the organ of Corti. Some of these results have been communicated in a preliminary form (Trigueiros-Cunha, 1998).

2. Results

The maternal weight gain of the animals treated with cocaine and pair-fed was determined by calculating the difference between the body weight at gestational day 1 (GD1) and GD21. There was no difference between the experimental groups in the weight gain of the mothers. No differences were detected in the number of pups per litter, in the ratio of male to female per litter, and in the mean body weight of the pups at PND1 between both groups. Though no extensive testing has been conducted, cocaine-treated and pair-fed pups showed no obvious difference in their behavior. In addition, no difference was noted in their reaction to environmental sounds at PND14 and PND30. Finally, the mesodermic glue disappeared from the middle ear of both the cocaine-treated and pair-fed pups between PND8 and 12, around the onset of hearing (Crowley and Hepp-Raymond, 1966; Puel and Uziel, 1987; Uziel et al., 1981).

2.1. *Effects of maternal cocaine treatment on the spiral ganglion of rat pups*

The spiral ganglion is formed by perikarya of ~90% type I neurons, whose dendrites innervate inner hair cells, and ~10% type II neurons, whose dendrites innervate outer hair cells. Type I neurons have big oval bipolar perikarya with a dark cytoplasm, a light nucleus, and a prominent nucleolus. Type II neurons are smaller, have round-shaped perikarya, a lighter cytoplasm, and a darker nucleus. They often lie in clusters of 2–3 neurons near the ganglion hillus (Schwartz et al., 1983). In both cell types, no images of cellular damage (vacuoles or nuclear degeneration) were observed.

The morphometric study showed no differences in both experimental groups at PND14 and PND30 when taking into account the mean spiral ganglion volume (Table 1). Similarly, no significant differences were found between the groups at both ages when considering the total number of primary auditory neurons (Table 1) or when determining the number of neurons per unit of volume in the basal, middle, and apical

Table 1 – Morphometric analysis of the spiral ganglion and primary auditory neurons of cocaine–treated and pair-fed rats at postnatal days (PND) 14 and 30

	Cocaine		Pair-fed	
	PND14	PND30	PND14	PND30
Spiral ganglion volume (mm^3, ±SD)	0.143 ± 0.018	0.151 ± 0.020	0.124 ± 0.013	0.148 ± 0.031
Total number of primary auditory neurons	13,997 ± 2946	15,038 ± 2416	15,176 ± 2546	16,247 ± 2425
Mean diameter (μm ± SD) of type I neurons perikarya	15.57 ± 0.63	15.39 ± 0.38	15.31 ± 0.57	15.85 ± 0.54
Mean diameter (μm ± SD) of type I neurons nucleus	7.67 ± 0.37	8.13 ± 0.29	7.88 ± 0.31	8.06 ± 0.38

No significant differences were found between the groups.