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Prenatal methylmercury exposure affects spatial vision in adult monkeys

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Abstract

Decades of research have demonstrated that exposure to methylmercury (MeHg), a ubiquitous environmental pollutant, can have both early and long-term neurobehavioral consequences in exposed offspring. The present study assessed visual functioning in adult macaque monkeys (*Macaca fascicularis*) exposed in utero to 0, 50, 70, or 90 μg/kg/day of MeHg hydroxide. Twenty-one full-term, normal birth weight offspring (9 controls, 12 exposed) were tested at approximately 11–14.5 years of age on a visual contrast sensitivity task. A forced-choice tracking procedure was utilized with spatial frequencies of 1, 4, 10, and 20 cycles per degree of visual angle. On each test session, a single spatial frequency was presented across five levels of contrast, each differing by 3 dB. Methylmercury-exposed monkeys exhibited reduced contrast sensitivity thresholds, particularly at the higher spatial frequencies. The degree of visual impairment was not related to MeHg body burden or clearance and almost half of the exposed animals were unimpaired. The results from this study demonstrate that chronic in utero MeHg exposure, at subclinical levels, is associated with permanent adverse effects on spatial vision in adult monkeys.

Keywords: Methylmercury; Prenatal exposure; Long-term effects; Spatial vision; Visual contrast sensitivity; Monkeys

Introduction

Methylmercury (MeHg) is an environmental pollutant that is found in many of the world's oceans and waterways. In aquatic environments, inorganic mercury (Hg) is converted to MeHg through the process of biomethylation and accumulates in the ascending food chain. These events can lead to high levels of MeHg in predatory fish and marine mammals, creating the principal means of current exposure for both humans and wildlife (National Research Council, 2000). In the last century, there have been incidents of high-dose human exposure to MeHg in Japan and Iraq (Bakir et al., 1973; Tokuomi et al., 1961). Strong evidence of fetal sensitivity to MeHg exposure was documented in both of these episodes (National Research Council, 2000) and women with few or no clinical signs of neurotoxicity delivered infants who clearly suffered from in utero MeHg poisoning (Bakir et al., 1973; Harada et al., 1968; Marsh et al., 1980). The catastrophic poisonings in Japan and Iraq provided evidence that susceptibility to MeHg exposure differs with life stage and that the fetus is at greatest risk for both functional and structural damage. Autopsy data from exposed children have demonstrated that developmental MeHg exposure results in widespread damage to the brain, primarily through hypoplasia and cell loss, and functional losses in highly exposed infants can be dramatic (e.g., cerebral palsy, mental retardation) (Kondo, 2000). Significant losses in visual and auditory functioning, including blindness and deafness, have also been documented in

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highly exposed infants and sensory disturbances are characteristic of both fetal and adult exposure (Amin-Zaki et al., 1974, 1981; Harada, 1995).

It is widely acknowledged that deficits in visual function are a hallmark of both adult and developmental exposure to MeHg. In a neurological study of 53 adult Iraqi patients with MeHg poisoning, 60% of subjects suffered from visual disturbances (Rustam and Hamdi, 1974). Common symptoms included constriction of the visual fields, reduced acuity, blindness, and abnormal fundi. In humans, high-level developmental exposure can result in oculomotor disturbances and blindness (Amin-Zaki et al., 1979; Harada, 1977; Marsh et al., 1980) while lower level exposure is associated with losses in visual acuity (Ishikawa et al., 1979) and constriction of the visual fields (Harada et al., 1968). Comparative work with nonhuman primates has provided important insights into the nature of early MeHg exposure and long-term effects on vision. In Canada, one cohort of *Macaca fascicularis* monkeys was treated with MeHg for 7 years after birth (50 μg/kg/day) while a second group was exposed in utero to 4–4.5 years after birth (10, 25, or 50 μg/kg/day. Impairments in spatial vision were found in both exposed groups (Rice and Gilbert, 1982, 1990), closely paralleling the visual deficits commonly observed in highly exposed humans (Rustam and Hamdi, 1974; Sabeliash and Himli, 1976). The findings from this longitudinal work provide strong evidence that, in the primate model, adult spatial vision is adversely affected by developmental MeHg exposure.

The macaque is considered an excellent model of human visual processing (Harwerth and Smith, 1985) and the normal development of contrast sensitivity has been well documented in both human and monkeys (Boothe et al., 1980; Hainline and Abramov, 1997; Kiorpes and Kiper, 1996). Tests of contrast sensitivity provide a valuable means of assessing spatial vision across a variety of object sizes under real-life conditions and offers more diagnostic information than simple measurements of visual acuity (Jindra and Zemon, 1989). Different pathological and refractive conditions can result in contrast sensitivity losses and this has been demonstrated in diseases such as Parkinson's, Alzheimer's, and multiple sclerosis (Bodis-Wollner, 1990; Cormack et al., 2000; Kupersmith et al., 1984). Deficits in contrast sensitivity can be due to changes in the optics of the eye, the retina, or the neurological pathways that serve central vision. When visual acuity is normal but contrast sensitivity is impaired, a deficit of neurological origin is suggested.

The present study assessed adult visual contrast sensitivity functioning in a cohort of macaque monkeys exposed to MeHg only through maternal ingestion during pregnancy. These animals are part of an on-going research program designed to study the effects of in utero MeHg exposure on neurobehavioral functioning across the life span. Adult female *M. fascicularis* monkeys were orally exposed to 0, 50, 70, or 90 μg/kg/day MeHg prior to and throughout pregnancy. Exposed offspring exhibited delays in the development of object permanence and visual recognition memory (Burbacher et al., 1986; Gunderson et al., 1986, 1988). The development of species-typical social behavior was also affected by MeHg exposure and treated infants showed reduced levels of social play and increased levels of self-directed behaviors (Burbacher et al., 1990). As adults, exposed monkeys exhibited subtle changes on a fixed interval/fixed ratio-learning task (Gilbert et al., 1996) but performance deficits were not observed on other assessments of learning memory and learning (Gilbert et al., 1993). These results provide a perspective on prenatal MeHg exposure that emphasizes deficits in memory and social behavior during infancy but competent performance on adult tests of cognition. To evaluate the long-term effects of in utero MeHg exposure on spatial vision, visual contrast sensitivity functioning was measured in our cohort when they reached adulthood. The results provide the first description of contrast sensitivity in a primate species whose history of exposure to MeHg was limited to the prenatal period, isolating the unique consequences of fetal exposure on adult sensory functioning.

Methods

Subjects. The animals in this study are the offspring of 21 adult female *M. fascicularis* monkeys who were exposed to 0, 50, 70, or 90 μg/kg/day MeHg prior to and throughout pregnancy (Burbacher et al., 1988). Briefly, exposure was achieved through maternal oral ingestion of MeHg hydroxide (97+%, Alfa Products, Thiokol/Ventron Division, Danvers, MA 01923) mixed with apple juice. Daily exposure of the adult females was based on maternal body weight prior to conception and dosing took place 7 days per week. Females were assessed weekly for behavioral changes associated with exposure and all dams delivering offspring remained symptom-free and healthy throughout pregnancy. To prevent postnatal exposure and allow for a controlled rearing environment, offspring were separated from their mothers at birth and housed in the Infant Primate Research Laboratory at the University of Washington according to standard laboratory protocol. Infants were tested on a comprehensive battery of behavioral assessments that focused on the development of social, cognitive, and motor skills during the first year of life (Burbacher et al., 1986, 1990; Gunderson et al., 1986, 1988). The experiment described in this manuscript took place when the monkeys were between 11 and 14.5 years of age (middle age for this species of monkey). The characteristics of the cohort, including dose group, age at test, and maternal and newborn blood mercury levels, are described in Table 1. The animals were single-cage housed in one large room at the Regional Primate Research Center at the University of Washington and fed a restricted diet of monkey chow, fruit, vegetables, and water. They were socialized with peers several times per week in a large exercise cage with ramps, swings, and toys.