AN OVERVIEW ON THE EFFECTS OF DIOXIN AND PCB EXPOSURE ON TEETH AND BONES

Miettinen HM[1], Alaluusua S[2], Sorvari R[3], Pulkkinen P[4], Tuukkanen J[4], Viluksela M[1]

[1] Department of Environmental Health, National Public Health Institute, P.O. Box 95, 70701, KUOPIO, FINLAND; [2]Department of Pediatric and Preventive Dentistry, Institute of Dentistry, P.O. Box 41, FIN-00014 University of Helsinki and Department of Oral and Maxillofacial Diseases, P.O. Box 263, FIN-00029 Helsinki University Central Hospital, Finland; [3]Department of Anatomy, P.O. Box 1627, FIN-70211, University of Kuopio, Finland; [4]Department of Anatomy and Cell Biology, University of Oulu, P.O. Box 5000, 90014

Introduction

Alterations in hard tissue development have long been neglected in toxicological studies with polychlorinated dibenzo-p-dioxins and –furans (PCDD/Fs), partly due to lack of feasible methods to study them. However, data gathered as side products of other studies and recent developmental studies show that the development of dentition is sensitive to TCDD and that bone development and homeostasis are disturbed after PCDD/F or PCB exposure. The aim of this article is to give an overview of PCDD/F or PCB induced alterations in mineralized tissues.

Studies in adult animals

Chronic exposure to TCDD altered bone geometry and reduced breaking force and stiffness of tibia with approximately 10-fold sensitivity difference in two rat strains with different TCDD sensitivity[1]. In the same study, lower incisors were affected in both strains without a clear sensitivity difference. The aberrations involved odontoblastic and pulpal cell death accompanied with arrested dentin formation. Furthermore, precocious squamous metaplasia was found in the postsecretory enamel organ[2]. In adult female rats, coplanar PCB126 reduced bone length, water content and torsional stiffness[3]. In female rats, PCB exposure increased osteoid surface, cortical thickness and organic content[4]. Nearly lethal PCB126 exposure via diet induced osteolysis in maxilla and mandible of juvenile minks[5]. A single TCDD dose of 1000 µg/kg to young adult males of a resistant rat strain hampered skull growth resulting in smaller skull size 16 weeks after dosing. In the same study, TCDD caused defective dentin formation and pulpal perforation of continuously erupting incisor teeth[6]. Cystic periodontal lesions around the unerupted tooth were found in rhesus macaques after a high dietary exposure to a PCB mixture containing mainly tetra-, penta- and tri-PCBs[7].

Studies in developing animals

PCB exposure arrests bone growth in birds. American kestrels, exposed after hatching to doses of PCB126 that did not significantly decrease body weight, exhibited significantly shorter crown-rump length and long bone length[8]. High maternal dietary exposure (59 ng TEQ/kg feed) resulted in decreased hatchability in association with feet and leg deformities as well as in malformed brain cases and poorly ossified skull bones in hen embryos and chicks[9]. Fish respond to TCDD with altered cartilage, bone and tooth development. TCDD reduced the length of craniofacial structures as well as total length of developing rainbow trout[10,11], and caused severe dysmorphogenesis in cranio-facial structures of zebrafish[12]. TCDD also disconcerted calcification in spinal cord and spines in medaka fish[13], retarded rib development in rainbow trout[11] and altered vertebral development in zebrafish[12]. Absence of teeth was reported in exposed sac fry of rainbow trout[11].

Very few developmental studies have reported the effect of TCDD on bones or teeth in mammals. A single maternal dose of 0.5 µg/kg or 1.0 µg/kg on gestation day 9 affected the shape and reduced the size of mandible in mouse offspring[14]. In mice, lactational exposure fastened incisor eruption[15]. The development of interfrontal bone was retarded in embryonic mice after a maternal dose of 25 µg/kg TCDD on gestation day 10[16]. High maternal exposure to a mixture of PCBs and organochlorines, excluding PCDD/Fs, resulted in facial malformations in rat offspring[17]. In rats, development of teeth appears to be as sensitive, if not more sensitive, to TCDD as reproductive organs. A single maternal dose as low as 0.03 µg/kg to pregnant rat dam affected tooth development in offspring. TCDD increased caries susceptibility, diminished molar size, retarded molar eruption but accelerated incisor eruption in rats exposed *in utero* and/or via lactation[18,19,20]. A maternal dose 1 µg/kg during gestation is sufficient to block third molar development in rat offspring, if the exposure occurs during gestation[18,19], and the same dose alters bone geometry, bone mineral density and mechanical properties of tibia and femur in offspring[21]. TCDD exposure during gestation and lactation to rhesus monkeys at a maternal dose of 0.3 µg/kg resulted in incomplete calcification, accelerated eruption of teeth as well as malshaped and missing teeth in the offspring. *In utero* exposure without lactational exposure was enough to induce these effects, as seen in a stillborn offspring[22]. Yasuda *et al.* have not yet reported possible effects of TCDD on bone development in this study. On the other hand, newborn rhesus and cynomolgus monkey neonates, exposed after birth to a similar PCB mixture via bottle feeding as the Canadian breast-fed infants via breast milk, exhibited no anomalies in their skeletal development or tooth eruption[23]. A high dose of TCDD (1000 µg/kg) to lactating rat dams blocked the development of offspring third molars, halted molar root formation and arrested dentinogenesis of the incisors[24]. In addition, enamel maturation in molars was impaired and dentin mineralization retarded. In enamel, TCDD caused a dose-dependent decrease in organic matrix degradation, a possibly permanent defect[25]. It appears that TCDD can totally block the development of third molars, whereas the incisors respond with deviated dentinogenesis and pulpal perforations, at least in rats[2,6,24]. Furthermore, the most sensitive time for third molar agenesis is during gestation, apparently during tooth initiation[19].

Wild-life studies

Some reports associate lesions observed in top-predator animals with environmental exposure to organochlorines. Baltic seals sampled during 1960-1985 - a period of heavy organochlorine contamination of the Baltic Sea - suffered from severe bone loss in skull[26]. Another study linked periodontitis and tooth loss, among other lesions, in beluga whales of St Lawrence Estuary with organochlorine exposure[27]. Bone mineral density in East Greenland polar bears correlated negatively with subcutaneous adipose tissue concentration of organochlorines, for example ΣPCB[28]. Artificially hatched eggs of tern collected from heavily organochlorine contaminated Great Lakes suffered from low hatchability, growth-retardation, and at necropsy, isolated cases of weak ossification and shortened mandible, even lack of jaw or skull bones was found in the chicks[29].

Effects of dioxin-like chemicals on human teeth and bone

High accidental exposure to PCBs and dioxin-like chemicals has led to oral lesions in humans. Two similar mass PCB poisonings of humans *via* contaminated cooking oil occurred in Japan and Taiwan. Japanese adults suffered from various symptoms, e.g. acneiform skin eruptions. Affected mothers gave birth to dark coloured babies that had precociously erupted teeth. Some of these babies had large and wide openings in frontal and occipital fontanels and sagittal suture was wider than normally, additionally calcification of the parieto-occipital area of the skull was deviated[30]. Broken teeth were found more often in patients exposed at age over 16 than in nonexposed subjects[31]. In Taiwan the symptoms involved chloracne and hyperpigmentation in adults. Nine percent of transplacentally exposed children had erupted teeth at birth, whereas none of the control subjects had any. Tooth chipping was found in 11% of the patients as opposed to control value 0% and caries in 68% vs 54% in exposed and control children, respectively[32]. Other studies revealed that Taiwanese children had abnormally shaped tooth roots, eruption of permanent teeth was retarded and they were missing permanent teeth germ at high frequency[33]. Accidental exposure

to TCDD occurred in Seveso, Italy after a chemical factory explosion. Missing permanent teeth, lateral incisors and second premolars, were recorded in Seveso subjects that were less than 9.5 years old at the time of exposure. In addition, developmental defects of enamel correlated with TCDD exposure[34]. Effects of high exposure to PCBs and dioxin-like chemicals on bones of adults have not been reported after Yusho, Yucheng or Seveso accidents.

Even occupational, environmental or dietary exposure may lead to alterations in mineralized tissues. Mothers working in a capacitor factory and exposed to PCBs reported carious teeth more often in their children breast-fed for more than 5 months. Some children had gingival pigmentation and mottled enamel[35]. Children living in a PCB contaminated area in Slovenia had more developmental defects of enamel mainly due to demarcated opacities and hypoplasia than controls. Most frequently affected teeth were incisors and premolars[36]. Background exposure to PCDD/Fs via mothers' milk in 1987 correlated with enamel hypomineralization of the first permanent molars that mineralize during the first 2 years of life. An important factor was the total exposure, dependent on the PCDD/F concentration of the milk and duration of lactation, which correlated with both the frequency and severity of the lesions[37]. Another Finnish study linked the duration of lactation with mineralization defects in children born in 1981-1984. The defects correlated clearly with the total exposure to PCDD/Fs, but only weakly with PCB exposure[38]. Organochlorines with hormone-like properties can be hypothesized to alter bone composition. An epidemiological study of Swedish fishermen and their wives suggested that those living next to the organochlorine contaminated Baltic Sea would have increased risk for vertebral fractures as compared to those from less contaminated Swedish West coast. However, smoking, a risk factor for osteoporosis, differed between exposed and controls, and individual exposures were not determined[39]. A more detailed study gave limited support to the earlier result proposing that females from the coastal regions of the Baltic Sea eating more than one fatty fishmeal a month had greater risk for osteoporotic fractures than those living on the West coast [40].

Summary

Taken together, available data show that TCDD affects both the development of dentition and bones, as well as the homeostasis of bones. Studies from our laboratory indicate that the development of teeth is among the most sensitive endpoints of TCDD induced toxicity. Bones appear to be slightly less sensitive than teeth, and constant remodelling remedies the TCDD induced defects. As teeth are not remodelled after formation, and because even background exposure has resulted in enamel defects in humans, enamel defects such as hypoplasy can be used as indicator for dioxin exposure.

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