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Characterization of Dioxin-induced Bone Tissue Modulations: Investigating the Role of AhR and the Retinoid System

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ABSTRACT

All individuals are exposed to a large number of chemicals from multiple sources, and concern is growing that many everyday chemicals, alone or in combination, contribute significantly to observed increases in public health diseases. Bone tissue has been identified as a target for effects of environmental chemicals, however, possible consequences for human and wildlife health as well as the underlying mechanisms behind these effects are not yet well known.

In the present thesis, bone tissue modulations following exposure to dioxins were characterized in experimental models, and the role of a functional aryl hydrocarbon receptor (AhR) for the observed effects, as well as for a normal bone phenotype, was investigated. The results show that exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) affects bone tissue in terms of altered geometrical, micro-structural, material and macro-mechanical properties. Osteoblast differentiation processes are affected by TCDD-exposure *in vitro*, which probably reflects one important cause for the disturbances of bone mineralization observed following *in vivo* exposure. Altered geometrical as well as densitometrical and micro-structural bone properties were associated with changes in circulating retinoid levels, which may reflect part of the observed bone modulations. Furthermore, altered expression of retinoid-related genes, as seen in osteoblastic cells following TCDD-exposure *in vitro*, might be a contributing mode-of-action underlying the disturbed osteogenesis process following dioxin exposure. A functional AhR is crucial for the manifestation of the observed dioxin-induced effects, and also impacts the normal bone phenotype as lack of AhR resulted in slightly modified bone tissue properties, both similar and opposite to effects of TCDD-exposure. Further, the outcome is clearly influenced by the timing of TCDD-exposure, as prenatal exposure resulted in delayed matrix maturation, while adult exposure caused a harder and stiffer bone matrix.

Based on the observations in the experimental models in this study, the overall results show that environmental contaminants, to which humans are continuously exposed, have the ability to modulate the osteogenesis process. The functional consequences of such modulations should be further elucidated in order to establish any causal links between exposure to everyday chemicals and effects on the bone tissue properties, and possible contribution to bone disorders.

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