C21 Species Specific Differences in Dioxin Toxicity: Differences in Gene Regulation?

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The goals of this presentation are to: (1) describe observed differences in dioxin-responsive element (DRE) prevalence and location in man and rat PEPCK gene sequences, (2) to clarify the nature and function of transcriptional enhancer elements in the control of gene transcription, and (3) to suggest a possible mechanism to explain why dioxin-mediated lethality in rats has not been observed in humans.

This presentation will impact the forensic science community by demonstrating the differential dioxin-mediated species toxicity, and how it may be dependent on dioxin's differential ability to regulate species-specific genes. Consequently, dioxin may not be as toxic to humans as regulators would have you believe.

Dioxin down regulation of the rat phosphoenolpyruvate carboxykinase (PEPCK) gene is the putative mechanism by which dioxin causes body weight loss, wasting, and death in rats. A search of the DNA sequence coding for the PEPCK gene, including significant non-coding flanking sequences, identified significant homology with the 10 base pair (bp) functional consensus sequence for the dioxin response element (DRE). Ten putative DREs with exact homology to the 5-bp core binding sequence (5′-GCGTG- 3′) and more than 70% homology to the functional consensus sequence (5′-T/GNGCGTGA/CG/C-3′) occur in close proximity to the PEPCK gene and within a region previously suggested to be of significance in this genes regulation. Eight of these DREs contain specific nucleotide substitutions known to abolish DRE functionality and are therefore not functional as enhancers of gene transcription. The remaining two putative DREs are potentially functional transcriptional enhancers. Two potentially functional DREs and four non-functional DREs are located in a unique overlapping arrangement within a 102-bp region downstream of the PEPCK gene in a manner that suggests coordinate regulation of the gene by the aryl hydro- carbon receptor (AhR). The location, binding affinity, and potential func- tionality of these putative DREs suggest a novel mechanism by which dioxin may regulate this genes transcription. In contrast, the available sequence of the human PEPCK gene does not contain similarly arraigned DREs, an observation which may explain the apparent lack of dioxin-mediated acute body weight loss, wasting, and death in humans.

Dioxin, Toxicity, Gene Regulation

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