Retinoid Teratogenesis: Toxicokinetics and Structure-Specificity

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It becomes increasingly clear that the dose is often an unsatisfactory correlate to the toxic effect produced by a drug or environmental agent. The effect in a particular target organ is strictly dependent on the concentration-time relationships of the drug and/or its active metabolite(s) in the target tissue, reactive metabolites formed or specific binding phenomena (Monro, 1992). Thus, an effect is dependent on the chemical structure of the xenobiotic (intrinsic activity), the exposure of the target tissue, and the susceptibility or sensitivity toward a particular insult (pharmacogenetics). This general concept will be discussed here with regard to drug teratogenesis, where it is particularly helpful to explain and overcome species differences, which are so extreme in this area of toxicology.

Species Differences

Species differences is still one of the most important problems in toxicology, and in particular teratology. Thalidomide was shown to produce characteristic limb defects in human and subhuman primates, but not in the rat and the mouse, even with doses several orders of magnitude above human therapeutic doses; the rabbit appears to be responsive to thalidomide, at least at high dosing (Neubert et al., 1988; Sterz et al., 1987; Schmahl et al., 1989). 13-Cis-retinoic acid (isotretinoin), a retinoid used for treatment of severe acne and other skin conditions, showed similar, if not as extreme species differences: The human was very sensitive toward this drug, followed by the monkey and the rabbit; the mouse and rat were again relatively insensitive (for recent reviews cf. Nau, 1990; 1993).

The reason behind the species difference of thalidomide teratogenesis is still unclear and pharmacokinetic studies have not yet added to our knowledge. Pharmacokinetic studies are well on the way to explain most, if not all of the major species differences in regard to 13-cis-retinoic acid teratogenicity.
Vitamin A and Retinoids

Retinoids are a family of substances which are structurally and functionally related to retinol (vitamin A) (cf. Blomhoff et al., 1992) (Fig. 1). They are required for a great range of biological processes including vision, reproduction, growth, differentiation and maintenance of epithelial tissues. All-trans-retinoic acid, formed intracellularly via oxidation of dietary vitamin A, is a principal regulatory retinoid which can substitute for retinol for nearly all vitamin A-related functions except vision and certain aspects of reproduction. Indeed, all-trans-retinoic acid is much more active than retinol in the control of differentiation and morphogenesis. The latter process appears to be of fundamental importance in the regulation of the pattern formation of the developing embryo. It is hypothesized that concentration gradients of all-trans-retinoic acid established within the developing limb bud and central nervous system are crucial morphogenetic events defining the three-dimensional structure of the developing embryo (Thaller and Eichele, 1987; Durston et al., 1989).

Figure 1 The main metabolic pathways of 13-cis-retinoic acid - depending on the species - consist of 4-oxidation (cytochrome P-450 dependent), β-glucuronidation (isoenzyme of the GT-1 family of glucuronyl transferases) and isomerization to the all-trans-retinoic acid.