

Retinoids As Teratogens

Vitamin A (retinol) is an essential vitamin in the daily functioning of human beings that helps regulate cellular differentiation of epithelial tissue. Studies have shown that an excess of vitamin A can affect embryonic development and result in teratogenesis, or the production of birth defects in a developing embryo. Excess intake of vitamin A and retinoids by pregnant women often results malformations to fetuses' skulls, faces, limbs, eyes, central nervous system. Additionally, doctors often use derivatives of vitamin A, known as retinoids, as medicine to treat a number of skin conditions and carcinomas, the most common form of human cancers.

The mammalian body transforms retinol, obtained dietarily, and stores it in the liver as retinyl esters. Esters are chemical compounds of acids condensed with alcohols. Those retinyl esters are then chemically transformed, through the process of hydrolysis, into retinol, which travels into the bloodstream for transport around the body. In humans bloodstreams, the retinol attaches to plasma retinol-binding proteins, the retinol transportation mechanism. Cells that require retinoic acid take up the retinol and convert it to retinoic acid, its metabolite, through two enzymes: retinol dehydrogenases (ROLDH) and retinal dehydrogenases (RALDH). The first enzyme, ROLDH, converts retinol to retinaldehyde. The second enzyme, RALDH, converts retinaldehyde into retinoic acid. Numerous forms of retinoic acid exist, including all-trans-RA, 9-cis-RA, didehydroRA, and 4-oxo-RA. In the nucleus of a cell, retinoic acid acts as a ligand, which is a molecule that binds to a site on a specific protein, to activate two families of transcriptional factors. These two families are the retinoic acid receptors (RAR) and retinoid X receptors (RXR), which bind to genes that respond to retinoic acid. There are three forms of RARs and three forms of RXR.

Studies with in vitro rat embryos have shown that retinoids act directly on the embryo, causing those embryo to develop abnormally. Developing organs partly depend on the amount of active retinoid that accumulates over time (concentration-time relationship) during stages of organ development. Factors that determine the amount of active retinoid in the embryo include the rate at which the maternal intestine absorbs retinoids, the maternal retinoid metabolism, the half-life of the retinoid in the maternal plasma, and the rate at which the placenta transfers retinoids from the pregnant female to her embryos or fetuses. The effects of one retinoid may vary from species to species; each species has unique embryonic tissue and therefore, different effects on developmental events may occur even when exposed to equal doses of the same retinoid.

Retinoic acid helps regulate embryonic development by activating gene transcription in different locations of the embryo. Cells will only respond to retinoic acid if the cells possess the appropriate receptors and if retinoic acid concentrations are within the appropriate range for the receptors. Because different levels of retinoic acid activate different genes, many doctors and pathologists study the precise control of the concentration of retinoic acid.

Retinoids contribute to expression of Hox genes in the early stages of human embryonic development, particularly the fourth week. Hox genes regulate the development of body-plan within the embryo. There are thirty-eight human Hox genes. In embryos exposed to excess retinoic acid, the Hox gene malfunction, which thereby disrupts the genetic control of body shape (axial patterning) in a developing embryo. Retinoic synthesis occurs in specific regions of the body that, as previously mentioned, must maintain exact levels of retinoic acid. Teratogenic retinoic acid may disrupt these levels. These disruptions can then lead to developmental defects, particularly in the embryonic spinal cord, central nervous system, and spinal cord, where retinoic acid synthesis and catabolic enzymes are located.

Sidney Q. Cohlman in 1953 observed that high doses of vitamin A in pregnant rats correlated with

teratogens in the offspring. Cohlan, working at the New York University School of Medicine in New York, New York, reported his results in a paper titled "Excessive Intake of Vitamin A as a Cause of Congenital Anomalies in the Rat." In the study, Cohlan fed pregnant rats with 35,000 IU (International Unit) of natural vitamin A per day. This dosage, an excess of over 32,000 IU from the dosage recommended for pregnant women, resulted in rats born with eye defects, cleft lips, cleft palates, exencephaly—a disorder in which the brain protruded outside of the skull, and shortness of the lower jaw (brachygnathia). Cohlan also noted that excess of vitamin A intake, on gestation days two through six, resulted in the highest number of fetal abnormalities. Researchers inferred from this data that developing embryos are particularly sensitive to the developmental effects of retinoids during early development.

Following Cohlan's experiment, hundreds of additional studies described more than seventy types of anomalies affecting almost every organ system related to excess intake of retinoids. These studies covered embryos from a variety of species, including monkeys, rabbits, rats, mice, and hamsters. The most common defects found across all species included central nervous system abnormalities such as an abnormally small head (microcephaly), incomplete development of the spinal cord (spina bifida), a brain disorder in which some part of the brain is located outside of the skull (exencephaly), and brain swelling due to buildup of fluid (hydrocephaly). Other common defects included the paralysis of facial nerves, underdevelopment of the upper jaw, cleft palate, cleft lip, absent or deformed ears, and shortened limbs.

Retinoids help treat skin diseases, as well as a variety of cancers including breast cancer, carcinomas of the respiratory tract, a subtype of leukemia, and ovarian cancer. The 13-cis-retinoic acid, a derivative of synthetic 13-cis-vitamin A, effectively treats psoriasis. In 1976 Gary Peck and Frank Yoder reported the first US study demonstrating those effects while working in Bethesda, Maryland, for the US National Institute of Health.

From 1982 to 1999, four retinoids were approved in the US for the treatment of dermatological conditions: 13-cis-retinoic acid isotretinoin (Accutane), etretinate (Tegison, Tigason), acitretin (Neotigason), and bexarotene (Targretin). Isotretinoin and etretinate were later marketed in the US with the warning that pregnant women should not use them. Malformations from exposure to 13-cis-retinoic acid causes defects, in developing fetuses, in the central nervous system, such as fluid buildup inside the brain, underdevelopment of the cerebellum, and structural malformation of the cerebral cortex. Use of 13-cis-retinoic acid by women during pregnancy also can result in developmental irregularities in fetuses and children, such as cleft palates, absent or abnormally small ears, heart defects, and thymus abnormalities. For children whose mother were exposed to Etretinate, which is similar to 13-cis-retinoic acid, they exhibit limb defects as well as cardiac and thymus abnormalities. The risk of fetal malformations from exposure to etretinate persists for a longer period of time after the pregnant women's exposure to the substance ends because etretinate stores in her deep body compartments, especially fat depots, and has an extremely long half life (120 days) in the human body. 13-cis-retinoic acid has a shorter half life than etretinate.

In 2002 the US Food and Drug Administration (FDA) in Washington D.C. placed strict risk management protocols upon each of these retinoids, such as isotretinoin and etretinate, so as to prevent the manifestation of their teratogenic effects. Doctors prescribe isotretinoin, the first retinoid approved for medical use in the US, to treat severe acne. The US FDA classified isotretinoin a Category X drug, which is the most severe pregnancy category assigned by the FDA. Category X includes drugs for which studies in animals or humans have displayed fetal abnormalities and that the risks of use of the drug by pregnant women clearly outweighs any potential benefits. US patients cannot receive isotretinoin unless enrolled in iPLEDGE, a comprehensive risk management program designed in 2006 to prevent fetal exposure to isotretinoin. Etretinate, which was approved by the US FDA on 30 September 1986, is a synthetic retinoid used to treat severe psoriasis. Due to its high incidence of teratogenic effects, etretinate was removed from the US market on 20 December 2002.

Sources

1. Brent, Robert. "In Memoriam: Dr. Sidney Q. Cohlan (1915-1999)." *Teratology* 62 (2000): 1-3.

2. Cohlman, Sidney. "Excessive Intake of Vitamin A as a Cause of Congenital Anomalies in the Rat." *Science* 117 (1953): 535-536.
3. Jick, Hershel. "Retinoids and Teratogenicity." *Journal of the American Academy of Dermatology* 39 (1998): S118-122.
4. Maden, Malcolm. "The Role of Retinoic Acid in Embryonic and Post-Embryonic Development." *Nutrition Society* 59 (2000): 65-73. <http://journals.cambridge.org/action/displayAbstract?fromPage=online&aid=796188> (Accessed February 28, 2014).
5. Pawson, Beverly A. "History of the Retinoids." *Journal of the American Academy of Dermatology* 6 (1982): 577-82.
6. Peck, Gary, and Frank Yoder. "Treatment of lamellar Ichthyosis and Other Keratinising Dermatoses with an Oral Synthetic Retinoid." *The Lancet* 308 (1976): 1172-1174.
7. Söderlund, Maria Berggren, Göran A. Fex, and Peter Nilsson-Ehle. "Concentrations of Retinoids in Early Pregnancy and in Newborns and their Mothers." *The American Journal of Clinical Nutrition* 81 (2005): 633-6. <http://ajcn.nutrition.org/content/81/3/633.full> (Accessed February 28, 2013).
8. Ross, Sharon A., Peter J. McCaffery, Ursula C. Dragner, and Luigi M. De Luca. "Retinoids in Embryonal Development." *Physiological Reviews* 80 (2000): 1022-46.
9. Soprano, Dianne Robert, and Kenneth J. Soprano. "Retinoids as Teratogens." *Annual Review of Nutrition* 15 (1995): 111-132.