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Researchers discover precisely how thalidomide causes birth defects

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Thalidomide may have been withdrawn in the early 1960s for use by pregnant women, but its dramatic effects remain memorable half a century later. Now, researchers have taken a major step toward understanding exactly how thalidomide causes the birth defects. This is important as thalidomide is still used to treat diseases like multiple myeloma and leprosy, and is being tested for cancers and autoimmune disorders. This discovery was recently published online in the *FASEB Journal*.

"The ability of thalidomide breakdown products to cause birth defects complicates our attempts to understand how the birth defects arise and the search for safer alternatives to thalidomide, although the rabbit embryo culture model will facilitate both processes," said Peter G. Wells, Pharm.D., a researcher involved in the work from the Department of Pharmacology and Toxicology at the University of Toronto in Ontario, Canada.

Specifically, Wells and colleagues found that birth defects result from not only thalidomide, but also from the compounds that it breaks down to in the body, which last up to 40 times longer in the body than thalidomide itself. These compounds ultimately lead to the production of highly toxic forms of oxygen, called "reactive oxygen species," (ROS) including hydrogen peroxide and free radicals that alter disrupt normal embryonic development, causing birth defects.

To make this discovery, the scientists developed a new animal model for

fetal thalidomide exposure by extracting rabbit embryos from pregnant mothers during the first trimester of pregnancy, when the limbs and other structures are developing. Then they cultured the embryos in dishes for one to two days, with or without exposure to thalidomide or one of its breakdown products. Front and hind limb deformities as well as other abnormalities were observed only in the embryos exposed to thalidomide or one of its products. DNA damage caused by ROS and free radicals was similarly increased only in the exposed embryos.

"Administering thalidomide to pregnant women remains was of the biggest mistakes made in modern medicine," said Gerald Weissmann, M.D., Editor-in-Chief of the FASEB Journal, "Yet we now use thalidomide and related products as effective therapies for serious diseases. This research not only explains what caused all that misery years ago, but promises to help us find safer alternatives to thalidomide in the future."

More information: Crystal J. J. Lee, Luisa L. Gonçalves, and Peter G. Wells. Embryopathic effects of thalidomide and its hydrolysis products in rabbit embryo culture: evidence for a prostaglandin H synthase (PHS)-dependent, reactive oxygen species (ROS)-mediated mechanism. FASEB J. doi:10.1096/fj.10-178814

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