OXIDATIVE STRESS AND HYPERSENSITIVITY RESPONSE TO PHENOLIC HAPTENS

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Phenolic haptens undergo oxidative metabolism and produce highly reactive quinone methides that can form conjugates with macromolecules of antigen–presenting cells (APC) and initiate sensitization. One electron oxidation intermediates of phenolic compounds, phenoxyl radicals, can be recycled by different physiological reductants, e.g., antioxidants. We hypothesized that reduction of phenoxyl radicals to their phenolic forms by antioxidants should inhibit/delay formation of quinone methides, and result in abrogation or lessening of the immune response. This effect should depend on the antioxidant/prooxidant status of the APC. We studied oxidation of eugenol (4-allyl-2-methoxyphenol) (EU) to its quinone methide by horseradish peroxidase/H_2O_2 (HRP/H_2O_2) and found that oxidation of EU was effectively inhibited by ascorbate. While dihydrolipoic acid (DHLA) alone was not able to efficiently inhibit oxidation of EU, it interacted synergistically with ascorbate, preventing HRP/H_2O_2-catalyzed oxidation of EU. In two murine models, we found that oxidation of EU in vivo affected the hypersensitivity response to hapten. Mice sensitized with oxidized EU revealed an enhanced cellular immune response to EU. In mice treated with an antioxidant, lipoic acid (LA), sensitization by EU caused a decreased inflammatory response. We further used vitamin E–deficient mice to test their susceptibility to isoeugenol (IEU)–induced hypersensitivity response. These mice showed decreased levels of vitamin E, GSH and total antioxidant reserves in skin, and elevated levels of mast cell mediated skin responses compared to controls (vitamin E–sufficient mice). We conclude that redox- and antioxidant status of skin are essential determinants of hypersensitivity response to phenolic haptens.

SAN FRANCISCO

12th INTERNATIONAL CONTACT DERMATITIS SYMPOSIUM

1st INTERNATIONAL SYMPOSIUM ON THE PREVENTION OF OCCUPATIONAL SKIN DISEASE IN HAIRDRESSERS

October 14-18, 1999

ABSTRACTS

SDEF SKIN DISEASE EDUCATION FOUNDATION