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National Institute of Toxicological Research, Korea Food and Drug Administration

The use of alpha-hydroxy acids(AHAs) containing cosmetics has aroused the public interest with their supposed ability to reduce wrinkles, roughness, age spots of skin and other signs of sunburn damages. The excessive and chronic use of AHA containing cosmetics could cause skin irritation, swelling and sunburn, and may increase photo-toxicity and photo-carcinogenesis. However, exact dose-response relationship, photo-toxic effects and skin toxic mechanisms have not been known. In the present study, dose and time effects of glycolic acid, one of the most commonly used AHAs, alone or combination with UVB on skin irritation and inflammatory response were examined. Skin irritation by glycolic acid and UVB alone was increased in dose and time-dependent manners. Higher dose of glycolic acid and UVB (3 J/cm2) treatment for 2 weeks caused severe skin irritation. Lower dose of glycolic acid and UVB (0.4 J/cm2) caused slight or mild irritation. However, lower glycolic acid enhanced UVB-induced skin irritation resulting in severe irritation. Histological examination showed that glycolic acid dose dependently reduced integrity of stratum corneun and increased skin thickness, and higher dose of glycolic acid destroyed epidermal layer without inflammatory response. UVB increased skin thickness, and caused condensed inner stratum corneum and reduced its integrity of outer layer. Glycolic acid enhanced UVB-induced the reduction of stratum corneum integrity. Completely lost of organization of stratum corneum was seen in UVB and glycolic acid combination treated skin. Glycolic acid did not change basal or UVB-induced PGE2 production and COX-2 protein expression. UVB,whereas,increased PGE2 (50% over control by higher dose of UVB) and COX-2 expression(2 and 3 fold). These results show that glycolic acid cause skin irritation in a dose and time dependent manners and enhance UVB-induced skin irritation, however glycolic acid-induced skin irritation may not be associated with inflammatory response.

[PA4-12] [10/19/2000 (Thr) 10:00 - 11:00 / [Hall B]]

Co-carcinogenic potential of glycolic acid in hairless mouse skin

Hong JT°, Ahn KS, Kim EJ, Jung KM, Park KS, Lee JK, YP Yun*, YK Kim, KW Ha and Lee SH

National Institute of Toxiological Research, KFDA and College of Pharmacy Chungbuk National University

Alpha-hydroxy acids (AHAs) are organic acids present in natural sources such as fruits, wine and milk.Such sources of AHAs have been used as cosmetic material for several years in the public with their supposed ability to reduce wrinkles, roughness, age spots of skin and other signs of sunburn damages. However. It is also true that the excessive and chronic use of AHAs containing cosmetics could cause skin irritation, swelling, sunburn, photo-toxicity, and that increase of photo-carcinogenesis has been suspected. Previous our study showed that glycolic acid, one of the most commonly used AHAs increased skin irritation dose dependently after treatment for 14 consecutive days. In the present study, we examined the tumor (anti)promoting ability of glycolic acid on two-stage carcinogenesis test using inbred hairless female mice (15/group) skin tumors either induced by 7,12-dimethylbenz[a]anthracene (DMBA) as an initiator and glycolic acid (twice a week) as a promoter, or induced by UVB followed glycolic acid (12.5 mg/cm2). Glycolic acid promoted parpilloma incidence and multiplicity initiated by DMBA similar to 12-O-tetradecanoyl phorbol-13-acetate (TPA), however, inhibited UVB-induced parpilloma formation. The expressions of PCNA, cyclins, cyclin dependent kinase and cyclooxygenase-2 , and the activation of transcription factor NF-kB and AP-1 were concomitantly decreased in glycolic acid treated skin compared to UVB treated skin. Change of these factors by glycolic acid may collectively contribute to during the skin carcinogenesis.

[PA4-13] [10/19/2000 (Thr) 10:00 - 11:00 / [Hall B]]

The Roles of ATP and Calcium in Morphology Changes and Cytotoxicity Induced by Benzoquinone in Platelets

Lee SK°, Chung SM, Lee MY, Chung JH

College of Pharmacy, Seoul National University, Seoul 151-742 Korea

To understand mechanism of benzoquinone-induced cytotoxicity, the roles of ATP and calcium in platelet toxicity and morphology changes was investigated. Using scanning electron microscopy, morphological changes to platelets following 1,4-benzoquinone exposure consisted of membrane blebbing at 5 min which was significantly different from shape changes (pseudopod formation) observed in response to physiological agonists. Benzoquinone-induced platelet membrane bleb formation was associated with rapid depletion of intracellular ATP and independent of presence of extracellular calcium. Benzoquinone-induced platelet lysis (LDH leakage) observed between 20-30 mins was dependent on extracellular calcium and associated with increased cytosolic calcium. Benzoquinone-induced cytotoxicity was inhibited by calmodulin antagonists, suggesting that calmodulin could play a major role in 1,4-benzoquinone toxicity via protease activation. These results suggested that the progression of events for quinone-induced cytotoxicity in platelets to be as follows: quinones deplete intracellular ATP; formation of blebs occurs; calcium homeostasis is disrupted, resulting activation of calmodulin-dependent proteases; irreversible cytotoxicity occurs.

[PA4-14] [10/19/2000 (Thr) 10:00 - 11:00 / [Hall B]]

TCDD induced micronuclei in estrogen receptor positive human breast cancer cells

Kim JW, Han ES, Park MS, Eom MO, Jun HS, Jung HK, Sim WS and Oh HY

Genetic Toxicology Division, National Institute of Toxicological Research, KFDA, Laboratory of Molecular Biology, Department of Biology, Korea University

Bisphenol A (BPA, Cas no. 80-05-7), di-2-ethylhexyl phthalte (DEHP, Cas no. 117-81-7), and 2,3,7,8-tetrachlorodibenzodioxin (TCDD, Cas no. 1746-01-6) were well known endocrine disrupting chemicals (EDCs). They showed all negative results in the Standard genetic toxicology test battery recommended by ICH guideline, i.e. bacterial reverse mutation assay, chromosome aberration assay, mouse lymphoma tk+/- assay and in vivo rodent micronucleus assay (MN). In our previous study, bisphenol A and di-2-ethylhexyl phthalte induced micronucleus formation in MCF-7 cells (estrogen receptor positive). In this study, to identify the relationship between MN formation and estrogen receptor (ER), TCDD was studied using micronucleus formation in human breast MCF-7 cells (ER positive). We also performed in vitro MN to identify the role of estrogen receptors with TCDD and tamoxifen, inhibitor of estrogen receptor, in MCF-7 cells during micronucleus formation. TCDD induced MN formation in MCF-7 cells (ER positive) was 6.60 fold higher than that of MCF-10A cells (ER negative). Though TCDD induced MN in MCF-10A cells, the frequencies were weak positive. Tamoxifen inhibited TCDD-induced MN formation up to 47.3% in MCF-7 cells.

[PA4-15] [10/19/2000 (Thr) 10:00 - 11:00 / [Hall B]]

Potentiation of Agonist-Induced Platelet Aggregation by Trivalent Arsenic

Lee MY°, Bae ON, Chung JH

College of Pharmacy, Seoul National University, Seoul 151-742 Korea

Chronic ingestions of arsenic by drinking water have been shown to induce cardiovascular disease