

**LE Magazine December 1999**

## ABSTRACTS

**FEATURED:**

- Glutathione
- Lipoic Acid
- Cyclo-oxygenases  
COX-1, COX-2

**Glutathione and the elderly**  
**Glutathione and morbidity in a community-based**  
**sample of elderly.**

*J Clin epidemiol 1994 Sep; 47(9): 1021-6*

This study examined the association of blood glutathione level, a potential marker of physiological/functional aging, with a number of biomedical/psychological traits in a subgroup (N = 33) of a representative sample of community-based elderly. Higher glutathione levels were associated with fewer number of illnesses ( $p < 0.05$ ), higher levels of self-rated health ( $p < 0.01$ ), lower cholesterol ( $p < 0.05$ ), lower body mass index, and lower blood pressures. Subjects with diagnoses of arthritis, diabetes, or heart disease (as assessed by physicians) had at least marginally significant lower glutathione levels than those who were disease free. Glutathione, together with age and a measure of suppressed anger, accounted for 39% of the variance of an index of morbidity. Glutathione, by itself, accounted for 24% of the variance. To our knowledge, this is the first evidence of an association of higher glutathione levels with higher levels of physical health in a sample of community-based elderly. Further studies in large samples are needed to investigate glutathione as a potential overall health risk factor for morbidity among the elderly.

## Effects of LA

### **Alpha-lipoic acid supplementation: tissue glutathione homeostasis at rest and after exercise.**

*J Appl Physiol* 1999 *Arp*; 86(4) 1191-6

Antioxidant nutrients have demonstrated potential in protecting against exercise-induced oxidative stress. Alpha-Lipoic acid (LA) is a proglutathione dietary supplement that is known to strengthen the antioxidant network. We studied the effect of intragastric LA supplementation (150 mg/kg, 8 wk) on tissue LA levels, glutathione metabolism, and lipid peroxidation in rats at rest and after exhaustive treadmill exercise. LA supplementation increased the level of free LA in the red gastrocnemius muscle and increased total glutathione levels in the liver and blood. The exercise-induced decrease in heart glutathione 5-transferase activity was prevented by LA supplementation. Exhaustive exercise significantly increased thiobarbituric acid-reactive substance levels in the liver and red gastrocnemius muscle. LA supplementation protected against oxidative lipid damage in the heart, liver, and red gastrocnemius muscle. This study reports that orally supplemented LA is able to favorably influence tissue antioxidant defenses and counteract lipid peroxidation at rest and in response to exercise.

## **Lipoic acid, a model compound**

### **The pharmacology of the antioxidant lipoic acid**

*Gen Pharmacol 1997 Sep; 29(3) 315-31*

1. Lipoic acid is an example of an existing drug whose therapeutic effect has been related to its antioxidant activity. 2. Antioxidant activity is a relative concept: it depends on the kind of oxidative stress and the kind of oxidizable substrate (e.g., DNA, lipid, protein). 3. In vitro, the final antioxidant activity of lipoic acid is determined by its concentration and by its antioxidant properties. Four antioxidant properties of lipoic acid have been studied: its metal chelating capacity, its ability to scavenge reactive oxygen species (ROS), its ability to regenerate endogenous antioxidants and its ability to repair oxidative damage. 4. Dihydrolipoic acid (DHLA), formed by reduction of lipoic acid, has more antioxidant properties than does lipoic acid. Both DHLA and lipoic acid have metal-chelating capacity and scavenge ROS, whereas only DHLA is able to regenerate endogenous antioxidants and to repair oxidative damage. 5. As a metal chelator, lipoic acid was shown to provide antioxidant activity by chelating  $Fe^{2+}$  and  $Cu^{2+}$ ; DHLA can do so by chelating  $Cd^{2+}$ . 6. As scavengers of ROS, lipoic acid and DHLA display antioxidant activity in most experiments, whereas, in particular cases, pro-oxidant activity has been observed. However, lipoic acid can act as an antioxidant against the pro-oxidant activity produced by DHLA. 7. DHLA has the capacity to regenerate the endogenous antioxidants vitamin E, vitamin C and glutathione. 8. DHLA can provide peptide methionine sulfoxide reductase with reducing equivalents. This enhances the repair of oxidatively damaged proteins such as  $\alpha$ -i antiprotease. 9. Through the lipoamide dehydrogenase-dependent reduction of lipoic acid, the cell can draw on its NADH pool for antioxidant activity additionally to its NADPH pool, which is usually consumed during oxidative stress. 10. Within drug-related antioxidant pharmacology, lipoic acid is a model compound that enhances understanding of the mode of action of antioxidants in drug therapy.

## **Human cancer cell growth**

### **Induction of cyclo-oxygenase-2 mRNA by prostaglandin E-2 in human prostatic carcinoma cells.**

*British Journal of cancer 75 (8):p 1111-11181997*

Abstract: Prostaglandins are synthesized from arachidonic acid by the enzyme cyclo-oxygenase. There are two isoforms of cyclo-oxygenases: COX-1 (a constitutive form) and COX-2 (an inducible form). COX-2 has recently been categorized as an immediate-early gene and is associated with cellular growth and differentiation. The purpose of this study was to investigate the effects of exogenous dimethylprostaglandin E-2 (dmPGE-2) on prostate cancer cell growth. Results of these experiments demonstrate that administration of dmPGE 2 to growing PC-3 cells significantly increased cellular proliferation (as measured by the cell number), total DNA content and endogenous PGE 2 concentration. DmPGE-2 also increased the steady-state mRNA levels of its own inducible synthesizing enzyme, COX-2, as well as cellular growth to levels similar to those seen with fetal calf serum and phorbol ester. The same results were observed in other human cancer cell types, such as the androgen-dependent LNCaP cells, breast cancer MDA-MB-134 cells and human colorectal carcinoma DiFi cells. In PC-3 cells, the dmPGE-2 regulation of the COX-2 mRNA levels was both time dependent, with maximum stimulation seen 2 h after addition, and dose dependent on dmPGE-2 concentration, with maximum stimulation seen at 5  $\mu$ -g ml<sup>-1</sup>. The non-steroidal anti-inflammatory drug flurbiprofen (5  $\mu$ -M), in the presence of exogenous dmPG-2, inhibited the up-regulation of COX-2 mRNA and PC- 3 cell growth. Taken together, these data suggest that PGE 2 has a specific role in the maintenance of human cancer cell growth and that the activation of COX-2 expression depends primarily upon newly synthesized PGE-2, perhaps resulting from changes in local cellular PGE-2 concentrations.

## **COX-2 and the human pancreas**

### **Cyclooxygenase-2 expression is up-regulated in human pancreatic cancer**

*Cancer Res 1999 Mar 1;59(5):98790*

A large body of evidence suggests that cyclooxygenase-2 (COX-2) is important in gastrointestinal cancer. The purpose of this study was to determine whether COX-2 was expressed in adenocarcinoma of the human pancreas. Quantitative reverse transcription-PCR, immunoblotting, and immunohistochemistry were used to assess the expression of COX-2 in pancreatic tissue. Levels of COX-2 mRNA were increased by >60-fold in pancreatic cancer compared to adjacent nontumorous tissue. COX-2 protein was present in 9 of 10 cases of adenocarcinoma of the pancreas but was undetectable in nontumorous pancreatic tissue. Immunohistochemical analysis showed that COX-2 was expressed in malignant epithelial cells. In cultured human pancreatic cancer cells, levels of COX-2 mRNA and protein were induced by treatment with tumor-promoting phorbol esters. Taken together, these results suggest that COX-2 may be a target for the prevention or treatment of pancreatic cancer.

## The role COX-2 plays in tumorigenesis

### COX-2 and colon cancer

*Inflammation Research 1998 Oct;47 Suppl 2:S112-6*

The role of cyclooxygenase-2 (CoX-2) in colorectal tumorigenesis in mice was studied by Oshima et al. to determine the effects of COX-2 gene knockouts and a new COX-2 inhibitor. In the study, heterozygous Apcdelta716 knockout mice, a mouse model of human familial adenomatous polyposis (FAP), were either crossed to COX-2 gene knockout mice, or fed chow containing the COX-2-selective inhibitor. Apcdelta716 litter mates were used as positive controls, which developed 652+/-198 (SD) polyps at 10 weeks. Introduction of a COX-2 gene mutation, or feeding with the COX-2-selective inhibitor to the Apcdelta716 knockout mice, reduced the number and size of intestinal polyps dramatically. The results provide direct genetic evidence that COX-2 plays a key role in tumorigenesis, and indicate that COX-2-selective inhibitors can be a new class of therapeutic agents for colorectal polyposis and cancer.

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