

## ANTIOXIDANTS AND INFLAMMATORY MEDIATORS IN AGING

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Dysregulated immune and inflammatory responses have been well documented in both aging humans and animals. Investigation into the cellular and molecular mechanism underlying these disorders has provided compelling evidence that upregulated cyclooxygenase (COX)-2 and its product, particularly prostaglandin (PG)E<sub>2</sub>, play a critical role in the age-associated dysregulation of the immune and inflammatory responses. In particular, several studies have shown that increased PGE<sub>2</sub> production in old macrophages (M $\phi$ ) contributes to the suppression of T cell function with aging. Furthermore, interventions targeted at decreasing PGE<sub>2</sub> production have been shown to enhance T cell mediated function. COX-2 and its catalytic products are also suggested to play a key role in age-related neuro-degenerative diseases such as Alzheimer's and Parkinson's disease. The administration of anti-inflammatory drugs that inhibit COX activity has been shown, by some investigators, to be beneficial in preventing and treating these diseases. It is thus important to understand the underlying mechanisms of age related COX-2 upregulation and to delineate the factors that contribute to the regulatory mechanisms governing this change. Increased PGE<sub>2</sub> production has been shown to be mainly due to an increase in COX activity, which is, in turn, a result of increased COX-2 protein and mRNA expression. Elevated COX-2 mRNA represents a higher transcription rate rather than an altered stability of COX-2 mRNA. Upon stimulation, M $\phi$  from old mice generate more sphingolipid ceramide than those from young mice. Ceramide has been shown to induce, by itself, and also augment, LPS-stimulated COX-2 expression and PGE<sub>2</sub> production. Several lines of evidence indicate that the higher ceramide level in old M $\phi$  is an important contributor to the age-associated upregulation of COX-2 in M $\phi$ . Ceramide induces upregulation in COX-2 transcription by increasing activation of transcription factor NF- $\kappa$ B. Current studies are determining the mechanisms of age related increase in NF- $\kappa$ B activation. Antioxidants such as vitamin E, green tea, and oat extracts have been shown to inhibit PGE<sub>2</sub> synthesis through decreasing COX activity. Vitamin E was shown to inhibit COX activity through reducing peroxynitrite formation without affecting COX-2 expression. This effect of vitamin E was associated with improvement in T cell mediated function. Preliminary experiments indicate that the effect of green tea and oat extract is also mediated through inhibiting COX activity. These preliminary findings need to be confirmed and the biological consequence of green tea- and oat extract-induced inhibition of COX activity needs to be determined. Supported by NIA grant 2R01 AG009140-10A1 and USDA Agreement # 58-1950-4-461.