Age-associated Inflammatory Changes: Role of Nutritional Intervention

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Accumulating evidence suggests that aging is associated with dysregulated immune and inflammatory responses. Investigation into the cellular and molecular mechanisms underlying this phenomenon suggests that an up-regulated cyclooxygenase (COX)-2 expression, and resulting increase in production of prostaglandin E₂ (PGE₂), is a critical factor. Macrophages from old mice have significantly higher levels of PGE₂ production compared with those from young mice, a result of increased COX-2 expression and protein levels leading to increased COX enzyme activity. Further, it is possible that the age-associated increase in macrophage PGE₂ production is due to ceramide-induced up-regulation of nuclear factor-kappa B activation. Such processes may also occur in cell types other than macrophages, lending further insight into potential mechanisms of age-related disease. More research is necessary to determine the efficacy of nutrient/dietary modifications, such as antioxidants and lipids, for reducing the age-related increase in COX activity and PGE₂ production that are associated with several disease states.

Key words: aging, inflammatory response, macrophages, ceramide, sphingomyelinase, cyclooxygenase 2, prostaglandin E₂, nuclear factor-kappa B.

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INTRODUCTION

Aging is associated with a number of chronic inflammatory conditions and a dysregulation of immune system function that increases risk of morbidity and mortality.¹ The upregulated production of prostaglandins, and particularly of the pro-inflammatory prostaglandin E₂ (PGE₂), is implicated in many of these age-related conditions including cardiovascular disease, Alzheimer’s disease, and type 2 diabetes as well as T-cell suppression associated with infectious disease and tumorigenesis.²⁻⁵ Many of these deleterious effects are attributed to excess PGE₂ production in macrophages (MΦ), which are a major source of inflammatory mediators.⁶ Nevertheless, the consequences of increased PGE₂ production depend largely on what target tissues are affected. For example, increased production of PGE₂ in MΦ localized to arterial plaques may be associated with plaque rupture in humans,⁷ while within the nervous system, it may contribute to neuropathic pain.⁸ Excess PGE₂ production can also result in suppression of T cell function. Thus, an understanding of the regulation of PGE₂ synthesis in MΦ may help elucidate the processes underlying several age-related diseases. Moreover, interventions to inhibit upregulation of PGE₂ may be explored as potential preventive and therapeutic strategies for such disease states.

CYCLOOXYGENASE-INDUCED INCREASE IN PGE₂ PRODUCTION WITH AGING

Age-associated increase in PGE₂ production has been demonstrated in a number of animal models⁹,¹⁰ and in humans.¹¹,¹² In one such study, peritoneal MΦ from aged (24-mo) and young (6-mo) mice were stimulated with lipopolysaccharide (LPS) and MΦ from aged mice produced significantly more PGE₂ compared with MΦ from young mice.¹³ The higher levels of PGE₂ production in the aged mice was attributed to increased cyclo-
oxygenase (COX) activity. COX is the rate-limiting enzyme in prostaglandin biosynthesis. It is now apparent that its inducible isofrom, COX-2, rather than its constitutively expressed isoform, COX-1, contributes to the increased PGE\(_2\) production with age. While COX-2 mRNA and protein expression were higher in M\(_\phi\) isolated from aged compared to young mice, no difference in COX-1 expression was observed between the two age groups. This increase in COX-2 mRNA expression is due to a higher rate of gene transcription in M\(_\phi\) isolated from aged mice, rather than an increased mRNA stability.

CERAMIDE IS A KEY FACTOR UNDERLYING INCREASED COX-2 EXPRESSION WITH AGING

Regulation of COX-2 expression involves complex interactions among a number of intracellular mediators (Figure 1), a key factor being the availability of ceramide, a sphingolipid second messenger formed by the action of the enzyme sphingomyelinase (SMase) on sphingomyelin, or by de novo synthesis. Addition of ceramide to the cultured mouse M\(_\phi\) increased COX-2 activity and, consequently, PGE\(_2\) production. In M\(_\phi\) of aged mice, ceramide levels were found to increase after LPS stimulation by a larger magnitude compared with M\(_\phi\) from young mice, consistent with the timing of enhanced COX-2 activity and PGE\(_2\) production. Although the precise mechanism underlying the increased generation of ceramide with aging is unknown, it may involve a reduction in glutathione concentrations, which normally exerts an inhibitory control over SMase.

The age-related increase in COX-2 expression and activity induced by ceramide is now known to be mediated by nuclear factor-kappa B (NF-κB), while other transcription factors including activator protein-1 (AP-1) and CRE-binding protein (CREB) do not appear to be involved. Thus, exogenously administered ceramide in the absence or presence of LPS was found to significantly increase NF-κB binding to the promoter region of the COX-2 gene, and binding of NF-κB to the COX-2 promoter was shown to occur at a faster rate in M\(_\phi\) from aged compared with young animals following LPS stimulation, presumably due to the increase in ceramide concentrations with aging. Although many of the intermediary processes involved in the regulation of NF-κB binding remain to be resolved, these findings suggest an altered activity of the inhibitory protein IkB, which normally anchors NF-κB in the cytoplasm until an activating signal is received. With aging, the cytoplasmic degradation of IkB is increased, resulting in an enhanced rate of NF-κB translocating into nucleus and binding to the COX-2 promoter in mouse M\(_\phi\). Such effects are blocked by the addition of Bay 11-7082, which prevents the phosphorylation and consequent degradation of IkB, or by administering an NF-κB decoy that competes for transcription site binding. Thus, applying these inhibitors is able to reduce the enhancement in COX-2 activity and PGE\(_2\) production typically observed in LPS-stimulated M\(_\phi\) of aged mice.

A number of studies have suggested that a similar inflammatory process may take place in cell types other than M\(_\phi\). Adipocytes are cells of particular interest, owing to their association with the development of insulin resistance in type 2 diabetes. The prevalence of type 2 diabetes increases with age, although it is not necessarily accompanied by an increase in weight. One avenue of research is the possibility that insulin resistance in aging individuals may be a consequence of increased production of inflammatory products within adipose tissue, without an increase in the size of fat mass.
INTERVENTIONS TO DECREASE AGE-RELATED INCREASE IN COX-2

Understanding the processes underlying the increased production of PGE₂ is important for developing rational intervention strategies. Although anti-inflammatory drugs that inhibit COX-1 and/or COX-2 activity and thereby reduce PGE₂ synthesis have shown some clinical benefit in several age-related diseases, their utility may be limited by concerns of unwanted effects.²⁷⁻²⁹ This has led to investigation of alternate therapies such as dietary/nutritional interventions that may reduce COX-2 activity and/or PGE₂ production.³⁰,³¹ One nutritional compound that appears to have some efficacy is vitamin E supplementation, which diminishes the increased PGE₂ production in Mφ of old mice by inhibiting COX activity, with negligible effects in young mice.³¹ A low-fat diet with high fish consumption for n-3 polyunsaturated fatty acid enrichment has also been shown to effectively reduce inflammatory products, lowering baseline PGE₂ production in elderly individuals by 63% over a 6-month period, compared with a 30% reduction in those with a lower fish intake.³⁰ Several studies are currently underway to explore the possible COX-2- and PGE₂-lowering benefits of various plant-derived phenolic compounds, or calorie-restriction, in aging individuals.

CONCLUSIONS

Aging is associated with a number of chronic inflammatory conditions and a dysregulation of immune system function. Mφ are a primary source of inflammatory mediators, and altered PGE₂ production with aging in these cells may contribute to the onset and progression of various age-related conditions. Mechanistic studies for the processes mediating increased PGE₂ production in Mφ with aging suggest that ceramide may serve as a triggering factor that induces increased binding of NF-κB to the nuclear transcription site of COX-2, resulting in a higher rate of COX-2 transcription and, eventually, excessive PGE₂ production. These same or similar mechanisms may occur in other cell types, and preliminary evidence suggests that higher levels of ceramide in adipocytes from old mice relative to those from young mice are a promising avenue for further study. Certain dietary/nutritional interventions appear to be effective in inhibiting the excessive production of PGE₂ seen in the aging, and may represent an important preventive and therapeutic strategy.

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