Therapeutic potential of dietary phase 2 enzyme inducers in ameliorating diseases that have an underlying inflammatory component[1]

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Abstract: Many diseases associated with ageing have an underlying oxidative stress and accompanying inflammatory component, for example, Alzheimer's disease or atherosclerosis. Reviewed in this manuscript are: the role of oxidative stress in activating the transcription factor nuclear factor kappa B (NFκB), the role of NFκB in activating pro-inflammatory gene transcription, strong oxidants produced by cells, anti-oxidant defense systems, the central role of phase 2 enzymes in the anti-oxidant defense, dietary phase 2 enzyme inducers and evidence that dietary phase 2 enzymes decrease oxidative stress. It is likely that a diet containing phase 2 enzyme inducers may ameliorate or even prevent diseases that have a prominent inflammatory component to them. Research should be directed into the potential therapeutic effects of dietary phase 2 enzyme inducers in ameliorating diseases with an underlying oxidative stress and inflammatory component to them.

Key words: Alzheimer's disease, atherosclerosis, diet, glutathione, inflammation, stroke.

Résumé : Un grand nombre de maladies associées au vieillissement ont un stress oxydatif sous-jacent accompagné d'une composante inflammatoire, par exemple l'athérosclérose. Dans cet article, nous réviserons les thèmes suivants : le rôle du stress oxydatif dans l'activation de la transcription du facteur nucléaire kappa B (FNκB), le rôle du FNκB dans l'activation de la transcription des gènes pro-inflammatoires, les puissants oxydants produits par les cellules, les systèmes de défense antioxydants, le rôle central des enzymes de phase 2 dans la défense antioxydante, les inducteurs d'enzymes de phase 2 alimentaires et la mise en évidence de la diminution du stress oxydatif par les enzymes de phase 2 alimentaires. Il semble très possible qu'un régime contenant des inducteurs d'enzymes de phase 2 puissent diminuer les symptômes des maladies ou même prévenir les maladies ayant une forte composante inflammatoire. Nous suggérons d'orienter la recherche vers l'étude des effets thérapeutiques potentiels des inducteurs d'enzymes de phase 2 alimentaires sur la diminution des symptômes des maladies ayant un stress oxydatif sous-jacent accompagné d'une composante inflammatoire.

Mots clés : maladie d'Alzheimer, athérosclérose, régime, glutathion, inflammation, accident vasculaire cérébral.

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Oxidative stress and disease

Introduction

Diseases with a chronic underlying oxidative stress and inflammatory components become more common with ageing. Examples of such diseases are Alzheimer's disease (Markesbery and Carney 1999; McGeer and McGeer 1999) and atherosclerosis (DeGraba 1997; Ross 1999). Oxidative stress, often with associated inflammation, also contributes to tissue damage in many other diseases including Parkinson's disease (Jenner and Olanow 1996; Shimura-Miura et al. 1999), Huntington's disease (Browne et al. 1999), amyo-

trophic lateral sclerosis (Cookson and Shaw 1999), multiple sclerosis (Bonetti et al. 1999), traumatic brain (Nonaka et al. 1999), spinal cord injury (Bethea et al. 1998), and diabetes (Brownlee 1995; Dominguez et al. 1998; Suzuki and Miyata 1999).

In recent years there has been much interest and research in the influence of diet on the diseases associated with ageing. There is evidence that intake of fruits and vegetables is inversely related to stroke incidence, both hemorrhagic and thrombotic (Gillman et al. 1995). Dietary flavonoids have been often implicated in providing some of the protective effects of fruits and vegetables. The Zutphen study showed a significant inverse correlation between flavonoid (mainly quercetin) intake and stroke incidence (Keli et al. 1996). Another study has demonstrated an inverse relationship between flavonoid intake and coronary heart disease (Yochum et al. 1999). Flavonoids are often stated to be cardiovascular-protective because of their anti-oxidant properties, possibly through the inhibition of low-density lipoprotein oxidation and the inhibition of platelet aggregation (Cook and Samman 1996). Vitamin E supplementation has also been demonstrated to protect against atherogenesis (Chan 1998;

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Hodis et al. 1995). An inverse correlation between serum selenium and risk of coronary heart disease has also been demonstrated (Suadicani et al. 1992).

There is also evidence that there is a correlation between diet and the chances of developing Alzheimer's disease (Grant 1997). Furthermore, there are several publications presenting data that intake of strawberries, blueberry and spinach extracts retards the onset, and even promotes the reversal, of age-related neuronal signal-transduction and cognitive behavioral deficits in the rat (Joseph et al. 1998, 1999).

What is the link, if any, amongst the various putative protective factors listed above?

There is also much interest in diet as a means to prevent cancer (American-Institute-for-Cancer-Research 1996; Longnecker et al. 1997; Shapiro et al. 1998; Steinmetz and Potter 1996; Wargovich 1997). Much of the focus of the interest in diet and cancer in recent years has revolved around dietary components that can induce anti-oxidant enzymes known as phase 2 enzymes (Fahey et al. 1997). The theoretical basis of this type of research is that oxidative stress can lead to DNA damage (Breen and Murphy 1995) which can lead to mutagenesis that in turn can lead to cancer formation. DNA-damaging oxidative stress can be mediated through a variety of oxidants including the hydroxyl radical (Giulivi et al. 1995), lipid peroxidation derivatives (de Kok et al. 1994), and peroxynitrous acid (Douki and Cadet 1996).

The objective of this article is to briefly review: (*i*) the role of oxidative stress and inflammation in several diseases associated with ageing, (*ii*) the role of oxidative stress in expression of pro-inflammatory diseases, (*iii*) the major mechanisms that result in oxidative stress, (*iv*) the strong-oxidant scavenging mechanisms, and (*v*) the role of phase 2 enzymes in strong-oxidant scavenging. Finally, I wish to bring attention to the possibility that dietary phase 2 enzyme inducers may have therapeutic potential in ameliorating diseases that have an underlying inflammatory component to them.

Alzheimer's disease

In Alzheimer's disease one indicator of increased oxidative stress is the presence of advanced glycation endproducts (AGEs) in the neurons of Alzheimer's patient brains (Munch et al. 1997); many of these AGEs are 4-hydroxynonenal derivatives (Sayre et al. 1997) that are indicative of extensive lipid peroxidation. A large increase in protein carbonyl formation, another indicator of oxidative stress, is also seen in brains of Alzheimer's patients (Smith et al. 1998). Furthermore, taking non-steroidal anti-inflammatory drugs retards the progression of Alzheimer's disease (Breitner et al. 1994; Rich et al. 1995; Stewart et al. 1997), suggesting that there is a prominent inflammatory component to the disease process. One of the therapeutic mechanisms of non-steroidal anti-inflammatory drugs is via inhibition of the activity of the pro-inflammatory enzyme cyclo-oxygenase-2 (COX-2) (Pasinetti 1998). This upregulation of COX-2 in Alzheimer's disease is likely mediated by the transcription factor complex nuclear factor kappa B (NFκB) because NFκB activation is upregulated in brains affected with Alzheimer's disease (Boissiere et al. 1997; Kitamura et al. 1997). Furthermore, there is a correlation between NFκB activation

and COX-2 expression in brains affected with Alzheimer's disease (Lukiw and Bazan 1998). Activation of NFκB is mediated, in part, by the amyloid β-peptide (Bales et al. 1998; Kuner et al. 1998). The role of inflammation in the progression of Alzheimer's disease has been summarized (McGeer and McGeer 1999). Similarly, the intake of vitamin E has been shown to retard progression of Alzheimer's disease (Sano et al. 1997). Increased vitamin E intake tends to inhibit lipid peroxidation. As discussed below, vitamin E plays an important, although limited, role in preventing lipid peroxidation.
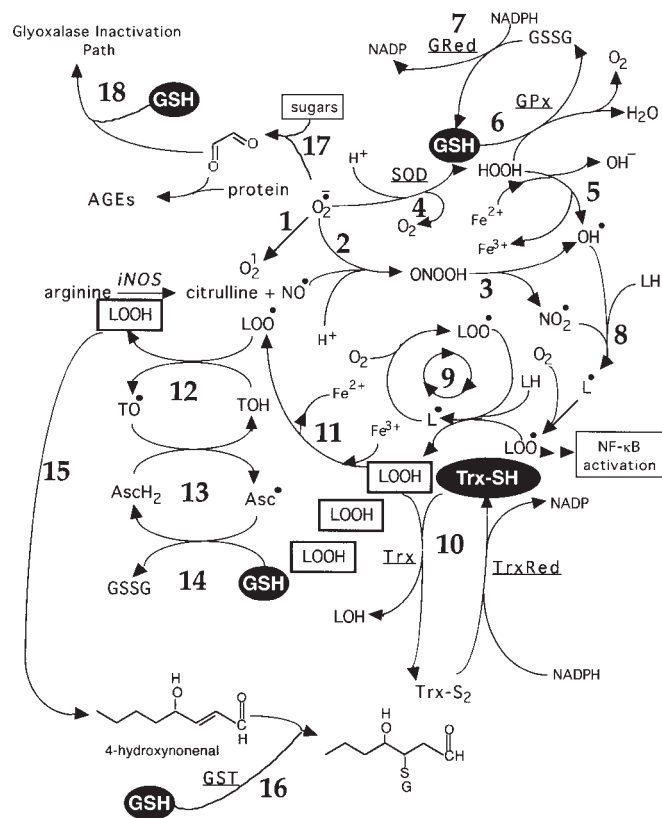
Atherosclerosis

The one common feature of the factors that predispose an individual to atherogenesis is that they all increase the oxidative stress experienced by the endothelium. Thus, both hypercholesterolemia and hypertension have been associated with endothelial oxidative stress (Nakazono et al. 1991; Ohara et al. 1993; Quyyumi 1998). Homocysteine auto-oxidizes, generating hydrogen peroxide causing oxidative stress at the level of the endothelium (Stamier et al. 1993; Loscalzo 1996; Welch et al. 1997; de Jong et al. 1998) and decreasing endothelial intracellular glutathione (GSH) (Hempel et al. 1998). Hyperglycemia associated with diabetes increases the formation of advanced glycation endproducts (AGEs) (Brownlee 1995; Cooper et al. 1997), which also causes increases in oxidative stress. Furthermore, lipopolysaccharide, the bacterial endotoxin, activates pro-inflammatory gene expression in endothelial cells (Seitz et al. 1996).

Endothelial oxidative stress results in (*i*) the activation of NFκB, (*ii*) the expression of pro-inflammatory cytokines and leukocyte chemotactic molecules (such as thrombin) and (*iii*) the expression of cell adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1); the outcome is leukocyte adherence (Griendling and Alexander 1996; Matthew et al. 1996; Dong and Wagner 1998). Leukocyte adherence is followed by the oxidation of low density lipoproteins (LDL) by hypochlorous acid, a product of leukocyte myeloperoxidase activity (Heinecke 1997; Jerlich et al. 1998). Oxidized LDL interacts with scavenger receptors (Steinbrecher 1999), promoting the establishment of a positive oxidative stress feedback loop that maintains the pro-inflammatory state characterized by macrophage recruitment (Steinberg et al. 1989) and maintains the upregulation of activated NFκB (Brand et al. 1996; Bourcier et al. 1997). Shearing forces often result in the rupture of an atherosclerotic lesion already weakened by matrix metalloproteinase activities of the macrophages within the plaque. This directly exposes procoagulant elements, such as macrophage-released tissue factor, to the blood, resulting in thrombus formation (Fuster 1998).

Increased intake of vitamin E has been associated with decreased atherogenesis (Rimm et al. 1993; Stampfer et al. 1993; Hodis 1995; Hodis et al. 1995; Chan 1998; Rimm and Stampfer 2000). Part of the therapeutic effect of vitamin E appears to be through a decrease in lipid peroxidation (Pratico et al. 1998). Aspirin intake also correlates with decreased cardiovascular risk (Ridker 1999); aspirin appears to act directly on the endothelium by preventing pro-

Fig. 1. Some pathways involved in generation and scavenging of strong oxidants. To reduce clutter, the reactions are not necessarily balanced and sometimes leave out intermediate steps. Superoxide can interact with another molecule of superoxide (1) to form the strong oxidant, singlet oxygen. Superoxide can also interact with nitric oxide to give rise to peroxynitrous acid (2) that in turn can give rise to strong oxidants such as the nitrogen dioxide and hydroxyl radicals (3). Superoxide is scavenged by superoxide dismutase (SOD) to form hydrogen peroxide and molecular oxygen (4). In the presence of transition metal ions, hydrogen peroxide can give rise to the hydroxyl radical (5). Hydrogen peroxide is scavenged by glutathione peroxidase (GPx) that requires GSH as the electron donor (6). The oxidized glutathione is reduced by glutathione reductase (GRed) that uses NADPH as the electron donor (7). The hydroxyl radical can abstract an electron from a polyunsaturated fatty acid (LH) to form a carbon-centred lipid radical (8). The lipid radical can interact with molecular oxygen to form a peroxyl radical that in turn can abstract an electron from a polyunsaturated fatty acid initiating a lipid peroxidation chain reaction (9). The oxidative stress that ensues can activate NFκB. The lipid peroxides that are formed are scavenged by either thioredoxin reductase using thioredoxin (TrSH2) as electron donor (10) or glutathione peroxidase using GSH as the electron donor (not presented). It is necessary to scavenge the lipid peroxides since they can interact with transition metal ions to give rise to new lipid peroxyl radicals (11) that can initiate new rounds of lipid peroxidation. Lipid peroxyl radicals are quenched by vitamin E (TOH) giving rise to an innocuous vitamin E radical (12). The vitamin E radical is reduced by ascorbic acid (13) and the oxidized ascorbate is reduced by GSH (14). Lipid peroxides can also break down into strong oxidants such as 4-hydroxynonenal (15) which is scavenged by gluta-

thione S-transferase (GST) by formation of an adduct with GSH (16). In the presence of transition metal ions, superoxide anion can also convert sugars to strong oxidants such as the dicarbonyl glyoxal (17). Dicarbonyls are scavenged by the glyoxalase pathway that uses GSH as a cofactor (18) – see Fig. 2.

inflammatory gene expression (Pierce et al. 1996; Husain et al. 1998), likely by inhibiting the activation of NFκB (Grilli et al. 1996; Pierce et al. 1996).

Because of the evidence of the efficacy of vitamin E and aspirin supplementation in reducing the rate of progression of Alzheimer's disease and atherosclerosis, it is becoming increasing popular to advocate intake of anti-oxidant vitamins or aspirin for preventing diseases that have an underlying oxidative stress component to them (Patrono 1998; Prasad et al. 1999; Vatassery et al. 1999). A better understanding of the role of vitamin E and aspirin in preventing lipid peroxidation may allow the design of more effective therapies in delaying, or possibly preventing, the progression of a number of diseases that have an underlying oxidative stress component.

Oxidative stress

Oxidative stress is a condition in which a greater amount of strong oxidants is produced than can be scavenged. Strong oxidants that can be produced include the hydroxyl radical, peroxynitrous acid, lipid peroxyl and alkoxyl radicals, α-oxo-aldehydes, and 4-hydroxyalkenals; these have been reviewed elsewhere (Juurlink 1999) and the pathways that produce such oxidants are illustrated in Figs. 1 and 2. Many of the cellular mechanisms that result in strong oxidant overproduction have been reviewed (Juurlink and Paterson 1998) and will not be dealt with in any length in this manuscript. It should be pointed out that strong oxidant production is a normal physiological phenomenon, what is important for normal cell function is that there are efficient mechanisms for scavenging such compounds, particularly the precursors to strong oxidants.

Superoxide anion and derivatives

Approximately 3% of oxygen respired is incompletely reduced to superoxide anions (Fridovich 1986). Superoxide production by mitochondria increases when intracellular Ca^{2+} rises and causes mitochondrial Ca^{2+} cycling (Richter and Kass 1991). Rises in intracellular Ca^{2+} also can activate Ca^{2+}-dependent enzymes such as phospholipase A2, resulting in the release of arachidonic acid (Daniel 1985) whose metabolism increases superoxide anion production (Kukreja et al. 1986). Arachidonic acid can be acted upon by COX-2 to produce pro-inflammatory prostanoids (Vane et al. 1998) and by 5-lipoxygenase to produce pro-inflammatory leukotrienes (Henderson 1994; Crooks and Stockley 1998). Other common sources of superoxide anions include the oxidoreductase activity present in peroxisomes (van den Bosch et al. 1992) and the activation of the membrane-bound NADPH oxidase that forms the respiratory burst of leukocytes (Chanock et al. 1994; Miesel et al. 1995).

Superoxide anions can give rise to strong oxidants such as singlet oxygen (Steinbeck et al. 1992; Steinbeck et al. 1993;

Fig. 2. Dicarbonyl production and scavenging. Glucose is converted to the trioses (1) glyceraldehyde 3-phosphate and dihydroxyacetone phosphate which can spontaneously give rise to methylglyoxal (#2). Methylglyoxal is very electrophilic and spontaneously reacts (3) with the electron-rich sulfur of glutathione (GSH) to form a hemithioacetyl. The efficiency of this reaction is dependent upon GSH concentration. The hemithioacetyl is acted upon by glyoxalase I (4) to give rise to (S)-D-lactoylglutathione. Glyoxalase II converts (S)-D-lactoylglutathione to GSH and the D-aldonic acid, D-lactic acid (5). Glucose can also be transition metal-mediated oxidized to the dicarbonyl glyoxal (6) that in turn reacts with GSH (7) and this hemithioacetyl can be metabolized by the glyoxalase pathway.
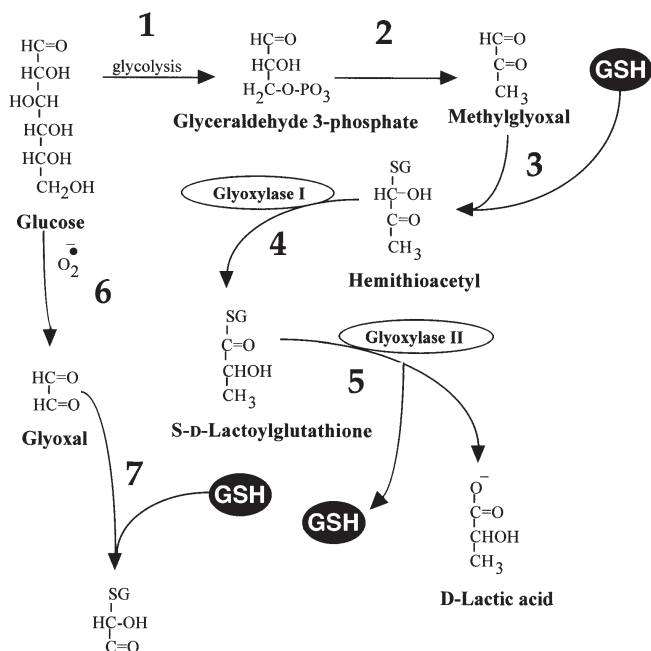
Khan and Kasha 1994) or interact with the nitric oxide radical to form the strong oxidant peroxynitrous acid (Crow et al. 1994; Squadrito and Pryor 1995). Hence, there are efficient mechanisms to scavenge superoxide anions; these are performed by a family of superoxide dismutase (SOD) enzymes that convert the superoxide anion to hydrogen peroxide (Fridovich 1995). There are three isoforms of SOD: (*i*) an extracellular Cu,Zn–SOD, (*ii*) a cytosolic Cu,Zn–SOD, and (*iii*) a mitochondrial Mn–SOD. Certain mutations of the Cu,Zn–SOD have been identified in a small subpopulation of amyotrophic lateral sclerosis patients (Rosen et al. 1993; Sapp et al. 1995); the effect of the mutation appears to be an increase in the pro-oxidant activity of the enzyme, resulting in a small increase in cellular oxidative stress (Yim et al. 1996) that does not affect function of motoneurons until the individual is usually in the fifth decade or later of life. This suggests that a slightly increased burden of oxidative stress results in cumulative deficits that become overtly deleterious after many decades of accumulation. This slow accumulation of functional deficits that interact to result in a progressive deterioration from homeostasis has been termed the 'deleterious network' (Ying 1996).

Lipid peroxidation

Hydrogen peroxide can react with transition metal ions to give rise to the hydroxyl radical, a powerful oxidant (Halliwell and Gutteridge 1989). Free transition metal ions tend to be localized to polyanionic charges, such as those present in the phosphate backbone of DNA and in phospholipids. The consequence of this is that there is a tendency for strong oxidants to be produced where they can cause the most damage. Consequences of hydroxyl radical formation are DNA damage and lipid peroxidation. Of these, I shall focus on lipid peroxidation as it has direct relevance to inflammation.

The hydroxyl radical can extract an electron from a polyunsaturated fatty acid, resulting in the formation of a carbon-centred lipid radical that can initiate a lipid peroxidation chain reaction (Braughler et al. 1986; Halliwell and Gutteridge 1989) by interacting with molecular oxygen and forming a lipid peroxyl radical (Fig. 1). The lipid peroxyl radical in turn can extract an electron from another polyunsaturated fatty acid giving rise to a new carbon-centred lipid radical and a lipid hydroperoxide, thereby initiating a chain of lipid peroxidations. Vitamin E plays a critical role in stopping this lipid peroxidation chain by interacting with a lipid peroxyl radical; this forms a lipid hydroperoxide and a vitamin E radical (Chan 1993). The vitamin E radical formed is reduced by ascorbate (Buettner 1993); the ascorbate is ultimately reduced by a GSH-dependent system (Rose and Bode 1995; Winkler et al. 1994) or by thioredoxin reductase using NADPH as the electron donor (May et al. 1998). Although vitamin E plays an important role in inhibiting lipid peroxidation, it is essential that the lipid peroxides are scavenged because the lipid hydroperoxide that is a byproduct of vitamin E inactivation of the lipid peroxyl radical can interact with transition metal ions, resulting in the formation of lipid alkoxyl and peroxyl radicals that can initiate new chains of lipid peroxidations.

Formation of lipid peroxides in membranes affects membrane structure. This results in altered membrane fluidity (McGrath et al. 1995), increased permeability of membranes (Subramaniam et al. 1997), and decreased membrane ATPase activity (Rauchova et al. 1995). Lipid radicals and lipid peroxides can also break down, forming pro-inflammatory isoprostanes (Liu et al. 1998) and isoleukotrienes (Harrison and Murphy 1995). Indicative of the important role that vitamin E has in preventing lipid peroxidation is that vitamin E intake reduces isoprostane formation in ApoE-deficient mice (Pratico et al. 1998). Lipid peroxidative products can also break down, forming strong oxidants including dicarbonyls such as malondialdehyde (Esterbauer et al. 1990) and 4-hydroxyalkenals such as 4-hydroxynonenal (Springer et al. 1997; Comporti 1998). These are strong oxidants that can interfere with critical cellular functions such as glutamate uptake (Springer et al. 1997; Blanc et al. 1998), maintenance of ion homeostasis (Mark et al. 1997), and mitochondrial respiration (Picklo et al. 1999), as well as alter membrane protein configuration (Subramaniam et al. 1997).

Peroxide scavenging

It is clear that there must be efficient mechanisms that scavenge both hydrogen peroxide and organic peroxides. There are two well-defined enzymatic mechanisms whereby

the cell can scavenge hydrogen peroxide: catalase and the glutathione peroxidase (GPx) systems. Of these, the GPx system appears to be the most important (Simmons and Jamall 1988; Michiels et al. 1994). This is likely because catalase is mainly restricted to peroxisomes and has a low affinity for hydrogen peroxide (Simmons and Jamall 1988). Furthermore, catalase can scavenge hydrogen peroxide but cannot scavenge organic peroxides. The GPx family of proteins are selenoproteins that can scavenge both hydrogen peroxide and organic peroxides, including lipid peroxides. Unlike catalase, these enzymes have a high affinity for their substrate (Paglia and Valentine 1967; Ursini et al. 1985; Saito et al. 1999). Well-characterized members of this enzyme family include: (*i*) a widely distributed cytosolic form (GPx1), (*ii*) a cytosolic form widely distributed in the gastrointestinal tract (GPx-GI, (*iii*) a membrane-associated GPx (GPx4) that scavenge membrane-bound phospholipid hydroperoxides as well as other organic peroxides and hydrogen peroxide, (*iv*) a plasma GPx (GPx3), and (*v*) a plasma GPx known as selenoprotein P (Ursini et al. 1995; Saito et al. 1999). GPx1, GPx-GI, GPx4, and selenoprotein P all use the tripeptide GSH as the electron donor in the scavenging of peroxides (Ursini et al. 1995; Saito et al. 1999), while GPx3 uses either the thiol protein thioredoxin or the thiol protein glutaredoxin as the electron donor in peroxide scavenging (Björnstedt et al. 1994). Increasing GSH concentrations markedly increases the peroxide scavenging efficiency (Carsol et al. 1997; as an example note Thorburne and Juurlink 1996) of the GSH-dependent GPx's because of the sequential reactions of two GSH molecules with glutathione peroxidase in the scavenging of peroxide.

Many lipid peroxides, as well as peroxide breakdown products such as 4-hydroxyalkenals, are scavenged by glutathione S-transferase which results in the formation of inactive glutathiyl adducts (Gulick and Fahl 1995; Hayes and Pulford 1995; Mantle 1995).

There is also a family of thioredoxin-dependent peroxidases that can reduce peroxides (Kang et al. 1998; Fisher et al. 1999). The importance of this family of enzymes to peroxide scavenging is not yet clear; however, they form approximately 1–2% of total soluble protein in neural cells (Juurlink et al. 1999).

As noted above, GSH plays several vital roles in minimizing oxidative stress; it is required for: (*i*) peroxide scavenging by GPx, (*ii*) scavenging of 4-hydroxyalkenals and other oxidants by glutathione S-transferase, and (*iii*) for the ultimate regeneration of vitamin E.

Dicarbonyls and advanced glycation endproducts

The dicarbonyls, α-oxo-aldehydes, are very electrophilic compounds that react readily with the nitrogen of protein-bound amino acids and of nucleic acids (Thornalley 1996) to give rise to advanced glycation endproducts (AGEs). As noted earlier, AGEs can also be formed by 4-hydroxyalkenals (Sayre et al. 1997). There are several pathways of dicarbonyl formation (Fig. 2). Glyoxal production is increased during oxidative stress by transition metal-mediated oxidation of the enediol form of glucose, while 3-deoxyglucosone is formed via the Amadori rearrangement of glucose (Wells-Knecht et al. 1995*a*, 1995*b*, 1996). Methyl-glyoxal is spontaneously formed from sugars principally by the base-

catalyzed phosphate elimination from the enediol forms of glyceraldehyde 3-phosphate and dihydroxyacetone phosphate (Thornalley 1990). Increased formation of dicarbonyls is thus associated both with oxidative stress and with hyperglycemia.

Effects of AGEs on cell function

AGEs affect cellular metabolism by the inactivation of affected proteins; for example, glycation of glutathione reductase inactivates this enzyme (Blakytny and Harding 1992) which plays an important role in reducing oxidized-glutathione. Indeed, a negative correlation exists between the extent of diabetic complications and the erythrocyte GSH level (Thornalley et al. 1996), which is possibly due, in part, to glutathione reductase inactivation. AGEs can also interact with several types of receptors. One receptor for AGEs (RAGE) has been characterized; it is comprised of a 45 kD membrane-spanning glycoprotein and an 80 kD lactoferrin-like protein (Thornalley 1998*a*). β-Amyloid peptide activation of RAGE has been implicated as part of the pathogenetic mechanism of Alzheimer's disease (Yan et al. 1996). Activation of RAGE results in increased production of reactive oxygen species that cause the activation of the p21^{ras}MAP kinase pathway (Yan et al. 1994) that in turn causes activation of NFκB (Bierhaus et al. 1997; Lander et al. 1997). Thus, RAGE activation is pro-inflammatory. The RAGE promoter has two NFκB binding sites, thereby enabling a positive feed-back cycle to be established. Furthermore, lipopolysaccharide-mediated increase in NFκB activation results in enhanced RAGE expression in vascular endothelial and smooth muscle cells (Li and Schmidt 1997). A second family of receptors with which AGEs can interact comprises the scavenger receptors (Li et al. 1998; Thornalley 1998*a*). Scavenger receptors also bind oxidized-LDL and activation of these receptors has been implicated in playing a role in the development of atherosclerosis (Yamada et al. 1998; Steinbrecher 1999). Scavenger receptors are present in a variety of cell types, including cells of the immune system, endothelial cells, and brain glial cells (Li et al. 1998; Thornalley 1998*a*). Activation of scavenger receptors causes release of arachidonic acid and reactive oxygen species (Hartung et al. 1986), thereby increasing oxidative stress.

AGEs have been shown to promote VCAM-1 expression in cultured human and murine endothelial cells (Schmidt et al. 1995) as well as in vivo upregulation of ICAM-1 and VCAM-1 in the endothelium of rabbits where it has been correlated with atherosclerotic lesion formation (Vlassara et al. 1995), likely via NFκB activation.

Dicarbonyl scavenging

GSH plays a major role in preventing the formation of AGE. Decreasing red blood cell GSH increases hemoglobin glycation (Jain 1998). The mechanism of action whereby GSH inhibits the formation of AGEs is likely via the glyoxalase pathway (Thornalley 1998*b*). This pathway converts α-oxo-aldehydes to corresponding aldonic acids. This has been most clearly demonstrated with methylglyoxal (Thornalley 1990; Thornalley 1998*b*). GSH spontaneously interacts with methylglyoxal to form a hemithioacetyl (Fig. 2). Glyoxylase I isomerizes the hemithioacetyl to S-D-lactoylglutathione which is converted to D-lactic acid and GSH by glyoxalase II. This is yet

another example of the many vital roles that GSH plays in minimizing oxidative stress.

Age and oxidative stress

Superoxide anion production (Sawada and Carlson 1987), hydrogen peroxide (Bejma and Ji 1999), hydroxyl radical production (Zhang et al. 1993) and tissue protein carbonyl content (Tian et al. 1998) increase with age in rodents. This is likely due to increased inefficiencies in mitochondrial respiration due, in part, to mitochondrial DNA damage (Richter 1995; Lenaz 1998). There is an increase in mitochondrial production of hydrogen peroxide with ageing (Sohal and Sohal 1991) in the housefly, and this increase in oxidative stress is associated with an increase in mitochondrial DNA damage (Lu et al. 1999). Similarly, there is an increase in mitochondrial DNA damage with age in humans. Thus, in human muscle tissue there are age-related increases in 8-hydroxy-2-deoxyguanosine, a marker of hydroxyl radical-mediated DNA damage (Giulivi et al. 1995), and this is associated with increased lipid peroxidation in muscle (Mecocci et al. 1999) and in skin (Lu et al. 1999).

In conjunction with the increased inefficiencies of mitochondrial respiration are reduced abilities by ageing cells to synthesize GSH, to reduce GSSG to GSH (Iantomasi et al. 1993), as well as decreased activities of GPx (Zhang et al. 1989; Tian et al. 1998; Lu et al. 1999), superoxide dismutase, and catalase (Tian et al. 1998; Lu et al. 1999). Catalase activities of peroxisomes decline with age (Périchon et al. 1998), suggesting an increase in the peroxisomal contribution to oxidative stress in cells. Peroxisomes are organelles whose oxidoreductases produce high amounts of hydrogen peroxide (van den Bosch et al. 1992; Lazarow 1995) that is scavenged by peroxisomally-localized catalase (de Duve and Baudhuin 1996).

It is likely that oxidative stress-mediated mitochondrial DNA damage that leads to inefficiencies in respiration resulting in increased oxidative stress plays a large role in the evolution of the 'deleterious network' described by Ying (1996).

Oxidative stress and inflammation

One consequence of oxidative stress is the establishment of a chronic low-grade inflammatory state, a condition that underlies many degenerative diseases that become more common as one ages. Oxidative stress causes the activation of the transcriptional factor NFκB that in turn upregulates pro-inflammatory gene expression (reviewed in Christman et al. 2000).

Activation of NFκB and pro-inflammatory gene expression

NFκB

NFκB is a DNA binding transcriptional factor complex that interacts with promoter elements in pro-inflammatory genes. Activated NFκB is a heterodimer comprised of two members of the NF-κB/Rel/Dorsal (NRD) family of proteins (Mercurio and Manning 1999). There are five known NRD members, RelA (also called p65), cRel, RelB, NF-κB1 (also called p50), and NF-κB2 (also called p52), with the classical activated NFκB being a heterodimer comprised of p50 and

p65. Inactive NFκB is a heterotrimer that contains a member of the inhibitory kappa B (IκB) family. There are six known members of the IκB family, IκBα, IκBβ, IκBγ, Bcl-3, plus p100 and p105 (the precursors for p50 and p52, respectively) (Baeuerle 1998a). The most common inactive NFκB heterotrimer is p65/p50/IκBα.

Potent inducers of NFκB activation are the gram-negative bacterial endotoxin lipopolysaccharide (LPS), and the cytokines tumour necrosis factor-α (TNF-α) and interleukin-1β (IL-1β). Receptor activation results in a phosphorylation cascade whose final component involves the IκB kinase that catalyzes the phosphorylation of serine residues on both IκBα and IκBβ; this is followed by polyubiquinatination of the IκB and subsequent degradation by the 26S proteasome (Traenckner et al. 1995; Baeuerle 1998b). IκB degradation unmasks a nuclear localization peptide sequence signal that allows NFκB to be translocated to the nucleus where NFκB binds to a cognate DNA sequence (5′-GGGPuNNPyPyCC-3′) and activates gene transcription (Baeuerle 1998a).

Oxidative stress and NFκB activation

Four areas of evidence indicate that the generation of reactive oxygen species is linked to NFκB activation. Treatment of cells with hydrogen peroxide directly activates NFκB in some cells (Schreck et al. 1992; Flohé et al. 1997) and overexpression of superoxide dismutase (SOD), the enzyme that converts superoxide anion to hydrogen peroxide, enhances the TNFα-induced activation of NFκB (Schmidt et al. 1996). Most of the known stimuli for NFκB activation, including LPS, TNFα, and IL-1β, produce oxidative stress in cells (Staal et al. 1990; Iuvone et al. 1998). Treatment with *N*-acetylcysteine, α-lipoic acid, membrane permeable hydroxyl scavengers, metallothionein, or the iron chelator PDTC blocks NFκB activation that is induced by a wide variety of stimuli (Pinkus et al. 1996; Flohé et al. 1997; Sakurai et al. 1999). The overexpression of catalase (Schmidt et al. 1996), an enzyme that scavenges hydrogen peroxide, as well as the overexpression of glutathione peroxidase (Kretz-Rémy et al. 1996), an enzyme that scavenges hydrogen peroxide as well as organic peroxides using GSH as an electron donor, inhibits the cytokine-induced activation of NFκB. Finally, over expression of γ-glutamylcysteine synthase, the rate-limiting enzyme for GSH synthesis, attenuates TNFα-induced NFκB activation (Manna et al. 1999). This latter observation points to a potential therapeutic approach for the inhibition of NFκB activation.

These observations suggest that strong oxidants act as a common second messenger following cellular exposure to agents that induce NFκB activation (Gius et al. 1999). However, the common point of the interaction between reactive oxygen species in the NFκB activation pathway has not been completely defined. Nevertheless, there is ample evidence that decreasing oxidative stress inhibits the activation of NFκB.

NFκB and pro-inflammatory gene expression

Activation of NFκB promotes transcription of pro-inflammatory genes that include: (*i*) cell adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) and VCAM-1, (*ii*) enzymes such as inducible nitric oxide

synthase (iNOS) and cycloxygenase-2 (COX-2), (*iii*) cytokines such as IL-1β, interleukin-6 (IL-6), and TNFα, and (*iv*) chemokines such as those that regulate normal T-cell expression and secreted protein (RANTES), monocyte chemo-attractant protein-1(MCP-1), and interleukin-8 (Baeuerle and Henkel 1994; Siebenlist et al. 1994; Verma et al. 1995; Baldwin 1996; Blackwell and Christman 1997; Christman et al. 1998).

NFκB is activated in Alzheimer's disease (Boissiere et al. 1997; Kitamura et al. 1997). This activation is correlated with the increased expression of ICAM-1 (Akiyama et al. 1993), iNOS (Baker et al. 1999), and COX-2 (Pasinetti 1998; Baker et al. 1999). Furthermore, there is a strong correlation between NFκB activation and COX-2 expression in brains affected by Alzheimer's disease (Lukiw and Bazan 1998).

Atherosclerosis is a fundamentally an inflammatory disease (Ross 1999; Whicher et al. 1999). NFκB activation is also seen in atherosclerosis (Brand et al. 1996; Bourcier et al. 1997). Such activation of NFκB results in the expression of pro-inflammatory cytokines and leukocyte chemotactic molecules such as thrombin as well as cell adhesion molecules such as VCAM-1, resulting in leukocyte adherence (Griendling and Alexander 1996; Matthew et al. 1996; Dong and Wagner 1998). ICAM-1 and TNFα are more upregulated in high-grade regions of atherosclerotic plaques human patients than in low-grade regions (DeGraba 1997), and have greater expression in symptomatic patients than in asymptomatic patients (DeGraba et al. 1998). Leukocyte adherence is followed by the oxidation of LDL by hypochlorous acid, a product of leukocyte myeloperoxidase activity (Heinecke 1997; Jerlich et al. 1998). Oxidized-LDL promotes the establishment of a positive oxidative stress feedback loop that maintains the pro-inflammatory state that is characterized by macrophage recruitment (Steinberg et al. 1989) and maintains the upregulation of activated NFκB (Brand et al. 1996; Bourcier et al. 1997). Shearing forces often results in the rupture of an atherosclerotic lesion already weakened by the matrix metalloproteinase activities of the macrophages within the plaque, thereby directly exposing procoagulant elements such as macrophage-released tissue factor to the blood, resulting in thrombus formation (Fuster 1998).

In principle, one should be able to inhibit inflammatory changes by inhibiting activation of NFκB. Decreasing the chances of activation of NFκB activation should be possible by promoting the scavenging of strong oxidants produced by normal and abnormal cellular metabolism. How to do this rationally requires an understanding of the critical components of the cellular anti-oxidant defense systems.
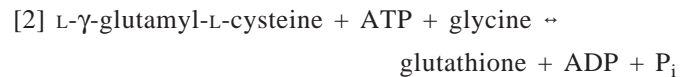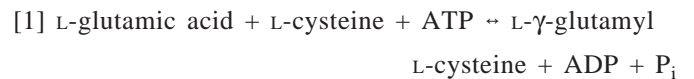
Critical components of the anti-oxidant defense system

It is clear from examining Fig. 1 that the critical components of the anti-oxidant defense system are : (*i*) scavenging of peroxides because peroxides can give rise to strong oxidants such as hydroxyl/peroxyl radicals, 4-hydroxyalkenals, and pro-inflammatory isoprostanoids; (*ii*) regeneration of vitamin E since vitamin E plays an essential role in preventing lipid peroxidation chain reactions; (*iii*) scavenging α-oxo-aldehydes because these strong oxidants can form AGEs; (*iv*) scaveng-

ing 4-hydroxyalkenals because these strong oxidants can also form AGEs and inactivate protein function through the formation of protein carbonyls; and (*v*) scavenging of quinone radicals. Thioredoxin-dependent peroxidases, which use thioredoxin as the electron donor, may also play an important role in scavenging peroxides (Chae et al. 1999). Glutathione S-transferases eliminate many electrophiles by catalyzing the formation of the glutathiyl adducts (Gulick and Fahl 1995). In addition, quinone reductase plays an important role in reducing quinones such aminochrome (Segura-Aguilar et al. 1998). GSH plays important roles in many of these scavenging activities, functioning as the electron donor in the reduction of oxidants or by forming glutathiyl adducts with the oxidants (Juurlink 1999).

Regulation of cellular GSH

GSH is synthesized according to the following two reactions (Meister 1983):

[1] L-glutamic acid + L-cysteine + ATP ↔ L-γ-glutamyl

$$\text{L-cysteine} + \text{ADP} + \text{P}_i$$

[2] L-γ-glutamyl-L-cysteine + ATP + glycine ↔

$$\text{glutathione} + \text{ADP} + \text{P}_i$$

Cysteine is the rate-limiting amino acid (Meister 1989). Cysteine readily auto-oxidizes to cystine; hence, plasma cysteine concentration is ~10 µM whereas plasma cystine is ~100 µM (cysteine equivalents) (Bannai 1984). Cellular cysteine content is regulated principally by the uptake of the oxidized form, cystine, since cysteine is readily oxidized. Cystine is taken up (or released) by the X_c^- antiporter in exchange for glutamate (Bannai 1984); intracellularly, 1 molecule of cystine is reduced to 2 molecules of cysteine. L-γ-Glutamyl-L-cysteine synthase (GCS: reaction 1) is the rate-limiting enzyme in regulating GSH levels (Meister 1989). GCS is a heterodimer comprised of a catalytic 73 kD heavy subunit and a regulatory 27.7 kD light subunit. It is a phase 2 enzyme and both subunits are under the control of the anti-oxidant response element (ARE) (Mulcahy and Gipp 1995; Galloway et al. 1997; Moinova and Mulcahy 1998; Wild et al. 1998).

Phase 1 and phase 2 enzymes

The terms phase 1 and phase 2 enzymes come from the perspective of xenobiotic metabolism. Xenobiotics are metabolized by enzymes placed into phase 1 (mono-oxygenases such as cytochrome P450s) and phase 2 categories (Nebert et al. 1990). The products of phase 1 enzyme activity are electrophiles that are acted upon by phase 2 enzymes. Members of the phase 2 enzymes include γ-glutamyl-cysteine synthase, quinone reductase, glutathione transferase, epoxide hydrolase, UDP-glucoronosyltransferase (Prestera et al. 1993*a*), and likely the selenoprotein family of thioredoxin reductases (Eftekharpour et al. 2000). Phase 2 enzymes generally play an important role, either directly or indirectly, in inactivating xenobiotics, often by forming conjugates such as glutathiyl–xenobiotic conjugates. In contrast, phase 1 enzymes generally oxidize or reduce xenobiotics, often to potentially harmful secondary products (Prestera et al. 1993*a*). There has been considerable research on phase 2

enzymes and their induction (particularly quinone reductase and glutathione S-transferases) in the context of cancer prevention (Benson et al. 1980; Prestera et al. 1993*a*; Talalay et al. 1995).

Phase 2 enzyme inducers

Phase 1 and phase 2 enzymes can be induced by compounds found in our diet. Such compounds can specifically induce phase 1 enzymes, phase 2 enzymes or both (Prestera et al. 1993*b*); the latter are referred to as bifunctional inducers. It is generally considered that it is undesirable to upregulate phase 1 enzymes because this increases the production of strong electrophiles thereby promoting carcinogenesis, whereas induction of phase 2 enzymes ought to decrease the incidence of cancer formation through enhanced scavenging of electrophilic compounds (Prestera et al. 1993*b*). Generally monofunctional phase 2 enzyme inducers are Michael reaction acceptors, quinones, and isothiocyanates (Talalay et al. 1995) that activate transcriptional factor complexes that bind to the ARE in the promoter regions of phase 2 enzyme genes (Jaiswal 1994). The ARE is also known as the electrophile responsive element (EpRE) (Moinova and Mulcahy 1998).

Monofunctional dietary phase 2 enzyme inducers

Phase 2 enzyme inducers can be encountered in our diet. These include, the isoflavonoid and phytoestrogen genistein (Wang et al. 1998); enterolactone (Wang et al. 1998), the phytoestrogenic metabolite of the major flax seed lignan secoisolariciresinol diglucoside; the flavonol kaempferol (Uda et al. 1997; Yannai et al. 1998) found in high amounts in kale (Uda et al. 1997); the polyphenolic ellagic acid (Barch and Rundhaugen 1994) found in high amounts in strawberries and raspberries and (or) blackberries (Daniel et al. 1989); sulforaphane, the isothiocyanate derivative of the glucosinlate glucoraphanin found in high amounts in broccoli sprouts (Zhang et al. 1992); the epicatechin flavonoids that are the major polyphenolics found in green tea (Khan et al. 1992; Stoner and Mukhtar 1995); and curcumin, a major component of turmeric (Dinkova-Kostova and Talalay 1999). Polymeric proanthocyanidin fractions from several *Vaccinium* species (low bush blueberry, cranberry, and lingonberry) also have potent phase 2 enzyme induction activities (Bomser et al. 1996).

Two widely used food additives are butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT). Dietary intake of BHA (McLellan et al. 1992; McLellan and Hayes 1989; Sharma et al. 1993) and BHT increases tissue phase 2 enzyme activities (McLellan et al. 1994). Phase 2 enzyme induction by BHA appears to be mediated by its metabolite BHT (Prestera et al. 1993*b*).

Dietary phase 2 enzyme inducers and tissue phase 2 enzyme activity

Can phase 2 enzyme inducers taken via the diet affect tissue phase 1 and 2 enzyme activities? The answer is yes. Ellagic acid can decrease cytochrome P450 11E1 (Wilson et al. 1992) and P450 1A1 activities (Barch et al. 1994) while increasing quinone reductase, glutathione S-transferase, and UDP-glucoronosyltransferase activities (Barch and

Rundhaugen 1994; Barch et al. 1995; Ahn et al. 1996). The isothiocyanate sulforaphane inhibits cytochrome P450 2E1 (Barcelo et al. 1996) (Maheo et al. 1997) and induces quinone reductase (Fahey et al. 1997) and glutathione S-transferase (Maheo et al. 1997). Oral intake of green tea polyphenolics have been shown to induce glutathione S-transferase and quinone reductase in a variety of tissues in mice (Khan et al. 1992). Soy intake increases quinone reductase and glutathione S-transferase in various tissues (Appelt and Reicks 1997).

Dietary flax seed inhibits atherogenesis in a rabbit model of atherosclerosis (Prasad 1997). The non-oil component of flax seed is responsible for this effect (Prasad et al. 1998). This effect is possibly mediated by enterolactone, the metabolite of secoisolariciresinol digucoside (SDG), the principal lignan found in flax seeds.

Can dietary phase 2 enzyme inducers have therapeutic effects?

Phase 2 enzyme inducers and cancer

A number of studies have shown that phase 2 enzyme inducers inhibit chemically-induced tumour formation. The principal lignan of flax, SDG, when taken in the diet has been demonstrated to inhibit dimethylbenzanthracene-induced (Thompson et al. 1996) and *N*-methyl-*N*-nitrosourea-induced tumours in rats (Rickard et al. 1999); it also inhibits melanoma metastasis in mice (Li et al. 1999). These effects may possibly be mediated by the phase 2 enzyme-inducing capability of enterolactone. Genistein administered intraperitoneally has also been shown to inhibit *N*-methyl-*N*-nitrosourea-induced tumours (Constantinou et al. 1996). Dietary intake of ellagic acid has been shown to decrease the tumourogenicity of benzo[a]pyrenete (Chang et al. 1985) and *N*-nitrosoethylamine (Khanduja et al. 1999), *N*-nitrosobenzylmethylamine (Mandal and Stoner 1990), 3-methylcholanthrene (Mukhtar et al. 1984; Mukhtar et al. 1986), and 16 α-fluoro-5-androsten-17-one (Rao et al. 1991). Green tea polyphenolics have been shown to inhibit a variety of chemically-induced tumours (Stoner and Mukhtar 1995). Sulforaphane has been demonstrated to inhibit 9,10-dimethyl-1,2-benzanthracene-induced tumours (Zhang et al. 1994; Fahey et al. 1997). Because of the high amount of glucoraphanin (from which sulforaphane is derived) in broccoli sprouts (Nestle 1998), there is now widespread public interest in the consumption of broccoli sprouts as a means to prevent cancer.

Curcumin as well as ellagic acid protects against whole body radiation-induced damage (Thresiamma et al. 1998; Dinkova-Kostova and Talalay 1999). Curcumin has also been demonstrated to inhibit inflammatory gene expression that normally occurs when colon epithelial cells are exposed to tumourogenic compounds (Plummer et al. 1999).

Phase 2 enzyme inducers and inflammation

As noted above, one of the consequences of oxidative stress is the activation of the transcriptional factor complex NFκB. The reason for this appears to be the fact that one part of the signal transduction cascade in the activation of NFκB involves a strong oxidant being produced, furthermore, anti-oxidant administration can counteract cytokine-induced activation of NFκB; this is reviewed in Christman et al.

(2000). That cytokine-induced NFκB activation can be ameliorated by increasing electrophilic scavenging ability of cells through overexpression of GCS (Manna et al. 1999) suggests the possibility that induction of phase 2 enzymes may ameliorate diseases that have an underlying inflammatory component.

Several studies on the spontaneously hypertensive stroke-prone rats are in support of my thesis that increased consumption of dietary phase 2 enzyme inducers may ameliorate inflammatory states. These animals are characterized by undergoing vascular changes that in many ways resemble human atherosclerosis. The endothelium of these animals is characterized by expression of pro-inflammatory genes such as ICAM-1 and vessel walls are characterized by infiltration of monocytes (Liu et al. 1996). Incorporating (–)-epigallocatechin-3-O-gallate, the major green tea polyphenolic, into the diet of the spontaneously hypertensive stroke-prone rats inhibited stroke and prolonged the life span of these animals without affecting blood pressure (Uchida et al. 1995). These authors attribute these effects to the ability of the flavonoid to scavenge free radicals directly; however, (–)-epigallocatechin-3-O-gallate is a potent phase 2 enzyme inducer. Another study has demonstrated that incorporating soy protein, rather than milk-based proteins, into the diet of the stroke-prone rats also greatly increased the lifespan of the animals (Sarwar et al. 1999). The authors suggest that this protective effect of soy proteins may be due to their higher arginine content. It is known that tightly bound to every gram of soy protein is one milligram of the potent phase 2 enzyme inducer genistein (Mazur et al. 1996); this suggests that the protective effect of soy flour may be mediated by upregulation of phase 2 enzymes by genistein.

Genistein has been demonstrated to ameliorate gut inflammation that was correlated with decreased iNOS expression (Sadowska-Krowicka et al. 1998). In one study this anti-inflammatory effect of genistein was attributed to its tyrosine kinase inhibitory activity (Corbett et al. 1996); however, these authors were not aware of the phase 2 enzyme-inducing ability of genistein. Curcumin and ellagic acid have been shown to inhibit lipid peroxidation and the necrosis of skin flaps in mice (Ashoori et al. 1994).

Finally I would like to end this section with a caveat. A number of dietary phase 2 enzyme inducers have been shown to inhibit specific cytochrome P450 isoenzymes. Depending upon which cytochrome P450 isoenzyme is inhibited, this may interfere with metabolism of drugs. As an example, it is known that grapefruit consumption can significantly decrease gut cytochrome P450 3A4 that in turn results in an increase of oral availability of felodipine (Lown et al. 1997). Hence, if it is shown that increased intake of dietary phase 2 enzyme inducers can ameliorate inflammatory states it becomes also important to determine whether such a diet may influence drug metabolism.

Concluding remarks and future directions

Most degenerative diseases of the cardiovascular system and the central nervous system become more common as we age. There are a number of known reasons for this, most of which are related to oxidative stress (Beal 1995; Benzi and Moretti 1995); these include increased inefficiencies in mito-

chondrial function leading to increased superoxide production (Sawada and Carlson 1987), decreased abilities to produce GSH and to reduce GSSG to GSH (Iantomasi et al. 1993), decreased activities of GPx (Zhang et al. 1989), etc. This change with age is likely due to a slow accumulation of functional deficits that interact resulting in a progressive deterioration from homeostasis, this has been termed the 'deleterious network' (Ying 1996).

A question that arises is whether these changes that appear to be driven by oxidative stress-mediated damage can be slowed through upregulation of phase 2 enzymes using a dietary source of phase 2 enzyme inducers? Several recent publications have demonstrated that intake of strawberries, blueberry, and spinach extracts retards the onset, and even promotes the reversal, of age-related neuronal signal-transduction and cognitive behavioral deficits in the rat (Joseph et al. 1998, 1999). It is known that strawberries contain large amounts of ellagic acid (Daniel et al. 1989), a potent phase 2 enzyme inducer. Furthermore, uncharacterized polyphenolic fraction from blueberries has also been described as having potent phase 2 enzyme inductive activities (Bomser et al. 1996). These experiments suggest that dietary components can slow what is often thought of as the normal ageing process.

There are already significant research activities directed towards investigating the potential of phase 2 enzyme inducers in preventing cancer formation. A very fruitful area of research may well be to determine whether dietary phase 2 enzyme inducers can prevent or retard the development of diseases that have an underlying oxidative stress and inflammatory component. As pointed out earlier, Alzheimer's disease and atherosclerosis have a prominent underlying inflammatory component. It seems very possible that relatively small changes in diet that include increased consumption of phase 2 enzyme inducers may ameliorate or even prevent atherosclerotic changes and thus greatly reduce the incidence of heart and brain attacks, and possibly even slow the progression of Alkzheimer's disease.

Acknowledgements

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