Red Wine Consumption and Brain Aging

Various epidemiologic studies in distinct populations have raised the hypothesis that moderate drinkers of red wine have significantly lower rates of mortality from coronary heart disease than those who abstain from alcohol and possibly those who consume liquors or beer. Red wine is a complex beverage, so it is difficult to establish whether its beneficial effects are attributable to alcohol or non-alcoholic components, mainly polyphenols. As Belleville points out (Nutrition, this issue), concommitant scientific findings suggest that the apparent superiority of red wine over other types of beverages lies mostly in ethanol because of its ability to increase levels of high-density lipoprotein, a protective factor against atherosclerotic cardiovascular diseases. However, in addition to increased high-density lipoprotein cholesterol levels, decreased platelet aggregation likely contributes to the cardioprotective effect of alcoholic beverages. Numerous studies have found that polyphenols exhibit consistent antithrombogenic effects, possibly through their anti-inflammatory activity, and reduce the susceptibility of low-density lipoprotein to oxidation, which likely contributes to atherosclerotic lesions (see, e.g., Hayek et al. and Levites et al.). Therefore, one cannot underestimate the inhibitory effects of polyphenols in the development of coronary heart disease.

As life expectancy increases, the aging of the population will increase the number of people affected by age-related neuro-psychiatric disorders. Currently, there are no established and fully validated strategies for the prevention or even the delay of the onset of these diseases, and no curative therapies are available. Interestingly, recent reports have associated a few glasses (three to four per day, i.e., 250 to 500 mL) of red wine with diminished risk of macular degeneration, Alzheimer’s disease, and cognitive deficits. Among the different types of alcohol tested, Obisean et al. found that the intake of wine rather than liquor and beer appears to have the strongest association with macular degeneration, whereas two other 3-y follow-up epidemiologic studies performed in a cohort of 225 to 3767 subjects reported an apparent protective effect of moderate wine drinking (250 to 500 mL/d) against Alzheimer’s disease, as estimated by the Deterioration Cognitive Observée and the Mini-Mental State Examination. Moreover, moderate alcohol drinkers (two to eight drinks per day in men), aged 55 to 88 y, displayed superior performance on various cognitive tests compared with abstainers. In a recent study performed in adults 65 y and older, moderate alcohol consumption (one to fewer than seven drinks per week) was associated with reduced white matter changes and infarcts, whereas the prevalence of brain atrophy was higher in drinkers with greater alcohol consumption (>15 drinks/). It is likely that at least some of the purported beneficial effects of red wine stem from its polyphenol constituents. A recent epidemiologic study in a cohort of 1367 subjects followed for 5 y found that the dietary intake of flavonoid-type polyphenols is inversely related to the risk of dementia. Animal studies have shown that polyphenols derived from fruits (e.g., blueberries) and vegetables (e.g., spinach) delay and even reverse age-related cognitive behavioral impairments or display neuroprotective abilities in various in vitro and animal models of neurotoxicities. These polyphenols include quercetin, the catechins, and the stilbene resveratrol. These studies also suggested that polyphenol compounds exert their activities by inhibiting the production of reactive oxygen species, whose accumulation is likely to play a
key deleterious role in brain aging, and modulating the activity of intracellular signal transduction molecules.\textsuperscript{10–12}

In addition to the existing literature on the cardiovascular benefits of red wine consumption, long-term extensive studies are very much needed to examine wine-related changes and possible side effects of ethanol on brain function in the elderly. Such studies are essential before recommending wine consumption as a prophylactic means of enhancing quality of life and protecting against neurodegeneration in older adults.

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\section*{Glutamine and Gut Barrier Function}

In 1978, Windmueller and Speth demonstrated that glucose, ketones, and glutamine are metabolic fuels for the postabsorptive small intestine.\textsuperscript{1} In 1980 Roediger demonstrated that butyrate is a metabolic fuel specific to the proximal and distal colon.\textsuperscript{2} These and other studies stimulated an enormous amount of research into the possibility of modulating clinical and metabolic functions by the use of organ-specific substrates. Perhaps the most investigated of these over the past 20 y and still the most controversial is the use of glutamine.

It is now generally accepted that glutamine is used as a major substrate by enterocytes and colonocytes to a lesser extent and by cells of the immune system. Skeletal muscle exports a large amount of glutamine after sepsis, trauma, operations, and other forms of catabolic stress resulting in a decrease in muscle and eventually blood glutamine. Studies have demonstrated increases in glutamine uptake and metabolism in glutamine-utilizing tissues such as the gut during stress. In animals, glutamine-supplemented parenteral and enteral nutrition enhances gut mucosal growth, repair, and function, decreases bacterial translocation, and improves nitrogen balance in animal models of intestinal atrophy injury and adaptation. There is some evidence from clinical studies that glutamine supplementation improves clinical outcomes in certain catabolic patient groups.

Concomitant with these findings concerning glutamine, the past 20 y or so has also seen an increasing recognition of the importance of the gut as a source of potentially pathogenic organisms. It is hardly surprising, therefore, that many investigators have pursued the attractively simple hypothesis that the use of glutamine might, as a trophic agent of the enterocyte, maintain gut mucosal integrity, thereby reducing the possibility of breakdown in barrier function and consequent translocation of bacteria, and, as such, be associated with improved clinical outcomes. In this issue of \textit{Nutrition}, Salvalaggio et al. make another contribution to this debate.\textsuperscript{3} They investigated the effect of supplemental glutamine on the rate of bacterial translocation in a rat model of intestinal obstruction. After ligating the terminal ileum, they injected a suspension of \textit{Escherichia coli} into the intestinal lumen. At 24 h all animals had microbiologic evidence of bacterial translocation to mesenteric lymph nodes. There was, however, a significant reduction in positive cultures from blood and distant organisms in animals that received glutamine as compared with controls (65.45\% versus 82.67\%, $P = 0.027$). Because the rate of bacterial translocation was unaltered in that study, the authors attributed the reduction in sepsis to glutamine-enhanced immune function rather than to enhanced barrier function.

That study raises some interesting philosophical questions that are apposite to this whole area of research endeavor. First, consider gut barrier function. The role of the gut as a barrier is to prevent the spread of intraluminal bacteria and endotoxins to systemic organs and tissues. Numerous defense mechanisms that function together have evolved to maintain this barrier. These include mechanical defenses, the stabilizing influence of a normal intestinal microflora, immunologic defenses, and the gut–liver axis. Clearly, investigators cannot measure all of these parameters in any individual study. Not surprisingly, therefore, surrogate endpoints are frequently employed. The most common of these are measurements of morphologic or biochemical parameters of the intestinal mucosa or determination of intestinal permeability. We and others, however, have shown that these measurements do not correlate with microbiologically confirmed bacterial translocation, so the significance of these parameters is open to question.\textsuperscript{4–6} This has led to the increasing use of sampling of mesenteric lymph nodes or other tissue from the reticuloendothelial system to obtain microbiological confirmation of bacterial translocation, which remains the gold standard measurement of breakdown in barrier function.\textsuperscript{7} One has to seriously question the significance of bacterial translocation when, in animal models, it occurs in 100\% of animals tested. Clearly, as a discriminant factor, it becomes worthless. Salvalaggio et al. appear to accept this in their study, recognizing that they can draw no conclusions with regard to the effect of glutamine in their animal model on gut-barrier function because translocation rates were so high. However, they do state that there

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