ELSEVIER

European Journal of Pharmacology 410 (2000) 161–163

ejp

www.elsevier.nl/locate/ejphar

The value of genotyping for apolipoprotein E alleles in relation to vitamin E supplementation

Stephen J. Peroutka*, Darlene M. Dreon

1025 Tournament Drive, Burlingame, CA 94010, USA

Accepted 17 October 2000

Abstract

The clinical utility of genotyping individuals for apolipoprotein E alleles remains controversial. The present summary reviews clinical and scientific data that suggest that vitamin E supplementation may be beneficial in individuals who carry the apolipoprotein E4 allele. We propose that early anti-oxidant intervention with vitamin E supplementation may have life-long beneficial effects for individuals who carry one or more apolipoprotein E4 alleles.

Keywords: Vitamin E; Atherosclerosis; Alzheimer's disease; Apolipoprotein E

1. Introduction

Significant evidence *exists* of the benefit of vitamin E supplementation in humans with coronary artery disease (Stampfer et al., 1993; Rimm et al., 1993; Luoma et al., 1995; Hodis et al., 1995; Losonczy et al., 1996; Stephens et al., 1996) and Alzheimer's Disease (Corrigan et al., 1991; Sano et al., 1997; Joseph et al., 1998; McIntosh et al., 1997). These common and serious medical disorders all have been similarly characterized by oxidative damage. Therefore, it follows logically that other conditions marked by oxidative damage might also respond to vitamin E supplementation and that, ideally, treatment could be initiated at the earliest stage of the disease. In theory, a test that could predict susceptibility to oxidative damage might provide a rationale for the early and asymptomatic use of vitamin E supplementation.

Indeed, such a test already exists in genotyping for apolipoprotein E alleles $\varepsilon 2$, $\varepsilon 3$, and $\varepsilon 4$. The $\varepsilon 4$ allele is unequivocally associated with a variety of medical disorders.

• *Alzheimer's Disease*—More than 50 studies have now demonstrated that the presence of an apolipoprotein E $\varepsilon 4$ allele is associated with a significant increase in late-onset Alzheimer's Disease (Corder et al., 1993). In addition, the $\varepsilon 4$ allele is a predisposing genetic marker for other non-Alzheimer's Disease dementias (Myers et al., 1996) and Parkinson's disease-related changes in Alzheimer's Disease (Gearing et al., 1995).

• *Chronic Temporal Lobe Epilepsy*—Apolipoprotein E $\varepsilon 4$ genotype may shorten the latency between initial injury and seizure onset (Briellmann et al., 2000).

• *Coronary Artery Disease*—The presence of the apolipoprotein E $\varepsilon 4$ allele, increases the risk for developing coronary artery disease by 1.3-fold (Stengard et al., 1995). Individuals with apolipoprotein E 2/2 are less at risk and those with apolipoprotein E 4/4 are more at risk for both coronary artery disease (Wilson et al., 1994, 1996) and Alzheimer's Disease (Corder et al., 1994) compared to those with the most common apolipoprotein E 3/3 genotype.

• *Head Trauma*—Patients who carry the apolipoprotein E $\varepsilon 4$ genotype are more likely to have a poor outcome from head injury than patients not possessing an $\varepsilon 4$ allele (Teasdale et al., 1997; Friedman et al., 1999).

• *Post-operative Cognitive Dysfunction*—The apolipoprotein E $\varepsilon 4$ allele is a significant predictor for post-operative cognitive dysfunction in patients undergoing a cardiac bypass operation (Newman et al., 1995)

* Corresponding author. Tel.: +1-650-574-2246; fax: +1-650-571-6433.

E-mail address: DrPeroutka@aol.com (S.J. Peroutka).

0014-2999/00/$ - see front matter
PII: S0014-2999(00)00813-X

• *Stroke*—Recent studies have suggested that the apolipoprotein E ε4 allele may also be a predisposing genetic marker for stroke (Kosunen et al., 1995).

2. Hypothesis

A common pathophysiological mechanism underlying these positive clinical associations with apolipoprotein E genotypes may relate to the endogenous anti-oxidant capability of an individual. Purified apolipoprotein E in vivo protects cells from hydrogen peroxide cytotoxicity and toxicity induced by β-amyloid peptides with $\varepsilon 2 > \varepsilon 3 > \varepsilon 4$ (Miyata and Smith, 1996; Barger and Matson, 1997). Increased levels of oxidative stress would be predicted to enhance β-amyloid peptide deposition (Sopher et al., 1996; Bales et al., 1997), a common pathological finding in Alzheimer's Disease (Bales et al., 1997).

Moreover, it has been observed that plasma lipoproteins from apolipoprotein E deficient mice are more susceptible to in vitro oxidation than the lipoproteins from wild-type mice (Selkoe, 1994). In addition, mice lacking apolipoprotein E are prone to atherosclerosis (Hayek et al., 1994; Breslow, 1996). Thus, taken together, these data indicate that humans with the apolipoprotein E 4/4 genotype have a significantly decreased endogenous anti-oxidation capacity than individuals who do not have an ε4 allele.

Therefore, it does seem reasonable to expect that *all* diseases associated with the ε4 allele might respond to anti-oxidant therapy. Apolipoprotein E alleles can be determined easily and at relatively low cost using either biochemical or genotypic assays. However, a consensus conference in 1995 (American College of Medical Genetics/American Society of Human Genetics Working Group on ApoE and Alzheimer Disease, 1995) concluded that although the apolipoprotein E ε4 allele "is strongly associated with Alzheimer's Disease", apolipoprotein E genotyping was "not recommended for use in routine clinical diagnosis nor should it be used for predictive testing". More recently, the 1997 Stanford University Program in Genomics, Ethics and Society Alzheimer Working Group concluded that "neither predictive nor diagnostic genetic testing for susceptibility genes (e.g., apolipoprotein E) should be encouraged at this time" (Lehrman, 1997).

However, these groups did not consider the fact that the determination of an individual's apolipoprotein E allele status appears to be an efficient method to objectively assess susceptibility to oxidative damage. Individuals at high risk for diseases characterized by oxidative damage (e.g., coronary artery disease, stroke, Alzheimer's Disease) *and* who have an apolipoprotein E ε4 allele might benefit significantly from vitamin E intervention at a relatively early and asymptomatic age. In such individuals, the key issue appears to be *when* to initiate anti-oxidant therapy since vitamin E supplementation is an extremely cost-effective and safe anti-oxidative therapy (Subcommittee on the Tenth Edition of the RDAs, Food and Nutrition Board, Commission on Life Sciences, National Research Council, 1989).

3. Conclusions

Clearly, prospective studies are needed to determine the clinical benefits of asymptomatic treatment with vitamin E or other anti-oxidants. Nonetheless, the existing data indicate that asymptomatic anti-oxidant therapy may have significant long-term medical benefits, especially for individuals with an apolipoprotein E ε4 allele. Therefore, we propose that prospective studies be designed to determine the value of genotyping for apolipoprotein E alleles as an indication to initiate early and asymptomatic vitamin E supplementation in the significant number of apolipoprotein E ε4 allele carriers who are more susceptible to oxidative damage, of varying causes, throughout their life.

References

American College of Medical Genetics/American Society of Human Genetics Working Group on ApoE and Alzheimer Disease, 1995. Statement on use of apolipoprotein E testing for Alzheimer disease. JAMA 274, 1627–1629.

Bales, K.R., Verina, T., Dodel, R.C., Du, Y., Altstiel, L., Bender, M., 1997. Lack of apolipoprotein E dramatically reduces amyloid β-peptide deposition. Nat. Genet. 17, 263–264.

Barger, S.W., Matson, M.P., 1997. Isoform-specific modulation by apolipoprotein E of the activities of secreted beta-amyloid precursor protein. J. Neurochem. 69, 60–67.

Breslow, J.L., 1996. Mouse models of atherosclerosis. Science 272, 685–688.

Briellmann, R.S., Torn-Broers, Y., Busuttil, B.E., Major, B.J., Kalnins, R.M., Olsen, M., Jackson, G.D., Frauman, A.G., Berkovic, S.F., 2000. ApoE ε4 genotype is associated with an earlier onset of chronic temporal lobe epilepsy. Neurology 55, 435–437.

Corder, E.H., Saunders, A.M., Strittmatter, W.J., Schmechel, D.E., Gaskell, P.C., Small, G.W., Roses, A.D., Haines, J.L., Pericak-Vance, M.A., 1993. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science 261, 921–923.

Corder, E.H., Saunders, A.M., Risch, N.J., Strittmatter, W.J., Schmechel, D.E., Gaskell, P.C., Rimmler, J.B., Locke, P.A., Conneally, P.M., Schmader, K.E., Small, G.W., Roses, A.D., Haines, J.L., Pericak-Vance, M.A., 1994. Protective effect of apolipoprotein E type 2 allele for late onset Alzheimer disease. Nat. Genet. 7, 180–184.

Corrigan, F.M., Van Rhijn, A., Horrobin, D.F., 1991. Essential fatty acids in Alzheimer's disease. Ann. N. Y. Acad. Sci. 640, 250–252.

Friedman, G., Froom, P., Sazbon, L., Grinblatt, I., Shochina, M., Tsenter, J., Babaey, S., Yehuda, B., Groswasser, Z., 1999. Apolipoprotein E-4 genotype predicts a poor outcome in survivors of traumatic injury. Neurology 52, 244–248.

Gearing, M., Schneider, J.A., Rebeck, G.W., Hyman, B.T., Mirra, S.S., 1995. Alzheimer's disease with and without coexisting Parkinson's disease changes: apolipoprotein E genotype and neuropathologic correlates. Neurology 45, 1985–1990.

Hayek, T., Oikinine, J., Brook, J.G., Avriam, M., 1994. Increased plasma and lipoprotein lipid peroxidation in apolipoprotein E deficient mice. Biochem. Biophys. Res. Commun. 201, 1567–1574.

Hodis, H.N., Mack, W.J., LaBree, L., Cashin-Hemphill, L., Sevanian, A.,

Johnson, R., Azen, S.P., 1995. Serial coronary angiographic evidence that antioxidant vitamin intake reduces progression of coronary artery atherosclerosis. JAMA 273, 1849–1854.

Joseph, J.A., Shukitt-Hale, B., Denisova, N.A., Prior, R.L., Cao, G., Martin, A., Taglialatela, G., Bickford, P.C., 1998. Long-term dietary strawberry, spinach, or vitamin E supplementation retards the onset of age-related neuronal signal-transduction and cognitive behavioral deficits. J. Neurosci. 18, 8047–8055.

Kosunen, O., Talasniemi, S., Lehtovirta, M., Heinonem, O., Helisalmi, S., Mannermaa, A., Paljarvi, L., Ryynanen, M., Riekkinen, P.J., Soinunen, H., 1995. Relation of coronary atherosclerosis and apolipoprotein E genotypes in Alzheimer patients. Stroke 26, 743–748.

Lehrman, S., 1997. Genetic testing for Alzheimer's disease 'not appropriate'. Nature 389, 898.

Losonczy, K.G., Harris, T.B., Havlik, R.J., 1996. Vitamin E and vitamin C supplement use and risk of all-cause and coronary heart disease mortality in older persons: the established populations for epidemiologic studies of the elderly. Am. J. Clin. Nutr. 64, 190–196.

Luoma, P., Nayha, S., Hassi, J., 1995. High serum concentrations of vitamin E and cholesterol and low mortality from ischaemic heart disease in northern Finland. Arct. Med. Res. 54, 26–28.

McIntosh, L.J., Trush, M.A., Troncoso, J.C., 1997. Increased susceptibility of Alzheimer's disease temporal cortex to oxygen free radical-mediated processes. Free Radical Biol. Med. 23, 183–190.

Miyata, M., Smith, J.D., 1996. Apolipoprotein E allele-specific antioxidant activity and effects on cytotoxicity by oxidative insults and β-amyloid peptides. Nat. Genet. 14, 55–61.

Myers, R.H., Schaefer, E.J., Wilson, P.F.W., D'Agostino, R., Ordovas, J.M., Espino, A., Au, R., White, R.F., Knoefel, J.E., Cobb, J.L., McNulty, K.A., Beiser, A., Wolf, P.A., 1996. Apolipoprotein E $\varepsilon 4$ association with dementia in a population-based study: the Framingham study. Neurology 46, 673–677.

Newman, M.F., Croughwell, N.D., Blumenthal, J.A., Lowry, E., White, W.D., Spillane, W., Davi, R.D., Glower, D.D., Smith, L.R., Mahanna, E.P., Reeves, J.G., 1995. Predictors of cognitive decline after cardiac operation. Ann. Thorac. Surg. 59, 1326–1330.

Rimm, E.B., Stampfer, M.J., Ascherio, A., Giovannucci, E., Colditz, G.A., Willett, W.C., 1993. Vitamin E consumption and the risk of coronary heart disease in men. N. Engl. J. Med. 328, 1450–1456.

Sano, M., Ernesto, C., Thomas, R.G., Klauber, M.R., Schafer, K., Grundman, M., Woodbury, P., Growdon, J., Cotman, C.W., Pfeiffer, E., Schneider, L.S., Thal, L.J., 1997. A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. The Alzheimer's disease cooperative study. N. Engl. J. Med. 336, 1216–1222.

Selkoe, D.J., 1994. Normal and abnormal biology of the beta-amyloid precursor protein. Annu. Rev. Neurosci. 17, 489–517.

Sopher, B.L., Fukuchi, K., Kavanagh, T.J., Furlong, C.E., Martin, G.M., 1996. Neurodegenerative mechanisms in Alzheimer disease. A role for oxidative damage in amyloid beta protein precursor-mediated cell death. Mol. Chem. Neuropathol. 29, 153–168.

Stampfer, M.J., Hennekens, C.H., Manson, J.E., Colditz, G.A., Rosner, B., Willett, W.C., 1993. Vitamin E consumption and the risk of coronary disease in men. N. Engl. J. Med. 328, 1444–1449.

Stengard, J.H., Zerba, K.E., Pekkanen, J., Ehnholm, C., Nissinen, A., Sing, C., 1995. Apolipoprotein E polymorphism predicts death from coronary heart disease in a longitudinal study of elderly Finnish men. Circulation 91, 265–269.

Stephens, N.G., Parsons, A., Schofield, P.M., Kelly, F., Cheeseman, K., Mitchinson, M.J., 1996. Randomized controlled trial of vitamin E in patients with coronary disease: Cambridge heart antioxidant study (CHAOS). Lancet 347, 781–786.

Subcommittee on the Tenth Edition of the RDAs, Food and Nutrition Board, Commission on Life Sciences, National Research Council, 1989. Recommended Dietary Allowances. 10th edn. National Academy Press, Washington, DC.

Teasdale, G.M., Nicoll, J.A.R., Murray, G., Fiddes, M., 1997. Association of apolipoprotein E polymorphism with outcome after headease injury. Lancet 350, 1069–1071.

Wilson, P.W.F., Myers, R.H., Larson, M.G., Ordovas, J.M., Wolf, P.A., Schaefer, E.J., 1994. Apolipoprotein E allele, dyslipidemia and coronary heart disease: the Framingham offspring study. JAMA 27, 1666–1671.

Wilson, P.W., Schaefer, E.J., Larson, M.G., Ordovas, J.M., 1996. Apolipoprotein E alleles and risk of coronary disease: a meta-analysis. Arterioscler., Thromb., Vasc. Biol. 16, 1250–1255.