Neurosteroids in the Retina
Neurodegenerative and Neuroprotective Agents in Retinal Degeneration

P. GUARNERI, a C. CASCIO, a D. RUSSO, a S. D’AGOSTINO, a G. DRAGO, a G. GALIZZI, a G. DE LEO, b F. PICCOLI, c M. GUARNERI, a AND R. GUARNERI a

aIstituto di Biomedicina e Immunologia Molecolare–CNR,
bSezione Biologia e Genetica, Dipartimento Biopatologia e Metodologie Biomediche, cIstituto di Neuropsichiatria, cFacoltà di Medicina e Chirurgia, Università di Palermo, 90146 Palermo, Italy

ABSTRACT: Steroids may have a powerful role in neuronal degeneration. Recent research has revealed that steroids may influence the onset and progression of some retinal disorders as well as neurodegenerative diseases and, as in brain, they accumulate in the retina via a local synthesis (neurosteroids) and metabolism of blood-circulating steroid hormones. Their crucial role as neurodegenerative and neuroprotective agents has been also upheld in a retinal excitotoxic paradigm. These findings are reviewed especially from the emerging perspective that after an insult local changes in steroidogenic responses and consequent neurosteroid availability might turn out to be offensive or defensive cellular adaptations for the potentiation or prevention of neuronal death.

KEYWORDS: pregnenolone sulfate; 17β-estradiol; DHEA; DHEAS; neurodegeneration; neuroprotection; retina
Serum dehydroepiandrosterone sulphate level in age-related macular degeneration.

Tamer C., Okay H., Sigipt S.
Ophthalmology Department, Mustafa Kemal University, Antakya, Turkey, cengaver01@gmail.com

Abstract

PURPOSE: To evaluate plasma dehydroepiandrosterone sulphate (DHEAS) levels in patients diagnosed with age-related macular degeneration (AMD) and controls.

DESIGN: Case-controlled, prospective, comparative noninterventional study.

METHODS: This study involved 32 men and 36 women with exudative AMD, 37 men and 38 women with nonexudative AMD, and 32 men and 32 women of an age-matched control group. The Wisconsin Age-Related Maculopathy Grading System was used to assess the severity of AMD lesions. DHEAS levels were measured and compared according to a gender-based subdivision. Analysis of variance was used to assess the association between DHEAS and AMD. Linear regression model was used to examine the relation among DHEAS level and AMD severity scale.

RESULTS: Mean ± SD of DHEAS levels in exudative AMD, nonexudative AMD, and controls in men was 2.67 ± 0.68 micromol/L, 2.89 ± 0.95 micromol/L, and 4.43 ± 1.44 micromol/L, respectively (P = .001), and in women was 1.64 ± 0.72 micromol/L, 1.85 ± 0.73 micromol/L, and 2.78 ± 0.91 micromol/L, respectively (P = .001). Post hoc Tukey analyses revealed a significant reduction in serum DHEAS level in both AMD groups, compared with controls for men and women (P = .001), while no difference was found between AMD groups in both men and women (P = .668 and 0.49, respectively). Regression analyses revealed an inverse correlation among serum DHEAS level and AMD severity scale both in men and women (P = .006 and .007, respectively).

CONCLUSIONS: This study suggests an inverse correlation between serum DHEAS level and AMD severity scale with a considerably reduced DHEAS level in AMD.

PMD: 17157799 [PubMed - indexed for MEDLINE]

Analysis of candidate genes for age-related macular degeneration subtypes in the Japanese population.

Department of Ophthalmology, Niho University School of Medicine, Tokyo, Japan.

Abstract

PURPOSE: Age-related macular degeneration (AMD) is thought to be a polygenic disease. It is divided into three subtypes: neovascular AMD (nAMD), polypoidal choroidal vasculopathy, and retinal angiomatosus proliferation (RAP). These subtypes are thought to have different pathophysiological and genetic backgrounds. We aimed to investigate the relationships between single nucleotide polymorphisms (SNPs) in candidate genes and subtypes of AMD in the Japanese population.

METHODS: We genotyped 685 AMD patients and 277 controls for four SNPs of the selected candidate genes: rs800292 in complement factor H, rs10490924 in age-related maculopathy susceptibility 2 (ARMS2), rs2010965 in elastin (ELN), and rs1801133 in methylenetetrahydrofolate reductase (MTHFR). Case-control studies were performed using these AMD subtypes. Logistic regression analysis was performed using a history of hypertension, diabetes mellitus, and smoking as cardiovascular risks.

RESULTS: The genotype-dominant or recessive distribution of all four SNPs differed significantly between the controls and the AMD patients. In the subtype analysis, there were significant differences between the controls and the AMD patients in genotype distributions. This was true for all AMD subtype analyses of both rs800292 (complement factor H) and rs10490924 (ARMS2). Logistic regression analysis indicated the TT genotype of the ARMS2 gene to be significantly more common in RAP patients (p=1.54×10^{-13}, odds ratio: 22.18). In contrast, there were significant differences in the genotype distribution between the controls and nAMD patients only for rs2010965 (ELN, p=0.022) and rs1801133 (MTHFR, p=2.50×10^{-3}).

CONCLUSIONS: Our results indicate that SNPs of the ARMS2 gene may serve as strong genetic markers of RAP, and that SNPs of the ELN and MTHFR genes are potential genetic markers for nAMD.

Folic acid, pyridoxine, and cyanocobalamin combination treatment and age-related macular degeneration in women: the Women's Antioxidant and Folic Acid Cardiovascular Study.

Christen WG, Glynn RJ, Chew EY, Albert DM, Manson JE
Division of Preventive Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, 600 Commonwealth Avenue E, Boston, MA 02215-1204, USA. wcg3p@rics.bwh.harvard.edu

Abstract

BACKGROUND: Observational epidemiologic studies indicate a direct association between homocysteine concentration in the blood and the risk of age-related macular degeneration (AMD), but randomized trial data to examine the effect of therapy to lower homocysteine levels in AMD are lacking. Our objective was to examine the incidence of AMD in a trial of combined folic acid, pyridoxine hydrochloride (vitamin B(6)), and cyanocobalamin (vitamin B(12)) therapy.

METHODS: We conducted a randomized, double-blind, placebo-controlled trial including 5442 female health care professionals 40 years or older with presexisting cardiovascular disease or 3 or more cardiovascular disease risk factors. A total of 5205 of these women did not have a diagnosis of AMD at baseline and were included in this analysis. Participants were randomly assigned to receive a combination of folic acid (2.5 mg/d), pyridoxine hydrochloride (50 mg/d), and cyanocobalamin (1 mg/d) or placebo. Our main outcome measures included total AMD, defined as a self-report documented by medical record evidence of an initial diagnosis after randomization, and visually significant AMD, defined as confirmed incident AMD with visual acuity of 20/30 or worse attributable to this condition.

RESULTS: After an average of 7.3 years of treatment and follow-up, there were 55 cases of AMD in the combination treatment group and 82 in the placebo group (relative risk, 0.66; 95% confidence interval, 0.47-0.93 [P = .02]). For visually significant AMD, there were 26 cases in the combination treatment group and 44 in the placebo group (relative risk, 0.59; 95% confidence interval, 0.36-0.95 [P = .03]).

CONCLUSIONS: These randomized trial data from a large cohort of women at high risk of cardiovascular disease indicate that daily supplementation with folic acid, pyridoxine, and cyanocobalamin may reduce the risk of AMD.

Parallel findings in age-related macular degeneration and Alzheimer's disease.

Ohno-Matsui K
Department of Ophthalmology and Visual Sciences, Tokyo Medical and Dental University, Yushima, Bunkyo-ku, Japan. kohno.oph@tmd.ac.jp

Abstract

Age is a common risk factor for Alzheimer's disease (AD) and age-related macular degeneration (AMD). Because of the increasing age of the population, these two age-related diseases have recently received a great deal of attention. In addition to age as a risk factor, AD and AMD have many characteristics in common. An important characteristic common to both diseases is the presence of amyloid β (Aβ) in the senile plaques of the AD brain and in the drusen of AMD patients. We have focused on the role of Aβ as a key regulator of the progression from drusen to AMD, and our results have shown that Aβ causes an imbalance of angiogenesis-related factors in the retinal pigment epithelial (RPE) cells. Mice that lack the Aβ-degrading enzyme neprilysin develop RPE degeneration, and the sub-RPE deposits that are formed have features similar to those of AMD in humans. These data suggest that a common pathogenic mechanism might exist between AMD and AD. Thus, therapeutic approaches that have targeted Aβ in patients with AD can also be applied to AMD. In this review, we summarise recent findings on the shared characteristics and perspectives between AMD and AD, beginning with the mechanism of Aβ deposition and including a discussion of Aβ-targeted therapeutic approaches for both AD and AMD.

Copyright © 2011 Elsevier Ltd. All rights reserved.

PMID: 21440663 [PubMed - indexed for MEDLINE]
Efficacy of various antioxidants in the protection of the retinal pigment epithelium from oxidative stress.

Kogan DB, Liu H, Huhnik CM.
Ivey Eye Institute, St Joseph’s Hospital, London, ON, Canada.

Abstract

BACKGROUND: Oxidative stress induced retinal pigment epithelium (RPE) dysfunction is hypothesized to be fundamental in the pathogenesis of age-related macular degeneration (AMD). This study investigated whether vitamin C, vitamin C phosphate, vitamin E, propofol, bexatol, and N-acetyl cysteine (NAC) protect human RPE cells from oxidative stress.

METHODS: ARPE-19 cells were pretreated with the compounds under investigation. The chemical oxidant tert-butyl hydroperoxide (t-BOOH) was used to induce oxidative stress. Cell viability was determined using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay.

RESULTS: Exposure to t-BOOH resulted in a dose- and time-dependent reduction in ARPE-19 cell viability. Compared with cells given t-BOOH alone, vitamin E and NAC pretreated cells had significantly improved viability, propofol and bexatol pretreated cells had no significant difference in viability, and vitamin C and vitamin C phosphate pretreated cells had significantly reduced viability.

CONCLUSION: Of the compounds studied, only vitamin E and NAC significantly mitigated the effects of oxidative stress on RPE cells. Because of their potential therapeutic value for AMD patients, these and other RPE protective compounds continue to merit further investigation.


Hypomethylation of IL17RC Promoter Associates with Age-related Macular Degeneration

Lai Wei, 1,2,3,* Baoying Liu, 1 Jingsheng Tuo, 1 Defan Shen, 1 Ping Chen, 1 Zhiyue Li, 1 Xunxian Liu, 3 Jin Ni, 1 Pradeep Dhar, 4 H. Nida San, 1 Shyamna Jawad, 1 Diamond Ling, 1 Stanley Pars, 1 Sagarika Chakraborty, 1 Catherine Meyerle, 5 Elwin Agron, 5 Frederik L. Fenn, 3rd, 5 Emily Y. Chew, 5 J. Philip McCoy, 4 Emily Blum, 5 Peter J. Francia, 5 Michael L. Klein, 5 Robyn H. Guymer, 7 Paul N. Baird, 7 Chi-Chao Chan, 1 and Robert B. Nussenblatt 1,2,3,*

Author information ► Copyright and License information ►

The publisher’s final edited version of this article is available at Cell Rep

SUMMARY

Age related macular degeneration (AMD) is the leading cause of irreversible blindness in the elderly population worldwide. While recent studies have demonstrated strong genetic associations of single nucleotide polymorphisms within a number of genes and AMD, other modes of regulation are also likely to play a role in its etiology. We identified a significantly decreased level of methylation on the IL17RC promoter in AMD patients. Further, we showed that hypomethylation of the IL17RC promoter in AMD patients led to an elevated expression of its protein and mRNA in peripheral blood as well as in the affected retina and choroid, suggesting that the DNA methylation pattern and expression of IL17RC may potentially serve as a biomarker for the diagnosis of AMD and likely plays a role in disease pathogenesis.
DNA methylation is associated with altered gene expression in AMD.

Hunter A. Spechler, PA, Cingrani A, Song Y, Zhang Z, Ying GS, Hunter AK, Dezoteux E, Duaeil L.

Helm Kirby Center for Molecular Ophthalmology, Scheie Eye Institute, University of Pennsylvania, Philadelphia, Pennsylvania 19104, USA. hunter.allen.a@gmail.com

Abstract

PURPOSE: Age-related macular degeneration (AMD) is the leading cause of blindness in the elderly. Evidence suggests oxidative stress plays a role in the disease. To assess the potential contribution of epigenetic regulation of antioxidant genes relevant to AMD pathogenesis, we evaluated DNA methylation, a tissue-specific genetic modulation that affects gene expression.

METHODS: Using the Illumina HumanMethylation27 bead platform, we performed DNA bisulfite sequencing to compare the methylation status in postmortem retina pigment epithelium (RPE)/choroid between patients with AMD and age-matched controls. Gene expression was assessed with the Affymetrix Exon Array. TaqMan gene expression assays were used for relative quantification (RT-qPCR) confirmation of the expression array results: Glutathione S-transferase isomorph mu1 (GSTM1) and mu5 (GSTM5) promoter methylation was confirmed by CGP island bisulfite pyrosequencing. To assess protein levels and localization, we used Western analysis, immunohistochemistry, and immunofluorescence with murine and human samples.

RESULTS: The mRNA levels of GSTM1 and GSTM5 were significantly reduced in AMD versus age-matched controls in RPE/choroid and neurosensory retina (NSR), which corresponded to hypomethylation of the GSTM1 promoter. mRNA and protein levels were decreased (RPE to a greater extent than NSR) in AMD postmortem samples, irrespective of age. Immunohistochemistry and immunofluorescence confirmed the presence of the enzymes in the NSR and RPE.

CONCLUSIONS: Comparison of DNA methylation, together with mRNA levels, revealed significant differences between AMD versus normal retinas. The evidence presented suggests that GSTM1 and GSTM5 undergo epigenetic repression in AMD RPE/choroid, which may increase susceptibility to oxidative stress in AMD retinas.

PMID: 22410570 [PubMed - indexed for MEDLINE]


Homocysteine, vitamin B12, and folic acid in age-related macular degeneration.


Pathophysiology Division, Department of Pathophysiology and Endocrinology, Medical University of Silesia, Zabrze, Poland. nowak-mar@wp.pl

Abstract

PURPOSE: Hyperhomocysteinemia is considered an independent risk factor for atherosclerosis and thrombosis. The purpose of this study was to evaluate plasma homocysteine, red blood cell folate, plasma folate, and plasma vitamin B12 concentration in patients with exudative age-related macular degeneration (AMD).

METHODS: The participants of this study included 30 patients aged 60 to 71 years (mean age 69.2±3.6) with exudative AMD. Plasma homocysteine levels were determined by high-performance liquid chromatography (HPLC). Red blood cell folate, plasma folate, and plasma vitamin B12 concentration were determined using a standard kit (Dualcount Solid Phase No Boril radioassay kit for B12/folic acid, DPC Diagnostic, USA) by radioassay method.

RESULTS: The plasma concentration of Hcy (14.88±6.23 micromol/L) in AMD patients was significantly increased (p=0.0001) compared with the control group (8.72±3.34 micromol/L). We found a not significant decrease of the plasma vitamin B12 concentration in the AMD group (478.86±220.91 pg/mL) compared with the control group (527.69±203.97 pg/mL). Red blood cell folate (158.44±56.30 ng/mL) and plasma folate (65.5±3.4 ng/mL) in AMD patients were also not significantly decreased when compared with the control group (168.86±59.33 ng/mL, and 7.90±2.90 ng/mL).

CONCLUSIONS: Hyperhomocysteinemia might be one of the risk factors for the exudative form of AMD.

PMID: 16320063 [PubMed - indexed for MEDLINE]


Plasma homocysteine, vitamin B12 and folate levels in age-related macular degeneration.

Kemalcioglu G, Gümüş C, Kuytulgililer B, Çiftçi B.

Department of Ophthalmology, Hacettepe University Hospital, 06100, Sihhiye, Ankara, Turkey.

Abstract

PURPOSE: The purpose of this study was to investigate the association of age-related macular degeneration (AMD) with plasma homocysteine, vitamin B12, and folate levels.

METHODS: Sixty patients diagnosed with AMD at our clinic between March 2004 and September 2004 were assessed in a prospective cross-sectional study. Plasma homocysteine, vitamin B12, and folate levels taken after 8 h of fasting from 30 patients with exudative AMD and 30 patients with dry AMD were compared with the results of 30 age- and sex-matched healthy participants.

RESULTS: Patients with both exudative and dry types of AMD had significantly higher plasma homocysteine levels (mean 14.19±3.11 micromol/L; 13.07±2.90 micromol/L, respectively) compared with the controls (mean 10.79±2.56 micromol/L; p=0.000 and p=0.008, respectively). Homocysteine levels were higher in the exudative AMD group compared with the dry AMD group, but the difference was not statistically significant (p=0.250). Plasma vitamin B12 levels were found to be significantly lower in the exudative AMD group (280.14±113.44 pg/mL) compared with the controls (436.17±264.12 pg/mL) and dry AMD group (443.47±190.83 pg/mL; p=0.000). Plasma folate levels were comparable among groups (p=0.168).

CONCLUSIONS: This study suggests an association between elevated plasma homocysteine and AMD regardless of the subtype. Further controlled prospective studies are needed to investigate the possible role of homocysteine in AMD and the effect of vitamin B12 and folate supplementation in this process.

PMID: 16853407 [PubMed - indexed for MEDLINE]
Visual impairment, age-related macular degeneration, cataract, and long-term mortality: the Blue Mountains Eye Study.

Centre for Vision Research, Department of Ophthalmology, Westmead Millennium Institute, University of Sydney, Westmead Hospital, Westmead, New South Wales, Australia.

Abstract

OBJECTIVE: To assess the association of visual impairment, age-related macular degeneration (ARMD), and cataract with long-term mortality.

METHODS: At baseline, 3054 persons 49 years and older were examined in the Blue Mountains Eye Study (1992-1994). Standardized photographic grading was used to assess ARMD and cataract. Mortality and causes of death occurring between baseline and December 31, 2003, were obtained via data linkage with the Australian National Death Index. Age-standardized mortality rates were calculated. Hazard ratios (HRs) and 95% confidence intervals (CIs) were assessed using Cox models. Results: Age-standardized mortality was higher in persons with vs without visual impairment (54.0% vs 34.9%), ARMD (45.6% vs 39.7%), and cataract (39.2% vs 29.9%). After adjusting for factors that predict mortality, neither visual impairment (HR, 1.3; 95% CI, 0.98-1.7) nor ARMD (HR, 1.0; 95% CI, 0.8-1.3) was significantly associated with all-cause mortality in all ages. Among persons younger than 75 years, however, ARMD predicted higher all-cause mortality (HR, 1.8; 95% CI, 1.0-2.4). Any cataract (HR, 1.3; 95% CI, 1.0-1.5) and cortical (HR, 1.2; 95% CI, 0.97-1.4), nuclear (HR, 1.2; 95% CI, 0.98-1.5), and posterior subcapsular (HR, 1.3; 95% CI, 1.0-1.7) cataract were also associated with higher all-cause mortality.

CONCLUSION: Cataract predicted increased mortality in persons 49 years and older, and ARMD predicted mortality in persons aged 49 to 74 years.

PMID: 17625571 [PubMed - indexed for MEDLINE]