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MD Research News

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Drug treatment

Semin Ophthalmol. 2013 Sep 6. [Epub ahead of print]

Pharmacogenetics of the Treatment Response of Age-Related Macular Degeneration with Ranibizumab and Bevacizumab.

Kanoff J, Miller J.

Department of Ophthalmology, Massachusetts Eye and Ear Infirmary, Harvard Medical School , Boston, Massachusetts , USA.

Abstract Introduction: Age-related macular degeneration is a major cause of blindness among people aged 50 and older in industrialized countries. Anti-VEGF therapy has been tremendously successful in the treatment of neovascular macular degeneration. Examining the pharmacogenetics of patients' response to the anti-VEGF molecules could allow for a tailored treatment strategy based on patients' underlying genetics rather than the "one-size fits all" approach currently used.

Methods: Review of the English literature for papers examining the pharmacogenetics of treatment response of neovascular macular degeneration to either ranibizumab or bevacizumab. Polymorphisms in CFH, ARMS2, HTRA1 and VEGF A were examined and reviewed.

Results: Patients with the high-risk CC genotype in complement factor H (CFH) had a worse response to therapy with ranibizumab and bevacizumab. No clear trends were found with ARMS2, HTRA1 and VEGF A.

Conclusions: The goal of personalized medicine is to craft a treatment program that is ideally suited to an individual patient's disease and genetic make-up rather than simply what works for a large population who share similar disease characteristics. Continued research is needed to achieve this goal for the treatment of age-related macular degeneration.

PMID: 24010796 [PubMed - as supplied by publisher]

PLoS One. 2013 Aug 27;8(8):e72755. doi: 10.1371/journal.pone.0072755.

Structural and Functional Measures of Efficacy in Response to Bevacizumab Monotherapy in Diabetic Macular Oedema: Exploratory Analyses of the BOLT Study (Report 4).

Sivaprasad S, Crosby-Nwaobi R, Esposti S, Peto T, Rajendram R, Michaelides M, Hykin P.

NIHR Moorfields Biomedical Research Centre, Moorfields Eye Hospital, London, United Kingdom.

BACKGROUND: To describe structural and functional changes associated with diabetic macular oedema (DMO) treated with intravitreal bevacizumab over 24 months.

METHODS: A post-hoc analysis of the data of 34 patients that completed 24 months follow-up in the intravitreal bevacizumab arm of a prospective, randomized controlled trial (BOLT study) was performed. The outcome measures previously used in clinical trials of intravitreal ranibizumab in DMO were employed to describe the visual acuity and macular thickness changes at 12 and 24 months.

RESULTS: The standard outcomes of mean change in best corrected visual acuity (BCVA) and central macular thickness (CMT) in participants treated with bevacizumab were comparable to those reported in association with ranibizumab. However, exploratory analyses showed that thick maculae at baseline defined as CMT of ≥400 μm, remained significantly thicker than those <400 μm with intensive bevacizumab therapy, despite a comparable gain in visual acuity at both 12 and 24 months. The proportion of subjects that attained a dry macula doubled in both CMT groups between the 12 and 24-month time-points.

CONCLUSIONS: These findings provide valuable information both for clinical practice and trials. Further studies are required to investigate the impact of intravitreal bevacizumab on retinal thickness profiles in DMO.

PMID: 24013651 [PubMed - in process] PMCID: PMC3754932

Other treatment & diagnosis

JAMA Ophthalmol. 2013 Sep 12. doi: 10.1001/jamaophthalmol.2013.4471. [Epub ahead of print]

Alteration of Travel Patterns With Vision Loss From Glaucoma and Macular Degeneration.

Curriero FC, Pinchoff J, van Landingham SW, Ferrucci L, Friedman DS, Ramulu PY.

Department of Environmental Health Sciences, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland2Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland.

IMPORTANCE: The distance patients can travel outside the home influences how much of the world they can sample and to what extent they can live independently. Recent technological advances have allowed travel outside the home to be directly measured in patients' real-world routines.

OBJECTIVE: To determine whether decreased visual acuity (VA) from age-related macular degeneration (AMD) and visual field (VF) loss from glaucoma are associated with restricted travel patterns in older adults.

DESIGN: Cross-sectional study.

SETTING: Patients were recruited from an eye clinic, while travel patterns were recorded during their real-world routines using a cellular tracking device.

PARTICIPANTS: Sixty-one control subjects with normal vision, 84 subjects with glaucoma with bilateral VF loss, and 65 subjects with AMD with bilateral or severe unilateral loss of VA had their location tracked every 15 minutes between 7 am and 11 pm for 7 days using a tracking device.

MAIN OUTCOMES AND MEASURES: Average daily excursion size (defined as maximum distance away from home) and average daily excursion span (defined as maximum span of travel) were defined for each individual. The effects of vision loss on travel patterns were evaluated after controlling for individual and geographic factors.

RESULTS: In multivariable models comparing subjects with AMD and control subjects, average excursion size and span decreased by approximately one-quarter mile for each line of better-eye VA loss (P≤ .03 for

both). Similar but not statistically significant associations were observed between average daily excursion size and span for severity of better-eye VF loss in subjects with glaucoma and control subjects. Being married or living with someone and younger age were associated with more distant travel, while less-distant travel was noted for older individuals, African Americans, and those living in more densely populated regions.

CONCLUSIONS AND RELEVANCE Age-related macular degeneration-related loss of VA, but not glaucoma-related loss of VF, is associated with restriction of travel to more nearby locations. This constriction of life space may impact quality of life and restrict access to services.

PMID: 24030033 [PubMed - as supplied by publisher]

J Vis. 2013 Sep 12;13(3). pii: 28. doi: 10.1167/13.3.28.

Contextual cueing impairment in patients with age-related macular degeneration.

Geringswald F, Herbik A, Hoffmann MB, Pollmann S.

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Abstract: Visual attention can be guided by past experience of regularities in our visual environment. In the contextual cueing paradigm, incidental learning of repeated distractor configurations speeds up search times compared to random search arrays. Concomitantly, fewer fixations and more direct scan paths indicate more efficient visual exploration in repeated search arrays. In previous work, we found that simulating a central scotoma in healthy observers eliminated this search facilitation. Here, we investigated contextual cueing in patients with age-related macular degeneration (AMD) who suffer from impaired foveal vision. AMD patients performed visual search using only their more severely impaired eye (n = 13) as well as under binocular viewing (n = 16). Normal-sighted controls developed a significant contextual cueing effect. In comparison, patients showed only a small nonsignificant advantage for repeated displays when searching with their worse eye. When searching binocularly, they profited from contextual cues, but still less than controls. Number of fixations and scan pattern ratios showed a comparable pattern as search times. Moreover, contextual cueing was significantly correlated with acuity in monocular search. Thus, foveal vision loss may lead to impaired guidance of attention by contextual memory cues.

PMID: 24029899 [PubMed - in process]

Prog Retin Eye Res. 2013 Sep 9. pii: S1350-9462(13)00056-6. doi: 10.1016/j.preteyeres.2013.08.003. [Epub ahead of print]

Cuticular Drusen: Stars in the sky.

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Abstract: Cuticular drusen is a specific clinical subtype of age-related macular degeneration (AMD). This subtype of AMD has an earlier age at onset, a stronger familial component, and genetic factors play a more prominent role in its development than in the general AMD population. In this review, we describe the clinical characteristics and differential diagnosis of cuticular drusen, as well as systemic associations including membranoproliferative glomerulonephritis type II. We discuss recent genetic and pathophysiological insights, and future therapeutic perspectives are highlighted.

PMID: 24028794 [PubMed - as supplied by publisher]

Front Psychol. 2013 Sep 3;4:579. doi: 10.3389/fpsyg.2013.00579.

Macular degeneration affects eye movement behavior during visual search.

Van der Stigchel S, Bethlehem RA, Klein BP, Berendschot TT, Nijboer TC, Dumoulin SO.

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Abstract: Patients with a scotoma in their central vision (e.g., due to macular degeneration, MD) commonly adopt a strategy to direct the eyes such that the image falls onto a peripheral location on the retina. This location is referred to as the preferred retinal locus (PRL). Although previous research has investigated the characteristics of this PRL, it is unclear whether eye movement metrics are modulated by peripheral viewing with a PRL as measured during a visual search paradigm. To this end, we tested four MD patients in a visual search paradigm and contrasted their performance with a healthy control group and a healthy control group performing the same experiment with a simulated scotoma. The experiment contained two conditions. In the first condition the target was an unfilled circle hidden among c-shaped distractors (serial condition) and in the second condition the target was a filled circle (pop-out condition). Saccadic search latencies for the MD group were significantly longer in both conditions compared to both control groups. Results of a subsequent experiment indicated that this difference between the MD and the control groups could not be explained by a difference in target selection sensitivity. Furthermore, search behavior of MD patients was associated with saccades with smaller amplitudes toward the scotoma, an increased intersaccadic interval and an increased number of eye movements necessary to locate the target. Some of these characteristics, such as the increased intersaccadic interval, were also observed in the simulation group, which indicate that these characteristics are related to the peripheral viewing itself. We suggest that the combination of the central scotoma and peripheral viewing can explain the altered search behavior and no behavioral evidence was found for a possible reorganization of the visual system associated with the use of a PRL. Thus the switch from a fovea-based to a PRL-based reference frame impairs search efficiency.

PMID: 24027546 [PubMed]

Sci Rep. 2013 Sep 12;3:2644. doi: 10.1038/srep02644.

In vivo Optical Coherence Tomography of Light-Driven Melanosome Translocation in Retinal Pigment Epithelium.

Zhang QX, Lu RW, Messinger JD, Curcio CA, Guarcello V, Yao XC.

Department of Biomedical Engineering, University of Alabama at Birmingham, Birmingham, AL 35294.

Abstract: Optical coherence tomography (OCT) may revolutionize fundamental investigation and clinical management of age-related macular degeneration and other eye diseases. However, quantitative OCT interpretation is hampered due to uncertain sub-cellular correlates of reflectivity in the retinal pigment epithelium (RPE) and photoreceptor. The purpose of this study was twofold: 1) to test OCT correlates in the RPE, and 2) to demonstrate the feasibility of longitudinal OCT monitoring of sub-cellular RPE dynamics. A high resolution OCT was constructed to achieve dynamic imaging of frog eyes, in which light-driven translocation of RPE melanosomes occurred within the RPE cell body and apical processes. Comparative histological examination of dark- and light-adapted eyes indicated that the RPE melanin granule, i.e., melanosome, was a primary OCT correlate. In vivo OCT imaging of RPE melanosomes opens the opportunity for quantitative assessment of RPE abnormalities associated with disease, and enables longitudinal investigation of RPE kinetics correlated with visual function.

PMID: 24025778 [PubMed - in process]

Phys Med Biol. 2013 Sep 12;58(19):6887-6896. [Epub ahead of print]

Influence of eye size and beam entry angle on dose to non-targeted tissues of the eye during stereotactic x-ray radiosurgery of AMD.

Cantley JL, Hanlon J, Chell E, Lee C, Smith WC, Bolch WE.

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Abstract: Age-related macular degeneration is a leading cause of vision loss for the elderly population of industrialized nations. The IRay® Radiotherapy System, developed by Oraya® Therapeutics, Inc., is a stereotactic low-voltage irradiation system designed to treat the wet form of the disease. The IRay System uses three robotically positioned 100 kVp collimated photon beams to deliver an absorbed dose of up to 24 Gy to the macula. The present study uses the Monte Carlo radiation transport code MCNPX to assess absorbed dose to six non-targeted tissues within the eye-total lens, radiosensitive tissues of the lens, optic nerve, distal tip of the central retinal artery, non-targeted portion of the retina, and the ciliary body--all as a function of eye size and beam entry angle. The ocular axial length was ranged from 20 to 28 mm in 2 mm increments, with the polar entry angle of the delivery system varied from 18° to 34° in 2° increments. The resulting data showed insignificant variations in dose for all eye sizes. Slight variations in the dose to the optic nerve and the distal tip of the central retinal artery were noted as the polar beam angle changed. An increase in non-targeted retinal dose was noted as the entry angle increased, while the dose to the lens, sensitive volume of the lens, and ciliary body decreased as the treatment polar angle increased. Polar angles of 26° or greater resulted in no portion of the sensitive volume of the lens receiving an absorbed dose of 0.5 Gy or greater. All doses to non-targeted structures reported in this study were less than accepted thresholds for post-procedure complications.

PMID: 24025704 [PubMed - as supplied by publisher]

Pathogenesis

Invest Ophthalmol Vis Sci. 2013 Sep 10. pii: iovs.13-12342v1. doi: 10.1167/iovs.13-12342. [Epub ahead of print]

Identification of vascular endothelial side population cells in the choroidal vessels and its potential role in age-related macular degeneration.

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Purpose: The neovascular form of age-related macular degeneration (AMD) is characterized by the growth of abnormal new blood vessels from the choroid, termed choroidal neovascularization (CNV). The origin of the new vessels in CNV, however, has not been fully elucidated. The purpose of this study is to identify vascular endothelial side population (SP) cells in the pre-existing choroidal vessels and investigate their potential role in age-related macular degeneration.

Methods: We made single cell suspensions of freshly isolated mouse choroidal, retinal, and brain tissue by enzymatic digestion. Vascular endothelial SP cells were isolated using flow cytometry based on the ability to efflux the DNA-binding dye Hoechst 33342 via ATP-binding cassette (ABC) transporters.

Results: In the choroid, 2.8% of CD31+ CD45- vascular endothelial cells (ECs) showed a typical SP staining pattern. They were not bone marrow-derived and possessed high colony-forming capacity in vitro. They proliferated during laser-induced CNV in vivo. In contrast, stereotypic SP staining pattern was not observed in retinal and brain ECs. Retinal and brain EC-SP cells included increased SP populations with less colony-forming capacity within the SP compartment because they contained both cells with and without

proliferative potential. The latter could still efflux the dye due to high levels of ABC transporters such as ABCB1a, ABCC4 and ABCC6.

Conclusions: EC-SP cells in the choroid may represent vessel-residing endothelial stem/progenitor cells contributing mainly to angiogenesis and may be useful for augmenting vascular regeneration or for developing new anti-angiogenic therapy in age-related macular degeneration.

PMID: 24022013 [PubMed - as supplied by publisher]

Exp Eye Res. 2013 Sep 7. pii: S0014-4835(13)00260-1. doi: 10.1016/j.exer.2013.08.021. [Epub ahead of print]

Retinal pigment epithelium cells produce VEGF in response to oxidized phospholipids through mechanisms involving ATF4 and protein kinase CK2.

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Department of Ophthalmology and Optometry, Medical University Vienna, Waehringer Guertel 18-20, 1090 Vienna, Austria.

Abstract: Oxidized phospholipids (OxPLs) are pleiotropic lipid mediators known to induce proangiogenic and proinflammatory cellular effects that are increasingly recognized to be involved in a number of physiologic and pathologic processes in the retina. Immunohistochemical studies have detected OxPLs in retinal structures, such as retinal pigment epithelium (RPE) or photoreceptor cells. This study analyzed whether OxPLs could play a role in upregulation of VEGF, which is a cause of pathological neovascularization characteristic of eye diseases such as age-related macular degeneration. We confirmed accumulation of OxPLs in the eye using reversed-phase liquid chromatography coupled to mass spectrometry. Multiple species of oxidized phosphatidylcholines (OxPCs) were detected in human vitreous, including biologically active fragmented species POVPC, PGPC, PONPC and PAzPC. In in vitro experiments human fetal RPE and primary RPE cells were stimulated with OxPLs. Primary RPE cells were transfected with small interfering RNAs targeting ATF4. mRNA levels of VEGF in fetal and primary RPE cells were determined by real-time quantitative PCR. VEGF protein concentrations were measured in culture medium by ELISA. We found that OxPCs and other classes of OxPLs upregulated the expression of VEGF in fetal and primary RPE cells, which critically depended on the ATF4. In addition, upregulation of VEGF in primary RPE cells was blocked by a chemical inhibitor of protein kinase CK2 known to suppress induction of ATF4 and VEGF by OxPLs. Our data show that different species of OxPLs, which are present in the human eye are capable of stimulating expression of VEGF in fetal and primary RPE cells via the ATF4-dependent mechanisms.

PMID: 24021586 [PubMed - as supplied by publisher]

J Clin Invest. 2013 Sep 9. pii: 67315. doi: 10.1172/JCI67315. [Epub ahead of print]

Retinal angiogenesis suppression through small molecule activation of p53.

Chavala SH, Kim Y, Tudisco L, Cicatiello V, Milde T, Kerur N, Claros N, Yanni S, Guaiquil VH, Hauswirth WW, Penn JS, Rafii S, De Falco S, Lee TC, Ambati J.

Abstract: Neovascular age-related macular degeneration is a leading cause of irreversible vision loss in the Western world. Cytokine-targeted therapies (such as anti-vascular endothelial growth factor) are effective in treating pathologic ocular angiogenesis, but have not led to a durable effect and often require indefinite treatment. Here, we show that Nutlin-3, a small molecule antagonist of the E3 ubiquitin protein ligase MDM2, inhibited angiogenesis in several model systems. We found that a functional p53 pathway was essential for Nutlin-3-mediated retinal antiangiogenesis and disruption of the p53 transcriptional network

abolished the antiangiogenic activity of Nutlin-3. Nutlin-3 did not inhibit established, mature blood vessels in the adult mouse retina, suggesting that only proliferating retinal vessels are sensitive to Nutlin-3. Furthermore, Nutlin-3 inhibited angiogenesis in nonretinal models such as the hind limb ischemia model. Our work demonstrates that Nutlin-3 functions through an antiproliferative pathway with conceivable advantages over existing cytokine-targeted antiangiogenesis therapies.

PMID: 24018558 [PubMed - as supplied by publisher]

Cell Rep. 2013 Sep 4. pii: S2211-1247(13)00426-9. doi: 10.1016/j.celrep.2013.08.002. [Epub ahead of print]

NLRP3 Inflammasome Blockade Inhibits VEGF-A-Induced Age-Related Macular Degeneration.

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Abstract: The NLRP3 inflammasome is activated in age-related macular degeneration (AMD), but it remains unknown whether its activation contributes to AMD pathologies. VEGF-A is increased in neovascular ("wet") AMD, but it is not known whether it plays a role in inflammasome activation, whether an increase of VEGF-A by itself is sufficient to cause neovascular AMD and whether it can contribute to nonexudative ("dry") AMD that often co-occurs with the neovascular form. Here, it is shown that an increase in VEGF-A results in NLRP3 inflammasome activation and is sufficient to cause both forms of AMD pathologies. Targeting NLRP3 or the inflammasome effector cytokine IL-1β inhibits but does not prevent VEGF-A-induced AMD pathologies, whereas targeting IL-18 promotes AMD. Thus, increased VEGF-A provides a unifying pathomechanism for both forms of AMD; combining therapeutic inhibition of both VEGF-A and IL-1β or the NLRP3 inflammasome is therefore likely to suppress both forms of AMD.

PMID: 24012762 [PubMed - as supplied by publisher]

PLoS One. 2013 Aug 27;8(8):e72737. doi: 10.1371/journal.pone.0072737.

Metabolome-wide association study of neovascular age-related macular degeneration.

Osborn MP, Park Y, Parks MB, Burgess LG, Uppal K, Lee K, Jones DP, Brantley MA Jr.

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PURPOSE: To determine if plasma metabolic profiles can detect differences between patients with neovascular age-related macular degeneration (NVAMD) and similarly-aged controls.

METHODS: Metabolomic analysis using liquid chromatography with Fourier-transform mass spectrometry (LC-FTMS) was performed on plasma samples from 26 NVAMD patients and 19 controls. Data were collected from mass/charge ratio (m/z) 85 to 850 on a Thermo LTQ-FT mass spectrometer, and metabolic features were extracted using an adaptive processing software package. Both non-transformed and log2 transformed data were corrected using Benjamini and Hochberg False Discovery Rate (FDR) to account for multiple testing. Orthogonal Partial Least Squares-Discriminant Analysis was performed to determine metabolic features that distinguished NVAMD patients from controls. Individual m/z features were matched to the Kyoto Encyclopedia of Genes and Genomes database and the Metlin metabolomics database, and metabolic pathways associated with NVAMD were identified using MetScape.

RESULTS: Of the 1680 total m/z features detected by LC-FTMS, 94 unique m/z features were significantly

different between NVAMD patients and controls using FDR (q=0.05). A comparison of these features to those found with log2 transformed data (n=132, q=0.2) revealed 40 features in common, reaffirming the involvement of certain metabolites. Such metabolites included di- and tripeptides, covalently modified amino acids, bile acids, and vitamin D-related metabolites. Correlation analysis revealed associations among certain significant features, and pathway analysis demonstrated broader changes in tyrosine metabolism, sulfur amino acid metabolism, and amino acids related to urea metabolism.

CONCLUSIONS: These data suggest that metabolomic analysis can identify a panel of individual metabolites that differ between NVAMD cases and controls. Pathway analysis can assess the involvement of certain metabolic pathways, such as tyrosine and urea metabolism, and can provide further insight into the pathophysiology of AMD.

PMID: 24015273 [PubMed - in process] PMCID: PMC3754980

Genetics

Mol Biol Rep. 2013 Sep 7. [Epub ahead of print]

Cumulative association between age-related macular degeneration and less studied genetic variants in PLEKHA1/ARMS2/HTRA1: a meta and gene-cluster analysis.

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Abstract: The objective of this study is to examine the cumulative effect of the less studied genetic variants in PLEKHA1/ARMS2/HTRA1 on age-related macular degeneration (AMD). We performed an extensive literature search for studies on the association between AMD and the less studied genetic variants in PLEKHA1/ARMS2/HTRA1. Multiple meta-analyses were performed to evaluate the association between individual genetic variants and AMD. A gene-cluster analysis was used to investigate the cumulative effect of these less studied genetic variants on AMD. A total of 23 studies from 20 published papers met the eligibility criteria and were included in our analyses. Several genetic variants in the gene cluster are significantly associated with AMD in our meta-analyses or in individual studies. Gene-cluster analysis reveals a strong cumulative association between these genetic variants in this gene cluster and AMD ($p < 10\text{-}5$). However, two previously suspected SNPs in ARMS2, including rs2736911, the SNP having the largest number of studies in our meta-analyses; and rs3793917, the SNP with the largest sample size, were not significantly associated with AMD (both p's > 0.12). Sensitivity analyses reveal significant association of AMD with rs2736911 in Chinese but not in Caucasian, with c.372_815del443ins54 in Caucasian but not in Chinese, and with rs1049331 in both ethnic groups. These less studied genetic variants have a significant cumulative effect on wet AMD. Our study provides evidence of the joint contribution of genetic variants in PLEKHA1/ARMS2/HTRA1 to AMD risk, in addition to the two widely studied genetic variants whose association with AMD was well established.

PMID: 24013816 [PubMed - as supplied by publisher]

Diet

J Food Sci. 2013 Sep 11. doi: 10.1111/1750-3841.12256. [Epub ahead of print]

Acute and Subacute Toxicity Assessment of Lutein in Lutein-Deficient Mice.

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Abstract: Dietary lutein consumption is lower than the actual recommended allowances to prevent macular degeneration; thus dietary lutein supplements have been recommended. This study aimed to investigate potential adverse effect of lutein from Tagetes erecta in lutein-deficient (LD) male mice. Preliminary acute toxicity study revealed that the LD50 exceeded the highest dose of 10000 mg/kg BW. In a subacute study, male mice were gavaged with 0, 100, 1000 mg/kg BW/day for a period of 4 wk. Plasma lutein levels increased dose dependently ($P < 0.01$) after acute and subacute feeding of lutein in LD mice. Compared to the control (peanut oil without lutein) group, no treatment-related toxicologically significant effects of lutein were prominent in clinical observation, ophthalmic examinations, body, and organ weights. Further, no toxicologically significant findings were eminent in hematological, histopathological, and other clinical chemistry parameters. In the oral subacute toxicity study, the no-observed-adverse-effect level (NOAEL) for lutein in LD mice was determined as 1000 mg/kg/day, the highest dose tested.

PMID: 24024482 [PubMed - as supplied by publisher]

J Pharm Pharm Sci. 2013;16(3):494-501.

Intracellular uptake mechanism of lutein in retinal pigment epithelial cells.

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Purpose: Lutein is a carotenoid mainly found in green leafy vegetables and is located in the macula lutea in the human eye. It has received much attention recently due to its preventive effect on age-related macular degeneration, and it has been consumed as a supplement. However, little information about the pharmacokinetic properties of lutein is available. Detailed knowledge of pharmacokinetic properties of lutein is needed for the development of pharmaceutics. In this study, we focused on the macular accumulation of lutein and investigated the uptake mechanism into human retinal pigment epithelial cells.

Methods: ARPE-19 cells were used for the study on the accumulation mechanism of lutein. The concentration of lutein was determined using an HPLC system. Involvement of scavenger class B type 1 (SR-B1) in the accumulation of lutein in ARPE-19 cells was suggested from the results of an inhibition study using block lipid transport 1 (BLT-1), a selective inhibitor of SR-B1. To investigate the involvement of SR-B1 in more detail, small interfering RNA (siRNA) was transfected and the mRNA and protein expression levels of SR-B1 were assessed by quantitative real-time reverse transcription polymerase chain reaction and Western blotting, respectively.

Results: We confirmed a sufficient siRNA knockdown effect in both mRNA and protein expression levels of SR-B1. We then found that lutein uptake was significantly decreased by siRNA knockdown of SR-B1.

Conclusion: The uptake of lutein was significantly decreased by 40% compared with the control uptake level. This suggested that active transport of lutein into ARPE-19 cells is mainly via SR-B1, given the result that lutein uptake at 4ºC was about 40% less that that at 37ºC. This article is open to POST-PUBLICATION REVIEW. Registered readers (see "For Readers") may comment by clicking on ABSTRACT on the issue's contents page.

PMID: 24021296 [PubMed - in process]

Redox Biol. 2013 Jan 31;1(1):125-130.

Oxysterols in the pathogenesis of major chronic diseases.

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Abstract: Pathological accumulation of 27-carbon intermediates or end-products of cholesterol metabolism, named oxysterols, may contribute to the onset and especially to the development of major chronic diseases in which inflammation, but also oxidative damage and to a certain extent cell death, are hallmarks and primary mechanisms of progression. Indeed, certain oxysterols exercise strong pro-oxidant and pro-inflammatory effects at concentrations detectable in the lesions typical of atherosclerosis, neurodegenerative diseases, inflammatory bowel diseases, age-related macular degeneration, and other pathological conditions characterized by altered cholesterol uptake and/or metabolism.

PMID: 24024145 [PubMed - as supplied by publisher] PMCID: PMC3757713