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<http://www.medscape.com/viewarticle/708545?src=emailthis>

Low Maternal Vitamin D Increases Risk of HIV Transmission to Offspring

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NEW YORK (Reuters Health) Sep 08 - In HIV-infected pregnant women, low levels of vitamin D are linked with a higher risk of virus transmission during pregnancy or breastfeeding, and also with an increase in infant mortality.

These findings are from a study in Tanzania that appears in the October issue of the Journal of Infectious Diseases.

"Vitamin D has been shown to improve cell-mediated immunity, phagocytic capacity of macrophages, and the cytolytic activity of natural killer cells," Dr. Saurabh Mehta from the Harvard School of Public Health in Boston told Reuters Health by email.

As a part of a clinical trial on the role of multivitamin supplements during pregnancy, Dr. Mehta and colleagues in Dar es Salaam evaluated outcomes of 855 offspring of HIV-infected women. Maternal 25 hydroxyvitamin D levels were estimated during pregnancy, and HIV tests were done in offspring at regular intervals. Vitamin D levels below 32 ng/ml were considered to be low.

Among babies born to the women with low vitamin D levels, HIV infection rates were 10.7% at birth, 21.7% at 6 weeks, and 35.2% at 2 years, Dr. Mehta and colleagues report. Corresponding infection rates

in offspring of women with adequate vitamin D were 6.5% at birth, 16.3% at 6 weeks, and 27% at 2 years.

On multivariate analysis, low maternal vitamin D was linked with a 50% higher risk of mother-to-child transmission of HIV at 6 weeks, a 200% higher risk of transmission during breastfeeding to babies who were uninfected at 6 weeks, and a 46% higher overall risk of acquiring HIV infection.

Furthermore, the investigators found, the children born to the HIV-infected women had "a 61% higher risk of dying during follow-up."

"By virtue of its ability to improve both innate and adaptive immunity in the mother and by helping in the development of the fetal immune system, vitamin D may help lower the risk of mother-to-child transmission of HIV," Dr. Mehta postulates.

While recommending further studies, Dr. Mehta concluded that "vitamin D supplementation may represent a low-cost method to reduce child mortality and to help decrease mother-to-child transmission of HIV as an adjunct to anti-retroviral therapy."

J Infect Dis 2009;200:1022-1030.

http://www.nlm.nih.gov/medlineplus/news/fullstory_88621.html

Wheat Consumption May Contribute to Diabetes

Overreaction in gut noted in study of people with type 1 version of disease

HealthDay

By Robert Preidt

Wednesday, August 26, 2009

WEDNESDAY, Aug. 26 (HealthDay News) -- An abnormal immune response to wheat proteins may contribute to type 1 diabetes, Canadian researchers say.

Their study of 42 people with type 1 diabetes found that nearly half had immune system T-cells that overreacted to wheat. The researchers also identified genes associated with this abnormal immune response.

"The immune system has to find the perfect balance to defend the body against foreign invaders without hurting itself or overreacting to the environment, and this can be particularly challenging in the gut, where there is an abundance of food and bacteria," study author Dr. Fraser Scott, a senior scientist at the Ottawa Hospital Research Institute and professor of medicine at the University of Ottawa, said in a hospital news release.

"Our research suggests that people with certain genes may be more likely to develop an overreaction to wheat and possibly other foods in the gut, and this may tip the balance with the immune system and make the body more likely to develop other immune problems, such as type 1 diabetes," he explained.

The study appears in the August issue of Diabetes.

"These observations add to the accumulating evidence that the gut is an active player in the diabetes disease process," Dr. Mikael Knip of Finland wrote in an accompanying editorial.

SOURCE: Ottawa Hospital Research Institute, news release, Aug. 20, 2009

HealthDay

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Toxicology and Applied Pharmacology

Volume 237, Issue 2, 1 June 2009, Pages 146-153

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Effects of wheat germ agglutinin on human gastrointestinal epithelium: Insights from an experimental model of immune/epithelial cell interaction

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revised 2 March 2009;

accepted 21 March 2009.

Available online 28 March 2009.

ESSENCE OF ARTICLE

“WGA is a toxic compound and an anti-nutritional...

WGA stimulates the synthesis of pro-inflammatory cytokines...

These results shed new light onto the molecular mechanisms underlying the onset of gastrointestinal disorders observed in vivo upon dietary intake of wheat-based foods.”

ARTICLE

Abstract

Wheat germ agglutinin (WGA) is a plant protein that binds specifically to sugars expressed, among many others, by human gastrointestinal epithelial and immune cells. WGA is a toxic compound and an anti-nutritional factor, but recent works have shown that it may have potential as an anti-tumor drug and as a carrier for oral drugs. To quantitate the toxicity threshold for WGA on normal epithelial cells we previously investigated the effects of the lectin on differentiated Caco2 cells, and showed that in the micromolar range of concentrations WGA could alter the integrity of the epithelium layer and increase its permeability to both mannitol and dextran. WGA was shown to be uptaken by Caco2 cells and only $\approx 0.1\%$ molecules were observed to cross the epithelium layer by transcytosis. Here we show that at nanomolar concentrations WGA is unexpectedly bioactive on immune cells. The supernatants of WGA-stimulated peripheral blood mononuclear cells (PBMC) can alter the integrity of the epithelium layer when administered to the basolateral side of differentiated Caco2 cells and the effects can be partially inhibited by monoclonal antibodies against IL1, IL6 and IL8. At nanomolar concentrations WGA stimulates the synthesis of pro-inflammatory cytokines and thus the biological activity of WGA should be reconsidered by taking into account the effects of WGA on the immune system at the gastrointestinal interface. These results shed new light onto the molecular mechanisms underlying the onset of gastrointestinal disorders observed in vivo upon dietary intake of wheat-based foods.

Keywords: Wheat germ agglutinin; Gastrointestinal epithelium; Caco2 cells; Peripheral blood mononuclear cells; Transepithelial electrical resistance; Pro-inflammatory cytokines

Fig. 1. The supernatants of PBMC treated with 14 nM WGA affect the integrity of the epithelium layer. TEER was measured to assay the integrity of the epithelium layer formed by differentiated Caco2 cells. At time 0 the medium in the bottom chamber was replaced with medium containing 14 nM WGA (closed circles), with the supernatants of unstimulated PBMC (closed squares) or with the supernatants of PBMC treated for 12 h with 14 nM (open circles).

Fig. 2. The supernatants of PBMC treated with 14 nM WGA affects the integrity of the epithelium layer. TEER was measured to assay the integrity of the epithelium layer formed by differentiated Caco2 cells. At time 0 the medium in the bottom chamber was replaced with medium conditioned by PBMC subjected to various treatments (+Sn) or with unconditioned fresh medium (-Sn). Top panel: the supernatants of WGA untreated PBMC were collected and administered to cells directly or after addition of irrelevant

antibodies (Abi), anti-IL1 β monoclonal antibody (Ab1), anti-IL6 antibodies (Ab6) and anti-IL8 antibodies (Ab8). Bottom panel: same as in top panel, but in this case PBMC were initially treated with 14 nM WGA (+WGA). The same data obtained with media –Sn and +Sn (–WGA –Ab) shown in the top panel are also reported for comparison purposes.

Fig. 3. Human recombinant cytokines affect the integrity of the epithelium layer. TEER was measured to assay the integrity of the epithelium layer formed by differentiated Caco2 cells. At time 0 human recombinant IL1 β , IL6 and IL8 were added at the indicated final concentrations to the bottom chamber of transwell cultures.

Fig. 4. Determining the purity of the WGA batch from endotoxin contamination by gel electrophoresis. WGA and ultrapure LPS from *E. coli* were separated by SDS-PAGE onto 16% polyacrylamide gels. Gels were then processed as described in Castellanos-Serra and Hardy (2006). A. Imidazole-zinc staining for proteins. Lanes are as follows: 1. WGA (10 μ g); 2. LPS (5 μ g); 3. molecular weight markers. B. Zinc-imidazole labelling of LPS carried out after acetonitrile–water treatment of the gels (Castellanos-Serra and Hardy, 2006). In this case the proteins appear as negatively stained bands. Lanes are as follows: 1. LPS (5 μ g); 2. LPS (0.5 μ g); 3. LPS (0.05 μ g); 4. LPS (0.005 μ g); 5. WGA (10 μ g).

<http://www.ajcn.org/cgi/content/abstract/61/5/1058>

American Journal of Clinical Nutrition, Vol 61, 1058-1061, Copyright © 1995 by The American Society for Clinical Nutrition, Inc

ORIGINAL RESEARCH COMMUNICATIONS

ESSENCE OF ARTICLE

“These findings demonstrate that a surprisingly small oral glutamine load is capable of elevating alkaline reserves as well as plasma growth hormone. “

ARTICLE

Increased plasma bicarbonate and growth hormone after an oral glutamine load

TC Welbourne

Department of Physiology, Louisiana State University College of Medicine, Shreveport 71130, USA.

An oral glutamine load was administered to nine healthy subjects to determine the effect on plasma glutamine, bicarbonate, and circulating growth hormone concentrations. Two grams glutamine were dissolved in a cola drink and ingested over a 20-min period 45 min after a light breakfast. Forearm venous blood samples were obtained at zero time and at 30-min intervals for 90 min and compared with time controls obtained 1 wk earlier. Eight of nine subjects responded to the oral glutamine load with an increase in plasma glutamine at 30 and 60 min before returning to the control value at 90 min. Ninety minutes after the glutamine administration load both plasma bicarbonate concentration and circulating plasma growth hormone concentration were elevated. These findings demonstrate that a surprisingly small oral glutamine load is capable of elevating alkaline reserves as well as plasma growth hormone.

This article has been cited by other articles:

M. Gleeson

Dosing and Efficacy of Glutamine Supplementation in Human Exercise and Sport Training

J. Nutr., October 1, 2008; 138(10): 2045S - 2049S.

[Abstract] [Full Text] [PDF]

A. J. A. H. van Vught, A. G. Nieuwenhuizen, R.-J. M. Brummer, and M. S. Westerterp-Plantenga

Effects of Oral Ingestion of Amino Acids and Proteins on the Somatotropic Axis

J. Clin. Endocrinol. Metab., February 1, 2008; 93(2): 584 - 590.

[Abstract] [Full Text] [PDF]

P. Klassen, M. Mazariegos, N. W. Solomons, and P. Fürst

The Pharmacokinetic Responses of Humans to 20 g of Alanyl-Glutamine Dipeptide Differ with the Dosing Protocol but Not with Gastric Acidity or in Patients with Acute Dengue Fever

J. Nutr., January 1, 2000; 130(2): 177 - 182.

[Abstract] [Full Text]

PMID: 19440038 [PubMed - indexed for MEDLINE]

1: Cell Cycle. 2009 Jul 1;8(13):2031-40. Epub 2009 Jul 21. Links

Comment in:

Cell Cycle. 2009 Sep 1;8(17):2681.

Metformin induces unique biological and molecular responses in triple negative breast cancer cells.

Liu B, Fan Z, Edgerton SM, Deng XS, Alimova IN, Lind SE, Thor AD.

Department of Pathology, University of Colorado Denver School of Medicine, Aurora, CO 80045, USA.

ESSENCE OF ARTICLE

”Given the unique anti-cancer activity of metformin against TN disease, both in vitro and in vivo, it should be explored as a therapeutic agent against this aggressive form of breast cancer.”

ARTICLE

Triple negative (TN) breast cancer is more frequent in women who are obese or have type II diabetes, as well as young women of color. These cancers do not express receptors for the steroid hormones estrogen or progesterone, or the type II receptor tyrosine kinase (RTK) Her-2 but do have upregulation of basal cytokeratins and the epidermal growth factor receptor (EGFR). These data suggest that aberrations of glucose and fatty acid metabolism, signaling through EGFR and genetic factors may promote the development of TN cancers. The anti-type II diabetes drug metformin has been associated with a decreased incidence of breast cancer, although the specific molecular subtypes that may be reduced by metformin have not been reported. Our data indicates that metformin has unique anti-TN breast cancer effects both in vitro and in vivo. It inhibits cell proliferation (with partial S phase arrest), colony formation and induces apoptosis via activation of the intrinsic and extrinsic signaling pathways only in TN breast cancer cell lines. At the molecular level, metformin increases P-AMPK, reduces P-EGFR, EGFR, P-MAPK, P-Src, cyclin D1 and cyclin E (but not cyclin A or B, p27 or p21), and induces PARP cleavage in a dose- and time-dependent manner. These data are in stark contrast to our previously published biological and molecular effects of metformin on luminal A and B, or Her-2 type breast cancer cells. Nude mice bearing tumor xenografts of the TN line MDA-MB-231, treated with metformin, show significant reductions in tumor growth ($p = 0.0066$) and cell proliferation ($p = 0.0021$) as compared to untreated controls. Metformin pre-treatment, before injection of MDA-MB-231 cells, results in a significant decrease in tumor outgrowth and incidence. Given the unique anti-cancer activity of metformin against TN disease, both in vitro and in vivo, it should be explored as a therapeutic agent against this aggressive form of breast cancer.

PMID: 19440038 [PubMed - indexed for MEDLINE]

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- Metformin inhibits breast cancer cell growth, colony formation and induces cell cycle arrest in vitro.

Cell Cycle. 2009 Mar 15; 8(6):909-15. Epub 2009 Mar 26.

[Cell Cycle. 2009]

- Short preoperative treatment with erlotinib inhibits tumor cell proliferation in hormone receptor-positive breast cancers.

J Clin Oncol. 2008 Feb 20; 26(6):897-906. Epub 2008 Jan 7.

[J Clin Oncol. 2008]

- Novel signaling molecules implicated in tumor-associated fatty acid synthase-dependent breast cancer cell proliferation and survival: Role of exogenous dietary fatty acids, p53-p21WAF1/CIP1, ERK1/2 MAPK, p27KIP1, BRCA1, and NF-kappaB.

Int J Oncol. 2004 Mar; 24(3):591-608.

[Int J Oncol. 2004]

- Anticancer effects of wogonin in both estrogen receptor-positive and -negative human breast cancer cell lines in vitro and in nude mice xenografts.

Int J Cancer. 2008 Feb 15; 122(4):816-22.

[Int J Cancer. 2008]

- ReviewThe mechanism of action of plitidepsin.

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PMID: 9535724 [PubMed - indexed for MEDLINE]

Dietary conjugated linoleic acid normalizes impaired glucose tolerance in the Zucker diabetic fatty fa/fa rat.

Houseknecht KL, Vanden Heuvel JP, Moya-Camarena SY, Portocarrero CP, Peck LW, Nickel KP, Belury MA.

Department of Animal Sciences, Purdue University, West Lafayette, Indiana 47907, USA.

ESSENCE OF ARTICLE

” The insulin sensitizing effects of CLA are due, at least in part, to activation of PPAR gamma since increasing levels of CLA induced a dose-dependent transactivation of PPAR gamma in CV-1 cells cotransfected with PPAR gamma and PPRE X 3-luciferase reporter construct. CLA effects on glucose tolerance and glucose homeostasis indicate that dietary CLA may prove to be an important therapy for the prevention and treatment of NIDDM..”

ARTICLE

Conjugated linoleic acid (CLA) is a naturally occurring fatty acid which has anti-carcinogenic and anti-atherogenic properties. CLA activates PPAR alpha in liver, and shares functional similarities to ligands of PPAR gamma, the thiazolidinediones, which are potent insulin sensitizers. We provide the first evidence that CLA is able to normalize impaired glucose tolerance and improve hyperinsulinemia in the pre-diabetic ZDF rat. Additionally, dietary CLA increased steady state levels of aP2 mRNA in adipose tissue of fatty ZDF rats compared to controls, consistent with activation of PPAR gamma. The insulin sensitizing effects of CLA are due, at least in part, to activation of PPAR gamma since increasing levels of CLA induced a dose-dependent transactivation of PPAR gamma in CV-1 cells cotransfected with PPAR gamma and PPRE X 3-luciferase reporter construct. CLA effects on glucose tolerance and glucose homeostasis indicate that dietary CLA may prove to be an important therapy for the prevention and treatment of NIDDM.

PMID: 9535724 [PubMed - indexed for MEDLINE]

ADDITIONAL REVIEW ARTICLE ON CLA

<http://www.ncbi.nlm.nih.gov/pubmed/12020636>

Biochim Biophys Acta. 2002 Apr 15;1581(3):89-99.

Conjugated linoleic acid decreases production of pro-inflammatory products in macrophages: evidence for a PPAR gamma-dependent mechanism.

Yu Y, Correll PH, Vanden Heuvel JP.

Department of Veterinary Science and Center for Molecular Toxicology and Carcinogenesis, 226 Fenske Laboratories, Penn State University, University Park, PA 16802, USA.

ESSENCE OF ARTICLE

“Conjugated linoleic acid (CLA) is a dietary fatty acid that has received considerable attention due to its unique properties in rodent models including anti-cancer, anti-atherogenic and anti-diabetic effects. The effects of CLA are similar to those seen with ligands for peroxisome proliferator-activated receptor (PPARs), most notably of the PPAR gamma subtype.”

ARTICLE

Conjugated linoleic acid (CLA) is a dietary fatty acid that has received considerable attention due to its unique properties in rodent models including anti-cancer, anti-atherogenic and anti-diabetic effects. The effects of CLA are similar to those seen with ligands for peroxisome proliferator-activated receptor (PPARs), most notably of the PPAR gamma subtype. With the recent observation of a role for PPAR gamma in regulation of immune responses, we suspected that CLA could affect immune function, in particular macrophage activity. The goal of our study was to examine whether this dietary fatty acid has anti-inflammatory properties similar to those reported for PPAR gamma activators such as 15-deoxy prostaglandin J(2) (PGJ(2)). In reporter assays, various CLA isomers activated PPAR gamma in RAW264.7 mouse macrophage (RAW) cells. CLA decreased the interferon-gamma (IFN gamma)-induced mRNA expression of mediators of inflammation including cyclooxygenase 2 (COX2), inducible NOS (iNOS), and tumor necrosis factor alpha (TNFalpha). Reporter assays also demonstrated reduced IFN gamma-stimulated transcriptional activity of the iNOS and COX2 promoters by CLA. Consequently, CLA decreased the production of PGE(2), TNFalpha and the inflammatory agent nitric oxide (NO) in RAW cells treated with IFN gamma. Other pro-inflammatory cytokines such as IL-1 beta and IL-6 were similarly decreased by CLA treatment of RAW cells. In addition, various CLA isomers induced HL60 cell differentiation along the monocytic lineage as assessed by measuring expression of the cell surface marker CD14. This differentiation process, as well as the regulation of iNOS and COX2 by 15dPGJ(2), is believed to involve PPAR gamma. Mutations of Leu(468) and Glu(471) to alanine in helix 12 of the ligand-binding domain of PPAR gamma resulted in a protein with strong dominant-negative activity (dnPPAR gamma). Transfecting dnPPAR gamma into RAW cells eliminated the ability of various CLA isomers to regulate the iNOS reporter construct. Taken together, these results suggest that CLA has anti-inflammatory properties that are mediated, at least in part, by the nuclear hormone receptor PPAR gamma.

PMID: 12020636 [PubMed - indexed for MEDLINE]

PMID: 14519781 [PubMed - indexed for MEDLINE]

Conjugated linoleic acid in humans: regulation of adiposity and insulin sensitivity.

Brown JM, McIntosh MK.

Department of Nutrition, University of North Carolina at Greensboro, Greensboro, NC 27402-6170, USA.

Conjugated linoleic acid (CLA) isomers, a group of positional and geometric isomers of linoleic acid [18:2(n-6)], have been studied extensively due to their ability to modulate cancer, atherosclerosis, obesity, immune function and diabetes in a variety of experimental models. The purpose of this review was to examine CLA's isomer-specific regulation of adiposity and insulin sensitivity in humans and in cultures of human adipocytes. It has been clearly demonstrated that specific CLA isomers or a crude mixture of CLA isomers prevent the development of obesity in certain rodent and pig models. This has been attributed mainly to trans-10, cis-12 CLA, both in vivo and in vitro. However, CLA's ability to modulate human obesity remains controversial because data from clinical trials using mixed isomers are conflicting. In support of some studies in humans, our group demonstrated that trans-10, cis-12 CLA prevents triglyceride (TG) accumulation in primary cultures of differentiating human preadipocytes. In contrast,

cis-9, trans-11 CLA increases TG content. Closer examination has revealed that CLA's antiadipogenic actions are due, at least in part, to regulation of glucose and fatty acid uptake and metabolism. This review presents our current understanding of potential isomer-specific mechanisms by which CLA reduces human adiposity and insulin sensitivity.

Publication Types:

- Review
- Review, Tutorial

PMID: 14519781 [PubMed - indexed for MEDLINE]

PMID: 14505483 [PubMed - in process]

2: Biochem Soc Trans. 2003 Oct;31(Pt 5):1075-9.

Regression of pre-established atherosclerosis in the apoE^{-/-} mouse by conjugated linoleic acid.

Toomey S, Roche H, Fitzgerald D, Belton O.

Department of Clinical Pharmacology, Royal College of Surgeons in Ireland, 123 St. Stephens Green, Dublin 2, Ireland.

Conjugated linoleic acid (CLA) refers to a group of positional and geometric isomers of linoleic acid that has been shown to suppress the development of atherosclerosis in a rabbit model. We investigated whether CLA acts as a cyclo-oxygenase (COX) inhibitor or as an agonist of the peroxisome-proliferator-activator receptor (PPAR) gamma in the ApoE^(-/-) mouse model. In vitro, a 9-cis, 11-trans isomer of CLA inhibited prostaglandin formation and oxygen consumption by both isoforms of COX, with no evidence by MS of alternative products being generated. In vivo, supplementation with CLA was found to induce resolution of atherosclerosis. The effect of CLA in vivo could not be explained by COX inhibition alone, as urinary prostaglandin levels were unchanged in animals receiving CLA supplementation, and administration of selective COX inhibitors did not induce lesion regression. There was however induction of PPAR gamma, a known response to agonists of this nuclear orphan receptor.

PMID: 14505483 [PubMed - in process]

PMID: 14505483 [PubMed - in process]

3: Clin Nutr. 2002 Dec;21(6):451-9.

Colonic anti-inflammatory mechanisms of conjugated linoleic acid.

Bassaganya-Riera J, Hontecillas R, Beitz DC.

Department of Animal Sciences, Iowa State University, Ames, Iowa 50011, USA.

Conjugated linoleic acid (CLA) is a mixture of positional (e.g. 7,9; 9,11; 10,12; 11,13) and geometric (cis or trans) isomers of octadecadienoic acid. This compound was first shown to prevent mammary carcinogenesis in murine models. Later investigations uncovered a number of additional health benefits, including decreasing atherosclerosis and inflammation while enhancing immune function. The mechanisms of action underlying these biological properties are not clearly understood. The aim of this review is to highlight recent advances in CLA research related to experimental inflammatory bowel disease. In addition, two possible mechanisms of action (i.e. endoplasmic and nuclear) were discussed in detail in the context of enteric inflammatory disorders. Conjugated linoleic acid was first implicated in down-regulating the generation of inducible eicosanoids (i.e. PGE(2) and LTB(4)) involved in early micro-inflammatory events (endoplasmic). More recently, CLA has been shown to modulate the expression of genes regulated by peroxisome proliferator-activated receptors (PPARs; nuclear). In pigs, prolonged dietary CLA treatment stimulated the expression of PPAR-gamma in the muscle. Thus, evidence supporting both mechanistic theories of CLA acting through eicosanoid synthesis and PPAR activity is available. The further understanding of the anti-inflammatory mechanisms of action of CLA may yield novel nutritional therapies for enteric inflammation.

Publication Types:

- Review
- Review, Tutorial

PMID: 14505483 [PubMed - in process]

PMID: 12431407 [PubMed - indexed for MEDLINE]

Comp Biochem Physiol B Biochem Mol Biol. 2002 Nov;133(3):395-404.

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Dietary conjugated linoleic acid reduces body fat mass and affects gene expression of proteins regulating energy metabolism in mice.

Takahashi Y, Kushiro M, Shinohara K, Ide T.

Division of Food Functionality, National Food Research Institute, 2-1-12 Kannondai, Tsukuba Science City, Ibaraki 305-8642, Japan.

ICR and C57BL/6J mice were fed experimental diets containing either a 2% fatty acid preparation rich in conjugated linoleic acid (CLA) or a preparation rich in linoleic acid and free of CLA for 21 days. CLA greatly decreased weights of white adipose tissue and interscapular brown adipose tissue in the two strains. CLA reduced mRNA levels of glucose transporter 4 (Glut 4) in white and brown adipose tissue of both strains. A CLA-dependent decrease in mRNA levels of peroxisome proliferator activated receptor (PPAR) gamma was seen in interscapular brown adipose tissue of both strains and in white adipose tissue of C57BL/6J but not ICR mice. Dietary CLA was found to cause a decrease in the mRNA levels of

uncoupling protein (UCP) 1 in brown adipose tissue when the value was corrected for the expression of a house-keeping gene (beta-actin) in the two strains. Uncorrected values were, however, indistinguishable between the animals fed the CLA diet and CLA-free diet. UCP 3 expression in brown adipose tissue was much lower in mice fed the CLA diet than in those fed the control diet in both strains. In contrast, CLA greatly up-regulated the gene expression of UCP 2 in brown adipose tissue. Dietary CLA also increased UCP 2 mRNA level in skeletal muscle. It is apparent that dietary CLA decreases white and brown adipose tissue mass, accompanying changes in the gene expression of proteins regulating energy metabolism in white and brown adipose tissues, and skeletal muscle of mice. Copyright 2002 Elsevier Science Inc.

PMID: 12431407 [PubMed - indexed for MEDLINE]

PMID: 12097686 [PubMed - indexed for MEDLINE]

J Nutr. 2002 Jul;132(7):2019-27.

Nutritional regulation of porcine bacterial-induced colitis by conjugated linoleic acid.

Hontecillas R, Wannemeulher MJ, Zimmerman DR, Hutto DL, Wilson JH, Ahn DU, Bassaganya-Riera J.

Veterinary Medical Research Institute, Nutritional Immunology, College of Veterinary Medicine, Ames, IA 50011, USA.

Excessive intake of saturated fatty acids and/or linoleic acid favors the induction of an array of lipid mediators and cytokines enhancing inflammatory responses. Conversely, dietary supplementation with (n-3) fatty acids or vitamin D ameliorates inflammation and autoimmune diseases. Although it was well accepted that conjugated linoleic acid (CLA) prevented diseases with a common inflammatory pathogenesis (i.e., cancer and atherosclerosis), no studies were available on the roles of CLA in mucosal inflammation. The present study was designed to investigate the anti-inflammatory actions and molecular mechanisms underlying the regulation of colonic health by CLA. We hypothesized that colonic inflammation can be ameliorated by dietary CLA supplementation. To test this hypothesis, inflammation of the colonic mucosa was triggered by challenging pigs fed either soybean oil-supplemented or CLA-supplemented diets with an enteric bacterial pathogen (i.e., *Brachyspira hyodysenteriae*). Immunoregulatory cytokines and peroxisome proliferator-activated receptor-gamma (PPAR-gamma) mRNA expression were assayed in colonic lymph nodes and colon of pigs. Colonic mucosal lesions and lymphocyte subset distribution were evaluated by histology and immunohistochemistry. Supplementation of CLA in the diet before the induction of colitis decreased mucosal damage; maintained cytokine profiles (i.e., interferon-gamma and interleukin-10) and lymphocyte subset distributions (i.e., CD4+ and CD8+), resembling those of noninfected pigs; enhanced colonic expression of PPAR-gamma; and attenuated growth failure. Therefore, CLA fed preventively before the onset of enteric disease attenuated inflammatory lesion development and growth failure.

PMID: 12097686 [PubMed - indexed for MEDLINE]

PMID: 12020636 [PubMed - indexed for MEDLINE]

Biochim Biophys Acta. 2002 Apr 15;1581(3):89-99.

Conjugated linoleic acid decreases production of pro-inflammatory products in macrophages: evidence for a PPAR gamma-dependent mechanism.

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Conjugated linoleic acid (CLA) is a dietary fatty acid that has received considerable attention due to its unique properties in rodent models including anti-cancer, anti-atherogenic and anti-diabetic effects. The effects of CLA are similar to those seen with ligands for peroxisome proliferator-activated receptor (PPARs), most notably of the PPAR gamma subtype. With the recent observation of a role for PPAR gamma in regulation of immune responses, we suspected that CLA could affect immune function, in particular macrophage activity. The goal of our study was to examine whether this dietary fatty acid has anti-inflammatory properties similar to those reported for PPAR gamma activators such as 15-deoxy prostaglandin J(2) (PGJ(2)). In reporter assays, various CLA isomers activated PPAR gamma in RAW264.7 mouse macrophage (RAW) cells. CLA decreased the interferon-gamma (IFN gamma)-induced mRNA expression of mediators of inflammation including cyclooxygenase 2 (COX2), inducible NOS (iNOS), and tumor necrosis factor alpha (TNFalpha). Reporter assays also demonstrated reduced IFN gamma-stimulated transcriptional activity of the iNOS and COX2 promoters by CLA. Consequently, CLA decreased the production of PGE(2), TNFalpha and the inflammatory agent nitric oxide (NO) in RAW cells treated with IFN gamma. Other pro-inflammatory cytokines such as IL-1 beta and IL-6 were similarly decreased by CLA treatment of RAW cells. In addition, various CLA isomers induced HL60 cell differentiation along the monocytic lineage as assessed by measuring expression of the cell surface marker CD14. This differentiation process, as well as the regulation of iNOS and COX2 by 15dPGJ(2), is believed to involve PPAR gamma. Mutations of Leu(468) and Glu(471) to alanine in helix 12 of the ligand-binding domain of PPAR gamma resulted in a protein with strong dominant-negative activity (dnPPAR gamma). Transfecting dnPPAR gamma into RAW cells eliminated the ability of various CLA isomers to regulate the iNOS reporter construct. Taken together, these results suggest that CLA has anti-inflammatory properties that are mediated, at least in part, by the nuclear hormone receptor PPAR gamma.

PMID: 12020636 [PubMed - indexed for MEDLINE]

PMID: 11932205 [PubMed - indexed for MEDLINE]

J Mol Endocrinol. 2002 Apr;28(2):79-86.

Related Articles, Links

Prolonged dietary treatment with conjugated linoleic acid stimulates porcine muscle peroxisome proliferator activated receptor gamma and glutamine-fructose aminotransferase gene expression in vivo.

Meadus WJ, MacInnis R, Dugan ME.

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Peroxisome proliferator activated receptors (PPARs) represent a family of DNA binding proteins that are activated by a variety of dietary and endogenous fatty acids. The PPAR proteins are expressed throughout the body and are the target of a variety of lipidaemic and insulin sensitizing drugs. Conjugated linoleic acid (CLA) is a collective name for octadecadienoic acid isomers with conjugated double bonds, which can also act as ligands for some of the PPAR family. To gain better understanding of the long-term effects of PPAR activation, CLA was fed at 11 g/kg of feed for 45 days to castrated male pigs (barrows). These barrows had a significant repartitioning of subcutaneous fat to lean tissue in the carcass: fat was reduced by 9 x 2% and lean muscle was increased by 3 x 5%, but intramuscular fat content was also increased by 14% (P<0 x 05). PPARgamma, glutamine-fructose aminotransferase (GFAT), adipocyte fatty acid binding protein (AFABP), but not PPARalpha mRNA levels were significantly increased (P<0 x 05) in the CLA-fed pigs. The increased expression of PPARgamma and AFABP indicates that CLA induced the development of preadipocytes from stromal-vascular (s-v) stem cells to promote intramuscular fat content. The increase in the expression of GFAT mRNA indicates that the glucose supply of the muscle cells had been increased with the CLA diet, possibly sparing intramuscular fatty acid reserves.

PMID: 11932205 [PubMed - indexed for MEDLINE]

PMID: 11795855 [PubMed - indexed for MEDLINE]

Lipids. 2001 Nov;36(11):1223-32.

Trans-10,cis-12 conjugated linoleic acid reduces triglyceride content while differentially affecting peroxisome proliferator activated receptor gamma2 and aP2 expression in 3T3-L1 preadipocytes.

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A series of experiments was conducted using 3T3-L1 preadipocytes as the cell model to determine: (i) whether the triglyceride (TG)-lowering effects of a crude mixture of conjugated linoleic acid (CLA) isomers were due to a specific isomer of CLA and the timing of treatment, (ii) if CLA reduced TG content by inhibiting a key regulator of adipogenesis, (iii) if CLA incorporated into either neutral lipid or phospholipid cell fractions, and (iv) whether the effects of CLA treatment were reversible. Trans-10,cis-12 CLA reduced TG content, whereas the cis-9,trans-11 isomer increased TG content compared to vehicle

[bovine serum albumin (BSA)] controls. Treatment with 50 microM trans-10,cis-12 CLA during the entire 6 d of differentiation reduced TG content to a greater extent than treatment during either the first 3 d or last 3 d of differentiation. Trans-10,cis-12 CLA treatment of preadipocyte cultures for 48 h increased peroxisome proliferator activated receptor gamma2 (PPARgamma2) protein expression compared to cultures treated with linoleic acid (LA) or the BSA controls. CLA had no effect on adipose P2 (aP2), a fatty acid-binding protein regulated by PPARgamma2. Both the cis-9,trans-11 and the trans-10,cis-12 isomers of CLA were incorporated into neutral lipids and phospholipids. However, cis-9,trans-11 CLA levels were one- to twofold higher than trans-10,cis-12 CLA levels. Moreover, trans-10,cis-12 CLA treatment reduced cis-11 18:1 concentrations in both neutral lipids and phospholipids while increasing cis-9 18:1 and 18:2 concentrations. Palmitoleic acid (16:1) levels were also lower in the neutral lipid fraction of cultures treated with trans-10,cis-12 CLA. Supplementing trans-10,cis-12 CLA-treated cultures (50 microM) with increasing levels of LA resulted in a dose-dependent increase in TG content compared to cultures treated with 50 microM CLA alone. LA supplementation also prevented some of the morphological changes associated with trans-10,cis-12 CLA treatment as seen with scanning electron microscopy. Treatment with 50 microM trans-10,cis-12 CLA for 6 d decreased PPARgamma2 levels, and supplementation of CLA-treated cultures with LA increased PPARgamma2 levels compared with cultures treated with CLA alone. Taken together, these data indicate that in cultures of 3T3-L1 preadipocytes: (i) trans-10,cis-12 CLA is the TG-lowering isomer of CLA, and its effects are dependent on dose, duration of treatment, and the amount of LA in the cultures; (ii) trans-10,cis-12 CLA treatment alters the monounsaturated fatty acid profile of neutral- and phospholipids of the cultures; and (iii) although acute (2-d) trans-10,cis-12 CLA treatment increased PPARgamma2 protein levels, chronic (6-d) treatment decreased PPARgamma2 levels.

PMID: 11795855 [PubMed - indexed for MEDLINE]

PMID: 11334420 [PubMed - indexed for MEDLINE]

Diabetes. 2001 May;50(5):1149-57.

Isomer-specific antidiabetic properties of conjugated linoleic acid. Improved glucose tolerance, skeletal muscle insulin action, and UCP-2 gene expression.

Ryder JW, Portocarrero CP, Song XM, Cui L, Yu M, Combatsiaris T, Galuska D, Bauman DE, Barbano DM, Charron MJ, Zierath JR, Houseknecht KL.

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Conjugated linoleic acid (CLA) isomers have a number of beneficial health effects, as shown in biomedical studies with animal models. Previously, we reported that a mixture of CLA isomers improved glucose tolerance in ZDF rats and activated peroxisome proliferator-activated receptor (PPAR)-gamma response elements in vitro. Here, our aim was to elucidate the effect(s) of specific CLA isomers on whole-body glucose tolerance, insulin action in skeletal muscle, and expression of genes important in

glucose and lipid metabolism. ZDF rats were fed either a control diet (CON), one of two CLA supplemented diets (1.5% CLA) containing differing isoforms of CLA (47% c9,t11; 47.9% c10,t12, 50:50; or 91% c9,t11, c9,t11 isomers), or were pair-fed CON diet to match the intake of 50:50. The 50:50 diet reduced adiposity and improved glucose tolerance compared with all other ZDF treatments. Insulin-stimulated glucose transport and glycogen synthase activity in skeletal muscle were improved with 50:50 compared with all other treatments. Neither phosphatidylinositol 3-kinase activity nor Akt activity in muscle was affected by treatment. Uncoupling protein 2 in muscle and adipose tissue was upregulated by c9,t11 and 50:50 compared with ZDF controls. PPAR-gamma mRNA was downregulated in liver of c9,t11 and pair-fed ZDF rats. Thus, the improved glucose tolerance in 50:50 rats is attributable to, at least in part, improved insulin action in muscle, and CLA effects cannot be explained simply by reduced food intake.

PMID: 11334420 [PubMed - indexed for MEDLINE]

PMID: 10985906 [PubMed - indexed for MEDLINE]

Med Hypotheses. 2000 Sep;55(3):187-8

Activation of PPARgamma may mediate a portion of the anticancer activity of conjugated linoleic acid.

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A number of human cancer cell lines express the PPARgamma transcription factor, and agonists for PPARgamma are reported to promote apoptosis in these cell lines and impede their clonal expansion both in vitro and in vivo. Conjugated linoleic acid (CLA) can activate PPARgamma in rat adipocytes, possibly explaining CLA's antidiabetic effects in Zucker fatty rats. It is thus reasonable to suspect that a portion of CLA's broad spectrum anticarcinogenic activity is mediated by PPARgamma activation in susceptible tumors.

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PMID: 10577045 [PubMed - indexed for MEDLINE]

J Nutr. 1999 Nov;129(11):2106.

Comment on:

- J Nutr. 1999 Mar;129(3):602-6.

CLA and PPARgamma activation.

Moya-Camarena SY, Belury MA.

Publication Types:

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- Letter

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J Lipid Res. 1999 Aug;40(8):1426-33.

Conjugated linoleic acid is a potent naturally occurring ligand and activator of PPARalpha.

Moya-Camarena SY, Vanden Heuvel JP, Blanchard SG, Leesnitzer LA, Belury MA.

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We have previously shown that a mixture of dietary conjugated derivatives of linoleic acid (conjugated linoleic acid, CLA) induces peroxisome proliferator-responsive enzymes and modulates hepatic lipid metabolism in vivo. The present studies demonstrate that CLA is a high affinity ligand and activator of peroxisome proliferator-activated receptor alpha (PPARalpha) and induces accumulation of PPAR-responsive mRNAs in a rat hepatoma cell line. Using a scintillation proximity assay (SPA), CLA isomers were shown to be ligands for human PPARalpha with a rank order of potency of (9Z,11E)>(10E,12Z)>(9E,11E)> furan-CLA (IC(50) values from 140 nm to 400 nm). Levels of acyl-CoA oxidase (ACO), liver fatty acid-binding protein (L-FABP), and cytochrome P450IVA1 (CYP4A1) mRNA were induced by CLA in FaO hepatoma cells. Even though linoleate and CLA were incorporated into lipids of hepatoma cells to the same extent, linoleate had little or no effect on ACO, CYP4A1, or L-FABP mRNA. In agreement with its binding potency, (9Z,11E)-CLA was the most efficacious PPARalpha activator in the mouse PPARalpha-GAL4(UAS)(5)-CAT reporter system. These data indicate that CLA is a ligand and activator of PPARalpha and its effects on lipid metabolism may be attributed to transcriptional events associated with this nuclear receptor. Also, (9Z,11E)-CLA is one of the most avid fatty acids yet described as a PPARalpha ligand.

PMID: 10428978 [PubMed - indexed for MEDLINE]

PMID: 17957784 [PubMed - indexed for MEDLINE]

1: Int J Cancer. 2008 Feb 15;122(4):816-22. Links

Anticancer effects of wogonin in both estrogen receptor-positive and -negative human breast cancer cell lines in vitro and in nude mice xenografts.

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ESSENCE OF ARTICLE

“As wogonin was effective both in vitro and in vivo, our novel findings open the possibility of wogonin as an effective therapeutic and/or chemopreventive agent against both ER-positive and -negative breast cancers, particularly against the more aggressive and hormonal therapy-resistant ER-negative types. (c) 2007 Wiley-Liss, Inc.”

ARTICLE

Wogonin is a plant monoflavonoid which has been reported to inhibit cell growth and/or induce apoptosis in various tumors. Herein, we investigated the in vitro and in vivo anticancer effects and associated mechanisms of wogonin in human breast cancer. Effects of wogonin were examined in estrogen receptor (ER)-positive and -negative human breast cancer cells in culture for proliferation, cell cycle progression, and apoptosis. The in vivo effect of oral wogonin was examined on tumor xenograft growth in athymic nude mice. The molecular changes associated with the biological effects of wogonin were analyzed by immunoblotting. Cell growth was attenuated by wogonin (50-200 microM), independently of its ER status, in a time- and concentration-dependent manner. Apoptosis was enhanced and accompanied by upregulation of PARP and Caspase 3 cleavages as well as proapoptotic Bax protein. Akt activity was suppressed and reduced phosphorylation of its substrates, GSK-3beta and p27, was observed. Suppression of Cyclin D1 expression suggested the downregulation of the Akt-mediated canonical Wnt signaling pathway. ER expression was downregulated in ER-positive cells, while c-ErbB2 expression and its activity were suppressed in ER-negative SK-BR-3 cells. Wogonin feeding to mice showed inhibition of tumor growth of T47D and MDA-MB-231 xenografts by up to 88% without any toxicity after 4 weeks of treatment. As wogonin was effective both in vitro and in vivo, our novel findings open the possibility of wogonin as an effective therapeutic and/or chemopreventive agent against both ER-positive and -negative breast cancers, particularly against the more aggressive and hormonal therapy-resistant ER-negative types. (c) 2007 Wiley-Liss, Inc.

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NEOPLASIA

Wogonin preferentially kills malignant lymphocytes and suppresses T-cell tumor growth by inducing PLC 1- and Ca²⁺-dependent apoptosis

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ESSENCE OF ARTICLE

“In this study, we show that Wogonin, derived from the traditional Chinese medicine Huang-Qin (*Scutellaria baicalensis* Georgi), induces apoptosis in malignant T cells in vitro and suppresses growth of human T-cell leukemia xenografts in vivo. Importantly, Wogonin shows almost no toxicity on T lymphocytes from healthy donors.....Taken together, our data show a therapeutic potential of Wogonin for the treatment of hematologic malignancies. “

ARTICLE

Herbs have successfully been used in traditional Chinese medicine for centuries. However, their curative mechanisms remain largely unknown. In this study, we show that Wogonin, derived from the traditional Chinese medicine Huang-Qin (*Scutellaria baicalensis* Georgi), induces apoptosis in malignant T cells in vitro and suppresses growth of human T-cell leukemia xenografts in vivo. Importantly, Wogonin shows almost no toxicity on T lymphocytes from healthy donors. Wogonin induces prolonged activation of PLC 1 via H₂O₂ signaling in malignant T cells, which leads to sustained elevation of cytosolic Ca²⁺ in malignant but not normal T cells. Subsequently, a Ca²⁺ overload leads to disruption of the mitochondrial membrane. The selective effect of Wogonin is due to its differential regulation of the redox status of malignant versus normal T cells. In addition, we show that the L-type voltage-dependent Ca²⁺ channels are involved in the intracellular Ca²⁺ mobilization in T cells. Furthermore, we show that malignant T cells possess elevated amounts of voltage-dependent Ca²⁺ channels compared with normal T cells, which further enhance the cytotoxicity of Wogonin for malignant T cells. Taken together, our data show a therapeutic potential of Wogonin for the treatment of hematologic malignancies.

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Flavonoid wogonin from medicinal herb is neuroprotective by inhibiting inflammatory activation of microglia¹

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ESSENCE OF ARTICLE

“Wogonin (5,7-dihydroxy-8-methoxyflavone) is a flavonoid derived from the root of *Scutellaria baicalensis* Georgi, a medicinal plant traditionally used in Oriental medicine. Based on the known anti-inflammatory activity of wogonin in macrophages and other cell types in periphery, we tested our hypothesis that wogonin may exert a similar anti-inflammatory effect in brain microglia and may be neuroprotective against brain injury where microglia-mediated inflammatory responses play an important pathogenic role. “

ARTICLE

SPECIFIC AIMS

Wogonin (5,7-dihydroxy-8-methoxyflavone) is a flavonoid derived from the root of *Scutellaria baicalensis* Georgi, a medicinal plant traditionally used in Oriental medicine. Based on the known anti-inflammatory activity of wogonin in macrophages and other cell types in periphery, we tested our hypothesis that wogonin may exert a similar anti-inflammatory effect in brain microglia and may be neuroprotective against brain injury where microglia-mediated inflammatory responses play an important pathogenic role.

PRINCIPAL FINDINGS

1. Flavonoid wogonin inhibited inflammatory activation of cultured brain microglia

Pretreatment of BV-2 mouse microglia cells or rat primary microglia cultures with wogonin (1–50 μ M) diminished lipopolysaccharide (LPS) -induced TNF- α , IL-1 β , and nitric oxide (NO) production in a dose-dependent manner (Fig. 1). Wogonin inhibition of LPS-induced NO production was accompanied by suppression of inducible NO synthase (iNOS) induction and NF- κ B activation in BV-2 microglia.

Figure 1. Wogonin inhibited inflammatory activation of cultured microglia. A) BV-2 cells were treated for 24 h with LPS (100 ng/mL) in the presence of NMMA (0.5 mM) or wogonin (1, 5, 25, 50 μ M), then NO production was assessed by Griess reaction. NMMA (NOS inhibitor) was used for comparison. NO production by LPS alone was set to 100%. Results are mean \pm SE of 4 independent experiments. Asterisks indicate significant differences from treatment with LPS alone ($P < 0.05$). B, C) Rat primary microglia cultures (B) or BV-2 cells (C) were treated for 72 (B) or 24 h (C) with LPS (100 ng/mL) in the absence or presence of wogonin (50 μ M), then production of NO or cytokines was

evaluated by Griess reaction or specific ELISA. Cells were pretreated with wogonin for 1 h before LPS stimulation. Asterisks indicate significant differences ($P < 0.05$).

2. Wogonin protected PC12 cells against microglial cytotoxicity

Coculture of microglia and neurons was used to determine whether wogonin inhibition of inflammatory activation of microglia could confer neuroprotection. Wogonin inhibition of microglial activation led to the reduction in microglial cytotoxicity toward cocultured PC12 cells, indicating a neuroprotective role for wogonin *in vitro*. Wogonin, however, did not influence NO donor-induced PC12 cell death.

3. Wogonin was protective against experimental brain injury *in vivo*

Wogonin (0.5–10 mg/kg) conferred neuroprotection against experimental brain injury by inhibiting inflammatory activation of microglia *in vivo*. In transient global ischemia (by 4-vessel occlusion), wogonin attenuated ischemic death of hippocampal neurons and reduced induction of inflammatory mediators such as iNOS and TNF- α in hippocampus. Wogonin was also neuroprotective against kainate (30 mg/kg)-induced excitotoxic brain injury (Fig. 2). Neuroprotection was accompanied by inhibition of microglial activation as determined by microglia-specific isolectin B4 histochemistry.

Figure 2. Neuroprotection by wogonin against kainate-induced excitotoxic brain injury. Compared to extensive hippocampal cell death by administration of kainate (B, E), pretreatment of wogonin (10 mg/kg) prior to kainate injection (C, F) afforded neuroprotection by attenuating hippocampal cell death both in CA1 and CA3. Neuronal loss or damage is not visible in saline-administered control animals (A, D). Panels D, E, and F (x200) are CA3 regions of panels A, B, and C (x40) as indicated by arrowheads, respectively. Photomicrographs are representative results of Cresyl violet staining performed 2 days after kainate injection.

CONCLUSIONS AND SIGNIFICANCE

In this work, we found that wogonin is a potent neuroprotector from natural source. Wogonin inhibited inflammatory activation of cultured brain microglia *in vitro* and provided neuroprotection in microglia/PC12 coculture by mitigating microglia-induced PC12 cell death. The neuroprotective effect of wogonin was further demonstrated *in vivo* using two experimental brain injury models; transient global ischemia by 4-vessel occlusion and excitotoxic injury by systemic kainate injection. In both animal models, wogonin conferred neuroprotection by attenuating the death of hippocampal neurons and the neuroprotective effect was associated with inhibition of the inflammatory activation of microglia. Taken together, our results indicate that wogonin exerts its neuroprotective effect by inhibiting microglial activation, which is a critical component of pathogenic inflammatory responses in neurodegenerative diseases. The current study emphasizes the importance of medicinal herbs and their constituents as an invaluable source for the development of novel neuroprotective drugs.

In neurodegenerative diseases, a pathogenic role of uncontrolled microglial activation is widely accepted. In search of neuroprotective agents, it is time to focus on killer cells (microglia) instead of killed cells (neurons); eliminating or at least suppressing killer microglial activation will provide a better chance for neuroprotection compared with just salvaging dying neurons. Now, our current work identified a potent

neuroprotector from natural source that inhibits the killer cell activity. Our work will certainly instigate further investigations in the related areas, which will ultimately lead to the successful development of novel neuroprotective drugs based on wogonin or other constituents of the medicinal herb *Scutellaria baicalensis*.

Figure 3. Microglia as a target of wogonin action. Resting microglia (ramified type) can be activated by inflammatory stimuli such as LPS and IFN- γ . Activated microglia (amoeboid type) produce a variety of inflammatory mediators, including nitric oxide, TNF- α , and IL-1 β , which cause neuronal injury (thereby resulting in neurodegeneration). Flavonoid wogonin may be neuroprotective by inhibiting the inflammatory activation of microglia.

FOOTNOTES

1 To read the full text of this article, go to <http://www.fasebj.org/cgi/doi/10.1096/fj.03-0057fje>; doi: 10.1096/fj.03-0057fje

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A Novel Neuroprotectant Granulocyte-Colony Stimulating Factor

Stroke, April 1, 2006; 37(4): 1123 - 1128.

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HEMATOPOIESIS

Comment on Fas et al, page 3700

A TRAIL to Chinese herbal medicine

Peter T. Daniel

HUMBOLDT UNIVERSITY

With apoptosis-targeting therapies coming of age, the report by Li-Weber and colleagues provides a novel molecular rationale for the evaluation of substances derived from traditional medicinal herbs in combination with biologicals to achieve a better response in anticancer therapy.

ESSENCE OF ARTICLE

“Here, the anti-inflammatory flavonoid wogonin is demonstrated to overcome a central, NF- B–mediated resistance mechanism in TRAIL (TNF-related apoptosis-inducing ligand)–induced apoptosis. Wogonin, derived from the traditional Chinese herbal medicine Huang-Qin (Baikal skullcap, *Scutellaria baicalensis*), strongly synergizes with TRAIL- or TNF –induced apoptosis. This is achieved by shifting the cellular redox equilibrium to a more reduced state. Wogonin thereby attenuates NF- B activity and interferes with antiapoptotic stress responses that follow death receptor ligation. Notably, wogonin spared nonmalignant cells, indicating promising perspectives for a clinical setting”

ARTICLE

Here, the anti-inflammatory flavonoid wogonin is demonstrated to overcome a central, NF- B–mediated resistance mechanism in TRAIL (TNF-related apoptosis-inducing ligand)–induced apoptosis. Wogonin, derived from the traditional Chinese herbal medicine Huang-Qin (Baikal skullcap, *Scutellaria baicalensis*), strongly synergizes with TRAIL- or TNF –induced apoptosis. This is achieved by shifting the cellular redox equilibrium to a more reduced state. Wogonin thereby attenuates NF- B activity and interferes with antiapoptotic stress responses that follow death receptor ligation. Notably, wogonin spared nonmalignant cells, indicating promising perspectives for a clinical setting. This has important implications, as clinical trials targeting receptors for the death ligand TRAIL (Apo-2L) have been

initiated. Whereas the natural ligand TRAIL (AMG-951) itself has only recently entered phase 1 trials, clinical development of agonistic TRAIL-mimicking antibodies is more advanced. Mapatumumab (HGS-ETR1) is an agonistic antibody against the TRAIL receptor I (death receptor 4, DR4). Phase 2 clinical trials of mapatumumab (HGS-ETR1) as monotherapy have been completed in patients with non-Hodgkin lymphoma, advanced colorectal cancer, and non-small cell lung cancer, and a randomized phase 2 study of HGS-ETR1 in combination with bortezomib in multiple myeloma is under way. Antibodies targeting TRAIL receptor II (DR5), HGS-ETR2, and HGS-TR2J are in phase 1. Results from these studies confirm a low toxicity profile but indicate at the same time that monotherapy targeting TRAIL receptors has only limited efficacy. This was expected, given the high rate of TRAIL-resistant tumor cell lines. Nevertheless, a far better, synergistic tumor cell killing can be achieved by combinations of TRAIL or the agonistic anti-DR4 and -DR5 antibodies with conventional chemo- or radiotherapy or some of the novel, targeted therapies including bortezomib.¹⁻³

NF- κ B-driven, antiapoptotic signaling by death receptors has only recently been recognized. Ligation of death receptors by their natural ligands or agonistic antibodies triggers a death signal through formation of a death-inducing signaling complex consisting of the receptor itself, the adaptor FADD binding to the cytosolic death domain, and an inducer caspase (caspase-8 and/or -10) that is recruited via the death effector domain found in both FADD and the caspase. In parallel, recruitment of TRAF family proteins via the adaptor TRADD promotes activation of the NF- κ B pathway that triggers survival signals by inducing expression of antiapoptotic factors. Whereas Bcl-2, Bcl-xL, and Bfl-1 interfere with the intrinsic, mitochondrial apoptosis machinery, induction of FLIP proteins blocks the extrinsic death pathway through interference with caspase-8 binding and activity. This allows cells with a dominant NF- κ B signal to evade death receptor-triggered apoptosis. Such antiapoptotic signaling becomes even more critical in cancer cells where cell death programs are often disturbed.^{2,3} In fact, there is evidence that many cancer cells even use antiapoptotic signaling by death receptors to promote growth and metastasis.^{4,5} Overcoming this survival strategy has important implications for the clinical use of TRAIL receptor-targeting drugs.

The author declares no competing financial interests.

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Related Article in Blood Online:

Wogonin sensitizes resistant malignant cells to TNF - and TRAIL-induced apoptosis

Stefanie C. Fas, Sven Baumann, Jia Yun Zhu, Marco Giaisi, Monika K. Treiber, Ulrich Mahlknecht, Peter H. Kramer, and Min Li-Weber

<http://www.tripanswers.org/Answer.aspx?qid=3142>

Lab Tests Online [3], reports that high levels of prolactin can be seen in PCOS.

We also found a 2007 article which aimed to identify the cause of hyperprolactinemia in polycystic ovary syndrome (PCOS) and to compare prolactin (PRL) levels between PCOS women without hyperprolactinemia and women with insulin resistance and without PCOS [4]. This concluded:

“This result leads us to conclude that PCOS patients with increased PRL levels must be investigated for other causes of hyperprolactinemia, because hyperprolactinemia is not a clinical manifestation of PCOS.”

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Original Article

Insulin-Lowering Agents Inhibit Synthesis of Testosterone in Ovaries of DHEA-Induced PCOS Rats

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Key Words

- Insulin-lowering agents
- Testosterone synthesis
- Polycystic ovary syndrome
- PCOS rat model

ESSENCE OF ARTICLE

Conclusion:

“ Insulin-lowering agents affected ovarian tissue by inhibiting testosterone biosynthesis in vivo.’

ARTICLE

Background: Insulin-lowering agents are reported to be useful in treating polycystic ovary syndrome (PCOS) anovulation. It has been suggested that lower insulin levels secondarily affect ovarian tissue, although the direct mechanism of action has not yet been verified. Here we investigated if these agents directly affect the ovary. Methods: Thirty female Wister rats were studied. Six control rats were injected subcutaneously with 0.2 ml sesame oil, while 24 rats used as PCOS models were injected subcutaneously with dehydroepiandrosterone (DHEA) and divided into four groups. Six rats were injected with only DHEA, while the remaining 18 rats received metformin, pioglitazone or troglitazone. The ovaries were immunohistochemically stained with anti- testosterone and anti-17 β -HSD antibodies, and then evaluated for morphological changes. Results: In the DHEA administration group, the number of atretic follicles significantly increased compared to that of control rats. The insulin-lowering agents did not improve the multicystic appearance. Serum testosterone concentrations significantly increased with DHEA administration, but the increase was inhibited by oral administration of insulin-lowering agents. Testosterone deposits in ovarian tissue were also reduced by feeding rats insulin-lowering agents. Conclusion: Insulin-lowering agents affected ovarian tissue by inhibiting testosterone biosynthesis in vivo.

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