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ABSTRACTS

The Benefits of Whey

Whey protein as cancer treatment adjuvant, antibiotic, and anti-aging agent

Whey and Chemotherapy

In vitro selective modulation of cellular glutathione by a humanized native milk protein isolate in normal cells and rat mammary carcinoma model

Baruchel S Viau G. In: Anticancer Res (1996 May-Jun) 16(3A):1095-9

We report the in vitro selective inhibitory activity of a humanized whey protein concentrate Immunocal on growth of mammary carcinoma cells and Jurkat T cells in comparison to normal peripheral blood mononuclear cells. We relate this inhibitory activity to a selective depletion of intracellular glutathione synthesis. The use of humanized whey protein concentrate as a food supplementation may have direct implication in clinical trial with adjuvant chemotherapy.

Whey and Diseases of Aging

The influence of dietary whey protein on tissue glutathione and the diseases of aging

Bounous G Gervais F Amer V Batist G Gold P. In: Clin Invest Med (1989 Dec) 12(6):343-9

This study compared the effects of a whey-rich diet (20 g/100 g diet), with that of Purina mouse chow or casein-rich diet (20 g/100 g diet), on the liver and heart glutathione content and on the survival of old male C57BL/6NIA mice.

The study was performed during a limited observation period of 6.3 months. In mice fed the whey protein-rich diet between 17 months and 20 months of age, the heart tissue and liver tissue glutathione content were enhanced significantly above the corresponding values of the casein diet-fed and Purina-fed mice.

Mice fed the whey protein diet at the onset of senescence at 84 weeks exhibited increased longevity as compared to mice fed Purina mouse chow over the 6.3-month observation period extending from the age of 21 months (corresponding to a human age of 55 years) to 26-27 months of age (corresponding to a human age of 80 years), during which time 55% mortality was observed. The corresponding mean survival time of mice fed the defined casein diet is almost identical to that of Purina-fed controls.

Body weight curves were similar in all three dietary groups. Hence a whey protein diet appears to enhance the liver and heart glutathione concentration in aging mice and to increase longevity over a 6.3-month observation period.

Whey and Cholesterol Concentrations

Lowering effect of dietary milk-whey protein v. casein on plasma and liver cholesterol concentrations in rats

Zhang X Beynen AC. In: Br J Nutr (1993 Jul) 70(1):139-46

The effect of dietary whey protein versus casein on plasma and liver cholesterol concentrations was investigated in female, weanling rats. Balanced, purified diets containing either whey protein or casein, or the amino acid mixtures simulating these proteins, were used.

The high-cholesterol diets (10 grams of cholesterol per kg feed) had either 150 or 300 grams protein or amino acids/kg feed. The diets were given for 3 weeks. At the low dietary protein level, whey protein versus casein did not affect plasma total cholesterol, but lowered the concentration of liver cholesterol.

At the high dietary-protein level, whey protein significantly lowered plasma and liver cholesterol and also plasma triacylglycerols. The hypocholesterolemic effect of whey protein was associated with a decrease in very-low-density-lipoprotein cholesterol.

At the high dietary protein concentration, whey protein reduced the fecal excretion of bile acids when compared with casein. The effects of intact whey protein versus casein were not reproduced by the amino acid mixtures simulating these proteins. It is suggested tentatively that the cholesterol-lowering effect of whey protein in rats is caused by inhibition of hepatic cholesterol synthesis.

Lactoferrin's Antibacterial Synergy

Damage of the outer membrane of enteric gram-negative bacteria by lactoferrin and transferrin

Ellison RT 3d Giehl TJ LaForce FM. In: Infect Immun (1988 Nov) 56(11):2774-81

We hypothesized that the iron-binding proteins could affect the gram-negative outer membrane in a manner similar to that of the chelator EDTA. The ability of lactoferrin and transferrin to release radiolabeled lipo polysaccharide (LPS) from a UDP- galactose epimerase deficient *Escherichia coli* mutant and from wild-type *Salmonella typhimurium* strains was tested. Initial studies in barbital-acetate buffer showed that EDTA and lactoferrin cause significant release of LPS from all three strains. Further studies found that LPS release was blocked by iron saturation of lactoferrin, occurred between pH 6 and 7.5, was comparable for bacterial concentrations from 10^4 to 10^7 CFU/ml, and increased with increasing lactoferrin concentrations. Studies using Hanks balanced salt solution lacking calcium and magnesium showed that transferrin also could cause LPS release. Additionally, both lactoferrin and transferrin increased the antibacterial effect of a subinhibitory concentration of rifampin, a drug excluded by the bacterial outer membrane. This work demonstrates that these iron-binding proteins damage the gram-negative outer membrane and alter bacterial outer membrane permeability.

Antibacterial Activity of Lactoferrin

Antibacterial activity of lactoferrin and a pepsin-derived lactoferrin peptide fragment

Yamauchi K Tomita M Giehl TJ Ellison RT 3d. In: Infect Immun (1993 Feb) 61(2):719-28

Recent work has indicated that in addition to binding iron, human lactoferrin damages the outer membrane of gram-negative bacteria. In this study, we determined whether bovine lactoferrin and a pepsin-derived bovine lactoferrin peptide (lactoferricin) fragment have similar activities. We found that both 20 microM bovine lactoferrin and 20 microM lactoferricin release intrinsically labeled [3H]lipopolysaccharide ([3H]LPS) from three bacterial strains, *Escherichia coli* CL99 1-2, *Salmonella typhimurium* SL696, and *Salmonella montevideo* SL5222. Under most conditions, more LPS is released by the peptide fragment than by whole bovine lactoferrin. In the presence of either lactoferrin or lactoferricin there is increased killing of *E. coli* CL99 1-2 by lysozyme. Like human lactoferrin, bovine lactoferrin and lactoferricin have the ability to bind to free intrinsically labeled [3H]LPS molecules. In addition to these effects, whereas bovine lactoferrin was at most bacteriostatic, lactoferricin demonstrated consistent bactericidal activity against gram-negative bacteria. This bactericidal effect is modulated by the cations Ca²⁺, Mg²⁺, and F³⁺ but is independent of the osmolarity of the medium. Transmission electron microscopy of bacterial cells exposed to lactoferricin show the immediate development of electron-dense "membrane blisters." These experiments offer evidence that bovine lactoferrin and lactoferricin damage the outer membrane of gram-negative bacteria. Moreover, the peptide fragment lactoferricin has direct bactericidal activity. As lactoferrin is exposed to proteolytic factors in vivo which could cleave the lactoferricin fragment, the effects of this peptide are of both mechanistic and physiologic relevance.

Whey's Antibacterial Spectrum

Antibacterial spectrum of lactoferricin B, a potent bactericidal peptide derived from the N-terminal region of bovine lactoferrin

Bellamy W Takase M Wakabayashi H Kawase K Tomita M. In: J Appl Bacteriol (1992 Dec) 73(6):472-9

A physiologically diverse range of Gram-positive and Gram-negative bacteria was found to be susceptible to inhibition and inactivation by lactoferricin B, a peptide produced by gastric pepsin digestion of bovine lactoferrin. The list of susceptible organisms includes *Escherichia coli*, *Salmonella enteritidis*, *Klebsiella pneumoniae*, *Proteus vulgaris*, *Yersinia enterocolitica*, *Pseudomonas aeruginosa*, *Campylobacter jejuni*, *Staphylococcus aureus*, *Streptococcus mutans*, *Corynebacterium diphtheriae*, *Listeria monocytogenes* and *Clostridium perfringens*. Concentrations of lactoferricin B required to cause complete inhibition of growth varied within the range of 0.3 to 150 micrograms/ml, depending on the strain and the culture medium used. The peptide showed activity against *E. coli* O111 over the range of pH 5.5 to 7.5 and was most effective under slightly alkaline conditions. Its antibacterial effectiveness was reduced in the presence of Na⁺, K⁺, Mg²⁺ or Ca²⁺ ions, or in the presence of various buffer salts. Lactoferricin B was lethal, causing a rapid loss of colony-forming capability in most of the species tested. *Pseudomonas fluorescens*, *Enterococcus faecalis* and *Bifidobacterium bifidum* strains were highly resistant to this peptide.

Garlic and Cancer

Effects of garlic thioallyl derivatives on growth, glutathione concentration, and polyamine formation of human prostate carcinoma cells in culture

Pinto JT Qiao C Xing J Rivlin RS Protomastro ML Weissler ML Tao Y Thaler H Heston WD. In: Am J Clin Nutr (1997 Aug) 66 (2):398-405

This study investigated whether naturally occurring garlic derivatives and synthetic S-cysteinyl compounds that resemble garlic constituents have antiproliferative effects on human prostate carcinoma (LNCaP) cells. Studies also examined whether S-allylmercaptocysteine and S-allylcysteine affect two important molecular targets, namely reduced glutathione and polyamines. Results showed that S-allylmercaptocysteine (50 mg/L) diminished LNCaP cell growth whereas the antiproliferative effect of S-allylcysteine was not as pronounced. Studies using synthetic S-cysteinyl analogues revealed that growth inhibition was most effective with compounds containing a disulfide or an active diallyl moiety. Marginal-to-no inhibitory effect was observed with monosulfenic analogues. Both S-allylmercaptocysteine and S-allylcysteine caused an increase in LNCaP cell reduced glutathione concentrations. Putrescine and spermine concentrations decreased and spermidine increased 3 days after S-allylmercaptocysteine treatment. At 5 days after S-allylmercaptocysteine treatment, polyamine concentrations were similar to those of saline-treated controls. Diminished cell growth and altered polyamine concentrations suggest that S-allylmercaptocysteine may impede the polyamine synthesizing enzyme, ornithine decarboxylase, either by enhancing the formation of reduced glutathione, a known inhibitor of ornithine decarboxylase, or by reacting directly with ornithine decarboxylase at its nucleophilic thiol moiety. Because S-allylcysteine also increases reduced glutathione formation but does not significantly inhibit growth, the latter mechanism may be more likely for this compound. These data provide further evidence that nonessential nutrients derived from garlic may modulate tumor growth.

Folic Acid, Gingival Overgrowth

Effect of folic acid on recurrence of phenytoin-induced gingival overgrowth following gingivectomy

Poppell TD Keeling SD Collins JF Hassell TM. In: J Clin Periodontol (1991 Feb) 18(2):134-9

This study examined the effect of folic acid supplementation on the recurrence of phenytoin-induced gingival overgrowth following gingivectomy. Eight residents of an institution for the developmentally disabled were randomly assigned to a treatment (N = 4) or control (N = 4) group. Subjects in the treatment group received an oral supplementation of 5 mg of folic acid daily during the study; those in the control group did not. A gingivectomy with an external beveled incision made to the crest of the alveolus was completed by quadrants. The following data were obtained prior to gingivectomy, 2 weeks following the last quadrant of surgery, and at 3 and 6 months post-surgery: plaque and gingival index scores, red blood cell folic acid levels, free phenytoin blood levels, photographs, and impressions. Percent change in overgrowth was determined from cross-sectional area measurements made on dies obtained from bucco-lingual cuts on stone models. The groups did not differ in plaque and gingival index scores or free phenytoin blood levels. The treatment group had significantly higher red blood cell folic acid levels (p less than or equal to 0.0001). Reduction in gingival overgrowth as a result of surgery was similar in both groups. Although the treatment group had significantly less recurrence of gingival overgrowth (p less than or equal to 0.05), the mean differences amounted to only 6-7% at 3 and 6 months.

Folate, Phenytoin Hyperplasia

Effect of folate on phenytoin hyperplasia

Drew HJ Vogel RI Molofsky W Baker H Frank O. In: J Clin Periodontol (1987 Jul) 14(6):350-6

There have been some reports that folic acid inhibits phenytoin-induced gingival hyperplasia. The purpose of this double-blind study was to quantify clinically the effects of both systemic and topical administration of folic acid on phenytoin-induced gingival overgrowth in man. For a period of 6 months, one group of phenytoin patients received 2 daily topical applications of a folate solution. An additional group received 2 daily doses of systemic folate while a control group received placebo medication. Results indicate that throughout the 180-day period of the study, the topical folate significantly inhibited gingival hyperplasia to a greater extent than either systemic folate or placebo groups.

Folate Mouthwash

Effects of folate mouthwash on experimental gingivitis in man

Pack AR .In: J Clin Periodontol (1986 Aug) 13(7):671-6

Although the experimental gingivitis model has been used extensively since 1965, some doubts exist concerning the nature of the tissue response in this model. Accordingly, the present study was designed to determine whether or not experimental gingivitis responded to 0.1% folate mouthwash (MW) in a similar manner to that already reported for established gingivitis. Twenty male dental students took part in a double blind cross-over study which involved two 3-week experimental periods with random allocation to folate or placebo MW. The experimental site was the lower anterior area and 24 points of gingival examination were made at baseline and weeks 1, 2 and 3. Inflammation was assessed by presence or absence of color change, and bleeding being slight, profuse or absent when gingivae were stroked with a blunt probe. A plaque sample was evaluated using dark field microscopy, and dry weight of accumulated plaque was measured at the end of each experimental period. Folate MW did not appear to have any statistically significant effects on accumulated plaque, or clinical signs of experimental gingivitis in this study. The different response of experimental gingivitis to folate MW, compared with the response of established gingivitis already reported, further suggests that experimental gingivitis may not represent an authentic replica of the cellular and immunological responses occurring in established gingivitis.

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