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ABSTRACTS

CLA

Building Muscle and Energy

Conjugated linoleic acid reduces arachidonic acid content and PGE(2) synthesis in murine keratinocytes
Cancer Letters, 1998, Vol 127, Iss 1-2, pp 15-22

Dietary conjugated linoleic acid (CLA) is associated with decreased 12-O-tetradecanoyl-phorbol-13-acetate (TPA)-induced tumor promotion in mouse skin. In addition, CLA decreases TPA-induced prostaglandin E synthesis and ornithine decarboxylase activity in cultured keratinocytes compared with linoleic acid (LA) and arachidonic acid (AA). When LA or CLA was added to keratinocyte cell cultures, the amounts of each of these cellular fatty acids increased significantly in a dose-dependent manner. Furthermore, LA treatment was associated with increased cellular AA while the AA content of keratinocytes was reduced when cultures were treated with CLA. Moreover, CLA (16 μ g/ml) was more potent than LA at decreasing the level of C-14-AA incorporated into cellular phosphatidylcholine. In order to determine the effect of CLA on arachidonate-derived PGE(2), the release of C-14-AA and C-14-PGE(2) synthesis was measured in cultures pre-treated with LA/C-14-AA or CLA/C-14-AA for 12 h. The amount of C-14-AA release induced by TPA in CLA/C-14-AA pre-treated cultures was significantly lower than cultures pre-treated with LA/C-14-AA. Furthermore, TPA-induced C-14-PGE(2) was significantly lower in cultures pre-treated with CLA/C-14-AA compared with cultures pre-treated with LA/C-14-AA. The effects of LA and CLA on AA composition of phospholipids and subsequent arachidonate-derived PGE(2) synthesis will provide insight into the anti-promoter mechanisms of CLA.

Glucose tolerance and CLA:

Dietary conjugated linoleic acid normalizes impaired glucose tolerance in the Zucker diabetic fatty rat
Biochem Biophys Res Commun 1998 Mar 27;244(3):678-82

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.

CLA increases lean body mass, decreases body fat

Effect of conjugated linoleic acid on body composition in mice
Lipids 1997 Aug;32(8):853-8

The effects of conjugated linoleic acid (CLA) on body composition were investigated. ICR mice were fed a control diet containing 5.5% corn oil or a CLA-supplemented diet (5.0% corn oil plus 0.5% CLA). Mice fed CLA-supplemented diet exhibited 57% and 60% lower body fat and 5% and 14% increased lean body mass relative to controls ($P < 0.05$). Total carnitine palmitoyltransferase activity was increased by dietary CLA supplementation in both fat pad and skeletal muscle; the differences were significant for fat pad of fed mice and skeletal muscle of fasted mice. In cultured 3T3-L1 adipocytes CLA treatment (1×10^{-4} M) significantly reduced heparin-releasable lipoprotein lipase activity (-66%) and the intracellular concentrations of triacylglyceride (-8%) and glycerol (-15%), but significantly increased free glycerol in the culture medium (+22%) compared to control ($P < 0.05$). The effects of CLA on body composition appear to be due in part to reduced fat deposition and increased lipolysis in adipocytes, possibly coupled with enhanced fatty acid oxidation in both muscle cells and adipocytes.

Inhibitory effects of CLA

Conjugated linoleic acid decreases hepatic stearoyl-CoA desaturase mRNA expression
Biochem Biophys Res Commun 1998 Jul 30;248(3):817-21

Conjugated dienoic derivatives of linoleic acid (CLA) is a collective term for positional and geometric isomers of linoleic acid that occur naturally in foods. The two predominant isomers of CLA are the c9,t11 and t10,c12. One of the effects of CLA is to modify membrane fatty acid composition by decreasing the activity of stearoyl-CoA desaturase enzyme activity. We analyzed the changes of stearoyl-CoA desaturase gene 1 (scd1) mRNA to further define the mechanism for the decrease in Scd enzyme activity by CLA. Mice fed for two weeks with either a fat-free high carbohydrate diet (CHO) or a 5.0% corn oil diet (CO), supplemented with 0.5% CLA had a 45% and 75% decrease respectively, in scd1 mRNA levels in the liver. Consistent with the effects observed in mice, 150 microM CLA suppressed the expression of scd1 mRNA in the H2.35 mouse liver cells by 60%. Further studies with enzymatically prepared c9,t11 isomer showed that the inhibitory effect of CLA on scd1 mRNA expression in H2.35 liver cells was by isomers other than the c9,t11-CLA.

Glycation via chronic hyperglycemia

Levels of lipid peroxidation product and glycated hemoglobin A1c in the erythrocytes of diabetic patients
Clin Chim Acta 1998 Aug 28;276(2):163-72

In diabetes, the glycation and subsequent browning (or glycooxidation) reactions are enhanced by elevated glucose concentrations. It is unclear whether or not the diabetic state per se also induces an increase in the generation of oxygen-derived free radicals (OFRs). There is some evidence, however, that glycation itself may induce the formation of OFRs. OFRs could cause oxidative damage to endogenous molecules. We examined the relationship between the levels of lipid peroxidation and the levels of glycated hemoglobin A1c (GHbA1c) in erythrocytes of diabetic and healthy subjects. Lipid peroxidation was assessed in erythrocyte membrane lipids by monitoring peak height ratios of conjugated linoleic acid (CLA), one of the products of lipid peroxidation, to linoleic acid (LA) using gas chromatography-mass spectrometry (GC/MS). CLA is a collective term used to designate a mixture of positional and geometric isomers of LA in which the double bonds are conjugated. The peak height ratio of CLA to LA was used as a biomarker of lipid peroxidation. GHbA1c, an index of glycemic stress, was measured by high-performance liquid chromatography. There were significantly increased ratios of CLA to LA in diabetic erythrocytes compared with control erythrocytes. These ratios of CLA to LA were also significantly correlated with GHbA1c values. This suggests that glycation via chronic hyperglycemia links lipid peroxidation in the erythrocytes of both diabetic and healthy subjects.

Fatty acids reduce CHD risk

A possible protective effect of nut consumption on risk of coronary heart disease
Arch Intern Med 1992 Jul;152(7):1416-24

Background: Although dietary factors are suspected to be important determinants of coronary heart disease (CHD) risk, the direct evidence is relatively sparse. Methods: The Adventist Health Study is a prospective cohort investigation of 31,208 non-Hispanic white California Seventh-Day Adventists. Extensive dietary information was obtained at baseline, along with the values of traditional coronary risk factors. These were related to risk of definite fatal CHD or definite nonfatal myocardial infarction. Results: Subjects who consumed nuts frequently (more than four times per week) experienced substantially fewer definite fatal CHD events (relative risk, 0.52; 95% confidence interval [CI], 0.36 to 0.76) and definite nonfatal myocardial infarctions (relative risk, 0.49; 95% CI, 0.28 to 0.85), when compared with those who consumed nuts less than once per week. These findings persisted on covariate adjustment and were seen in almost all of 16 different subgroups of the population. Subjects who usually consumed whole wheat bread also experienced lower rates of definite nonfatal myocardial infarction (relative risk, 0.56; 95% CI, 0.35 to 0.89) and definite fatal CHD (relative risk, 0.89; 95% CI, 0.60 to 1.33) when compared with those who usually ate white bread. Men who ate beef at least three times each week had a higher risk of definite fatal CHD (relative risk, 2.31; 95% CI, 1.11 to 4.78), but this effect was not seen in women or for the nonfatal myocardial infarction end point. Conclusions: Our data strongly suggest that the frequent consumption of nuts may protect against risk of CHD events. The favorable fatty acid profile of many nuts is one possible explanation for such an effect.

Dietary enrichment of LDL with oleic acid

LDL isolated from Greek subjects on a typical diet or from American subjects on an oleate-supplemented diet induces less monocyte chemotaxis and adhesion when exposed to oxidative stress
Arterioscler Thromb Vasc Biol 1999 Jan;19(1):122-30

The mechanisms underlying the cardiovascular benefits of Mediterranean-style diets are not fully understood. The high content of monounsaturated fatty acids in Mediterranean-style diets derived from oleate-rich olive oil may be beneficial in reducing low density lipoprotein (LDL) oxidation and its subsequent development of atherogenic properties. This study sought to assess the proinflammatory potential of LDL isolated from subjects consuming a diet naturally rich in olive oil. LDL was isolated from 18 Greek, 18 American, and 11 Greek-Americans subjects, all of whom were living in the United States.

Fatty acid composition and vitamin E levels of LDL were determined, as was the extent of copper-mediated LDL oxidation. LDL was also mildly oxidized by exposure to fibroblasts overexpressing 15-lipoxygenase and tested in vitro for bioactivity by determining its ability to stimulate monocyte chemotaxis and adhesion to endothelial cells. To confirm that dietary fatty acids influence the proinflammatory properties of mildly oxidized LDL, LDL was also isolated from 13 healthy American subjects after consumption of an 8-week liquid diet supplemented with either oleic (n=6) or linoleic (n=7) acid and tested for bioactivity in a similar fashion. There were no differences in the baseline lipid profiles among the Greeks, Americans, or Greek-Americans. Oleic acid content in LDL was 20% higher in the Greek compared with the American or Greek-American subjects ($P<0.001$). The extent of in vitro LDL oxidation, measured by conjugated diene formation, was lower in the Greek subjects ($P<0.02$), but there was no difference in the lag time. Induction of monocyte chemotaxis and adhesion by mildly oxidized LDL was decreased by 42% in the Greek group compared with the American subjects ($P<0.001$). There was an inverse correlation between the oleic acid content of LDL and stimulation of monocyte chemotaxis ($r=-0.64$, $P<0.001$) and a positive correlation between the polyunsaturated fatty acid content of LDL (total linoleate and arachidonic acids levels in LDL) and stimulation of monocyte chemotaxis ($r=0.51$, $P<0.01$) in the entire cohort. There were no differences in LDL vitamin E content between the groups. In the liquid-diet groups, the oleic acid-supplemented group had a 113% higher oleic acid content in LDL and a 46% lower linoleic acid content in LDL than the linoleate-supplemented group ($P<0.001$), whereas the vitamin E content in LDL was equal in both groups. When exposed to oxidative stress, the LDL enriched in oleic acid promoted less monocyte chemotaxis (52% lower) and reduced monocyte adhesion by 77% in comparison with linoleate-enriched LDL ($P<0.001$). There was a strong, negative correlation between oleic acid LDL content and monocyte adhesion ($r=-0.73$, $P<0.001$) and a strong, positive correlation between polyunsaturated fatty acid LDL content and monocyte adhesion ($r=0.87$, $P<0.001$). This study demonstrates that dietary enrichment of LDL with oleic acid is realistic and readily achieved by using diets currently in use in Mediterranean countries. In addition, these data suggest that LDL enriched with oleic acid and reduced in polyunsaturated fatty acids may be less easily converted to a proinflammatory, minimally modified LDL.

Steatorrhea and enzyme replacement therapy

Pancreatic enzyme replacement therapy: comparative effects of conventional and enteric-coated microspheric pancreatin and acid-stable fungal enzyme preparations on steatorrhea in chronic pancreatitis
Hepatology 1985 Apr;32(2):97-102

The therapeutic effectiveness of a conventional (Pankreon-Granulat) and an acid-protected (Kreon) porcine pancreatic enzyme preparation, and an acid-stable fungal enzyme preparation (Nortase) in the treatment of severe pancreatogenic steatorrhea was investigated. The study comprised 17 patients with chronic pancreatitis and exocrine pancreatic insufficiency with (A) or without (B) a previous Whipple's procedure (B II resection + partial duodenopancreatectomy). With all three enzyme preparations, a significant (p less than 0.05) reduction in the total fecal fat excretion/day was achieved. In therapy group A, this reduction was, on average, 58% for Kreon (100,000 U lipase/day), 67% for Pankreon-Granulat (360,000 U lipase/day) and 54% for Nortase (75,000 U lipase/day), the respective figures for therapy group B being 58%, 52% and 46% at identical dosages. Thus, in both groups, the effect produced by the conventional porcine pancreatic enzyme preparation and the acid-protected porcine or the acid-stable fungal enzyme preparation was largely equivalent, although the latter two preparations were administered at only 1/4 of the dosages of the former preparation. On the basis of the respective average reduction in total fecal fat excretion and average number of stools/day, it would appear that in patients with chronic pancreatitis and prior Whipple's procedure, Pankreon-Granulat should be administered for enzyme replacement while in patients with an intact upper gastrointestinal tract, Kreon should be administered, in the treatment of steatorrhea in chronic pancreatitis.

Enzyme replacement therapy and chronic pancreatitis

Management of chronic pancreatitis. Focus on enzyme replacement therapy
Int J Pancreatol 1989;5 Suppl:17-29

The goals of treatment with pancreatic extracts in patients with chronic relapsing pancreatitis are twofold: pain relief and control of maldigestion caused by exocrine pancreatic insufficiency. Experience with the use of pancreatic enzymes for analgesic purposes suggests that the less severe the pain, the greater the analgesic effect of these enzymes. However, the number of trials, as well as the number of patients treated, is fairly small and more studies in larger patient populations are needed. The use of pancreatic enzymes for maldigestion owing to exocrine pancreatic insufficiency which is secondary to chronic pancreatitis, pancreatectomy, cystic fibrosis, or GI bypass surgery incurs several problems. These problems are primarily caused by gastric inactivation of the enzymes, low enzyme activity of many commercial preparations and/or poor patient compliance. Treatment with conventional enzyme products (powdered extracts, enteric-coated tablets or capsules) has been disappointing. At best, results were inconsistent, showing a high degree of individual variation. The introduction of enzyme preparations in the form of pH-sensitive enteric-coated microspheres in hard gelatin capsules represents a significant advance. These microspheres are superior to conventional enzyme preparations in improving the symptoms of pancreatic insufficiency, particularly steatorrhea, where low doses of microspheres are as effective as large doses of conventional enzyme preparations. Steatorrhea, however, is rarely completely resolved. In cases refractory to therapy, treatment with the combination of pH-sensitive enteric-coated microspheres and H₂-antagonists or prostaglandins has met with some success.

Reduction of nutrient malabsorption

Pancreatic enzymes: secretion and luminal nutrient digestion in health and disease
J Clin Gastroenterol 1999 Jan;28(1):3-10

Severe pancreatic exocrine insufficiency leading to malabsorption of nutrients is one of the most important late features of chronic pancreatitis. In contrast to other key enzymes, pancreatic synthesis and secretion of lipase is impaired more rapidly, its intraluminal survival is shorter due to its higher susceptibility against acidic and proteolytic denaturation, and its luminal digestive action is hardly compensated by nonpancreatic mechanisms. As a consequence, steatorrhea is in general more severe and occurs several years before clinical malabsorption of protein or starch. Apart from the detrimental effects of nutrient deficiency, profound alterations of upper gastrointestinal secretory and motor functions may be an additional and hitherto underestimated consequence of increased nutrient delivery to distal intestinal sites. Effective reduction of nutrient malabsorption in pancreatic insufficiency requires delivery of sufficient enzymatic activity into the duodenal lumen simultaneously with meal nutrients. Modern enteric-coated pancreatin microsphere preparations attempt to achieve this by optimizing the size of individual microspheres and chemical properties of the coating. However, lipid digestion cannot be completely normalized in most patients by current standard therapy. In the future, acid and protease stable bacterial and fungal lipases with additional pH optima in the acidic milieu or animal or bioengineered human gastric lipase preparations may offer superior therapeutic alternatives. This review first summarizes current knowledge about secretion and luminal fate of pancreatic enzymes and their effects on nutrient digestion in health and chronic pancreatitis. Second, rationale, current standards, options, and future aspects of enzyme replacement therapy are discussed.

Enzymes and nutrients

Effect of dietary or abomasal supplementation of exogenous polysaccharide- degrading enzymes on rumen fermentation and nutrient digestibility
J Anim Sci 1998 Dec;76(12):3146-56

The effect of site of supplementation of a mixture of two crude preparations (Enzyme C and Enzyme X) of exogenous polysaccharide-degrading enzymes (EPDE) was studied in vivo using four ruminally and duodenally cannulated heifers (Exp. 1). The treatments were as follows: control (no EPDE), EPDE supplied through the diet (EF, 47.0 g/d), and EPDE infused continuously into the abomasum (EA, 41.6 g/d). Enzyme treatment increased the concentration of soluble reducing sugars ($P < .05$) and decreased NDF content ($P < .05$) in the treated feed, but this did not increase the rate or extent of in sacco disappearance of DM from the feed. Compared with control, ruminal fermentation was not affected by EF, but abomasal infusion increased ($P < .05$) rumen ammonia levels and shifted ruminal VFA patterns. Ruminal carboxymethylcellulase (CMCase) and xylanase activities were not affected by treatment. Abomasal infusion increased ($P < .05$) duodenal xylanase activity as compared with control and EF, but apparent digestion of DM, NDF, and CP were not affected by treatment. Negligible levels of CMCase and amylase reached the duodenum. During an in vitro experiment (Exp. 2), abomasal stability of the two EPDE was studied over a range of pH from 3.39 to .85, with or without pepsin. Carboxymethylcellulase activity (in Enzymes C and X) and beta-glucanase activity (in Enzyme C) were largely unstable against pepsin proteolysis ($P < .001$) and low pH ($P < .001$). Xylanase and amylase activities were resistant to pepsin but irreversibly inactivated at low pH. These two experiments showed that abomasal supplementation of EPDE did not successfully supply cellulases and amylases to the intestine, due partially to their limited resistance to low pH and pepsin proteolysis. Although EPDE significantly increased the level of xylanase activity at the duodenum, this did not significantly improve total tract digestion.

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