

Liver Cirrhosis

ABSTRACTS

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Hepatoprotective activity of polyphenolic compounds from *Cynara scolymus* against CCl₄ toxicity in isolated rat hepatocytes.

Adzet T, Camarasa J, Laguna JC. Departamento de Farmacognosia y Farmacodinamia, Facultad de Farmacia, Nucleo Universitario de Pedralbes, Barcelona, Spain.

J Nat Prod. 1987 Jul-Aug;50(4):612-7

The hepatoprotective activity against CCl₄ toxicity in isolated rat hepatocytes of some polyphenolic compounds, such as cynarin, isochlorogenic acid, chlorogenic acid, luteolin-7-glucoside, and two organic acids, caffeic and quinic, from *Cynara scolymus*, is tested. Only cynarine and, to a lesser extent, caffeic acid showed cytoprotective action. The possible relationship between the molecular structure and the protective effect found is discussed.

Preventive effect of malotilate on carbon tetrachloride-induced liver damage and collagen accumulation in the rat.

Ala-Kokko L, Stenback F, Ryhanen L. Collagen Research Unit, Biocenter, Oulu, Finland.

Biochem J. 1987 Sep 1;246(2):503-9

Malotilate is a new drug suggested for use in chronic liver diseases. It is shown here to prevent liver damage caused by CCl₄. The concomitant administration of malotilate with CCl₄ significantly decreased hydroxyproline accumulation in the liver, liver prolyl 4-hydroxylase and liver and serum galactosylhydroxylsyl glucosyltransferase activities. However, it had no effect on the daily urinary hydroxyproline excretion or the hydroxyproline content of the skin, liver or lungs in normal young growing rats. It also had no specific inhibitory effect on hydroxyproline synthesis or secretion in fibroblast cultures, and did not affect the amount of procollagen-alpha 1(I)-specific mRNAs in these cultures. Thus it seems to have no direct inhibitory effect on collagen metabolism. In addition to inhibition of liver collagen accumulation, malotilate was also able to prevent the development of morphological changes in the liver such as focal necrosis, fatty infiltration and inflammatory changes. It also normalized almost completely the standard liver-function tests. It is possible that malotilate may prevent excessive collagen deposition by inhibiting the inflammation caused by CCl₄-induced liver damage.

Preventive effect of malotilate on dimethylnitrosamine-induced liver fibrosis in the rat.

Ala-Kokko L, Stenback F, Ryhanen L. Department of Medical Biochemistry, University of Oulu, Finland.

Dimethylnitrosamine-induced liver damage, which leads to hepatic failure and death of the animal, was prevented by treatment with malotilate. The accumulation of collagen and the morphologic changes caused by dimethylnitrosamine, such as inflammatory cell accumulation and fibrosis, were also prevented by this drug. Malotilate drastically reduced the increases in the amount of type I procollagen alpha 2-chain mRNA and activities of the enzymes prolyl 4-hydroxylase and galactosylhydroxylsyl glucosyltransferase, which are early events in liver fibrosis preceding the deposition of collagen. Even when started 14 days after dimethylnitrosamine induction, malotilate treatment was able to reduce liver damage. We suggest that the effect of malotilate is a result of the inhibition of inflammation.

Polyenylphosphatidylcholine prevents carbon tetrachloride-induced lipid peroxidation while it attenuates liver fibrosis.

Aleynik SI, Leo MA, Ma X, Aleynik MK, Lieber CS. Alcohol Research Center, Veterans Affairs Medical Center, Bronx, New York 10468, USA.

J Hepatol. 1997 Sep;27(3):554-61

BACKGROUND/AIMS: Polyenylphosphatidylcholine protects against alcoholic cirrhosis in the baboon and carbon tetrachloride-induced cirrhosis in rats. This study addresses the possible mechanism of the protective effect of polyenylphosphatidylcholine.

METHODS: For 8 weeks, rats were injected with either carbon tetrachloride in peanut oil or peanut oil alone (control), and pair-fed nutritionally adequate liquid diets with equivalent amounts of linoleic acid either as polyenylphosphatidylcholine or as safflower oil. Other rats were injected for 9 weeks with heterologous albumin and fed the same liquid diets. Lipid peroxidation was measured by F2-isoprostanes and 4-hydroxynonenal.

RESULTS: Carbon tetrachloride-induced lipid peroxidation was strikingly attenuated with polyenylphosphatidylcholine supplementation. Levels of hepatic F2-isoprostanes and 4-hydroxynonenal paralleled liver fibrotic scores and collagen accumulation. Polyenylphosphatidylcholine also attenuated the fibrosis induced in rats with human albumin, but in this case, levels of hepatic 4-hydroxynonenal did not change, nor were they significantly affected by polyenylphosphatidylcholine. Neither carbon tetrachloride injection nor polyenylphosphatidylcholine treatment changed the arachidonic acid content (a major precursor of F2-isoprostanes and 4-hydroxynonenal) in liver phospholipids, and hepatic vitamin E was not significantly altered.

CONCLUSIONS: The hepatic protection of polyenylphosphatidylcholine against carbon tetrachloride appears to be due, at least in part, to an antioxidant effect, whereas the protection against heterologous albumin-induced fibrosis suggests that an additional mechanism, such as stimulation of collagenase activity, may also be responsible.

Gallstones: A National Health Problem

ALF.

2002. New York: American Liver Foundation.

Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease.

Alter, M.J., Margolis, H.S., Bell, B.P. et al.

MMWR 1998 Sep 16; 47(RR-19): 1-39.

No Abstract Available

Nutritional support of the pediatric surgical patient.

Amii LA, Moss RL. Division of Pediatric Surgery, Stanford University School of Medicine, Packard Children's Hospital, Palo Alto, CA 94304, USA.

Curr Opin Pediatr. 1999 Jun;11(3):237-40

This review discusses the important developments in pediatric surgical nutrition over the past year. Sepsis and total parenteral nutrition-associated cholestasis remain complex problems for patients on total parenteral nutrition. Investigations suggest that

total parenteral nutrition may compromise bactericidal activity, increasing the risk of sepsis. Sepsis possibly sensitizes the liver to cholestatic injury. Small volume enteral feeds may restore immune system function. Current research does not support an association between phytosterols in parenteral lipid solutions and total parenteral nutrition-associated cholestasis. Methionine has been identified as a potential hepatotoxin. Ursodeoxycholic acid and S-adenosyl-L-methionine are the most promising treatments of total parenteral nutrition-associated cholestasis. Small bowel transplant is now a reasonable option for patients with irreversible intestinal failure. Patient and graft survival rates have improved with FK-506 (Tacrolimus) immunosuppression. Isolated intestinal grafts have the best survival rate (92% at 1 year). Most surviving graft recipients are weaned off of total parenteral nutrition. The Cox Proportional Hazard model may help to identify candidates for small bowel transplant. This equation predicts the duration of dependence on total parenteral nutrition. Patients with irreversible intestinal failure can then be referred for early small bowel transplantation.

Holistic Health Encyclopedia

Anon.

2002. Oakford, PA: Telstar Innovations.

Lipoic acid prevents suppression of connective tissue proliferation in the rat liver induced by n-3 PUFAs. A pilot study.

Arend A, Zilmer M, Vihalemm T, Selstam G, Sepp E. Department of Anatomy, University of Tartu, Estonia. arend@ut.ee

Ann Nutr Metab. 2000;44(5-6):217-22

As previously shown, dietary n-3 polyunsaturated fatty acids (n-3 PUFAs) suppress connective tissue proliferation in the rat liver wound concurrent with an elevated level of lipid peroxidation. The present study was undertaken to investigate the influence of alpha-lipoic acid (LA), a natural anti-oxidant, on these effects of n-3 PUFAs. Rats were fed with a commercial pellet diet (control group) or with diets enriched with 10% of sunflower oil (n-6 group) or 10% of fish oil (n-3 group) for 8 weeks followed by addition of LA to the same diets for 10 days. Then a liver thermic wound was induced and the administration of LA was continued for 6 days. The proliferation of the connective tissue, the level of lipid peroxidation and their peroxidizability and the content of prostaglandins E2 and F2alpha were measured in the liver wounds. LA prevented the suppression of connective tissue proliferation in the healing wound induced by n-3 PUFAs, avoided the increase in peroxidation of lipids, reduced peroxidizability of lipids and modulated the decrease in PGE2 and PGF2alpha. The results indicate that dietary LA may prevent the suppression of liver wound healing induced by n-3 PUFAs.

Taurine has a protective effect against thioacetamide-induced liver cirrhosis by decreasing oxidative stress.

Balkan J, Dogru-Abbasoglu S, Kanbagli O, Cevikbas U, Aykac-Toker G, Uysal M. Department of Biochemistry, Istanbul Medical Faculty, University of Istanbul, Capa, Turkey.

Hum Exp Toxicol. 2001 May;20(5):251-4

Thioacetamide (TAA) administration (0.3 g/l of tap water for a period of 3 months) to rats resulted in hepatic cirrhosis as assessed by biochemical and histopathological findings. This treatment caused an increase in the levels of malondialdehyde (MDA) and diene conjugates (DCs) and a decrease in the levels of glutathione (GSH), vitamin E, vitamin C and the activities of glutathione peroxidase (GSH-Px) in the liver of rats. Superoxide dismutase (SOD) activities were unchanged. Taurine (2% w/w, added to the chow diet) was administered together with TAA (0.3 g/l of drinking water) for 3 months. Taurine was found to decrease TAA-induced hepatic lipid peroxidation and to increase TAA-depleted vitamin E levels and GSH-Px activities. Histopathological findings also suggested that taurine has an inhibitive effect on TAA-induced hepatic cirrhosis. These results indicate that taurine treatment has a protective effect against TAA-induced liver cirrhosis by decreasing oxidative stress.

Double-blind trial of silymarin vs. placebo in the treatment of chronic hepatitis.

Berenguer, J. et al.

Munch. Med. Wochenschr. 1977; 119: 240 60.

No Abstract Available

The pharmacology of the antioxidant lipoic acid.

Gen Pharmacol. 1997 Sep;29(3):315-31

Lipoic acid is an example of an existing drug whose therapeutic effect has been related to its antioxidant activity. 2. Antioxidant activity is a relative concept: it depends on the kind of oxidative stress and the kind of oxidizable substrate (e.g., DNA, lipid, protein). 3. In vitro, the final antioxidant activity of lipoic acid is determined by its concentration and by its antioxidant properties. Four antioxidant properties of lipoic acid have been studied: its metal chelating capacity, its ability to scavenge reactive oxygen species (ROS), its ability to regenerate endogenous antioxidants and its ability to repair oxidative damage. 4. Dihydrolipoic acid (DHLA), formed by reduction of lipoic acid, has more antioxidant properties than does lipoic acid. Both DHLA and lipoic acid have metal-chelating capacity and scavenge ROS, whereas only DHLA is able to regenerate endogenous antioxidants and to repair oxidative damage. 5. As a metal chelator, lipoic acid was shown to provide antioxidant activity by chelating Fe²⁺ and Cu²⁺; DHLA can do so by chelating Cd²⁺. 6. As scavengers of ROS, lipoic acid and DHLA display antioxidant activity in most experiments, whereas, in particular cases, pro-oxidant activity has been observed. However, lipoic acid can act as an antioxidant against the pro-oxidant activity produced by DHLA. 7. DHLA has the capacity to regenerate the endogenous antioxidants vitamin E, vitamin C and glutathione. 8. DHLA can provide peptide methionine sulfoxide reductase with reducing equivalents. This enhances the repair of oxidatively damaged proteins such as alpha-1 antiprotease. 9. Through the lipoamide dehydrogenase-dependent reduction of lipoic acid, the cell can draw on its NADH pool for antioxidant activity additionally to its NADPH pool, which is usually consumed during oxidative stress. 10. Within drug-related antioxidant pharmacology, lipoic acid is a model compound that enhances understanding of the mode of action of antioxidants in drug therapy.

The Miracle Nutrient: Coenzyme Q10

Bliznakov, E.G.

1987. New York: Bantam.

Effect of the flavanolignans of *Silybum marianum* L. on lipid peroxidation in rat liver microsomes and freshly isolated hepatocytes.

Bosisio E, Benelli C, Pirola O. Institute of Pharmacological Sciences, Faculty of Pharmacy, University of Milan, Italy.

Pharmacol Res. 1992 Feb-Mar;25(2):147-54

The effect of several flavanolignans (silicristin, silidianin, silybin and isosilybin) present in silymarin, the extract of *Silybum marianum* fruits, was tested on lipid peroxidation in rat liver microsomes and freshly isolated hepatocytes. In microsomes lipid peroxidation was generated by ADP/Fe²⁺ and NADPH. All flavanolignans inhibited peroxidation in a concentration dependent manner. In hepatocytes lipid peroxidation was induced by ADP/Fe³⁺ complex and cell damage was evaluated as LDH activity released in the medium. The inhibition of the peroxidative process by flavanolignans was also evident in this model, even if with a potency order different from that found in microsomes. In contrast, the effect on LDH release was significant only for silybin and isosilybin, the other compounds being inactive on this parameter.

Hepatitis C.

Buggs, A.M.

eMed. J. 2002 April 26 (<http://www.emedicine.com/aaem/topic247.htm>).

Lecithin and choline in human health and disease.

Canty DJ, Zeisel SH. Department of Nutrition, Food, and Hotel Management at New York University, NY.

Nutr Rev. 1994 Oct;52(10):327-39

Choline is involved in methyl group metabolism and lipid transport and is a component of a number of important biological compounds including the membrane phospholipids lecithin, sphingomyelin, and plasmalogen; the neurotransmitter acetylcholine; and platelet activating factor. Although a required nutrient for several animal species, choline is not currently designated as essential for humans. However, recent clinical studies show it to be essential for normal liver function. Additionally, a large body of evidence from the fields of molecular and cell biology shows that certain phospholipids play a critical role in generating second messengers for cell membrane signal transduction. This process involves a cascade of

reactions that translate an external cell stimulus such as a hormone or growth factor into a change in cell transport, metabolism, growth, function, or gene expression. Disruptions in phospholipid metabolism can interfere with this process and may underlie certain disease states such as cancer and Alzheimer's disease. These recent findings may be appropriate in the consideration of choline as an essential nutrient for humans.

Severe recurrent hepatic encephalopathy that responded to oral branched chain amino acids.

Chalasani N, Gitlin N. Division of Digestive Diseases, Emory University School of Medicine, Atlanta, Georgia 30322, USA.

Am J Gastroenterol. 1996 Jun;91(6):1266-8

Hepatic encephalopathy is a neuropsychiatric syndrome occurring in patients with acute or chronic liver disease. Its pathogenesis remains unclear; however, it appears to be multifactorial. There are several conventional treatments for this condition, such as lactulose, neomycin, and protein restriction. There is significant controversy regarding the role of branched chain amino acids in the treatment of chronic hepatic encephalopathy. We describe a patient who had hepatic encephalopathy secondary to Budd-Chairi syndrome and a mesoatrial shunt that failed vigorous conventional therapy. She required multiple hospitalizations for severe recurrent encephalopathy. The patient was considered for a colonic exclusion procedure for the management of intractable encephalopathy. However, branched amino acid therapy was instituted as a last measure before the contemplated surgery, and the patient's encephalopathy responded in dramatic fashion, and she remained free from encephalopathy during a prolonged follow-up.

The American Medical Association Encyclopedia of Medicine

Clayman, C.B.

1989. New York: Random House.

Early diagnosis and treatment of hepatocellular carcinoma.

Columbo, M.

Leadership Medica 2001 Jan (<http://info@leadershipmedica.com>).

Alpha-Lipoic acid protects against hemolysis of human erythrocytes induced by peroxy radicals.

Constantinescu A, Tritschler H, Packer L. Department of Molecular and Cell Biology, University of California Berkeley 94720.

Biochem Mol Biol Int. 1994 Jul;33(4):669-79

The azo initiator of peroxy radicals 2,2'-azobis (2-amidinopropane) dihydrochloride (AAPH) induces oxidative hemolysis in human erythrocytes and subsequent hemoglobin oxidation. Using the degree of hemolysis versus time as an indication of the oxidative damage it was found that i) both reduced and oxidized alpha-lipoic acid protected against oxidative damage; ii) simultaneous treatment of erythrocytes with ascorbate and dihydrolipoate or alpha-lipoate has a synergistic tendency to protect cells against hemolysis; iii) glutathione in combination with dihydrolipoic acid or alpha-lipoic acid has an additive effect on hemolysis protection. The spin trapping reagent 5,5-dimethyl-1-pyrroline N-oxide (DMPO) formed an adduct with the peroxy/alkoxy radicals produced by thermal decomposition of AAPH in the presence of oxygen. The formation of this adduct was prevented by reduced or oxidized lipoic acid, reduced glutathione or ascorbate. It is concluded that AAPH-peroxy radicals progressively damage the cells and the released hemoglobin is subsequently oxidized to methemoglobin which might further enhance the oxidative damage. The protective effect of antioxidants is exerted outside the cells by directly scavenging AAPH-alkoxy radicals.

Close relation between cirrhosis and gallstones: cross-sectional and longitudinal survey.

Conte D, Fraquelli M, Fornari F, Lodi L, Bodini P, Buscarini L. IRCCS Maggiore Hospital, Milan, Italy.
Gastrbia@imiucca.csi.unimi.it

Arch Intern Med. 1999 Jan 11;159(1):49-52

BACKGROUND: Increased gallstone prevalence and incidence in cirrhosis have already been reported in different series, including a limited number of patients with cirrhosis.

OBJECTIVE: To evaluate the frequency of gallstones and related risk factors in a large series of patients with cirrhosis.

PATIENTS AND METHODS: The cross-sectional study involved 1010 patients with cirrhosis related to alcohol abuse, chronic viral infection, or miscellaneous causes (42%, 48%, and 10%, respectively) in Child class A, B, or C (48%, 36%, and 16%, respectively). In the longitudinal study gallstone development was monitored ultrasonographically in 618 patients free of gallstones at enrollment.

RESULTS: The overall prevalence of gallstone(s) was 29.5% and increased significantly with age without differences according to sex or cause of cirrhosis. Multiple logistic regression analysis showed that only Child classes B and C were significantly related to a higher risk of gallstone (odds ratio, 1.63 for class C vs class A and 1.91 for class B vs class A; $P = .001$). During a mean \pm SD follow-up of 50 months \pm 9 months, 141 (22.8%) of 618 patients developed gallstone(s), with an estimated cumulative probability of 6.5%, 18.6%, 28.2%, and 40.9% at 2, 4, 6, and 8 years, respectively. Multivariate analysis showed that Child class (hazard ratio, 2.8 for class C vs class A and 1.8 for class B vs class A; $P = .002$ and $P = .001$, respectively) and high-body mass index (hazard ratio, 1.31; $P = .04$) carried a significantly greater risk of gallstone formation.

CONCLUSION: Cirrhosis per se represents a major risk factor for gallstones whose prevalence and incidence were far higher than those reported in a general population from the same area.

Who gets alcoholic liver disease: nature or nurture?

Day CP. Newcastle upon Tyne and Freeman Hospital. c.p.day@ncl.ac.uk

J R Coll Physicians Lond. 2000 Nov-Dec;34(6):557-62

The factors determining why fewer than 10% of drinkers develop advanced alcoholic liver disease remain largely unknown. There is a weak relationship between disease risk and the dose and pattern of alcohol consumed. Obesity increases the risk of all stages of alcoholic liver disease, probably reflecting the role of steatosis in the pathogenesis of more advanced disease. Women develop disease at a lower intake than men due, in part, to their lower volume of distribution for alcohol, but also potentially to increased gut permeability to endotoxin. Recent studies suggest a non-gender-linked genetic component to disease susceptibility and recent case-control studies have suggested that polymorphisms of genes encoding cytokines and other immunoregulatory molecules may exert a significant effect. The pattern of polymorphisms associated with risk suggests that antibody-mediated mechanisms play a role in disease pathogenesis. This has implications for treatment and for identifying high risk individuals at an early stage.

The effects of silymarin on experimental phalloidine poisoning.

Desplaces A, Choppin J, Vogel G, Trost W.

Arzneimittelforschung. 1975 Jan;25(1):89

The hepatoprotective action of silymarin, the active principle extracted from the fruit of *Silybum marianum* (L.) Gaertn., in animals (dogs, rabbits, rats, mice) intoxicated with phalloidine is evident, both after protective and curative treatment. A dose of 15 mg/kg of silymarin protects every animal when given 60 min before the toxin. When injected 10 min after phalloidine, a dose of 100 mg/kg of silymarin again provides total protection. However, as the time span between administration of the toxic substance and start of treatment increases, so the efficacy of silymarin decreases; after 30 min its curative effect is negligible. The histochemical and histoenzymological studies show that during intoxication of the mice by phalloidine, silymarin inhibits the effect of the toxic substance and regulates the functions of the hepatocyte, when given either 60 min before or 10 min after phalloidine.

Protective effect of N-acetylcysteine on rat liver cell membrane during methanol intoxication.

Dobrzynska I, Skrzydlewska E, Kasacka I, Figaszewski Z. Institute of Chemistry, University in Bialystok, Poland.

J Pharm Pharmacol. 2000 May;52(5):547-52

Methanol is oxidized in-vivo to formaldehyde and then to formate, and these processes are accompanied by the generation of free radicals. We have studied the effect of N-acetylcysteine on liver cell membrane from rats intoxicated with methanol (3.0 g/kg (-1)). Evaluation of the effect was achieved by several methods. Lipid peroxidation and surface charge density were measured. An ultrastructural study of the liver cells was undertaken. The concentration of marker enzymes of liver damage (alanine aminotransferase and aspartate aminotransferase) in blood serum was measured. Methanol administration caused an increase in lipid peroxidation products (approximately 30%) as well as in surface charge density (approximately 60%). This might have

resulted in the membrane liver cell damage visible under electron microscopy and a leak of alanine aminotransferase and aspartate aminotransferase into the blood (increase of approximately 70 and 50%, respectively). Ingestion of N-acetylcysteine with methanol partially prevented these methanol-induced changes. Compared with the control group, lipid peroxidation was increased by approximately 3% and surface charge density by approximately 30%. Alanine aminotransferase and aspartate aminotransferase activity increased by 9 and 8%, respectively, compared with the control group. The results suggested that N-acetylcysteine was an effective antioxidant in methanol intoxication. It may have efficacy in protecting free radical damage to liver cells following methanol intoxication.

Randomized controlled trial of silymarin treatment in patients with cirrhosis of the liver.

Ferenci P, Dragosics B, Dittrich H, Frank H, Benda L, Lochs H, Meryn S, Base W, Schneider B. 1st Department of Gastroenterology and Hepatology, University of Vienna, Austria.

J Hepatol. 1989 Jul;9(1):105-13

Silymarin, the active principle of the milk thistle *Silybum marianum*, protects experimental animals against various hepatotoxic substances. To determine the effect of silymarin on the outcome of patients with cirrhosis, a double blind, prospective, randomized study was performed in 170 patients with cirrhosis. 87 patients (alcoholic 46, non-alcoholic 41; 61 male, 26 female; Child A, 47; B, 37; C, 3; mean age 57) received 140 mg silymarin three times daily. 83 patients (alcoholic 45, non-alcoholic 38; 62 male, 21 female; Child A, 42; B, 32; C, 9; mean age 58) received a placebo. Non-compliant patients and patients who failed to come to a control were considered as 'drop outs' and were withdrawn from the study. All patients received the same treatment until the last patient entered had finished 2-years of treatment. The mean observation period was 41 months. There were 10 drop outs in the placebo group and 14 in the treatment group. In the placebo group, 37 (+2 drop outs) patients had died, and in 31 of these, death was related to liver disease. In the treatment group, 24 (+4 drop outs) had died, and in 18 of these, death was related to liver disease. The 4-year survival rate was 58 +/- 9% (S.E.) in silymarin-treated patients and 39 +/- 9% in the placebo group (P = 0.036). Analysis of subgroups indicated that treatment was effective in patients with alcoholic cirrhosis (P = 0.01) and in patients initially rated 'Child A' (P = 0.03). No side effects of drug treatment were observed. (ABSTRACT TRUNCATED AT 250 WORDS)

Motonuclear changes after cranial nerve injury and regeneration.

Fernandez E, Pallini R, Lauretti L, La Marca F, Scogna A, Rossi GF. Center for Research in Regeneration of the Nervous System, Catholic University Medical School, Rome, Italy.

Arch Ital Biol. 1997 Sep;135(4):343-51

Little is known about the mechanisms at play in nerve regeneration after nerve injury. Personal studies are reported regarding motonuclear changes after regeneration of injured cranial nerves, in particular of the facial and oculomotor nerves, as well as the influence that the natural molecule acetyl-L-carnitine (ALC) has on post-axotomy cranial nerve motoneuron degeneration after facial and vagus nerve lesions. Adult and newborn animal models were used. Massive motoneuron response after nerve section and reconstruction was observed in the motonuclei of all nerves studied. ALC showed to have significant neuroprotective effects on the degeneration of axotomized motoneurons. Complex quantitative, morphological and somatotopic nuclear changes occurred that sustain new hypotheses regarding the capacities of motoneurons to regenerate and the possibilities of new neuron proliferation. The particularities of such observations are described and discussed.

Protective antioxidant effect of vitamins C and E in streptozotocin induced diabetic rats.

Garg MC, Bansal DD. Department of Biochemistry, Panjab University, Chandigarh 160 014, India.

Indian J Exp Biol. 2000 Feb;38(2):101-4

We have investigated the protective effect of vitamin C and E together supplementation on oxidative stress and antioxidant enzyme activities in the liver of streptozotocin-induced diabetic rats, unsupplemented diabetic and control rats. We also determined the levels of both the vitamins and oxidative stress in plasma. Vitamin supplementation in diabetic rats lowered plasma and liver lipid peroxidation, normalised plasma vitamin C levels and raised vitamin E above normal levels. In liver, the activity of glutathione peroxidase was raised significantly and that of glutathione-S-transferase was normalised by vitamin supplementation in diabetic rats. The levels of lipid peroxidation products in plasma and liver of vitamin-supplemented diabetic rats and activities of antioxidant enzymes in liver suggest that these vitamins reduce lipid peroxidation by quenching free radicals.

Artischockenblatterextrakt: in vitro Nachweis einer Hemmwirkung auf die cholesterin-Biosynthese.

Gebhardt, R.

Med. Welt. 1995; 46: 393 5.

No Abstract Available

Protective effect of exogenous coenzyme Q in rats subjected to partial hepatic ischemia and reperfusion.

Genova ML, Bonacorsi E, D'Aurelio M, Formiggini G, Nardo B, Cuccomarino S, Turi P, Pich MM, Lenaz G, Bovina C. Department of Biochemistry G. Moruzzi, University of Bologna, Italy.

Biofactors. 1999;9(2-4):345-9

In a surgical model of liver ischemia lipid peroxidation occurs, as shown by increase of lipid peroxidation end products, endogenous CoQ9 is oxidized and mitochondrial respiration is lowered; however, pre-treatment of the rats by i.p. injection of CoQ10 for 14 days normalizes the above parameters, presumably by way of the observed high extent of reduction of the incorporated quinone; moreover, liver homogenates of the CoQ10-treated rats are more resistant than those of non-treated rats to oxidative stress induced by an azido free radical initiator. This preliminary study suggests that CoQ10 pre-treatment can be of beneficial effect against oxidative damage during liver surgery transplantation.

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Acetyl-L-carnitine fed to old rats partially restores mitochondrial function and ambulatory activity.

Hagen TM, Ingersoll RT, Wehr CM, Lykkesfeldt J, Vinarsky V, Bartholomew JC, Song MH, Ames BN. Department of Molecular and Cell Biology, University of California, Berkeley, CA 94720, USA.

Proc Natl Acad Sci U S A. 1998 Aug 4;95(16):9562-6

Mitochondrial function and ambulatory activity were monitored after feeding old rats acetyl-L-carnitine (ALCAR). Young (3-5 mo) and old (22-28 mo) rats were given a 1.5% (wt/vol) solution of ALCAR in their drinking water for 1 mo, were sacrificed, and their liver parenchymal cells were isolated. ALCAR supplementation significantly reverses the age-associated decline of mitochondrial membrane potential, as assessed by rhodamine 123 staining. Cardiolipin, which declines significantly with age, is also restored. ALCAR increases cellular oxygen consumption, which declines with age, to the level of young rats. However, the oxidant production per oxygen consumed, as measured by 2',7'-dichlorofluorescein fluorescence levels, is approximately 30% higher than in untreated old rats. Cellular glutathione and ascorbate levels were nearly 30% and 50% lower, respectively, in cells from ALCAR-supplemented old rats than in untreated old rats, further indicating that ALCAR supplementation might increase oxidative stress. Ambulatory activity in young and old rats was quantified as a general measure of metabolic activity. Ambulatory activity, defined as mean total distance traveled, in old rats is almost 3-fold lower than in young animals. ALCAR supplementation increases ambulatory activity significantly in both young and old rats, with the increase being larger in old rats. Thus, ALCAR supplementation to old rats markedly reverses the age-associated decline in many indices of mitochondrial function and general metabolic activity, but may increase oxidative stress.

Mitochondrial decay in aging. Reversal through supplementation of acetyl-L-carnitine and N-tert-butyl-alpha-phenyl-nitron.

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tory.hagen@orst.edu

Ann N Y Acad Sci. 1998 Nov 20;854:214-23

We show that mitochondrial function in the majority of hepatocytes isolated from old rats (24 mo) is significantly impaired. Mitochondrial membrane potential, cardiolipin levels, respiratory control ratio, and overall cellular O₂ consumption decline, and the level of oxidants increases. To examine whether dietary supplementation of micronutrients that may have become essential with age could reverse the decline in mitochondrial function, we supplemented the diet of old rats with 1% (w/v) acetyl-L-carnitine (ALCAR) in drinking water. ALCAR supplementation (1 month) resulted in significant increases in cellular respiration, mitochondrial membrane potential, and cardiolipin values. However, supplementation also increased the rate of oxidant production, indicating that the efficiency of mitochondrial electron transport had not improved. To counteract the potential increase in oxidative stress, animals were administered N-tert-butyl-alpha-phenyl-nitron (30 mg/kg) (PBN) with or without ALCAR. Results showed that PBN significantly lowered oxidant production as measured by 2,7'-dichlorofluorescein diacetate (DCFH), even when ALCAR was coadministered to the animals. Thus, dietary supplementation with ALCAR, particularly in combination with PBN, improves mitochondrial function without a significant increase in oxidative stress.

Antihepatotoxic actions of flavonolignans from *Silybum marianum* fruits.

Hikino H, Kiso Y, Wagner H, Fiebig M.

Planta Med. 1984 Jun;50(3):248-50

No Abstract Available

The effect of polyene phosphatidylcholine (Essentiale forte) in the treatment of liver steatosis and ultrasound findings?preliminary study. [Article in Czech]

Horejsova M, Urban J. II. interni klinika, Institutu postgradualniho vzdelavani ve zdravotnictvi, Praha.

Cas Lek Cesk. 1994 Jun 13;133(12):366-9

BACKGROUND. Steatosis of the liver is the most frequent diffuse liver disease and its detection increased markedly due to ultrasonography. The presence of lipid particles in hepatocytes alters the ultrastructure of cellular membranes. The damaged cell is unable to meet adequately the energy requirements of phospholipid synthesis, the latter being the basic component of cellular and subcellular membranes. Substitution of "essential" phospholipids plays an important role in their regeneration.

OBJECTIVE. The objective of the open trial without controls was to obtain preliminary information on the effectiveness of Essentiale forte cps. in the treatment of steatosis of the liver of varying etiology in a group of 30 women, focused on changes in the ultrasonic pictures and a parallel follow-up of laboratory findings and subjective feelings, to be followed subsequently by a placebo controlled double blind trial.

METHODS AND RESULTS. Ultrasonic examinations were made using a Hewlett-Packard apparatus (77065AR). The sonographic criterium of steatosis was the finding of a diffusely enhanced echogenicity of the liver parenchyma associated as a rule with varying degrees of hepatomegaly with a smooth rounded margin and readily apparent hepatic veins with a normal lumen. The preparation Essentiale forte, cps. Rhone-Poulenc Rorer Co., contains natural "essential" phospholipids, diglyceride esters of cholinephosphoric acid (enriched with unsaturated fatty acids (linolic, linoleic, oleic) 300 mg, vitamin B1 6 mg, vitamin B2 6 mg, vitamin B6 6 mg, vitamin B12 6 micrograms, nicotinamide 30 mg, vitamin E 6 mg. Six tablets per day (2 x 3 tablets) were administered for six months. The clinical, ultrasonic and laboratory examination were made at the onset of the trial and then after the second and sixth month. From the total number of 28 women who completed treatment in 29 % (8 woman) were free from sonographic signs of steatosis and only in 25 % (7 women) the finding remained unaltered. In the remainder the ultrasonic picture improved only partly, in 10 of 11 women (91 %) the non-homogeneity of the parenchyma disappeared, in 3 of 12 women (25 %) the conduction of acoustic signals improved. The authors recorded also regression of hepatomegaly from 12.9 +/- 1.5 cm to 11.4 +/- 1.0 cm (p < 0.0001). There was also a significant decline of laboratory values: ALT from 1.650 +/- 1.612 mu kat/l to 0.812 +/- 0.392 mu kat/l (p < 0.0014), AST from 1.308 +/- 1.341 mu kat/l to 0.613 +/- 0.206 mu kat/l (p < 0.0038), GMT from 2.525 +/- 3.374 mu kat/l to 0.976 +/- 0.727 mu kat/l (p < 0.0078). A statistically significant decline was also found in mean values of total bilirubin (p < 0.0316), cholesterol (p < 0.0129) and triglycerides (p < 0.001). In all patients subjective sensations improved (p < 0.05).

CONCLUSIONS. The authors provided evidence that in 53.6 % of patients the effect of six-month treatment with Essentiale forte was very good (improvement of all investigated parameters), partial in 42.9 % (improvement of laboratory findings and subjective complaints) and not quite satisfactory in 3.6 % (only improvement of subjective feelings).

Folate depletion and elevated plasma homocysteine promote oxidative stress in rat livers.

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J Nutr. 2001 Jan;131(1):33-8

This study was designed to determine whether nutritional folate depletion exerts hepatic oxidative stress in relation to elevated plasma homocysteine. To mimic various extents of folate depletion status in vivo, male Wistar rats were fed an amino acid-defined diet containing either 8 (control), 2, 0.5, or 0 mg folic acid/kg diet. After a 4-wk feeding period, the plasma and hepatic folate concentrations of the rats decreased significantly with each decrement of dietary folate. Folate depletion did not significantly affect two major liver antioxidants: reduced glutathione and alpha-tocopherol. Conversely, folate depletion decreased Cu-Zn superoxide dismutase and glutathione peroxidase activities, but had no effect on catalase activity in liver homogenates. Lipid peroxidation products, as measured by thiobarbituric acid-reactive substances, were significantly higher in livers of folate-depleted rats than in those of the controls. This occurrence of hepatic oxidative stress in folate-depleted rats was confirmed by demonstrating an increased susceptibility of livers of folate-depleted rats to lipid peroxidation induced by additional H₂O₂ or Fe (2+) treatments compared with the controls. Decreasing dietary folate intake resulted in graded increases in plasma homocysteine concentrations of folate-depleted rats. Elevated plasma homocysteine and decreased plasma and hepatic folate concentrations in folate-depleted rats were all strongly and significantly correlated with increased liver lipid peroxidation ($r > 0.58$, $P < 0.0003$). These data demonstrate that folate depletion and elevated plasma homocysteine promote oxidative stress in rat livers.

Regulation of methionine adenosyltransferase activity by the glutathione level in rat liver during ischemia-reperfusion.

Ito K, Miwa N, Hagiwara K, Yano T, Shimizu-Saito K, Goseki N, Iwai T, Horikawa S. Department of Surgery, Tsuchiura Kyodo Hospital, Tsuchiura 300-0053, Japan.

Surg Today. 1999;29(10):1053-8

Hepatic ischemia was induced by clamping the hepatic artery, portal vein, and bile duct. After 15 min of ischemia, the hepatic glutathione (GSH) content rapidly decreased. On the other hand, after the start of reperfusion, the hepatic GSH levels promptly increased and reached a peak at about 1 h, and thereafter decreased to a minimum level by 2 h. Under such conditions, we examined the changes in the methionine adenosyltransferase (MAT) activity in the liver. Though the time course of MAT activity was somewhat delayed compared with that of the hepatic GSH levels, both patterns were substantially similar during ischemia-reperfusion. In contrast to the changes in the MAT activity during ischemia-reperfusion, the levels of MAT protein were unchanged during these periods. When endogenous antioxidant coenzyme Q(10) (CoQ(10)) was administered to rats prior to ischemia, both the reduction in the MAT activity and hepatic GSH levels induced by ischemia-reperfusion were protected. Our findings suggest that CoQ(10) may posttranslationally regulate the MAT activity via the changes in the GSH level in the liver.

Preferential use of branched-chain amino acids as an energy substrate in patients with liver cirrhosis.

Kato M, Miwa Y, Tajika M, Hiraoka T, Muto Y, Moriwaki H. First Department of Internal Medicine, Gifu University School of Medicine.

Intern Med. 1998 May;37(5):429-34

We analyzed basal energy metabolism in 20 healthy volunteers and 41 cirrhotic patients by indirect calorimetry. Subjects were then given either glucose, branched-chain amino acids (BCAA) or fatty acids as an energy substrate. Resting energy expenditure (REE), nonprotein respiratory quotient (npRQ), and oxidation rates of glucose (% CHO), protein (% PRO) and fat (% FAT) were analyzed. REE and %FAT were significantly higher and % CHO and %PRO were significantly lower in cirrhosis than in controls. These changes correlated with disease severity. Glucose and BCAA were utilized efficiently as energy substrates and reduced %FAT in cirrhosis. Energy efficacy (increased energy expenditure/energy equivalent of the supplemented nutrient) was significantly higher in BCAA (96 +/- 16%) than in glucose (41 +/- 8%) ($p < 0.01$) and fatty acids (27 +/- 13%) ($p < 0.05$). Patients with cirrhosis have an increased energy requirement. BCAA seems to be the preferred substrate to meet this demand, because its energy efficacy is higher than glucose or fatty acids in cirrhosis.

Antiviral effect of flavonoids on human viruses.

Kaul TN, Middleton E Jr, Ogra PL.

J Med Virol. 1985 Jan;15(1):71-9

The effect of several naturally occurring dietary flavonoids including quercetin, naringin, hesperetin, and catechin on the infectivity and replication of herpes simplex virus type 1 (HSV-1), polio-virus type 1, parainfluenza virus type 3 (Pf-3), and respiratory syncytial virus (RSV) was studied in vitro in cell culture monolayers employing the technique of viral plaque reduction. Quercetin caused a concentration-dependent reduction in the infectivity of each virus. In addition, it reduced intracellular replication of each virus when monolayers were infected and subsequently cultured in medium containing quercetin. Preincubation of tissue culture cell monolayers with quercetin did not affect the ability of the viruses to infect or replicate in the tissue culture monolayers. Hesperetin had no effect on infectivity but it reduced intracellular replication of each of the viruses. Catechin inhibited the infectivity but not the replication of RSV and HSV-1 and had negligible effects on the other viruses. Naringin had no effect on either the infectivity or the replication of any of the viruses studied. Thus, naturally occurring flavonoids possess a variable spectrum of antiviral activity against certain RNA (RSV, Pf-3, polio) and DNA (HSV-1) viruses acting to inhibit infectivity and/or replication.

Alpha-lipoic acid supplementation: tissue glutathione homeostasis at rest and after exercise.

Khanna S, Atalay M, Laaksonen DE, Gul M, Roy S, Sen CK. Department of Physiology, Faculty of Medicine, University of Kuopio, 70211 Kuopio, Finland.

J Appl Physiol. 1999 Apr;86(4):1191-6

Antioxidant nutrients have demonstrated potential in protecting against exercise-induced oxidative stress. alpha-Lipoic acid (LA) is a proglutathione dietary supplement that is known to strengthen the antioxidant network. We studied the effect of intragastric LA supplementation (150 mg/kg, 8 wk) on tissue LA levels, glutathione metabolism, and lipid peroxidation in rats at rest and after exhaustive treadmill exercise. LA supplementation increased the level of free LA in the red gastrocnemius muscle and increased total glutathione levels in the liver and blood. The exercise-induced decrease in heart glutathione S-transferase activity was prevented by LA supplementation. Exhaustive exercise significantly increased thiobarbituric acid-reactive substance levels in the liver and red gastrocnemius muscle. LA supplementation protected against oxidative lipid damage in the heart, liver, and red gastrocnemius muscle. This study reports that orally supplemented LA is able to favorably influence tissue antioxidant defenses and counteract lipid peroxidation at rest and in response to exercise.

Silymarin inhibits the development of diet-induced hypercholesterolemia in rats.

Krecman V, Skottova N, Walterova D, Ulrichova J, Simanek V. Institute of Medical Chemistry, Medical Faculty, Palacky University, Olomouc, Czech Republic.

Planta Med. 1998 Mar;64(2):138-42

To study the ability of silymarin, a standardized mixture of antioxidant flavonolignans from the medicinal plant *Silybum marianum*, and of silybin, the main flavonolignan of silymarin, to inhibit the development of diet-induced hypercholesterolemia the rats were fed high cholesterol diet (HCD). Silymarin or silybin were given as dietary supplements, and their influences on serum cholesterol levels were compared to those of probucol, an antioxidant hypocholesterolemic drug. Anticholesterolemic effect of silymarin was parallel to that of probucol, and dose-dependent at dietary drug concentrations of 0.1-0.5-1.0% (w/w). However, in contradistinction to probucol, silymarin caused an increase in high density lipoprotein (HDL)-cholesterol and a decrease in liver cholesterol content, changes considered to be of benefit. In addition to its anticholesterolemic effect silymarin partially prevented the HCD-induced decrease in liver reduced glutathione, an endogenous antioxidant. Silybin was not so effective as silymarin suggesting that either other constituent(s) of silymarin may be responsible for its anticholesterolemic effect or the bioavailability of silybin alone might be lower than that of silybin as a compound of silymarin.

Subchronic inhalation toxicity of nitromethane and 2-nitropropane.

Lewis TR, Ulrich CE, Busey WM.

J Environ Pathol Toxicol. 1979 May-Jun;2(5):233-49

Nitromethane (NM) and 2-nitropropane (2-NP) are versatile compounds employed in a wide variety of industrial applications, thus providing ample opportunity for occupational exposure. The purpose of this study was to determine the subchronic inhalation

toxicity of NM and 2-NP in order to recommend acceptable exposure levels in the workplace. Fifty male rats and 15 male rabbits were exposed to either 98 ppm or 745 ppm of NM or 27 or 207 ppm of 2-NP 7 hours/day, 5 days/week, for periods up to 24 weeks. Fifty rats and 15 rabbits were exposed to filtered air for similar lengths of time and served as controls. Ten rats from each exposure and control group were sacrificed following 2 days, 10 days, 1 month, 3 months, and 6 months of exposure. Five rabbits from each exposure or control group were sacrificed at 1, 3, and 6 months of exposure. Effects relating to exposure to NM were decreased body weight gain in rats following 8 weeks of exposure to 745 ppm, and a thyroid effect evidenced by an increased thyroid weight and decreased serum thyroxin levels, most notable in rabbits. Liver weights were significantly elevated in rats exposed to 207 ppm of 2-NP for 1, 3, and 6 months. No exposure-related gross or microscopic alterations were seen in any of the tissues examined for rats and rabbits exposed to 745 and 98 ppm of NM and 27 ppm of 2-NP or in tissues of rabbits exposed to 207 ppm of 2-NP. Liver neoplasms were seen in all 10 rats killed following 6 months of exposure to 207 ppm of 2-NP, indicating that 2-NP is a potent carcinogen in the rat.

Inhibition of nitric oxide synthesis in primary cultured mouse hepatocytes by alpha-lipoic acid.

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Chem Biol Interact. 2000 Jan 3;124(1):53-60

Recent work shows that septic or endotoxic shock is associated with lipopolysaccharide and cytokine mixture-induced nitric oxide (NO) synthesis in liver. Here we found that DL-alpha-lipoic acid inhibited but other thiol-containing antioxidants such as glutathione and N-acetylcysteine enhanced lipopolysaccharide and cytokine mixture (referred as LPS/CM)-induced NO synthesis in hepatocytes. The inhibitory action of alpha-lipoic acid on hepatocyte NO synthesis was as potent as that of NG-monomethyl-L-arginine without obvious cytotoxicity. Deletion by diethylmaleate or inhibition by buthionine sulfoximine of intracellular glutathione caused a significant decrease in hepatocyte NO synthesis, implying that increased intracellular reduced glutathione levels could not be the reason for alpha-lipoic acid inhibited NO synthesis. alpha-Lipoic acid inhibition of NO synthesis seems to be from alpha-lipoic acid improved carbohydrate metabolism in hepatocytes. Since alpha-lipoic acid is an essential compound existing naturally in physiological systems, it may serve as both a research and therapeutic agent for sepsis.

Prevention and treatment of liver fibrosis based on pathogenesis.

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Alcohol Clin Exp Res. 1999 May;23(5):944-9

Multiple agents have been proposed for the prevention and treatment of fibrosis. S-adenosylmethionine was reported to oppose CCl₄-induced fibrosis in the rat, to attenuate the consequences of the ethanol-induced oxidative stress, and to decrease mortality in cirrhotics. Anti-inflammatory medications and agents that interfere with collagen synthesis, such as inhibitors of prolyl-4-hydroxylase and antioxidants, are also being tested. In nonhuman primates, polyenylphosphatidylcholine (PPC), extracted from soybeans, protected against alcohol-induced fibrosis and cirrhosis and prevented the associated hepatic phosphatidylcholine (PC) depletion by increasing 18:2 containing PC species; it also attenuated the transformation of stellate cells into collagen-producing transitional cells. Furthermore, it increased collagen breakdown, as shown in cultured stellate cells enriched with PPC or pure dilinoleoyl PC, the main PC species present in the extract. Because PPC and dilinoleoyl PC promote the breakdown of collagen, there is reasonable hope that this treatment may be useful for the management of fibrosis of alcoholic, as well as nonalcoholic, etiologies and that it may affect not only the progression of the disease, but may also reverse pre-existing fibrosis, as demonstrated for CCl₄-induced cirrhosis in the rat and as presently tested in an ongoing clinical trial.

Protective effect of melatonin against oxidative stress induced by ligation of extra-hepatic biliary duct in rats: comparison with the effect of S-adenosyl-L-methionine.

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J Pineal Res. 2000 Apr;28(3):143-9

In the present research, we studied the effect of the administration of melatonin or S-adenosyl-L-methionine (S-AMe) on oxidative stress and hepatic cholestasis produced by double ligation of the extra-hepatic biliary duct (LBD) in adult male Wistar rats. Hepatic oxidative stress was evaluated by the changes in the amount of lipid peroxides and by the reduced glutathione content (GSH) in lysates of erythrocytes and homogenates of hepatic tissue. The severity of the cholestasis and hepatic injury were determined by the changes in the plasma enzyme activities of alanine aminotransferase (ALT), aspartate aminotransferase

(AST), alkaline phosphatase (AP), g-glutamyl-transpeptidase (GGT), and levels of albumin, total bilirubin (TB) and direct bilirubin (DB). Either melatonin or S-AMe were administered daily 3 days before LBD, and for 10 days after biliary obstruction. LBD caused highly significant increases in plasma enzyme activities and in bilirubin and lipid peroxides levels in erythrocytes and hepatic tissue. At the same time, this procedure produced a notable decrease in the GSH pools in these biological media. Both melatonin and S-AMe administration were effective as antioxidants and hepatoprotective substances, although the protective effects of melatonin were superior; it prevented the GSH decrease and reduced significantly the increases in enzyme activities and lipid peroxidation products produced by biliary ligation. S-AMe did not modify the increased GGT activity nor did it decrease greatly the TB levels (43% melatonin vs. 14% S-AMe). However, S-AMe was effective in preventing the loss of GSH in erythrocytes and hepatic tissue, as was melatonin. The obtained data permit the following conclusions. First, the LBD models cause marked hepatic oxidative stress. Second, the participation of free radicals of oxygen in the pathogenesis and severity of cholestasis produced by the acute obstruction of the extra-hepatic biliary duct is likely. Third, the results confirm the function of S-AMe as an antioxidant and hepatoprotector. Finally, melatonin is far more potent and provides superior protection as compared to S-AMe. Considering the decrease in oxidative stress and the intensity of cholestasis, these findings have interesting clinical implications for melatonin as a possible therapeutic agent in biliary cholestasis and parenchymatous liver injury.

Age-associated decline in ascorbic acid concentration, recycling, and biosynthesis in rat hepatocytes-reversal with R alpha lipoic acid supplementation.

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FASEB J. 1998 Sep;12(12):1183-9

Ascorbic acid recycling from dehydroascorbic acid and biosynthesis from gulono-1,4-lactone were used as measures of cellular response capacity to increased oxidative stress induced by tert-butylhydroperoxide. The hepatic ascorbic acid concentration was 54% lower in cells from old rats when compared to cells isolated from young rats ($P < 0.0005$). Freshly isolated hepatocytes from old rats exhibited a significantly decreased ascorbic acid recycling capacity in response to oxidative stress ($P < 0.005$) compared to cells from young rats. Ascorbic acid synthesis in these cells from old animals was unaffected by various concentrations of tert-butylhydroperoxide, but amounted to only approximately half of the biosynthetic rate when compared to cells from young animals ($P < 0.001$). Cells from young animals were not significantly affected by the tert-butylhydroperoxide treatments. The results demonstrate a declining ability with age to respond to increased oxidative stress. (R)-alpha-Lipoic acid, a mitochondrial coenzyme, is a powerful antioxidant. A two-week dietary supplementation of old animals with 0.5% (R)-alpha-lipoic acid prior to cell isolation almost completely reversed the age-associated effects on ascorbic acid concentration ($P < 0.0001$), recycling ($P < 0.05$) and biosynthesis after oxidative stress. These results provide further evidence for the potential of alpha-lipoic acid in treatment of diseases related to oxidative stress. Furthermore, the study extends the value of ascorbic acid as a biomarker of oxidative stress.

Polyenylphosphatidylcholine attenuates non-alcoholic hepatic fibrosis and accelerates its regression.

Ma X, Zhao J, Lieber CS. Alcohol Research and Treatment Center, Bronx V.A. Medical Center, NY 10468, USA.

J Hepatol. 1996 May;24(5):604-13

BACKGROUND/AIMS: Polyenylphosphatidylcholine protects against alcoholic cirrhosis in the baboon. This study assesses whether the antifibrotic effect also pertains to a species other than the baboon and to agents other than alcohol.

METHODS: Rats were injected with either CC14 in peanut oil or peanut oil alone, and pair-fed nutritionally adequate liquid diets, with or without polyenylphosphatidylcholine. Other rats were injected with heterologous albumin instead of CC14. To assess whether polyenylphosphatidylcholine is active on established fibrosis, rats were also given CC14 for 8 weeks, and then divided into two groups and pair-fed a diet with or without polyenylphosphatidylcholine.

RESULTS: After 8 weeks of CC14, the animals were sacrificed; chromotrope aniline blue and Sirius red stains of liver revealed fibrosis or cirrhosis in animals given CC14 alone, whereas the effect was attenuated in the polyenylphosphatidylcholine-supplemented animals. Hepatic collagen content was decreased by 25 to 32% ($p < 0.05$) and serum ALT and AST were significantly less increased. The expression of liver collagen type I mRNA was significantly increased in CC14 treated rats and was not significantly affected by polyenylphosphatidylcholine although there was a trend towards a lesser increase. Polyenylphosphatidylcholine also attenuated liver fibrosis produced by the injection of heterologous albumin. CC14-induced liver fibrosis regressed more rapidly in polyenylphosphatidylcholine-treated animals than controls, both histologically and by measurement of collagen ($p < 0.05$).

CONCLUSIONS: Polyenylphosphatidylcholine (a) attenuates hepatic fibrosis induced by CC14 or human albumin in rats; and (b)

accelerates the regression of pre-existing fibrosis.

Effects of Cynara scolymus extracts on the regeneration of rat liver.

Maros T, Racz G, Katonai B, Kovacs VV.

Arzneimittelforschung. 1966 Feb;16(2):127-9

No Abstract Available

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ABSTRACTS

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Attenuation of alcohol-induced apoptosis of hepatocytes in rat livers by polyenylphosphatidylcholine (PPC).

Mi LJ, Mak KM, Lieber CS. Alcohol Research and Treatment Center, Bronx Veterans Affairs Medical Center, New York, New York 10468, USA.

Alcohol Clin Exp Res. 2000 Feb;24(2):207-12

BACKGROUND: Alcohol consumption increases apoptosis of hepatocytes. This effect appears to be mediated by the induction of hepatic cytochrome P-4502E1(CYP2E1) and its generation of free radicals, which results in an enhanced lipid peroxidation that initiates apoptosis. Because polyenylphosphatidylcholine (PPC), a soybean extract rich in polyunsaturated phosphatidylcholines, decreases the induction of ethanol-specific CYP2E1 and opposes oxidative stress, we hypothesized that PPC supplementation may attenuate hepatocyte apoptosis caused by ethanol ingestion.

METHODS: Twenty-eight male Sprague Dawley rats were pair-fed Lieber-DeCarli liquid diets containing 36% of energy as alcohol or an isocaloric amount of carbohydrate for 28 days. Half of the rats were given PPC (3 g/liter), whereas the other half received the same amount of linoleate (as safflower oil) and of choline as the bitartrate. An additional dose of alcohol (3 g/kg) was given intragastrically 90 min before the livers were removed. We assessed apoptosis in formalin-fixed, paraffin-embedded liver sections by using the TUNEL (terminal transferase dUTP nick end labeling) assay. Apoptotic hepatocytes were identified by positive TUNEL staining in conjunction with condensation of nucleoplasm or margination of chromatin. In each rat, 20,000 to 60,000 hepatocytes were counted by light microscopy by using Image-Pro Plus computer software, and the incidence of apoptosis was expressed as the percentage of total hepatocytes.

RESULTS: Alcohol feeding resulted in a 4.5-fold increase in apoptosis of hepatocytes compared to pair-fed control rats; PPC supplementation decreased the alcohol-induced apoptosis to less than half. No difference in the incidence of apoptosis between the control and PPC-supplemented rats was found in the absence of alcohol. Apoptosis was distributed randomly in the liver lobules of the rats fed the control diet, whereas the alcohol-induced apoptosis was significantly increased in the perivenular area. PPC supplementation strikingly reduced this effect.

CONCLUSIONS: PPC attenuates alcohol-induced apoptosis of hepatocytes; this effect may provide a mechanism for PPC's protection against liver injury, possibly in association with its antioxidative action via the down-regulation of ethanol-mediated CYP2E1 induction.

Alcoholic hepatitis.

Mihas, A.A., Heuman, D.M.

eMed. J. 2002 Jan 2; 3(1) (<http://www.emedicine.com/med/topic101.htm>).

Deaths: preliminary data for 2000.

Minino, A.M., Smith, B.L.

Natl. Vital Stat. Rep. 2001 Oct 9; 49(12): 1-40.

Effect of malotilate on ethanol-induced gastric mucosal damage in capsaicin-pretreated rats.

Mirossay L, Kohut A, Mojzis J. Department of Pharmacology, Faculty of Medicine, Safarik University, Kosice, Slovak Republic. mirossay@central.medic.upjs.sk

Physiol Res. 1999;48(5):375-81

We studied the role of afferent sensory neurons in malotilate-mediated gastric mucosal protection. Intact and capsaicin sensory-denervated rats were used in the experiments. Gross gastric mucosal injury was assessed and evaluated as a main criterion of the gastroprotective effect of the tested substances. Besides malotilate, methyl-prostaglandin E2 was applied alone or in combination with malotilate to compare the effects and the mechanism of action of both substances. The results revealed that both malotilate as well as methyl-prostaglandin E2 exerted a significant protective action on 96% ethanol-induced gastric mucosal damage. However, there were no significant differences between intact and capsaicin-denervated rats. Only the use of 50% ethanol as a milder mucosal irritating agent resulted in significant differences in both groups of animals. We propose that malotilate (like methyl-prostaglandin E2) has a gastroprotective effect on ethanol-induced gastric mucosal injury. This effect is partly dependent on the sensory nervous system and the combination of both above substances has an additive effect.

Gastroprotective effect of malotilate in indomethacin- and ethanol-induced gastric mucosal damage.

Mirossay L, Mojzis J, Sallingova Z, Bodnar J, Benicky M, Boor A, Kohut A. Department of Pharmacology, Faculty of Medicine, Safarik University, Kosice, Slovak Republic.

Physiol Res. 1996;45(5):405-11

Malotilate as a synthetic substance shares comparable hepatoprotective properties with various flavonoids. The gastroprotective effect of some flavonoids prompted us to ascertain the similar effectiveness of malotilate. The possible gastroprotectivity was examined in gastric mucosal damage in rats induced by indomethacin (20 mg.kg⁻¹) or ethanol (96%). Oral pretreatment with malotilate (25, 50, 100, 200 and 400 mg.kg⁻¹) reduced the extent of lesions induced by both indomethacin and ethanol. Histological analyses also revealed a mitigating effect on the severity of gastric mucosal lesions. Similar results were obtained in the group of rats pretreated with 5 mg.kg⁻¹ indomethacin followed by oral administration of 96% ethanol. This finding suggests that the effect of malotilate on rat gastric mucosa is independent of endogenous prostaglandin production.

Peroxisome proliferator-activated receptors and hepatic stellate cell activation.

Miyahara T, Schrum L, Rippe R, Xiong S, Yee HF Jr, Motomura K, Anania FA, Willson TM, Tsukamoto H. Departments of Medicine and Pathology, Keck School of Medicine of the University of Southern California, Los Angeles, California 90033, USA.

J Biol Chem. 2000 Nov 17;275(46):35715-22

The present study examined the roles of peroxisome proliferator-activated receptors (PPAR) in activation of hepatic stellate cells (HSC), a pivotal event in liver fibrogenesis. RNase protection assay detected mRNA for PPAR γ 1 but not that for the adipocyte-specific γ 2 isoform in HSC isolated from sham-operated rats, whereas the transcripts for neither isoforms were detectable in HSC from cholestatic liver fibrosis induced by bile duct ligation (BDL). Semi-quantitative reverse transcriptase-polymerase chain reaction confirmed a 70% reduction in PPAR γ mRNA level in HSC from BDL. Nuclear extracts from

BDL cells showed an expected diminution of binding to PPAR-responsive element, whereas NF-kappaB and AP-1 binding were increased. Treatment of cultured-activated HSC with ligands for PPARgamma (10 microm 15-deoxy-Delta(12,14)-PGJ(2) (15dPGJ(2)); 0.1 approximately 10 microm BRL49653) inhibited DNA and collagen synthesis without affecting the cell viability. Suppression of HSC collagen by 15dPGJ(2) was abrogated 70% by the concomitant treatment with a PPARgamma antagonist (GW9662). HSC DNA and collagen synthesis were inhibited by WY14643 at the concentrations known to activate both PPARalpha and gamma (>100 microm) but not at those that only activate PPARalpha (<10 microm) or by a synthetic PPARalpha-selective agonist (GW9578). 15dPGJ(2) reduced alpha1(I) procollagen, smooth muscle alpha-actin, and monocyte chemotactic protein-1 mRNA levels while inducing matrix metalloproteinase-3 and CD36. 15dPGJ(2) and BRL49653 inhibited alpha1(I) procollagen promoter activity. Tumor necrosis factor alpha (10 ng/ml) reduced PPARgamma mRNA, and this effect was prevented by the treatment with 15dPGJ(2). These results demonstrate that HSC activation is associated with the reductions in PPARgamma expression and PPAR-responsive element binding in vivo and is reversed by the treatment with PPARgamma ligands in vitro. These findings implicate diminished PPARgamma signaling in molecular mechanisms underlying activation of HSC in liver fibrogenesis and the potential therapeutic value of PPARgamma ligands for liver fibrosis.

Extending effects of phospholipids, cholesterol, and ethanolamines on survival of adult rat hepatocytes in serum-free primary culture.

Miyazaki M, Bai L, Namba M. Department of Pathology, Okayama University Medical School, Japan.

Res Exp Med (Berl). 1991;191(2):77-83

In a serum-free primary culture, membrane lipids, such as phosphatidylethanolamine, phosphatidylcholine, or cholesterol, effectively prolonged the survival of adult rat hepatocytes. These lipids effectively prevented hepatocytes from morphologic degeneration observed in control cultures, such as enlargement of cell surface, degranulation of cytoplasm, and multinucleation. The maintenance effect of phospholipid precursors, ethanolamine, or phosphoethanolamine on the primary-cultured hepatocytes was similar to that of phospholipids. These effects appear to be due to stabilization of the plasma membrane.

Acetyl-L-carnitine treatment stimulates oxygen consumption and biosynthetic function in perfused liver of young and old rats.

Mollica MP, Iossa S, Soboll S, Liverini G. Department of General and Environmental Physiology, University of Naples Federico II, Italy.

Cell Mol Life Sci. 2001 Mar;58(3):477-84

The effect of treatment with acetyl-L-carnitine on hepatic mitochondrial respiration and biosynthetic function in perfused liver from young (90 days) and old (22-24 months) rats was studied. Rats were given a 1.5% (w/v) solution of acetyl-L-carnitine in their drinking water for 1 month and oxygen consumption together with the rate of gluconeogenesis, urea synthesis, and ketogenesis with and without added substrates were measured in perfused liver. Mitochondrial oxygen consumption was also assessed in liver homogenate and isolated mitochondria to determine the maximal capacity for oxidative phosphorylation. Acetyl-L-carnitine treatment almost completely restored the age-dependent decline in oxygen consumption, gluconeogenesis, urea synthesis, and ketogenesis found in perfused liver of old rats to the levels found in young rats. In addition, acetyl-L-carnitine treatment increased oxygen consumption and biosynthetic function in perfused liver from young rats. After acetyl-L-carnitine treatment, we found detectable 3-oxoacyl-CoA-transferase activity associated with a consumption of ketone bodies in young and old rats. Finally, oxygen consumption measured in homogenate and isolated mitochondria did not change with age and acetyl-L-carnitine treatment. Our results show that in perfused liver, acetyl-L-carnitine treatment slows the age-associated decline in mitochondrial respiration and biosynthetic function. In addition, treatment of young rats with acetyl-L-carnitine has a stimulating effect on liver metabolism, probably through an increase in ATP production.

Polyenylphosphatidylcholine attenuates alcohol-induced fatty liver and hyperlipemia in rats.

Navder KP, Baraona E, Lieber CS. Alcohol Research and Treatment Center, Bronx Veterans Affairs Medical Center, New York, New York, USA.

J Nutr. 1997 Sep;127(9):1800-6

Chronic administration of a soybean-derived polyenylphosphatidylcholine (PPC) extract prevents the development of cirrhosis in alcohol-fed baboons. To assess whether this phospholipid also affects earlier changes induced by alcohol consumption (such as fatty liver and hyperlipemia), 28 male rat littermates were pair-fed liquid diets containing 36% of energy either as ethanol or as additional carbohydrate for 21 d, and killed 90 min after intragastric administration of the corresponding diets. Half of the rats were given PPC (3 g/l), whereas the other half received the same amount of linoleate (as safflower oil) and choline (as bitartrate

salt). PPC did not affect diet or alcohol consumption [15.4 +/- 0.5 G/(kg.d)], but the ethanol-induced hepatomegaly and the hepatic accumulation of lipids (principally triglycerides and cholesterol esters) and proteins were about half those in rats not given PPC. The ethanol-induced postprandial hyperlipemia was lower with PPC than without, despite an enhanced fat absorption and no difference in the level of plasma free fatty acids. The attenuation of fatty liver and hyperlipemia was associated with correction of the ethanol-induced inhibition of mitochondrial oxidation of palmitoyl-1-carnitine and the depression of cytochrome oxidase activity, as well as the increases in activity of serum glutamate dehydrogenase and aminotransferases. Thus, PPC attenuates early manifestations of alcohol toxicity, at least in part, by improving mitochondrial injury. These beneficial effects of PPC at the initial stages of alcoholic liver injury may prevent or delay the progression to more advanced forms of alcoholic liver disease.

Oxidation of LDL in baboons is increased by alcohol and attenuated by polyenylphosphatidylcholine.

Navder KP, Baraona E, Leo MA, Lieber CS. Alcohol Research and Treatment Center, Bronx Veterans Affairs Medical Center and Mount Sinai School of Medicine, New York, NY 10468, USA.

J Lipid Res. 1999 Jun;40(6):983-7

Alcohol taken in moderation may prevent atherosclerosis, whereas heavy drinking has the opposite effect, in part by promoting oxidation of low density lipoproteins (LDL), a pathogenetic factor in atherogenesis. We assess here: 1) whether similar alterations can be reproduced in baboons fed 50% of energy as ethanol (the average intake of alcoholics) for 7- 8 years, and 2) whether such alterations are affected by supplementation with polyenylphosphatidylcholine (PPC), a mixture of polyunsaturated phosphatidylcholines, shown to prevent alcoholic fatty liver, fibrosis, and cirrhosis. Ten animals were given the ethanol-containing diet and ten were pair-fed isocaloric control diets. In half of the pairs, the diets were supplemented with 2.8 g of polyenylphosphatidylcholine/1000 kcal. Alcohol feeding increased LDL-lipoperoxides and made LDL-proteins more negatively charged, changes that were attenuated or prevented by PPC. The oxidizability of LDL was determined in vitro by the formation of conjugated dienes after oxidation with copper. Alcohol shortened the lag time (which measures LDL antioxidant capacity); this effect was normalized by PPC supplementation. By contrast, PPC produced no changes in the controls. Thus polyenylphosphatidylcholine, by markedly attenuating the ethanol-induced increase in LDL oxidation, opposes one of the effects whereby alcohol promotes atherosclerosis.

Effect of polyunsaturated phosphatidylcholine on immune mediated hepatocyte damage.

Neuberger J, Hegarty JE, Eddleston AL, Williams R.

Gut. 1983 Aug;24(8):751-5

Studies were carried out to investigate the mechanisms underlying the reduction of hepatocellular necrosis observed when polyunsaturated phosphatidylcholine was administered to patients with HBsAg negative chronic active hepatitis. After oral administration of the agent, the susceptibility of rabbit hepatocytes to both antibody dependent cell mediated cytotoxicity and mitogen induced lymphocyte cytotoxicity was substantially reduced. Short term in vitro incubation of either the hepatocytes or lymphocytes with polyunsaturated phosphatidylcholine had no effect on antibody dependent cell mediated cytotoxicity. As it has been shown that orally administered polyunsaturated phosphatidylcholine can be incorporated into the liver cell membrane, it is possible that polyunsaturated phosphatidylcholine exerts its effect by blocking the interaction between immune effector cells and hepatocytes.

Hepatitis C.

NIDA.

NIDA Community Drug Alert Bulletin 2002 Feb 21. Bethesda, MD: National Institute on Drug Abuse/National Institutes of Health/Department of Health and Human Services.

Cirrhosis of the Liver

NIDDK.

2000 Jan. NIH Publ. No. 00-1134. Bethesda, MD: National Institute of Diabetes and Digestive and Kidney Diseases/National Institutes of Health.

How is cirrhosis diagnosed?

Nidus.

Well-Connected Report: Cirrhosis 1999a Mar. New York: Nidus Information Services (www.well-connected.com).

What are the primary treatments for cirrhosis?

Nidus.

Well-Connected Report: Cirrhosis 1999b Mar. New York: Nidus Information Services (www.well-connected.com).

Effect of dietary zinc deficiency on alkaline phosphatase and nucleic acids in rats.

Okegbile EO, Odunuga O, Oyewo A. Department of Biochemistry, Ogun State University, Ago-Iwoye, Nigeria.

Afr J Med Med Sci. 1998 Sep-Dec;27(3-4):189-92

Weanling male albino rats were randomly allotted to zinc deficient fed (ZnDF) pair-fed (ZnPF) or ad libitum-fed (ZnAL) dietary treatments. The rats were fed diets with either low (5 micrograms/g) or adequate (100 micrograms/g) zinc for 28 days. Zinc deficiency significantly reduced growth rate by 60% and was associated with a significantly low feed intake when compared with ZnPF and ZnAL groups. DNA and RNA contents of the liver were used as indication of nitrogen metabolism. DNA content was similar for both ZnPF and ZnAL groups (1.90 and 2.20 mg/g wet weight, respectively), but significantly different from ZnDF (1.42 mg/g wet weight). Liver RNA values of ZnAL, ZnPF and ZnDF groups similarly varied (25.0, 20.2 and 14.8 mg/g wet weight, respectively). Liver, muscle, spleen, femur and serum zinc concentrations were lowest in rats fed ZnDF relative to adequate zinc levels. The levels of the alkaline phosphatase activity was highest in the serum and lowest in the brain (spleen value was greater than that of the liver). Alkaline phosphatase activity was similar in ZnAL and ZnPF groups, but significantly different from ZnDF. In conclusion, the constitutively expressed growth rate, DNA level, RNA level, organ/serum zinc contents and alkaline phosphatase activities were markedly affected by zinc deficiency in rats.

Antioxidant properties of lipoic acid and its therapeutic effects in prevention of diabetes complications and cataracts.

Packer L. Department of Molecular and Cell Biology, University of California at Berkeley 94720.

Ann N Y Acad Sci. 1994 Nov 17;738:257-64

No Abstract Available

Neuroprotection by the metabolic antioxidant alpha-lipoic acid.

Packer L, Tritschler HJ, Wessel K. Department of Molecular and Cell Biology, University of California, Berkeley 94720-3200, USA.

Free Radic Biol Med. 1997;22(1-2):359-78

Reactive oxygen species are thought to be involved in a number of types of acute and chronic pathologic conditions in the brain and neural tissue. The metabolic antioxidant alpha-lipoate (thioctic acid, 1, 2-dithiolane-3-pentanoic acid; 1, 2-dithiolane-3 valeric acid; and 6, 8-dithiooctanoic acid) is a low molecular weight substance that is absorbed from the diet and crosses the blood-brain barrier. alpha-Lipoate is taken up and reduced in cells and tissues to dihydrolipoate, which is also exported to the extracellular medium; hence, protection is afforded to both intracellular and extracellular environments. Both alpha-lipoate and especially dihydrolipoate have been shown to be potent antioxidants, to regenerate through redox cycling other antioxidants like vitamin C and vitamin E, and to raise intracellular glutathione levels. Thus, it would seem an ideal substance in the treatment of oxidative brain and neural disorders involving free radical processes. Examination of current research reveals protective effects of these compounds in cerebral ischemia-reperfusion, excitotoxic amino acid brain injury, mitochondrial dysfunction, diabetes and diabetic neuropathy, inborn errors of metabolism, and other causes of acute or chronic damage to brain or neural tissue. Very few neuropharmacological intervention strategies are currently available for the treatment of stroke and numerous other brain disorders involving free radical injury. We propose that the various metabolic antioxidant properties of alpha-lipoate relate to its possible therapeutic roles in a variety of brain and neuronal tissue pathologies: thiols are central to antioxidant defense in brain and other tissues. The most important thiol antioxidant, glutathione, cannot be directly administered, whereas alpha-lipoic acid can. In vitro, animal, and preliminary human studies indicate that alpha-lipoate may be effective in numerous neurodegenerative disorders.

The effect of aging and acetyl-L-carnitine on the pyruvate transport and oxidation in rat heart mitochondria.

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FEBS Lett. 1999 Jul 9;454(3):207-9

The effect of aging and acute treatment with acetyl-L-carnitine on the pyruvate transport and oxidation in rat heart mitochondria was studied. The activity of the pyruvate carrier as well as the rates of pyruvate-supported respiration were both depressed (around 40%) in heart mitochondria from aged rats, the major decrease occurring during the second year of life. Administration of acetyl-L-carnitine to aged rats almost completely restored the rates of these metabolic functions to the level of young control rats. This effect of acetyl-L-carnitine was not due to changes in the content of pyruvate carrier molecules. The heart mitochondrial content of cardiolipin, a key phospholipid necessary for mitochondrial substrate transport, was markedly reduced (approximately 40%) in aged rats. Treatment of aged rats with acetyl-L-carnitine reversed the age-associated decline in cardiolipin content. As the changes in cardiolipin content were correlated with changes in rates of pyruvate transport and oxidation, it is suggested that acetyl-L-carnitine reverses the age-related decrement in the mitochondrial pyruvate metabolism by restoring the normal cardiolipin content.

Carnitine: an essential nutrient?

Plawecki, K.

Nutrition Notes 2001 Sep. Northbrook, IL: Weeks Publishing.

Alpha-lipoic acid supplementation prevents symptoms of vitamin E deficiency.

Podda M, Tritschler HJ, Ulrich H, Packer L. Department of Molecular and Cell Biology, University of California at Berkeley, 94720-3200.

Biochem Biophys Res Commun. 1994 Oct 14;204(1):98

alpha-Lipoic acid, an essential cofactor in mitochondrial dehydrogenases, has recently been shown to be a potent antioxidant in vitro, as well as being capable of regenerating vitamin E in vitro. In this study, using a new animal model for rapid vitamin E deficiency in adult animals and a new technique for tissue extraction of oxidized and reduced alpha-lipoic acid, we examined the antioxidant action of alpha-lipoic acid in vivo. Vitamin E-deficient adult hairless mice displayed obvious symptoms of deficiency within five weeks, but if the diet was supplemented with alpha-lipoic acid the animals were completely protected. At five weeks on a vitamin E-deficient diet animals exhibited similar decreases in tissue vitamin E levels, whether supplemented or unsupplemented with alpha-lipoic acid: vitamin E levels in liver, kidney, heart, and skin decreased 70 to 85%; levels in brain decreased only 25%. These data show that there was no effect of alpha-lipoic acid supplementation on vitamin E tissue concentrations, arguing against a role for alpha-lipoic acid in regenerating vitamin E in vivo.

Dilinoleoylphosphatidylcholine decreases hepatic stellate cell activation.

Poniachik J, Baraona E, Zhao J, Lieber CS. Alcohol Research and Treatment Center, Bronx Veterans Affairs Medical Center, Bronx, NY 10468, USA.

J Lab Clin Med. 1999 Apr;133(4):342-8

The prevention of cirrhosis in alcohol-fed baboons by the administration of a soybean extract-43% to 50% of which was dilinoleoyl-phosphatidylcholine (DLPC) and 24% of which was 1,palmitoyl 2,linoleoyl-phosphatidylcholine (PLPC)-was associated with a significant reduction in the number of stellate cells transformed to myofibroblast-like cells. To study whether these two major phospholipids affect the similar transformation that occurs by culturing stellate cells on uncoated plastic, we assessed their effects on proliferation (by (methyl-3H)-thymidine incorporation into DNA), expression of alpha-smooth muscle actin and type I procollagen (by densitometry of Western blots), and collagen synthesis (by incorporation of tritiated proline into collagenase-digestible proteins). These manifestations of stellate cell activation were decreased by 10 micromol/L DLPC but not by 10 micromol/L PLPC when compared with controls incubated either with 17 mmol/L ethanol (used as solvent for the phospholipids) or without addition. These agents did not affect cell viability, contamination with other cells, or the capacity of stellate cells to synthesize protein. Thus DLPC specifically decreases the in vitro activation of stellate cells, as judged by the decreases in proliferative activity, alpha-smooth muscle actin and procollagen I expressions, and collagen synthesis, whereas PLPC did not show such effects. alpha-Procollagen (type I) mRNA was not affected by DLPC, suggesting a post-translational effect. The reduction in the activation of hepatic stellate cells by DLPC may be responsible for, or at least contribute to, the

prevention of fibrosis by the polyenylphosphatidylcholine mixture administered in vivo.

(+)-Cyanidanol-3 changes functional properties of collagen.

Pontz BF, Krieg T, Muller PK.

Biochem Pharmacol. 1982 Nov 15;31(22):3581-9

About 6-7 (+)-cyanidanol-3 molecules are bound per collagen alpha-chain. The (+)-cyanidanol-3 treated collagen contains an increased number of pepsin-resistant cross-links, is less susceptible to attack by mammalian collagenase, has a higher shrinkage temp and forms unstructured aggregates. Cell and organ culture studies show that these biological systems produce less protein and collagen in the presence of (+)-cyanidanol-3 and that the newly synthesized collagen is less soluble.

Transection of the oesophagus for bleeding oesophageal varices.

Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R.

Br J Surg. 1973 Aug;60(8):646-9

No Abstract Available

S-adenosyl-L-methionine for alcoholic liver diseases.

Rambaldi A, Gluud C. Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen University Hospital, H:S Rigshospitalet, Blegdamsvej 9, Copenhagen, Denmark, DK-2100. arambaldi@hotmail.com

Cochrane Database Syst Rev. 2001;(4):CD002235

BACKGROUND: Alcohol is a major cause of liver disease in the Western world today. S-adenosyl-L-methionine (SAME) acts as a methyl donor for all known biological methylation reactions and participates in the synthesis of glutathione, the main cellular anti-oxidant. Randomised clinical trials have addressed the question whether SAME has any efficacy in patients with alcoholic liver diseases.

OBJECTIVES: The objectives were to assess the efficacy of SAME on mortality, clinical symptoms, complications, liver biochemistry, and liver histology in patients with alcoholic liver diseases. Adverse events were also analysed.

SEARCH STRATEGY: The Cochrane Hepato-Biliary Group Controlled Trials Register, The Cochrane Library, MEDLINE, EMBASE, and full text searches were combined.

SELECTION CRITERIA: Randomised clinical trials studying patients with alcoholic liver diseases were included. Interventions encompassed peroral or parenteral administration of SAME at any dose versus placebo or no intervention. The trials could be double blind, single blind, or unblinded. The trials could be unpublished or published as an article, an abstract, or a letter, and no language limitations were applied.

DATA COLLECTION AND ANALYSIS: All analyses were performed according to the intention-to-treat method. The statistical package (RevMan and MetaView) provided by the Cochrane Collaboration was used. The methodological quality of the randomised clinical trials was evaluated by components of quality and the Jadad-score.

MAIN RESULTS: Eight placebo-controlled randomised clinical trials including a heterogeneous sample of 330 patients with alcoholic liver disease were identified. Only one trial including 123 patients with alcoholic cirrhosis used adequate methodology and reported clearly on mortality and liver transplantation. It demonstrated no significant effects of SAME on mortality (Peto odds ratio (OR) 0.53, 95% confidence interval (CI) 0.22 to 1.29), liver related mortality (OR 0.63, 95% CI 0.25 to 1.58), mortality or liver transplantation (OR 0.47; 95% CI 0.20 to 1.09), or patients without complications (OR 0.63, 95% CI 0.30 to 1.31). SAME was not significantly associated with adverse events (OR 3.95, 95% CI 0.77 to 20.24).

REVIEWER'S CONCLUSIONS: This systematic review could not demonstrate any significant effect of SAME on mortality, liver related mortality, mortality or liver transplantation, and liver complications of patients with alcoholic liver disease. SAME should not be used for alcoholic liver disease outside randomised clinical trials.

N-acetylcysteine increases liver blood flow and improves liver function in septic shock patients: results of a

prospective, randomized, double-blind study.

Rank N, Michel C, Haertel C, Lenhart A, Welte M, Meier-Hellmann A, Spies C. Department of Anesthesiology and Operative Intensive Care Medicine, University Hospital Benjamin Franklin, Freie Universitat Berlin, Germany.

Crit Care Med. 2000 Dec;28(12):3799-807

OBJECTIVE: In septic shock, decreased splanchnic blood flow is reported, despite adequate systemic hemodynamics. Acetylcysteine (NAC) was found to increase hepatosplanchnic blood flow in experimental settings. In septic shock patients, NAC improved the clearance of indocyanine green and the relationship of systemic oxygen consumption to oxygen demand. We investigated the influence of NAC on liver blood flow, hepatosplanchnic oxygen transport-related variables, and liver function during early septic shock.

DESIGN: Prospective, randomized, double-blind study.

SETTING: Septic shock patients admitted to an interdisciplinary surgical intensive care unit.

PATIENTS: We examined 60 septic shock patients within 24 hrs after onset of sepsis. They were conventionally resuscitated with volume and inotropes and were in stable condition. A gastric tonometer was inserted into the stomach and a catheter into the hepatic vein. Microsomal liver function was assessed by using the plasma appearance of monoethylglycinexylidide (MEGX).

INTERVENTIONS: Subjects randomly received either a bolus of 150 mg/kg iv NAC over 15 mins and a subsequent continuous infusion of 12.5 mg/kg/hr NAC over 90 mins (n = 30) or placebo (n = 30).

MEASUREMENTS AND MAIN RESULTS: Measurements were performed before (baseline) and 60 mins after beginning the infusion (infusion). After NAC, a significant increase in absolute liver blood flow index (2.7 vs. 3.3 L/min/m²; p = .01) and cardiac index (5.0 vs. 5.7 L/min/m²; p = .02) was observed. Fractional liver blood flow index (cardiac index-related liver blood flow index) did not change. The difference between arterial and gastric mucosal carbon dioxide tension decreased (p = .05) and MEGX increased (p = .04). Liver blood flow index and MEGX correlated significantly (r(s) = .57; p < or = .01).

CONCLUSIONS: After NAC treatment, hepatosplanchnic flow and function improved and may, therefore, suggest enhanced nutritive blood flow. The increase of liver blood flow index was not caused by redistribution to the hepatosplanchnic area, but by an increase of cardiac index. Because of its correlation with liver blood flow index, MEGX may be helpful in identifying patients who benefit from NAC treatment in early septic shock.

Reduction in the MK-801 binding sites of the NMDA sub-type of glutamate receptor in a mouse model of congenital hyperammonemia: prevention by acetyl-L-carnitine.

Rao KV, Qureshi IA. Division of Medical Genetics, Sainte-Justine Hospital, Montreal, Que, Canada.

Neuropharmacology. 1999 Mar;38(3):383-94

Our earlier studies on the pharmacotherapeutic effects of acetyl-L-carnitine (ALCAR), in sparse-fur (spf) mutant mice with X linked ornithine transcarbamylase deficiency, have shown a restoration of cerebral ATP, depleted by congenital hyperammonemia and hyperglutaminemia. The reduced cortical glutamate and increased quinolinate may cause a down-regulation of the N-methyl-D-aspartate (NMDA) receptors, observed by us in adult spf mice. We have now studied the kinetics of [3H]-MK-801 binding to NMDA receptors in spf mice of different ages to see the effect of chronic hyperammonemia on the glutamate neurotransmission. We have also studied the Ca²⁺-dependent and independent (4-aminopyridine (AP) and veratridine-mediated) release of glutamate and the uptake of [3H]-glutamate in synaptosomes isolated from mutant spf mice and normal CD-1 controls. All these studies were done with and without ALCAR treatment (4 mmol/kg wt i.p. daily for 2 weeks), to see if its effect on ATP repletion could correct the glutamate neurotransmitter abnormalities. Our results indicate a normal MK-801 binding in 12-day-old spf mice but a significant reduction immediately after weaning (21 day), continuing into the adult stage. The Ca²⁺-independent release of endogenous glutamate from synaptosomes was significantly elevated at 35 days, while the uptake of glutamate into synaptosomes was significantly reduced in spf mice. ALCAR treatment significantly enhanced the MK-801 binding, neutralized the increased glutamate release and restored the glutamate uptake into synaptosomes of spf mice. These studies point out that: (a) the developmental abnormalities of the NMDA sub-type of glutamate receptor in spf mice could be due to the effect of sustained hyperammonemia, causing a persistent release of excess glutamate and inhibition of the ATP-dependent glutamate transport, (b) the modulatory effects of ALCAR on the NMDA binding sites could be through a repletion of ATP, required by the transporters to efficiently remove extracellular glutamate.

Subclinical hepatic encephalopathy predicts the development of overt hepatic encephalopathy.

Romero-Gomez M, Boza F, Garcia-Valdecasas MS, Garcia E, Aguilar-Reina J. Hepatology Unit, Hospital Universitario de Valme, Sevilla, Spain.

Am J Gastroenterol. 2001 Sep;96(9):2718-23

OBJECTIVES: In patients with compensated liver cirrhosis the clinical repercussions of detecting subclinical hepatic encephalopathy (SHE) are unclear. We present a long-term follow-up study in cirrhotic patients to examine the relationship between SHE and subsequent episodes of overt hepatic encephalopathy.

METHODS: A total of 63 cirrhotic patients were studied by Number Connection Test and auditory evoked potentials. We determined glutamine, ammonia, zinc, glutamate, urea, and ratio of branched chain amino acids to aromatic amino acids, and Child-Pugh classification.

RESULTS: Of 63 patients, 34 (53%) exhibited SHE. Nineteen out of 63 (30%) developed overt hepatic encephalopathy during follow-up. Hepatic encephalopathy in follow-up was related to alcoholic etiology, ammonia, glutamine, zinc, ratio of branched chain amino acids to aromatic amino acids, liver function, presence of esophageal varices, and detection of SHE (84% of patients who exhibited hepatic encephalopathy in follow-up showed SHE). In Cox-regression, glutamine levels, SHE, esophageal varices, and Child-Pugh class were the independent variables related to hepatic encephalopathy in follow-up.

CONCLUSIONS: SHE (defined on the basis of number connection test or auditory evoked potentials alteration) could predict a subsequent episode of overt hepatic encephalopathy. Lower glutamine levels, presence of esophageal varices, and liver dysfunction were also related to the development of overt hepatic encephalopathy.

The effect of malotilate on type III and type IV collagen, laminin and fibronectin metabolism in dimethylnitrosamine-induced liver fibrosis in the rat.

Ryhanen L, Stenback F, Ala-Kokko L, Savolainen ER. Department of Internal Medicine, University of Oulu, Finland.

J Hepatol. 1996 Feb;24(2):238-45

BACKGROUND/AIMS: Dimethylnitrosamine-induced liver damage was used as an experimental model to study the effect of malotilate on liver fibrosis.

METHODS: Deposition of type III and IV collagens, laminin and fibronectin were studied from liver section by immunohistochemical techniques using specific antibodies. Serum concentrations of aminoterminal propeptide of type III procollagen, and aminoterminal and carboxyterminal domains of type IV collagen were determined by radioimmunoassays from both malotilate-treated and untreated animals with dimethylnitrosamine injury.

RESULTS: A significant elevation of all three serum parameters was observed after 3 weeks of hepatic injury in animals without malotilate treatment, and a constant increase was noted in the amounts of hepatic type III and IV collagens, laminin and fibronectin. Malotilate prevented increases in serum markers of type III and IV collagen synthesis as well as accumulation of the collagens, laminin and fibronectin in the liver.

CONCLUSIONS: The results suggest that serum marker determinations can be used to monitor changes in type III and IV collagen synthesis in the liver. The data indicate that malotilate has a preventive effect in dimethylnitrosamine-induced experimental hepatic fibrosis.

Effect of silymarin on chemical, functional, and morphological alterations of the liver. A double-blind controlled study.

Salmi HA, Sarna S.

Scand J Gastroenterol. 1982 Jun;17(4):517-21

One hundred and six consecutive patients with liver disease were selected on the basis of elevated serum transaminase levels. The patients were randomly allocated into a group treated with silymarin (treated) and a group receiving placebo (controls). Ninety-seven patients complete the 4-week trial-47 treated and 50 controls. In general, the series represented a relatively slight acute and subacute liver disease, mostly induced by alcohol abuse. There was a statistically highly significantly greater decrease of S-SGPT (S-ALAT) and S-SGOT (S-ASAT) in the treated group than in controls. Serum total and conjugated bilirubin decreased more in the treated than in controls, but the differences were not statistically significant. BSP retention returned to

normal significantly more often in the treated group. The mean percentage decrease of BSP was also markedly higher in the treated. Normalization of histological changes occurred significantly more often in the treated than in controls.

The influence of 1,5-dicaffeoylquinic acid on serum lipids in the experimentally alcoholized rat.

Samochowicz, L., Wojcicki, J., Kadykow, M.

Panminerva Med. 1971; 13(11): 87.

No Abstract Available

An experimental and clinical study of energy-protein metabolism and host defense-repair mechanism in postoperative period--a significance of administration of branched chain amino acid. [Article in Japanese]

Shimazu Y. First Department of Surgery, Sapporo Medical College, Japan.

Nippon Geka Gakkai Zasshi. 1990 Oct;91(10):1534-47

The aim of this study is to evaluate in vivo the effect of branched chain amino acid (BCAA). Experimentally, hepatic energy production and protein synthetic rate were measured in gastrectomized rat which was infused BCAA postoperatively. Clinically, following indices were examined in prospectively randomized patients who underwent abdominal operation and were administered with conventional total parenteral nutrition keeping Calorie/N ratio about 150, including nitrogen balance, urinary 3-methylhistidine, retinol binding protein, B lymphocyte percentage and lymphocyte blastogenesis by phytohemagglutinin. Furthermore, plasma BCAA with their keto-analog level, Factor XIII and opsonic activity were determined in another group of patients who received full strength load of BCAA immediately after subtotal or total gastrectomy, in a controlled prospective randomized double-blinded manner. Results obtained from above mentioned measurements exhibited significant improvement by the administration of BCAA. From these findings, it is suggested that BCAA sustains energy-protein metabolism, supports immunocompetence and promotes wound healing under moderately stressed condition where catabolic response is physiologically compensated.

Biochemical effects of the flavonolignane silibinin on RNA, protein and DNA synthesis in rat livers.

Sonnenbichler J, Zetl I.

Prog Clin Biol Res. 1986;213:319-31

No Abstract Available

Hepatitis C.

Strickland, D.K.

eMed. J. 2002 Jan 16 (<http://www.emedicine.com/ped/topic979.htm>).

Malotilate completely inhibits CCl4-induced liver cirrhosis in rats: biochemical and morphological analysis.

Suzuki T. Department of Pathology II, Fukushima Medical College, Japan.

Fukushima J Med Sci. 1992 Jun;38(1):19-33

Malotilate, diisopropyl 1,3-dithiol-2-ylidenemalonate, is a relatively recently synthesized hepatotropic chemical substance. Its inhibitory effect on rat liver cirrhosis induced by carbon tetrachloride (CCl₄) was biochemically and morphologically investigated for 10 weeks, since this chemical had been reported to suppress liver damage caused by CCl₄ or in vitro collagenogenesis of human fibroblasts. Concomitant administration of malotilate with CCl₄ completely suppressed liver cell necrosis and markedly inhibited fatty change of hepatocytes in the first three weeks of the experiment. During the six to ten weeks of the experimental period, liver cirrhosis was perfectly inhibited by malotilate. Previously established liver cirrhosis, however, could not be normalized by malotilate treatment. Precise mechanism of the inhibitory effect of malotilate on liver cirrhosis is not elucidated, but this substance is clearly effective for preventing liver cell damage and/or liver cirrhosis caused by CCl₄.

Effects of malotilate treatment on alcoholic liver disease.

Alcohol. 1989 May-Jun;6(3):219-22

Malotilate, a new hepatotrophic drug, improves serum transaminase levels and the markers of protein metabolism in the liver in chronic liver diseases. However, the effects of malotilate on alcoholic liver disease are not well known. In the present study, the effects of this drug on the recovery process of alcoholic liver disease after abstinence were analyzed. Many hepatic test values were significantly improved after abstinence from alcohol in both the malotilate-treated and nontreated control groups. However, the Normotest values improved significantly only in the malotilate group, and not in the control group. The improvement rates for choline esterase activity were significantly greater in the malotilate group than in the control group. Serum albumin levels significantly increased in the malotilate group but not in the control group. Changes in the serum markers of hepatic fibrogenesis were not different between the 2 groups. These results indicate that malotilate accelerates the recovery of impaired protein metabolism in alcoholic liver disease and that this drug may be useful for the treatment of alcoholic liver diseases.

N-Acetylcysteine induces shedding of selectins from liver and intestine during orthotopic liver transplantation.

Taut FJ, Schmidt H, Zapletal CM, Thies JC, Grube C, Motsch J, Klar E, Martin E. Department of Anaesthesiology, University of Heidelberg, Heidelberg, Germany. taut@narkose.net

Clin Exp Immunol. 2001 May;124(2):337-41

In orthotopic liver transplantation (OLT), N-acetylcysteine (NAC) reduces ischaemia/reperfusion (I/R) injury, improves liver synthesis function and prevents primary nonfunction of the graft. To further elucidate the mechanisms of these beneficial effects of NAC, we investigated influence of high-dose NAC therapy on the pattern of adhesion molecule release from liver and intestine during OLT. Nine patients receiving allograft OLT were treated with 150 mg NAC/kg during the first hour after reperfusion; 10 patients received the carrier only. One hour after reperfusion, samples of arterial, portal venous and hepatic venous plasma were taken and blood flow in the hepatic artery and the portal vein was measured. Absolute concentrations of sICAM-1, sVCAM-1, sP-selectin and sE-selectin were not markedly different. However, balance calculations showed release of selectins from NAC-treated livers as opposed to net uptake in controls ($P < \text{or} = 0.02$ for sP-selectin). This shedding of selectins might be a contributing factor to the decrease in leucocyte adherence and improved haemodynamics found experimentally with NAC-treatment.

Liver, transplant.

Thomas, G., McNamara, R.M.

eMed. J. 2001 November 19, 2001 (<http://www.emedicine.com/aaem/topic458.htm>).

Blood viscosity and red cell morphology in subjects suffering from cirrhosis before and after treatment with S-adenosyl-L-methionine (S-AMe).

Turchetti V, Bellini MA, Leoncini F, Petri F, Trabalzini L, Guerrini M, Forconi S. Istituto di Medicina Interna e Geriatria, Università degli Studi di Siena, Italy. images@unisi.it

Clin Hemorheol Microcirc. 2000;22(3):215-21

Alterations of fluidity of the hepatocytic membrane and of the transport related systems are the basis of the cholestatic syndrome and favour the tissue accumulation of cytotoxic metabolites. S-Adenosyl-L-Methionine (SAM) is a natural molecule which acts as a giver of methyl groups and as an enzymatic activator in several enzymatic actions of transmethylation and of transsulphuration and plays a key role in biochemical processes of hepatic cell. The aim of our study was to evaluate the effects of SAM on the restoration of the membrane fluidity and on the hepatic function in general. In studying the fluidity of the cell membrane we evaluated some hemorheological parameters (total blood viscosity and red cell morphology). Fluidity of the red cell membrane is one of the most important elements of red cell rheology. We studied 15 patients (Group A) suffering from micro- and macro-nodular cirrhosis verified through hepatic biopsy, with alcoholic or post-viral causes. We evaluated the values of: blood viscosity (with a cone-plate rheometer by Carri-med), haematocrit, plasma fibrinogen and the erythrocytic morphology at the optical microscope with the Zipursky-Forconi method before and after 7 days of therapy with SAM i.v.. Data were compared with those of a similar group (Group B) treated with traditional therapy only (hyposodic and hypoprotein diet supplemented with multivitamin preparations, vitamin K in particular, if necessary, and potassium sparing diuretics). We also measured biliary salts, alkaline phosphatase, transaminase and gamma-GT. In the first group we observed a statistically significant reduction of blood viscosity, haematocrit didn't change significantly; biliary salts reduced in a statistically significant way. Evaluation of red cell morphology showed in all cases a pathological percentage (>15%) of echinocytes and knizocytes

which reduced to a mean of 5% after SAM therapy. We observed no further modifications of the other hemorheological parameters. Results demonstrate that SAM has a positive action on the fluidity of the membrane, as indicated by the improvement of haemorheological parameters and by the significant decrease of biliary salts, indicating the presence of cholestasis.

Evidence of hepatic endogenous hydrogen peroxide in bile of selenium-deficient rats.

Ueda Y, Matsumoto K, Endo K. Department of Physical Chemistry, Showa Pharmaceutical University, 3-3165, Higashi-Tamagawagakuen, Machida, Tokyo, 194-8543, Japan.

Biochem Biophys Res Commun. 2000 May 19;271(3):699-702

Hepatic endogenous hydrogen peroxide (H₂O₂) in bile of selenium-deficient rats (SeD) was for the first time found using the electron spin resonance (ESR) spin-trap technique, and the relationship between glutathione peroxidase (GPX) activity and H₂O₂ amount is discussed. Normal rats and four groups of rats fed a selenium-deficient diet with different feeding periods were examined. The results showed that the GPX activity decreased depending on the feeding period with the selenium-deficient diet and that the hepatic endogenous H₂O₂ amount in the bile of the rats fed the selenium-deficient diet for the longest period (a week before birth to 8 weeks old) was drastically higher than those in other groups of rats (P < 0.005). We found that generation of H₂O₂ due to the decrease in the GPX activity has a threshold value. The results suggest that an exposure to selenium deficiency for long term will cause oxidative stress. Copyright 2000 Academic Press.

Selectivity of silymarin on the increase of the glutathione content in different tissues of the rat.

Valenzuela A, Aspillaga M, Vial S, Guerra R.

Planta Med. 1989 Oct;55(5):420-2

Silymarin, a flavonoid extracted from the seeds of the milk thistle, *Silybum marianum*, increases the redox state and the total glutathione content of the liver, intestine, and stomach of the rat. The same treatment does not affect the levels of the tripeptides in the kidney, lung, and spleen. This selective effect of the flavonoid on the digestive organs is ascribed to its pharmacokinetics on the digestive track, where the biliary concentration of silymarin is increased and maintained via the entero-hepatic circulation.

Gallstones: Cause

WebMD.

2002 Jul 19 (last update, 12/31/01) (<http://webmd.lycos.com/content.healthwise/141/35096.htm>).

Lung preconditioning with N-acetyl-L-cysteine prevents reperfusion injury after liver no flow-reflow: a dose-response study.

Weinbroum AA, Kluger Y, Ben Abraham R, Shapira I, Karchevski E, Rudick V. Department of Anesthesiology, Tel Aviv Sourasky Medical Center, Israel. draviw@tasmc.health.gov.il

Transplantation. 2001 Jan 27;71(2):300-6

BACKGROUND: Circulating xanthine oxidase activity and the generated oxidants have been linked to lung reperfusion injury from no flow-reflow conditions in other organs after organ transplantation or surgery. N-acetyl-L-cysteine (NAC), an oxidant scavenger, promotes glutathione in its reduced form (GSH) that is depleted during ischemia. We have recently demonstrated its efficacy in protecting lungs from reperfusion injury if administered during reperfusion of postischemic liver. We now investigated whether preconditioning of lungs with NAC could attenuate lung respiratory or vascular derangement after no flow-reflow (ischemia-reperfusion, IR) and if this depends on lung GSH levels.

METHODS: Rat isolated livers were stabilized and perfused with modified Krebs-Henseleit solution (KH) (control, n=12) or made ischemic (no flow, IR-0, n=12) for 2 hr. Meanwhile, lungs were isolated, ventilated, and stabilized (KH+bovine albumin 5%). Serial perfusion (15 min) of liver+lung pairs took place followed by lung only recirculation (45 min) with the accumulated solution. Another three controls and three ischemic groups included lungs treated during stabilization with NAC at 100 mg x kg⁻¹, 150 or 225 mg x kg⁻¹ (in 2.5, 3.7 or 5.5 mmol solutions, respectively). Results. Ischemic liver damage, expressed by circulating hepatocellular constituents, was associated with pulmonary artery and ventilatory pressure increases by 70-100% of baseline, abnormal wet-to-dry weight ratio, and abnormal bronchoalveolar lavage volume and content in the IR-0 (nontreated) and the IR-100 and IR-225 pretreated lungs. NAC-150 pretreatment afforded preservation for most parameters. GSH content in the IR-150

lung tissue was only 11% higher than that of IR-225, but 2-fold that in IR-0 and IR-100 GSH lungs.

CONCLUSION: Lung preconditioning with NAC prevents reperfusion injury but not in a dose-related manner. Although enhanced GSH tissue content explains lung protection, GSH-independent NAC activity is another possibility.

Effects of 1,5-dicaffeoylquinic acid (cynarin) on cholesterol levels in serum and liver of acute ethanol-treated rats.

Wojcicki J.

Drug Alcohol Depend. 1978 Mar;3(2):143-5

The effect of 1,5-dicaffeoylquinic acid (Cynarine) on total cholesterol levels in serum and liver of acute ethanol-treated rats was studied. Male Wistar rats were administered ethyl alcohol, 6 g/kg per day by gavage over three days. In rats treated with ethanol alone, the serum and hepatic cholesterol showed a significant rise of 44 and 75%, respectively. In rats receiving ethanol and Cynarine simultaneously, a distinct reduction of the serum and hepatic cholesterol levels was observed.

Cirrhosis.

Wolf, D.C.

eMed. J. 2001 Sep 6 (<http://www.emedicine.com/med/topic3183.htm>).

Cirrhosis and its disorders.

Workman, J.J.

Liver Disorders Sourcebook 1999, p. 48. Los Angeles: Lowell House.

Eds. Biomedical and Clinical Aspects of Coenzyme Q

Yamamura, Y., Folkers, K., Ito, Y.,

Volume 2 1980. Amsterdam: Elsevier.

Plant proteins in relation to human protein and amino acid nutrition.

Young VR, Pellett PL. Clinical Research Center, Massachusetts Institute of Technology, Cambridge 02142.

Am J Clin Nutr. 1994 May;59(5 Suppl):1203S-1212S

Plant protein foods contribute approximately 65% of the per capita supply of protein on a worldwide basis and approximately 32% in the North American region. These sources of protein are discussed in relation to their amino acid content, human amino acid requirements, and dietary protein quality. Mixtures of plant proteins can serve as a complete and well-balanced source of amino acids for meeting human physiological requirements. This short review ends with a list of series of myths and realities concerning the relationship between plant protein and human nutrition and a list of some nutritional issues of concern to the health professional and informed consumer.

Protective role of selenium against hepatitis B virus and primary liver cancer in Qidong.

Yu SY, Zhu YJ, Li WG. Cancer Institute, Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing, China.

Biol Trace Elem Res. 1997 Jan;56(1):117-24

High rates of hepatitis B virus (HBV) infection and primary liver cancer (PLC) are present in Qidong county. Epidemiological surveys demonstrated an inverse association between selenium (Se) level and regional cancer incidence, as well as HBV infection. Four-year animal studies showed that dietary supplement of Se reduced the HBV infection by 77.2% and liver precancerous lesion by 75.8% of ducks, caused by exposure to natural environmental etiologic factors. An intervention trial was undertaken among the general population of 130,471. Individuals in five townships were involved for observation of the preventive effect of Se. The 8-yr follow-up data showed reduced PLC incidence by 35.1% in selenized table salt supplemented vs the nonsupplemented population. On withdrawal of Se from the treated group, PLC incidence rate began to increase. However, the

inhibitory response to HBV was sustained during the 3-yr cessation of treatment. The clinical study among 226 Hepatitis B Surface Antigen (HBsAg)-positive persons provided either 200 micrograms of Se in the form of selenized yeast tablet or an identical placebo of yeast tablet daily for 4 yr showed that 7 of 113 subjects were diagnosed as having PLC in the placebo group, whereas no incidence of PLC was found in 113 subjects supplemented with Se. Again on cessation of treatment, PLC developed at a rate comparable to that in the control group, demonstrating that a continuous intake of Se is essential to sustain the chemopreventive effect.

Effect of N-acetylcysteine and deferoxamine on endogenous antioxidant defense system gene expression in a rat hepatocyte model of cocaine cytotoxicity.

Zaragoza A, Diez-Fernandez C, Alvarez AM, Andres D, Cascales M. Instituto de Bioquímica (CSIC-UCM), Facultad de Farmacia, Universidad Complutense, Plaza de Ramon y Cajal sn, 28040, Madrid, Spain.

Biochim Biophys Acta. 2000 Apr 17;1496(2-3):183-95

In the present study we investigated on cultures of hepatocytes from phenobarbital-pretreated rats, the effect of the antioxidants, 0.5 mM N-acetylcysteine (NAC) or 1.5 mM deferoxamine (DFO), previously incubated for 24 h and coincubated with cocaine (0-1000 microM) for another 24 h. Cocaine cytotoxicity was monitored by either the lysis of the cell membranes or apoptosis. Lysis of the cell membranes was evidenced by lactate dehydrogenase leakage, apoptosis was observed by detecting a hypodiploid peak (<2C) in DNA histograms obtained by flow cytometry, peroxide production was quantified with 2', 7'-dichlorodihydrofluorescein diacetate and gene expression of the antioxidant enzymes: Mn- and Cu,Zn-superoxide dismutases, catalase and glutathione peroxidase were measured by Northern blot analysis. NAC and DFO significantly decreased the extent of lysis of cell membranes and apoptosis, and the antiapoptotic effect was parallel to peroxide generation. By the effect of NAC and DFO, significant increases were detected in the levels of mRNA of catalase, manganese superoxide dismutase and glutathione peroxidase. From these results we conclude that NAC or DFO, when incubated in the presence of cocaine, exerted a protective effect against cocaine toxicity at the level of both lysis of the membranes and apoptosis. This protective effect, in the case of NAC, was directed towards an increase in antioxidant enzyme expression, and in the case of DFO against reactive oxygen species generation.

The effect of folic acid on the drug metabolizing liver function in man with viral hepatitis.

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Exp Toxicol Pathol. 1999 Jul;51(4-5):455-7

The investigations were carried out on 31 patients (16 men and 15 women, at the age of 20-50) with viral hepatitis. The all patients were divided at two groups. The first group (12 man) received usual treatment (diet, corsil), the second group (19 man) received in addition to the base treatment folic acid (5 mg per day, 10 days). It was found, that at patients with viral hepatitis was decreased the activity of monooxygenase system of liver. So, period of semielimination (T1/2) of antipyrine (AP) was greater in 1,4 time, area under the pharmacokinetic curve - 1,5 time and clearance was below by 39% than in volunteers (29 man). On day of treatment only by corsil, the rate of elimination of AP and clearance were increased by 34 and 31% (p < 0.05) respectively, T1/2 was decreased by 23% (p < 0.05) and area under the pharmacokinetic curve - 17 %. On 10 day of treatment by corsil with folic acid (5 mg per day), the rate of elimination of AP and clearance was increased by 43% (p < 0.05), area under the pharmacokinetic curve and T 1/2 were decreased by 30 and 33% (p < 0.05) respectively. The positive effect of folic acid in treatment of hepatitis at restoration period may be cause participating its derivatives in de novo nucleotide synthesis.

