

Liver Degeneration

ABSTRACTS

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Protective effect of N-acetylcysteine in isoniazid induced hepatic injury in growing rats.

Attri S, Rana SV, Vaiphie K, Katyal R, Sodhi CP, Kanwar S, Singh K.

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Indian J Exp Biol 2001 May;39(5):436-40

Status of oxidative/antioxidative profile was the mechanistic approach to inumerate the nature of protection by N-acetylcysteine (NAC) in isoniazid (INH) exposed experimental animals. Analysis of lipid peroxidation, thiol levels, cytochrome P450, superoxide dismutase (SOD), catalase, glutathione peroxidase, reductase and transferase were estimated in liver along with the body and liver weight of animals and histological observations. Isoniazid exposure to animals resulted in no change in body and liver weights. Thiols, lipid peroxidation, catalase, SOD glutathione peroxidase, reductase, transferase and cytochrome P450 levels were altered with INH exposure. supplementation of NAC with INH protected the animals against hepatotoxic reactions by minimizing the free radical induced tissue injury and overall maintenance of the endogenous scavengers of free radicals.

Itching in Liver Disease

Bergasa, N.V.

Steatohepatitis-inducing drugs cause mitochondrial dysfunction and lipid peroxidation in rat hepatocytes.

Berson A, De Beco V, Letteron P, Robin MA, Moreau C, El Kahwaji J, Verthier N, Feldmann G, Fromenty B, Pessayre D.

INSERM Unite 481 and Centre de Recherche sur les Hepatites Virales (Association Claude Bernard), Hopital Beaujon, Clichy, France.

Gastroenterology. 1998 Apr;114(4):764-74.

BACKGROUND & AIMS: 4,4'-Diethylaminoethoxyhexestrol (DEAEH), amiodarone, and perhexiline cause steatohepatitis in humans. The mechanisms of these effects are unknown for DEAEH and have not been completely elucidated for amiodarone and perhexiline. The aim of this study was to determine these mechanisms.

METHODS: Rat liver mitochondria, cultured rat hepatocytes, or rats were treated with these drugs, and the effects on mitochondrial respiration, beta-oxidation, reactive oxygen species formation, and lipid peroxidation were determined.

RESULTS: DEAEH accumulated in mitochondria and inhibited carnitine palmitoyl transferase I and acyl-coenzyme A dehydrogenases; it decreased beta-oxidation and caused lipid deposits in hepatocytes. DEAEH also inhibited mitochondrial respiration and decreased adenosine triphosphate (ATP) levels in hepatocytes. DEAEH, amiodarone, and perhexiline augmented the mitochondrial formation of reactive oxygen species and caused lipid peroxidation in rats.

CONCLUSIONS: Like amiodarone and perhexiline, DEAEH accumulates in mitochondria, where it inhibits both beta-oxidation (causing steatosis) and respiration. Inhibition of respiration decreases ATP and also increases the mitochondrial formation of reactive oxygen species. The latter oxidize fat deposits, causing lipid peroxidation. We suggest that ATP depletion and lipid peroxidation may cause cell death and that lipid peroxidation products may account, in part, for other steatohepatitis lesions.

The pharmacology of the antioxidant lipoic acid.

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Leiden/Amsterdam Center for Drug Research, Vrije Universiteit, Department of Pharmacochemistry, The Netherlands.

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

1. 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-I 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.

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

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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.

Liver in obesity.

Braillon A, Capron JP, Herve MA, Degott C, Quenum C.

Gut. 1985 Feb;26(2):133-9.

We report on clinical, nutritional, and hepatic histological findings in 50 non-selected obese subjects (mean overweight +74%; range +21-138%). The pathogenesis of the liver damage was assessed with the help of multidimensional analysis of a number of clinical variables. According to the severity of the hepatic lesions, the patients have been ranged in five groups: O (normal liver) 10%; I (fatty liver) 48%; II (fatty hepatitis) 26%; III (fatty fibrosis) 8%; IV (fatty cirrhosis) 8%. The more severe changes (groups III and IV) were constantly associated with excessive alcohol intake. The multidimensional analysis was unable to find a relationship between obesity and the development of fibrosis and cirrhosis whereas it showed that: (a) there was a highly significant correlation between the daily ethanol intake and the degree of overweight, (b) severe fatty metamorphosis was significantly associated with the degree of overweight, the existence of diabetes mellitus, and the amount of alcohol and fat intake, (c) nutritional factors, in particular deficient protein intake, have only an accessory effect in the development of mild inflammation and fibrosis, (d) the consumption of potentially hepatotoxic drugs, very high in the obese (about five drugs per day) could have a role in the development of cirrhosis. In conclusion in our study, there was no evidence that obesity per se could result in severe liver damage.

Diagnosis and treatment of Wilson's disease.

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Semin Neurol. 1999;19(3):261-70.

Wilson's disease is due to an inherited defect in copper excretion into the bile by the liver. The resulting copper accumulation and copper toxicity results in liver disease, and in some patients, brain damage. Patients present, generally between the ages of 10 and 40 years, with liver disease, neurological disease of a movement disorder type, or behavioral abnormalities, and often with a combination of these. Because Wilson's disease is effectively treated, it is extremely important for physicians to learn to recognize and diagnose the disease. Treatment options have evolved rapidly in the last few years, with zinc now being the drug of choice in most situations.

Role of free radicals in liver diseases and hepatic fibrosis.

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Department of Internal Medicine, St. Louis University Health Sciences Center, Missouri.

Hepatology. 1994 Aug;41(4):343-8.

An increased production of free radicals in the liver has been implicated in a variety of liver diseases. Free radicals can damage cellular macromolecules and, therefore, may participate in hepatocellular injury when produced in excess. Strong evidence exists for hepatic free radical production in animal models of iron and copper overload, ethanol consumption, and ischemia-reperfusion. Although less is known about the situation in humans with liver diseases, the available evidence is consistent with the findings in animal experiments. Treatments that reduce free radical production and/or levels have protective effects in hepatic ischemia-reperfusion. Free radical-initiated lipid peroxidation may play a role in hepatic fibrogenesis, perhaps through an effect of aldehydic peroxidation products on Kupffer cells and lipocytes. This hypothesis is supported by the observation that dietary supplementation with vitamin E has a protective effect on carbon tetrachloride-induced hepatic fibrosis. While cellular damage in human liver diseases is probably multifactorial, free radicals may play important roles in initiating and/or perpetuating this damage.

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

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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.

Folate deficiency-induced oxidative stress and apoptosis are mediated via homocysteine-dependent overproduction of hydrogen peroxide and enhanced activation of NF-kappaB in human Hep G2 cells.

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Biomed Pharmacother. 2001 Oct;55(8):434-42.

Folate coenzymes are critical for de novo synthesis of purine and thymidine, and for interconversion of amino acids. Folate deficiency inhibits cellular proliferation, disturbs cell cycling, causes genetic damage and eventually results in cell death. Previously, we demonstrated that the demise of human hepatoma Hep G2 cells mediated by folate deficiency proceeded via a p53-independent apoptosis, and the perturbation of intracellular calcium homeostasis was also shown to be involved. To further delineate the mechanism associated with this observed phenomenon, Hep G2 cells were cultivated in the control or folate-deficient media (control media lacking folate, glycine, thymidine and hypoxanthine) for 4 weeks. At the end of this cultivation period, we found that TBARS (an index of lipid peroxidation) concentrations in the folate-deficient cells were drastically increased as compared to the control cells (0.04 vs 0.01 nmole/10(6) cells), indicating that a severe oxidative stress of the former cells had occurred. This phenomenon was also shown to coincide with the ability of these folate-deficient cells to elaborate increased amounts of H₂O₂ as compared to its folate-supplemented cells (2.87 vs 0.98 nmole/10(5) cells/h). Furthermore, the accelerated production of H₂O₂ by the folate-deficient cells was also closely correlated with the elevated homocysteine concentrations released in the culture medium (15.37 +/- 2.4 vs 3.58 +/- 2.4 micromole/L; P < 0.001). Finally, we demonstrated that folate deficiency was indeed capable of activating a redox-sensitive transcription factor, NF-kappaB, which is crucial in the control of a reactive oxygen species-mediated apoptosis. In summary, we show that folate deficiency-induced apoptosis is proceeded via the enhanced activation of NF-kappaB, which is the resulting form of the homocysteine-mediated overproduction of hydrogen peroxide.

The biochemistry of alcohol-induced fatty liver.

Day, C.P., Yeaman, S.J.

Biochem. Biophys. Acta 1994 Nov 17; 1215(1-2): 33-48.

No abstract available.

S-adenosylmethionine prevents hepatic tocopherol depletion in carbon tetrachloride-injured rats.

Deulofeu R, Pares A, Rubio M, Gasso M, Roman J, Gimenez A, Varela-Moreiras G, Caballeria J, Ballesta AM, Mato JM, Rodes J. Laboratory of Biochemistry, Hospital Clinic i Provincial, University of Barcelona, Barcelona, Spain.

Clin Sci (Lond). 2000 Oct;99(4):315-20.

In various experimental models, S-adenosylmethionine (S-AdoMet) has been shown to reduce liver injury by preventing depletion of glutathione, one of the antioxidant systems that plays a critical role in defence against oxidative stress. On the other hand, alpha-tocopherol may be decreased in liver diseases, and treatment with this vitamin reduces liver injury in CCl₄-treated rats. Since there is a close relationship among the different antioxidant systems (mainly glutathione, alpha-tocopherol and ascorbic acid), we have

assessed

whether, as well as restoring hepatic glutathione content, SAME has any effect on liver alpha-tocopherol and ascorbic acid levels in CCl(4)-injured rats. Four groups of seven male Wistar rats treated for 9 weeks were studied: rats induced to cirrhosis with CCl(4), rats induced to cirrhosis plus SAME administration (10 mg x kg(-1) x day(-1)) and their respective controls. Liver samples were obtained for measuring levels of glutathione, alpha-tocopherol, ascorbic acid and thiobarbituric acid-reactive substances (TBARS), and hydroxyproline concentration as an index of collagen content. The hydroxyproline content was higher in CCl(4)-injured rats than in the control group (4.4+/-1.8 and 1.1+/-0.3 micromol/g respectively; P<0.05). In CCl(4)-injured rats, SAME administration decreased collagen content (2.7+/-1.0 micromol/g; P<0.05) and TBARS, and corrected glutathione depletion. alpha-Tocopherol was significantly lower in CCl(4)-injured rats than in controls (17.3+/-4.9 and 23.0+/-4.0 micromol/g respectively; P<0.05). By contrast, alpha-tocopherol levels were similar (23.8+/-5.1 micromol/g) in CCl(4)-injured rats receiving SAME and in controls. In CCl(4)-injured rats, liver ascorbic acid was decreased in comparison with controls (4.9+/-1.8 and 8.2+/-1.0 micromol/g respectively; P<0.05), levels which were not replenished by SAME (4.6+/-0.4 micromol/g). In conclusion, SAME not only decreases fibrosis and protects against hepatic glutathione depletion, but has a further antioxidant effect of preventing alpha-tocopherol depletion in CCl(4)-injured rats.

Role of free-radical reactions in liver diseases.

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Hungary.

Acta Physiol Hung. 1992;80(1-4):351-61.

Role of free-radical reactions is most significant in toxic liver injuries. Two traditional groups of liver injuries induced by drugs and chemicals are distinguished, 1. direct toxic type and 2. idiosyncratic type. Liver injury of direct toxic type is generally developed following toxin exposure, it is dose dependent, incubation period is short, and the injury often affects other organs (e.g. kidney). Direct toxins frequently cause typical zonal necrosis usually without concomitant signs of hypersensitivity. It is typical of idiosyncratic reaction that it appears only in a shorter period of exposure, it cannot be predicted, it is not dose-dependent, its incubation period varies and sometimes (in one-fourth of cases) it is accompanied by extrahepatic symptoms of hypersensitivity (fever, leukocytosis, eosinophilia, rashes), its morphologic picture shows great variety. A part of direct toxins is toxic itself, in the other part the basic compound is not toxic but it changes into toxic metabolites in the liver. Liver is well-protected against free-radicals developing in the organism: it is one of our best antioxidant supplied organs. It is probably due to the one of the important tasks of liver, namely detoxication of drugs, chemicals and toxic materials, with subsequent release of free-radicals. It is proved by the fact that in normal bile peroxidized lipids produced by free-radical chain reactions can also be detected. The pathologic free-radical reactions and one of their sequelae, peroxidation of lipids (LPO) do not necessarily cause cell and tissue damage. Antioxidant protection of cells and tissues is able to prevent free-radical injury and it enables, that the already developed damages become reversible. According to recent investigations, the lipid peroxidation, caused by free-radical reactions, or covalent binding of radical products to biomolecules does not lead directly to cellular destruction, only via further reactions. Such intermediary steps can be the phospholipase A2 activation, accumulation of lysophosphatides, poly-ADP-ribose polymerase repair enzyme activation, following oxidative damage of DNA, with subsequent NAD and ATP depletion. Its significance may be that the irreversible cellular and tissue damage can be prevented perhaps not only by administration of antioxidants, but also by compounds (e.g. phospholipase A2 inhibitors) affecting the above-mentioned biochemical mechanisms.

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.

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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.

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.

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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.

Mosby Medical Encyclopedia, Revised Edition 1996.

Glanze, W.D., Ed.

St. Louis, MO: C.V. Mosby.

Advances in antiviral agents for hepatitis B virus.

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Antivir Chem Chemother. 2001;12 Suppl 1:93-117.

Hepatitis B virus (HBV) is the third most common disease after venereal diseases and chickenpox. HBV currently infects 2 billion people in the world, of which 350 million are chronic carriers. At least 1 million chronically infected individuals die each year due to HBV-related diseases, especially cirrhosis and liver cancer. The greatest concern about the diffusion of this virus is in endemic regions in central and southern Africa, South-East Asia and South America, where neonatal exposure results in high mortality rates. Anti-HBV therapy has made important progresses in the last decade, with two approved drugs and a number of other potent agents in the pharmaceutical industry pipeline. Nevertheless, resistance and viral rebound are still major issues in devising a winning strategy, and there is a continuous need of developing new active compounds, as well as therapeutic protocols based on combination therapy and a prophylactic approach. This review will summarize the latest advances in anti-HBV therapy, with particular regard to the latest clinical data on the most significant anti-HBV agents. Issues such as viral resistance and combination therapy will be highlighted.

[About paracetamol again.] [Article in Hungarian]

Hazai E, Monostory K, Bakos A, Zacher G, Vereczkey L.

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Orv Hetil 2001 Feb 18;142(7):345-9

The mechanism of hepatotoxicity caused by paracetamol (acetaminophen) overdose and the treatment of patients is reviewed. Paracetamol is widely used over-the-counter drug with analgesic and antipyretic properties. Although it is considered to be safe at therapeutic doses, the incidence of hepatotoxicity caused by overdose or inadvertent application has been increasing lately. N-acetyl-p-benzoquinonimine, one of the metabolites formed from paracetamol is responsible for the hepatotoxicity. Until now there is no complete therapeutic strategy for the effective treatment of hepatotoxicity caused by paracetamol. Gut decontamination, N-acetylcysteine antidote administration and enhancement of elimination is used for the management of paracetamol overdose. Those with severe hepatotoxicity and neurological symptoms can benefit from removal of necrotic liver and undergo transplantation.

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.
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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.

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

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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 5-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.

[Clinical aspects and therapy of viral hepatitis] [Article in German]

Lammert F, Busch N, Matern S.
Medizinische Klinik III, Universitätsklinikum der RWTH Aachen.

Chirurg. 2000 Apr;71(4):381-8.

Acute hepatitis can be caused by the enterically spread hepatitis A and E viruses and the parenterally spread hepatitis B, C or D viruses. The clinical features of acute viral hepatitis are similar among the five viruses and include non-specific symptoms and icterus. In general, a specific therapy is not necessary, but patients with fulminant hepatitis may require liver transplantation. For acute hepatitis C, the effect of interferon-alpha on the risk of chronicity is evaluated in clinical trials. Chronic hepatitis is defined as inflammatory reaction in the liver that continues without improvement for at least 6 months after infection with hepatitis B, C or D viruses. Hepatitis B resolves in more than 90% of the patients, but chronic infection can lead to liver cirrhosis and hepatocellular carcinoma. Chronic hepatitis C is an insidious disease, because early diagnosis is missed easily due to asymptomatic presentation and about 70% of infected patients develop chronic hepatitis. The benefits of interferon-alpha and/or nucleoside analogues have been proven in recent clinical trials that show sustained responses in more than a third of all patients with chronic viral hepatitis. The future treatment of chronic viral hepatitis will likely include immunomodulation and gene therapy.

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.

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.

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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.

Chronic hepatitis B virus infection: treatment strategies for the next millennium.

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Medical Center, Dallas 75390-9151, USA.

Ann Intern Med. 2000 May 2;132(9):723-31.

Chronic hepatitis B virus (HBV) infection is a leading cause of cirrhosis and hepatocellular carcinoma worldwide. Its prevalence approaches 10% in hyperendemic areas, such as southeast Asia, China, and Africa. Although chronic HBV infection is seen less frequently in North America and Europe, an estimated 1.25 million persons in the United States are infected. In the past decade, revolutionary strides have been made toward the treatment of chronic HBV infection. Interferon-alpha was once the only available therapy but has recently been joined by the nucleoside analogues, the most extensively studied of which is lamivudine. Interferon therapy continues to have a role in the treatment of a carefully selected group of patients. Lamivudine therapy, which has less stringent selection criteria, suppresses HBV DNA in almost all treated patients: Seventeen percent to 33% experience loss of hepatitis B e antigen, and 53% to 56% have a histologic response. Extended lamivudine treatment leads to the development of a specific lamivudine-resistant virus with base-pair substitutions at the YMDD locus of the DNA polymerase. Newer nucleoside analogues and other immunomodulator therapies are being investigated. In the future, combination therapy with different classes of agents may yield improved response rates and delay the development of resistance.

Mutations in the basal core promoter and precore/core gene of hepatitis B virus in patients with chronic active but not acute hepatitis B.

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Eur J Clin Microbiol Infect Dis. 1999 Dec;18(12):871-8.

Around 5-10% of adults infected with hepatitis B virus (HBV) develop a chronic liver disease such as chronic active hepatitis (CAH), and it is unclear whether the clinical outcome depends solely on the immune response or whether viral factors also play a role. In this study, a search was therefore made for nucleotide mutations in the basic core promoter (BCP) and amino-acid substitutions in the precore/core region of HBV infecting patients with CAH or with acute hepatitis. The nucleotide sequences of the BCP and of the precore/core region were determined in virus from ten patients with CAH and ten with acute hepatitis. The precore/core sequences were also analysed in 14 additional patients (6 with CAH, 8 with acute hepatitis). In seven of the ten patients with CAH, five types of mutations were found in the BCP. Deletions in the precore/core region were observed in six patients. In all six patients where only the precore/core region was studied, amino-acid substitutions were present. In contrast, in the ten patients with acute hepatitis studied for BCP, a mutation was found in the BCP of one patient only. Of the 18 patients in whom the precore/core was studied, three had an amino-acid substitution in this region. The results show a clear link between CAH and both HBV BCP and precore/core region mutations, suggesting these mutations may play a role in the persistence of HBV infection.

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.
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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.

Vitamin E as an antioxidant agent in CAPD patients.

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Int J Artif Organs. 2002 May;25(5):373-8.

Oxidative stress, increased lipid peroxidation and decreased activity of antioxidant systems may contribute to the accelerated development of atherosclerosis in chronic renal failure patients during renal replacement therapy. The aim of the study was to investigate the influence of vitamin E (400 mg/day) on some antioxidant defense parameters in CAPD patients. In fourteen CAPD patients, erythrocyte antioxidant enzymes, superoxide dismutase (SOD), glutathione peroxidase (GPX) and catalase (CAT), the concentration of plasma malondialdehyde (MDA), vitamin A, vitamin C and vitamin E were investigated. The study was divided into two periods. Each period lasted six weeks. In the first period patients received orally vitamin E 400 mg/day, in the second period they did not receive vitamin E or other antioxidant drugs. Each parameter was determined at the beginning of the study and at the end of each period. Six CAPD patients were treated by erythropoietin (EPO) and received orally pyridoxine 20 mg/day and the others without EPO treatment received pyridoxine 5 mg/day. Six-week treatment by vitamin E (400 mg/day) led to the significant increase of serum vitamin E (from 33.6±9.0 to 49.3±15.5 micromol/L) and to the significant decrease of MDA (from 2.62±0.5 to 2.36±0.4 micromol/L). The mean values of erythrocyte enzymes were in or under the lower margin of normal range and were not influenced by vitamin E in CAPD patients. The results of our study showed that orally administered vitamin E is a very important antioxidant agent for CAPD patients.

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.

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 2000 Jan.

NIDDK.

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

What are the primary treatments for cirrhosis?

Nidus.

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

Viral hepatitis and its prevention.

Ou, J.H.J.

Infection Control Today Magazine 2002.

Phoenix, AZ: Virgo Publishing.

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.

Dilinoleoylphosphatidylcholine decreases hepatic stellate cell activation.

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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 polyenyolphosphatidylcholine mixture administered in vivo.

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.

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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.

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

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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.

Roles of selenium in endotoxin-induced lipid peroxidation in the rats liver and in nitric oxide production in J774A.1 cells.

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Toxicol Lett 2000 Dec 20;118(1-2):69-77

We examined the role of selenium (Se) in the mechanism of oxidative stress caused by endotoxin by feeding rats deficient a diet in

this element. In rats fed the Se-deficient diet (concentration of Se, less than 0.027 microg g(-1)) for 10 weeks, Se level and glutathione peroxidase (GSH-Px) activity in the liver were about 47 and 43% lower, respectively, than those in rats fed a Se-adequate diet (Se, 0.2 microg g(-1)). Rat fed the Se-deficient diet and given endotoxin (6 mg kg(-1), i.p.) showed a mortality rates of about 43% at 18 h. Nevertheless, no lethality was observed with endotoxin (4 mg kg(-1), i.p.) challenge. Levels of serum lactate dehydrogenase and acid phosphatase leakage were significantly higher in Se-deficient rats than those in Se-adequate diet 18 h after endotoxin (4 mg kg(-1), i. p.) challenge. Superoxide anion generation and lipid peroxide formation in the liver of Se-deficient rat were markedly increased 18 h after endotoxin (4 mg kg(-1), i.p.) injection compared with those in the endotoxin/Se-adequate diet group, whereas non-protein sulfhydryl level in the liver after administration of endotoxin to Se-deficient rats was lower than that in Se-adequate rats treated with endotoxin. We investigated whether Se can suppress nitric oxide (NO) generation and cytotoxicity in endotoxin-treated J774A.1 cells. Treatment with Se (10(-6) M) markedly inhibited endotoxin (0.1 microg ml(-1))-induced NO production in J774A.1 cells. Se induced an increased activity of GSH-Px in cells after 24 h of incubation, suggesting that the preventive effect of Se on NO production in endotoxemia is due to the induction of Se-GSH-Px activity. However, Se did not affect endotoxin-induced cytotoxicity in J774A.1 cells. These findings suggested that the oxidative stress caused by endotoxin may be due, at least in part, to changes in Se regulation during endotoxemia.

[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]

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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.

Stimulatory effect of silibinin on the DNA synthesis in partially hepatectomized rat livers: non-response in hepatoma and other malign cell lines.

Sonnenbichler, J., Goldberg, M., Hane, L., Madubunyi, I., Vogl, S., Zetl, I.

Biochem. Pharmacol. 1986a Feb 1; 35(3): 538-41.

No abstract available.

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

Sonnenbichler, J., Zetl, I.

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

No abstract available.

Hepatitis C.

Strickland, D.K.

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

Effects of malotilate treatment on alcoholic liver disease.

Takase S, Matsuda Y, Yasuhara M, Takada A.
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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.

Effects of coenzyme Q10 on changes in the membrane potential and rate of generation of reactive oxygen species in hydrazine- and chloramphenicol-treated rat liver mitochondria.

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Arch Biochem Biophys. 1999 Jun 1;366(1):157-67.

Effects of CoQ10 and cycloheximide (CHX) on hydrazine- and chloramphenicol (CP)-induced morphological and some functional changes of mitochondria using cultured rat hepatocytes and effects on the process of recovery from CP intoxication using mouse liver were examined. Results obtained are summarized as follows: (1) The formation of megamitochondria induced in the hepatocytes cultured for 22 h in the presence of 2 mM hydrazine or CP (300 microgram/ml) was suppressed by pretreatment of hepatocytes with CoQ10 (1 microM) or CHX (0.5 microgram/ml). This was proved by electron microscopic analysis of mitochondria. (2) Treatment of hepatocytes with hydrazine for 48 h or longer caused decreases in the membrane potential of mitochondria, which were suppressed by CoQ10. (3) Treatment of hepatocytes with hydrazine for 22 h or longer caused remarkable increases in intracellular levels of reactive oxygen species in hepatocytes, which were suppressed by CoQ10. (4) The process of recovery from the CP-induced changes of mitochondria in mouse liver was accelerated by CoQ10 and CHX. Copyright 1999 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.

Bladder cancer and smoking in males: types of cigarettes, age at start, effect of stopping and interaction with occupation.

Vineis P, Esteve J, Terracini B.

Int J Cancer. 1984 Aug 15;34(2):165-70.

A case-control study of 512 male cases of bladder cancer and 596 male hospital controls (all living in the province of Turin, Northern Italy) has been analyzed for cigarette smoking. Relative risks (RRs) decreased with years since stopping, whereas they seemed not to change with age starting to smoke. A multiplicative effect of RRs for smoking and high-risk occupations was suggested. Filters exerted a protective effect (RR = 0.3 for smokers of filter-tip cigarettes only vs. smokers of non-filter-tip cigarettes). A previously unreported difference was noticed between black types and blond types of tobacco (RR = 0.4 for smokers of the blond types only vs. smokers of the black types, adjusted for age, average daily amount, years since stopping, occupation and use of filter).

Occupation and bladder cancer in males: a case-control study.

Vineis P, Magnani C.

A case-control study of 512 male cases of bladder cancer and 596 male hospital controls (all living in the province of Turin, Northern Italy, an area with a high proportion of car workers) has been analyzed for occupations. Relative risks were 1.8 (95% c.i. 0.9-3.6) for the textile industry, 3.8 (1.3-11.5) for the leather industry, 1.8 (0.8-4.0) for printing, 8.8 (2.7-28.6) for dyestuff production, 1.2 (0.6-2.4) for tire production and 2.5 (1.0-6.0) for other rubber goods, 2.0 (0.9-4.5) for brickyards and related activities. A relative risk of 3.1 (0.9-10.5) was found for turners having started work before 1940 and with at least 10 years of activity. For truck drivers the relative risk was 1.2 (0.6-2.5). A job-exposure matrix was developed for the development of new hypotheses; an association with bladder cancer was found for aromatic amines only. The attributable risk percent in the population was estimated as 10%, when only those occupations consistently associated with bladder cancer were considered.

The influence of personal activities on exposure to volatile organic compounds.

Wallace LA, Pellizzari ED, Hartwell TD, Davis V, Michael LC, Whitmore RW.
U.S. Environmental Protection Agency, Washington, D.C. 20460.

Environ Res. 1989 Oct;50(1):37-55.

Seven persons volunteered to perform 25 common activities thought to increase personal exposure to volatile organic chemicals (VOCs) during a 3-day monitoring period. Personal, indoor, and outdoor air samples were collected on Tenax cartridges three times per day (evening, overnight, and daytime) and analyzed by GC-MS for 17 target VOCs. Samples of exhaled breath were also collected before and after each monitoring period. About 20 activities resulted in increasing exposure to one or more of the target VOCs, often by factors of 10, sometimes by factors of 100, compared to exposures during the sleep period. These concentrations were far above the highest observed outdoor concentrations during the length of the study. Breath levels were often significantly correlated with previous personal exposures. Major exposures were associated with use of deodorizers (p-dichlorobenzene); washing clothes and dishes (chloroform); visiting a dry cleaners (1,1,1-trichloroethane, tetrachloroethylene); smoking (benzene, styrene); cleaning a car engine (xylenes, ethylbenzene, tetrachloroethylene); painting and using paint remover (n-decane, n-undecane); and working in a scientific laboratory (many VOCs). Continuously elevated indoor air levels of p-dichlorobenzene, trichloroethylene, 1,1,1-trichloroethane, carbon tetrachloride, decane, and undecane were noted in several homes and attributed to unknown indoor sources. Measurements of exhaled breath suggested biological residence times in tissue of 12-18 hr and 20-30 hr for 1,1,1-trichloroethane and p-dichlorobenzene, respectively.

Cirrhosis.

Wolf, D.C.

eMed. J. 2001 Sep 6; 2(9) (<http://www.emedicine.com/med/topic3183.htm>).

Obesity increases sensitivity to endotoxin liver injury: implications for the pathogenesis of steatohepatitis.

Yang SQ, Lin HZ, Lane MD, Clemens M, Diehl AM.
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Genetically obese fatty/fatty rats and obese/obese mice exhibit increased sensitivity to endotoxin hepatotoxicity, quickly developing steatohepatitis after exposure to low doses of lipopolysaccharide (LPS). Among obese animals, females are more sensitive to endotoxin liver injury than males. LPS induction of tumor necrosis factor alpha (TNF alpha), the proven affecter of endotoxin liver injury, is no greater in the livers, white adipose tissues, or sera of obese animals than in those of lean controls. Indeed, the lowest serum concentrations of TNF occur in female obese rodents, which exhibit the most endotoxin-induced liver injury. Several cytokines that modulate the biological activity of TNF are regulated abnormally in the livers of obese animals. After exposure to LPS, mRNA of interferon gamma, which sensitizes hepatocytes to TNF toxicity, is overexpressed, and mRNA levels of interleukin 10, a TNF inhibitor, are decreased. The phagocytic activity of liver macrophages and the hepatic expression of a gene encoding a macrophage-specific receptor are also decreased in obesity. This new animal model of obesity-associated liver disease demonstrates that hepatic macrophage dysfunction occurs in obesity and suggests that this might promote steatohepatitis by sensitizing hepatocytes to endotoxin.

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