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S-GH-7

NITRIC OXIDE SYNTHASE (NOS) EXPRESSION AND NITRIC OXIDE (NO) PRODUCTION IN CCL_4-INDUCED HEPATOTOXICITY OF RATS

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Background. Some chronic liver diseases such as hepatitis B, alcoholic liver diseases can cause liver cirrhosis. Cirrhosis is irreversible and the liver becomes permanently injured and scarred. Nitric oxide (NO) is an L-arginine derived, short-lived free-radical which is synthesized by three nitric oxide synthase (NOS) isoforms : constitutive endothelial NOS (eNOS), inducible NOS (iNOS) and neuronal NOS. NO is highly unstable in oxygenated, aqueous solution and will be oxidized to more stable nitrite (NO_2^-) and nitrate (NO_3^-). In normal liver, only eNOS is present and NO produced here is to regulate the hepatic blood flows. Under certain circumstances iNOS expression is increased. This in turn produces more NO inside the liver.Method. Severe liver damage / cirrhosis is induced in phenobarbital-primed rats intragastrically (group G) and intraperitoneally (group P) by CCl_4 together with corn oil (1:1) once weekly for twelve weeks and twice weekly for eight weeks respectively. Their drinking water was supplemented with phenobarbital sodium salt (350mg/L) throughout the cirrhosis induction period. A third group of rats, phenobarbital control rats (group C), was given phenobarbital sodium salts in their drinking water and treated with corn oil. A fourth group of untreated rats was taken as normal control (group N). Immunocytochemical staining (ICC), electron paramagnetic resonance (EPR) spectroscopy and nitric oxide analyzer (NOA) using chemiluminescence detection were applied in liver tissues and serum to indicate the relative amount / concentration of NOS, cyclooxygenase (Cox1 and Cox2), NO and NO_2^- together with NO_3^-. Liver tissues for light microscopy study were stained with haematoxylin and eosin (H&E) and trichrome. Liver histology was assessed using light microscopy. The degree of liver fibrosis was classified as grade 0 (normal liver) – grade 4 (cirrhosis), according to the severity of liver damage (Knodell's scoring system for fibrosis).Results. All CCl_4-treated rats developed hepatotoxicity with at least grade 3 fibrosis.

	Group N	Group C	Group (P + G)
No. of rats used	6	10	20
Mean grade of fibrosis	0	0	3.7±0.5
EPR intensity (cm)	1.35±0.67	0.76±0.15a	0.59±0.22a
NO_2^- / NO_3^- conc. (uM)	22.21±4.33	26.86±6.83b	17.97±7.36b
eNOS expression (%area)		5.73±0.26c	5.22±2.13c
iNOS expression (%area)		7.64±0.32d	6.63±2.48d

For a, p =not significant; b, p = 0.008; c, p = not significant; d, p = 0.001

When compared to Group P rats, Group G rats had lower EPR signal intensity (p = 0.0001), NO_2^-/NO_3^- concentration (p = 0.002), eNOS expression (p = 0.03) and iNOS expression (p = 5E-10). Conclusion And Hypothesis. CCl_4-induced hepatotoxicity in rats (Group G and Group P rats) reduced NO_2^-/NO_3^- concentration and iNOS expression, eNOS expression also showed a trend in reduction. We postulate that the reduction in iNOS expression is related to the loss of detoxification function in endstage liver damage. The trend in reduction of eNOS expression may be the result of damage to the microcirculation.

S-G-1

LOW DOSE RECOMBINANT HUMAN GROWTH HORMONE IN THE TREATMENT OF MALNOURISHED ELDERLY PATIENTS.

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High dose human growth hormone (rhGH) has been shown to improve nutritional status of malnourished older adults. It was uncertain whether low dose rhGH was effective and whether its effect on nutritional status would lead to improvement in physical function. The purpose of the present study was to determine the efficacy of low dose rhGH in treating malnourished geriatric patients and its effect on the physical function of these patients. Nineteen stable malnourished geriatric patients were randomized into two groups - low dose rhGH or placebo. Patients with cancer, infections, untreated depression or other secondary causes for malnutrition were excluded. In the rhGH group, 0.09 IU/Kg 3 times weekly were given together with appropriate dietary intervention as prescribed by our dietitian. In the placebo group, equal volume of normal saline 3 times weekly were given together with dietary intervention. There was no statistically significant difference in baseline demographic, nutritional, IGF-1 and physical function variables between the two groups. The GH treated group showed a more rapid gain in body weight, total lean body mass (i.e. +1.41 vs. -0.49 Kg., change in total lean body mass after 3 weeks- by bio-impedance method; p=0.007, unpaired t-test) and a faster improvement in 5-meter walking time (decrease in 5-m. walking time 27.45 vs. 0.45 sec. after 4 weeks; p=0.026, unpaired t-test) than the placebo group. The rise in IGF-1 at 4 week was significantly greater in the GH treated group (i.e. 49.07 vs. 17.52; p=0.04, unpaired t-test). There is no statistically significant difference for other nutritional variables. Conclusions: In our study, low dose rhGH was an effective adjuvant therapy for stable malnourished geriatric patient. It led to a faster gain in lean body mass, which was associated with greater improvement in walking speed when compared with dietary intervention alone.