

TOP Journal Club

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Chemoprevention of Helicobacter pylori-associated Gastric Carcinogenesis in a Mouse Model: Is It Possible?

Reference: J Biochem Mol Biol 2003 Jan;36(1):82-94

Although debates still exist whether Helicobacter pylori infection is really class I carcinogen or not, H. pylori has been known to provoke precancerous lesions like gastric adenoma and chronic atrophic gastritis with intestinal metaplasia as well as gastric cancer. Chronic persistent, uncontrolled gastric inflammations are possible basis for ensuing gastric carcinogenesis and H. pylori infection increased COX-2 expressions, which might be the one of the mechanisms leading to gastric cancer. To know the implication of long-term treatment of antiinflammatory drugs, rebamipide or nimesulide, on H. pylori-associated gastric carcinogenesis, we infected C57BL/6 mice with H. pylori, especially after MNU administration to promote carcinogenesis and the effects of the long-term administration of rebamipide or nimesulide were evaluated. C57BL/6 mice were sacrificed 50 weeks after H. pylori infection. Colonization rates of H. pylori, degree of gastric inflammation and other pathological changes including atrophic gastritis and metaplasia, serum levels and mRNA transcripts of various mouse cytokines and chemokines, and NF-kappaB binding activities, and finally the presence of gastric adenocarcinoma were compared between H. pylori infected group (HP), and H. pylori infected group administered with long-term rebamipide containing pellet diets (HPR) or nimesulide mixed pellets (HPN). Gastric mucosal expressions of ICAM-1, HCAM, MMP, and transcriptional regulations of NF-kappaB binding were all significantly decreased in HPR group than in HP group. Multi-probe RNase protection assay showed the significantly decreased mRNA levels of apoptosis related genes and various cytokines genes like IFN-gamma, RANTES, TNF-alpha, TNFR p75, IL-1beta in HPR group. In the experiment designed to provoke gastric cancer through MNU treatment with H. pylori infection, the incidence of gastric carcinoma was not changed between HP and HPR group, but significantly decreased in HPN group, suggesting the chemoprevention of H. pylori-associated gastric carcinogenesis by COX-2 inhibition. Long-term administration of antiinflammatory drugs should be

considered in the treatment of H. pylori since they showed the molecular and biologic advantages with possible chemopreventive effect against H. pylori-associated gastric carcinogenesis. If the final concrete proof showing the causal relationship between H. pylori infection and gastric carcinogenesis could be obtained, that will shed new light on chemoprevention of gastric cancer, that is, that gastric cancer could be prevented through either the eradication of H. pylori or lessening the inflammation provoked by H. pylori infection in high risk group.

Hepatic amino-acid metabolism in liver cirrhosis and in the long-term course after liver transplantation.

Reference: Transpl Int 2003 Jan;16(1):1-8

The aim of this study was to investigate the impact of orthotopic liver transplantation (OLT) on plasma levels and splanchnic turnover of key amino acids for muscular (branched-chain amino acids: BCAAs) and hepatic metabolism (aromatic amino acids (AAAs) and methionine) in 48 patients with cirrhosis, 14 patients after OLT, and 46 controls. Also, hepatic amino-acid supply and resting energy expenditure were measured.

BCAA levels (no hepatic uptake) decreased in cirrhosis ($P < 0.001$) and were improved, although not normalized, after OLT ($P < 0.001$). AAA and methionine levels were raised in cirrhosis ($P < 0.001$) and normalized after OLT ($P < 0.001$). Hepatic supply of these amino acids increased in patients graded Child B and C and decreased significantly after OLT. Splanchnic uptake of AAAs and methionine increased significantly in Child-B and decreased in Child-C patients. After OLT, splanchnic extraction of AAAs and methionine was as in Child A. Circulating AAAs and methionine correlated with indocyanine-green half-life ($r = 0.71$, $P < 0.001$) and resting energy expenditure ($r = 0.50$, $P < 0.001$), indicating that levels of circulating AAAs and methionine in cirrhosis are determined by hepatic and extra-hepatic metabolic factors.

This study demonstrates persistent changes in muscular metabolism of BCAAs after OLT, while the hepatic amino-acid metabolism is normalized due to (1) a significant reduction in the rate of peripheral proteolysis, and (2) improved liver function compared with that in patients with cirrhosis.

Severe catabolic state after prolonged fasting in cirrhotic patients: effect of oral branched-chain amino-acid-enriched nutrient mixture.

Reference: J Gastroenterol 2002;37(7):531-6.

BACKGROUND: Cirrhotic patients frequently undergo various medical procedures, such as diagnostic gastrointestinal endoscopy, without taking breakfast. The aim of the present study was to clarify the effect of longer fasting (> 12 h) on energy metabolism, and to test whether supplementation of an oral branched-chain amino-acid-enriched nutrient mixture (BCAA mixture), which contains various nutrients in addition to BCAA, could improve the catabolic state.

METHODS: Metabolic measurement was performed in 30 cirrhotic patients and 13 normal subjects, using indirect calorimetry.

RESULTS: Compared with that in the normal subjects, the respiratory quotient (RQ) was significantly lower after an overnight fast in the cirrhotic patients, indicating accelerated fat oxidation and a catabolic state. In addition, RQ in cirrhotic patients (n = 7) decreased rapidly with longer fasting, whereas that in the normal subjects (n = 5) showed relatively stable values. These results indicate that special care should be taken with medical procedures that are carried out in patients who have fasted. The effect of oral glucose, a carbohydrate-rich snack (rice ball), and the BCAA mixture (each, 210 kcal) on RQ was studied in 6 normal subjects and 6 patients with liver cirrhosis after an overnight fast. Supplementation of the carbohydrate-rich snack and the BCAA mixture (210 kcal each) elevated RQ and blood glucose levels to a similar degree in the cirrhotic patients. Oral administration of glucose (210 kcal) led to significantly greater elevation of blood glucose level than the other snacks, which may be unfavorable for cirrhotic patients, who frequently have glucose intolerance. In the 30 cirrhotic patients, supplementation with the BCAA mixture in the late evening significantly improved RQ in the early morning.

CONCLUSIONS: Carbohydrate-rich meals are used as a late evening snack in cirrhotic patients, but our study indicates that supplementation with a BCAA mixture can also be used to reduce fat oxidation in the early morning, with results similar to those with carbohydrate-rich snacks.

Effects of Cilostazol, a Selective Cyclic AMP Phosphodiesterase Inhibitor on Isolated Rabbit Spinal Arterioles.

Reference: Jpn J Physiol 2002 Oct;52(5):471-477

Cilostazol, a potent inhibitor of guanosine 3':5'-cyclic monophosphate (cGMP)-inhibited adenosine 3':5'-cyclic monophosphate (cAMP) phosphodiesterase (PDE3), has been used clinically for the treatment of chronic peripheral arterial occlusive disease. The beneficial effect of cilostazol is attributed to both anti-platelet aggregating activity and vasodilation. However, the effect of cilostazol on resistance-sized vasculature is not well documented. Furthermore, mechanisms of vasodilation and influence on endothelium function are not fully understood. Thus, we investigated the vasodilator action of cilostazol using isolated, pressurized rabbit spinal arterioles with special reference to the functional endothelium. Cilostazol, acetylcholine (ACh), isocarbacyclin (prostacyclin analogue), and sodium nitroprusside (SNP) all produced concentration-dependent vasodilations of isolated spinal arterioles with endogenous myogenic tone. The order of potency of these agonists was isocarbacyclin>ACh>SNP>cilostazol. Indomethacin (10 μ M, a cyclo-oxygenase inhibitor), N(omega)-nitro-L-arginine methyl ester (L-NAME, a nitric oxide synthase inhibitor, 30 μ M), or chemical denudation of the endothelial cells did not significantly alter the cilostazol-induced arteriolar dilation.

Furthermore, stimulating the release of endothelium-derived relaxing factors by administering ACh (100 nM), or treating with isocarbacyclin (1 nM) or SNP (3 nM) did not significantly modify the cilostazol-induced vasodilation. These results suggest that cilostazol produces the vasodilation of isolated, pressurized rabbit spinal arterioles independent of the functional endothelium. We infer that the vasodilator action of cilostazol in the spinal arterioles may be attributed to a yet unknown mechanism that is independent of the PDE3 inhibition.

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