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Dipeptides for the erosive colitis treatment and intestinal permeability stabilization: an experimental preclinical evaluation.

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Aim: Evaluate threonine dipeptides [threonil-threonine(THL) and threonil-threonine-Zinc(ThL-Z)] efficacy and safty at the dextran sulfate sodium (DSS) model of experimental mouse and rats erosive colitis(DSS-EC).

Material and Methods: This study consists of several phases.

Phase 1: Highly purified dipeptides synthesis.

Phase 2: Hypothesis confirmation that dipeptides THL and THL-Z have enteroprotective action. Phase 3: Toxicological screening by up-and-down (UDP) method with dose levels of 5, 50, 500, and 2000 mg/kg and calculate on ROC analysis, calculate No Observed Adverse Effect Level (NOAEL) and Lowest Observed Adverse Effect Level (LOAEL).

Phase 4: Dipeptides specific effect testing in mice and rats with DSS-EC model.

Phase 5: Complete standard toxicological assessment.

Phase 6: Publications on dipeptides THL and THL-Z search and analysis.

Phase 7: Final assessment of the efficacy and safety of the substance containing an equal proportion of the THL(10 mg) and THL-Z dipeptide (10 mg) [S-THL+THL-Z]. The study was conducted after approval by the local ethics committee. Data analysis and comparison was carried out using statistical processing software Statistica-6, version 6.1, series 1203d and Winpepi.

Results: Synthesized dipeptides with 98.5% purity. Both dipeptides administration does not worsen the model-specific changes in the intestine, liver, kidnes and does not metabolic disorders, does not increase the general manifestations histological changes severity of bowel mucous membrane. It was found that mucous membrane excessive permeability is significantly more common at the DSS-EC: 49.8% versus 6.2% with Chi-square: p = 0.0027, Fisher coefficient (bilateral assessment) p = 0.01. Dipeptides THL and THL-Z have shown efficacy: decrease disease activity index (DAI) and istological activity index (HAI). Toxicological data have shown a high degree of safety without mortalities caused by the investigational product at dose 5000 mg/ kg body weight for both THL and THL-Z. NOEL and LOEL parameters allowed calculating the therapeutic dose were determined. On DSS chronic colitis (28 days, with adition increased mucosal damage by rectal administration of 30% ethyl alcohol) treatment with S-THL+THL-Z give the following data: positive response Odds Ratio (OR) was 59.18, in the absence of signivicants adverse reactions (benefit 59 times the risk); complete remission came by the 2nd week according to DAI, and persisted by the 4th week; excessive permeability is significantly redused.

Conclusion: This study first time clearly demonstrated that threonine's dipeptides has positive efficacy at the experimental induced colitis and it may be very promising as a new medication for Inflammatory Bowel Disease.

Biography

Dr. Yury Marakhouski. approved as Professor of Clinical Medicine in 2005 year by the Higher Certification Commission of the Council of Ministers of the Republic of Belarus. He is head of the Department Gastroenterology and Nutrition of the Byelorussian Medical Academy of Postgraduate Education. He has published more than 30 papers in reputed journals and serving as a member of the editorial board of several reputed journals (predominantly in Russia and Belarus). His Current Position is Head of Department of Gastroenterology and Nutrition, Byelorussian Medical Academy Postgraduate Education (BelMAPE).He is principal investigator on numerous clinical (18) and preclinical (6) studies and has been involved in the study of many medication including mesalazine, amino acids, anti-TNF.