ヒドロキシプロリルセリン誘導体(JBP923と485)はラットで腸管吸収後、抗肝炎作用を示す

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Hydroxyprolylserine Derivatives JBP923 and JBP485 Exhibit the Antihepatitis Activities after Gastrointestinal Absorption in Rats

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Abstract: It had been a desire to develop orally effective therapeutic agents that restore the liver function in chronic injury. Here we demonstrated that *trans*-4-L-hydroxyprolyl-L-serine (JBP923) and cyclo-*trans*-4-L-hydroxyprolyl-L-serine (JBP485), which was previously isolated from hydrolysate of human placenta, exhibit potent antihepatitis activity after their oral administration. The increase in bilirubin concentration and activities of liver cytosolic enzymes in serum caused by α-naphthylisothiocyanate intoxication in rats were significantly countered both after i.v. and oral administration of these dipeptides, whereas glycyrrhizin, which has been used in the treatment of chronic hepatitis, is active only after its i.v. administration. Antihepatitis activity of dipeptides results, at least partially, from their direct effect on hepatocytes because glutamic-oxaloacetic transaminase and lactate dehydrogenase activities in the medium of hepatotoxin-exposed primary cultured hepatocytes were reduced by these compounds. When comparing the plasma concentration-time profile of JBP923 after its i.v., oral, and portal vein injection, it is suggested that JBP923 is almost completely absorbed from gastrointestinal lumen, and hepatic first-pass removal is minor. JBP923 inhibited the proton-dependent transport

of glycylsarcosine in brush-border membrane vesicles, suggesting that peptide transport system(s) may recognize JBP923. Thus, these dipeptides are potent antihepatitis reagents that are still active after oral administration and may be useful for clinical applications.

抄録 ヒト胎盤水解物より単離されたt-4-L-Hyp-L-Serとcyclo(t-4-L-Hyp-L-Ser)は経口投与で培養肝細胞の増殖を示した。α－ナフチルイソチオシアナートによる肝毒性で、ビリルビンや肝血漿中の逸脱酵素の流出が起きたラットで、これらペプチドのi.v.やp.o.投与で、その修復が認められた。これらペプチドの肝組織修復作用は直接効果によるのであることが、初代培養肝細胞中のグルタミン－オギザロ酢酸転移酵素や乳酸デヒドロゲナーゼの血漿中での減少によって証明された。t-4-L-Hyp-L-Serはラット小腸ブラシボーダ膜を通じてのプロトン依存グリシルサルコスチンの輸送を阻害するので、このペプチドはトランスポータを経て吸収されたと考えられる。

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