グルタチオン－デキストラン結合体のアセトアミノフェン肝障害に対する保護効果は分子量に依存する

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A Protective Effect of Glutathione–Dextran Macromolecular Conjugates on Acetaminophen-Induced Hepatotoxicity Dependent on Molecular Size

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Glutathion (GSH) was covalently attached to dextrans with various molecular weights of 2, 5, 10, 40, and 70 kDa by the cyanogen bromide activation method. The conjugates obtained synthetically were white or pale yellowish powders containing 6–10% (w/w) of GSH. The average moleular weights of the conjugates were estimated to be larger and the molecular weight distribution was a little broader than that of each original dextran. The conjugates signicantly stabilized GSH and liberated it gradually under physiological conditions ($t_{1/2}$=0.99–1.6h). Mice depleted of GSH by treatment with buthionine sulfoximine, a potent inhibitor of γ-glutamylcysteine synhetase, exhibited a significant increase in hepatic GSH level after intravenous injection of the conjugates. In mice given a hepatotoxic dose of acetaminophen, the survival rate increased progressively with coadministration of the conjugates, whereas a small improvement was found when free GSH was given. The conjugate of GSH attached to dextran with the molecular weight of 40 kDa exhibited the highest prophylactic effect on acetaminophen-induced hepatotoxicity in mice. The prolonged retention of the conjugates of large molecular weight in the circulation would cause a higher hepatic accumulation. These results Suggested that molecular size would be the most critical factor in the delivery of GSH, as a dextran conjugate, into the liver.

臭化シアン活性化法により、グルタチオン(GSH)と各種分子量のデキストランとの結合体を合成した。これらの結合体は生理的条件下でGSHを遊離放出した。GSHを枯渇させたマウスへ結合体を投与すると、肝のGSHレベルは顕著に上昇した。アセトアミノフェン急性肝毒性マウスに対して、結合体は延命効果を示した。この効果は分子量40kDaのデキストランを用いた結合体で最も高かった。これらの知見から、結合体の分子量を増大させることにより、体内滞留性が向上し、肝への集積性が高まると考えられた。