グルタチオン-デキストラン結合体の結合様式と高分子プロドラッグとしての性質

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Properties of soluble glutathione–dextran conjugates as a macromolecular prodrug dependent on the linkage structure

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GSH was covalently attached to dextran (T-40) by both the CNBr activation method and the $NaIO_4$ oxidation method. The conjugates, D-GSH(CNBr) and D-GSH($NaIO_4$), were water-soluble powder containing 10 and 25 w/w% of GSH, resectively, Mice were depleted of GSH by treatment with buthionine sulfoximine, a potent inhibitor of γ-glutamylcysteine synthetase. Intravenous administration of D-GSH(CNBr) led to a marked increase in the lever of GSH. However, administration of D-GSH($NaIO_4$) or free GSH had no significant effect on the hepatic GSH. In mice given a lethal dose of acetaminophen, the survival rate increased progressively with coadministration of D-GSH(CNBr), whereas little improvement was found when D-GSH($NaIO_4$) or free GSH was given. This was due to the distinction of the linkage structure between the conjugates;D-GSH($NaIO_4$) was too stable to release free GSH. The conjugate was transported into hepatic cells and, in the case of D-GSH(CNBr), was intracellulary hydrolyxed to free form, which protected mice from hepatotoxicity of acetaminophen.

These results suggested that the linkage structre would be the most critical in the delivery of GSH, as a dextran conjugate, into the liver.

臭化シアン活性化法及びメタ過ヨウ素酸酸化法により、グルタチオン(GSH)とデキストランの結合体（それぞれD-GSH(CNBr)及びD-GSH($NaIO_4$)を合成した。そ

れぞれ，10%及び25%のGSHを含有する結合体が得られた。GSHを枯渇させたマウスに静注すると、D-GSH(CNBr)では肝のGSHレベルが上昇した。致死量のアセトアミノフェンと同時に投与すると、D-GSH(CNBr)群の生存率はコントロールに比べて顕著に増大した。これらの効果は、D-GSH($NaIO_4$)やGSHの投与群では認められなかった。安定性の検討から、インビボ系での効果の違いは、結合体からのGSHの遊離放出性の差によるものと考えられた。