ラットにおけるフルオレセイン標識アラビノガラクタンの薬物速度論と体内挙動

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International Journal of Pharmaceutics, **201**, 59–69(2000)

Pharmacokinetics and Biodisposition of Fluorescein-labeled Arabinogalactan in Rats

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ABSTRACT: Fluorescein-labeled arabinogalactan (FA) was prepared by the reaction with FITC in methyl sulphoxide according to the method of deBelder and Granath. A systemic kinetic analysis of FA in rats was carried out by using a specific high-performance size-exclusion chromatography. Intravenous administered FA was rapidly eliminated from the blood circulation followed by an appreciable distribution to the liver and kidney. FA was accumulated in these organs over a long period whereas negligible levels of FA were detected in the other organs. A marked dose-dependency was seen in the hepatic uptake of FA which was markedly reduced by coinjected asialofetuin whereas the renal uptake of FA was not altered. Measurement of the hepatocellular localization demonstrated the overwhelming distribution of FA in the parenchymal liver cell fraction. Furthermore, the microscopic examination revealed FA that was effectively endocytosed by the parenchymal liver cells. These results suggested that FA which is bound to the asialoglycoprotein receptor with a high affinity is subsequently internalized to the hepatocyte *via* receptor-mediated endocytosis. FA was partially activated by periodate oxidation in order to acquire aldehyde groups to which guest molecules can be bound. A 12.5% oxidized arabinogalactan keeping a hepatocellular targetability showed a good conjugating reactivity to guest molecules *via* Schiff-base formation or by reductive amination. It was suggested that arabinogalactan can serve as a

potential carrier for the delivery of enzymes and drugs to the parenchymal liver cells *via* the asialoglycoprotein receptor.

抄録 deBelderらの方法により，フルオレセイン標識アラビノガラクタン（FA）を合成した．高速排除クロマトグラフ法によりラットにおけるFAの速度論的解析を行った．FAは静注後，肝と腎へ顕著にかつ長期間に亘って分布し，循環血液中からは速やかに消失した．FAの肝取り込みには，著しい投与量依存性が認められるとともに，アシアロフェツインの同時投与による阻害が確認された．肝細胞分布を検討したところ，FAの大部分は肝実質細胞に局在することが明らかになった．さらに，蛍光顕微鏡によってもFAは肝実質細胞へ効率よく取り込まれることが観察された．これらの知見は，アラビノガラクタンがアシアロ糖蛋白質受容体と結合し，肝細胞内へ取り込まれることを示唆するものであった．アラビノガラクタンにゲスト分子を結合させる目的で，過ヨウ素酸酸化を行った．12.5%酸化したアラビノガラクタンは肝への送達性を保持しつつ，シッフ塩基の生成あるは還元アミノ化によるゲスト分子との結合反応性を有していた．これらより，アラビノガラクタンはアシアロ糖蛋白質受容体を介した肝実質細胞への酵素や薬物の送達用運搬体として機能することが示唆された．