

Development of A Long Retention Drug Delivery System via Disulfide Bond and Hydrophobic Interaction with Serum Albumin

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論 文 名 : Development of A Long Retention Drug Delivery System via Disulfide Bond and Hydrophobic Interaction with Serum Albumin
(血清アルブミンとのジスルフィド結合および疎水性相互作用を利用した長時間保持型薬物送達システムの開発)

区 分 : 甲

論 文 内 容 の 要 旨

One of the greatest challenges to overcome in small therapeutics(<70kda) are the short resident time in blood due to the fast renal clearance. Human serum albumin (HSA) has been proven to be an excellent natural carrier to extend the drug plasma half-life for its abundance in blood (~600 μ M) as well as a long half-life more than 20 days. Because its ability to bind with neonatal fragment crystallizable receptor (FcRn) allows it to be recycled through the endosomal pathway rather than being broken down. To bind therapeutics with HSA in blood, hydrophobic interactions between an alkyl chain and the hydrophobic pockets of HSA have been used. Analogs of insulin and glucagon-like peptide-1 (GLP-1) which are applied to the treatment of diabetes utilize this strategy to extend their blood half-life. Despite the high affinity of the alkyl chain with HSA, the half-life extension achieved by this reversible hydrophobic interaction remains limited. In contrast, covalent binding with Cys34 of HSA has the potential to extend the half-life considerably. Disulfide bond formation with Cys34 was used with GLP-1, which contains activated disulfide, to form a disulfide exchange reaction with Cys34. However, these strategies targeting Cys34 with thiol-reactive groups may have a relatively slow rate of reaction with Cys34 of HSA in the blood, leading to undesired initial renal clearance. In this study, I developed a novel ligand with both a disulfide bond and fatty acid, which could interact with Cys34 and the hydrophobic pocket of HSA, respectively. It has the potential to be an ultra-long retention DDS.

In Chapter 2, I developed a novel long-acting drug delivery system based on HSA. The newly designed ligand features a fatty acid side chain and a pre-organized disulfide bond, enabling it to simultaneously bind to HSA's hydrophobic pockets and Cys34. Through fluorescence-labeled ligands, in vitro and in vivo, proof-of-concept experiments were completed. This dual-binding approach, relying on both covalent and non-covalent interactions, demonstrates a longer half-life compared to single-binding strategies, making it a promising platform for drug delivery.

In Chapter 3, GLP-1 was chosen as the first experimental drug for the system developed in Chapter 2. Three new GLP-1 analog suyamaglutides were designed and developed, and a ligand-modified GLP-1 synthesis route was explored. Challenges encountered during the synthesis and their solutions were discussed. Suyamaglutide Ver 1 is found to be difficult to obtain as the final product yield remained low. Suyamaglutide Ver 2 is successfully synthesized, also a suyamaglutide Ver 3 was proposed and expected to give a better therapeutic effect.

In Chapter 4, the author summarized the conclusion of this thesis and gave a future perspective.

The new strategy in this thesis may provide a fresh perspective into the development of long term drug delivery system based on HSA. This system could be the platform to extend small molecule drug half-life and treat several diseases.