Design of Ligand-polyrotaxane Conjugates for Controlling Biomolecular Interactions

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This dissertation describes structural design of ligand-polyrotaxane conjugate to control biomolecular interactions. The method of control of biomolecular interaction is classified two types. One is directly control of interaction between biomolecular and substrate by inducing of structure change of biomolecular or substrate. Second is control of interaction between binding sites and ligand by using more strongly ligand conjugates. Many ligand-polymer conjugates were studied for control biomolecular interactions. However, the structure and amount of the biomolecules are changing every time in the living body. This changing cannot be conformed by ligand-polymer (polymer chemistry). Therefore, ligand-polyrotaxane conjugates having supramolecular structure were chosen for control biomolecular interaction. The structures of chemical modified polyrotaxane (ligand-polyrotaxane) were controlled by the number of ligand, α-CD and/or molecular weight of PEG.

Carboxyethylester (CEE)-polyrotaxanes were designed for calcium chlation to inhibit of trypsin activity. The CEE-polyrotaxanes with the smallest number of CEE-α-CDs showed temporal interaction with trypsin, which might be main inhibition mechanism. The CEE-polyrotaxanes with the highest number of CEE-α-CDs showed greater inhibition of trypsin activity than PAA. Therefore, the mechanism and extent of trypsin inhibition can be controllable by the design of CEE-polyrotaxanes.

Maltose-polyrotaxane conjugates (MW of PEG 20,000) were designed for enhancing multivalent interactions with concanavalin A (Con A). Con A-induced hemagglutination was greatly inhibited by polyrotaxanes with 38% α-CDs threading. Spin-spin relaxation time (T_2) of maltose C (1) proton in the polyrotaxane by using ^{1}H-NMR at a typical α-CD threading 38 % was significantly larger than any other conjugates, which was well related to the inhibitory multivalent effect.

Sodium salts of Val-Lys(VK)-polyrotaxane conjugate were designed as a non-absorptive inhibitor for human peptide transporter hPEPT1. From the results of in vitro study, a VK-polyrotaxane conjugate using high molecular weight PEG (MW: 100,000) exhibited high inhibitory effect when many hPEPT1s were expressed HEK293 cells. From the results of *in vivo* study, the VK-polyrotaxane sodium salt conjugate was also effective on inhibition inhibiting the absorption of a model peptide (cefixime). Thus, it is concluded that the number of α-CD threading and molecular weight of PEG were important factors on the design of polyrotaxane conjugates to control biomolecular interactions.