Molecular Mechanism for Apolipoprotein E-Glycosaminoglycan Interaction

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The interaction of apolipoprotein E (apoE) with cell-surface heparan sulfate proteoglycans is an important step in the uptake of lipoprotein remnants by the liver. ApoE interacts predominantly with heparin through the N-terminal binding site spanning residues around 136-150. In this work, surface plasmon resonance (SPR) analysis was employed to investigate how amphipathic α-helix properties and basic residue organization in this region modulate binding of apoE to heparin. The apoE-heparin interaction involves a two-step process: apoE initially binds to heparin with fast association and dissociation rates, followed by a step exhibiting much slower kinetics. Circular dichroism and SPR experiments using a disulfide-linked mutant in which opening of the N-terminal helix bundle was prevented demonstrated that there is no major secondary or tertiary structural change in apoE upon heparin binding. Mutations of Lys-146, a key residue for the heparin interaction, greatly reduced the favorable free energy of binding of the first step without affecting the second step, suggesting that electrostatic interaction is involved in the first binding step. Discoidal apoE3/phospholipid complexes using a substitution mutant (K143R/K146R) showed similar binding affinity to wild type apoE3, indicating that basic residue specificity is not required for the effective binding of apoE to heparin, unlike to the low density lipoprotein receptor. In addition, disruption of α-helix structure in the apoE heparin binding region led to an increased favorable free energy of binding in the second step, suggesting that hydrophobic interactions contribute to the second binding step. Based on these results, it seems that cell-surface heparan sulfate proteoglycan localizes apoE-enriched remnant lipoproteins to the vicinity of receptors by fast association and dissociation.