Effects of Heparin on the Conformational Ensemble of R3 Fragment from Tau Protein

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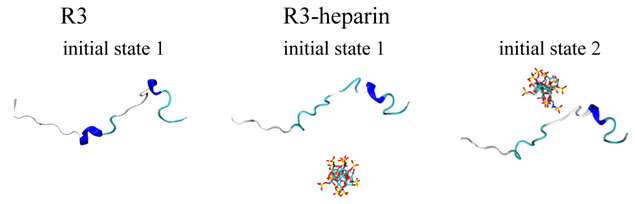
Introduction

The neurofibrillary tangles formed by abnormal aggregation of Tau inside neurons are involved in several neuronal diseases. R3, the third repeat fragment of Tau in microtubule-binding domain is critical to the formation of fibrillar aggregates of Tau[1]. Experimental studies indicate that the achievement of Tau aggregation needs the assistance of other molecules[2]. Heparin, a kind of polyanions, is widely used to promote the aggregation of Tau[3]. However, the mechanism underlying the Tau-heparin interaction remain mostly unclear. Here, we perform all-atom replica exchange molecular dynamics (REMD) simulations to investigate the molecular mechanism of R3-heparin interaction and conformational ensemble of R3 monomer at the atomic level.

Models and Methods

R3: VQIVYKPVDLSKVTSK CGSLGNIHHKPGGGQ
Heparin: $C_{12}H_{19}NO_{20}S_3$
Water Model: explicit water (TIP3P)
Method: REMD in NPT ensemble, temperature: 310 – 430 K
Force field: AMBER99SB-ILDN



Results

1. Isolated R3 monomer mainly adopts disordered coil conformations and the probability of β-structure is significantly reduced by heparin.

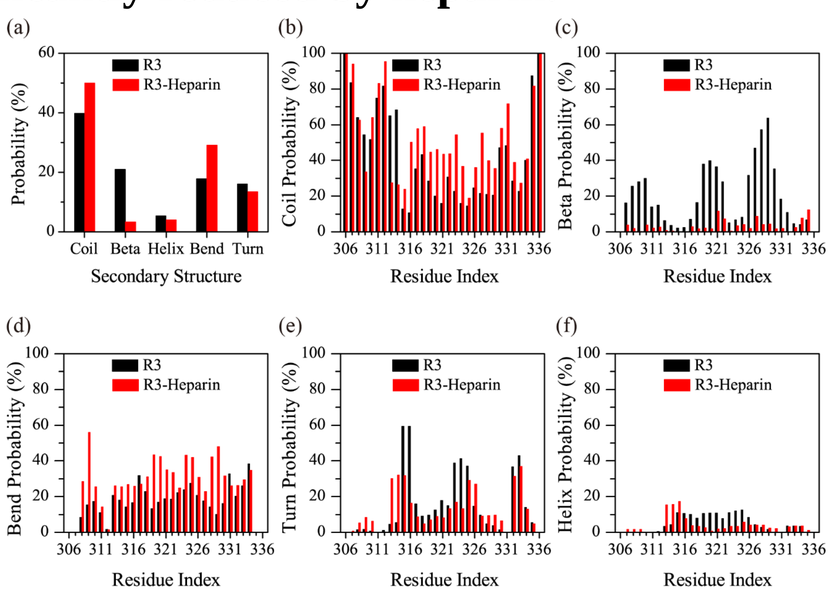


Figure 1. Secondary structure probability of R3 and R3-heparin.

2. Conformational ensemble of isolated R3 is larger than that of R3 with heparin.

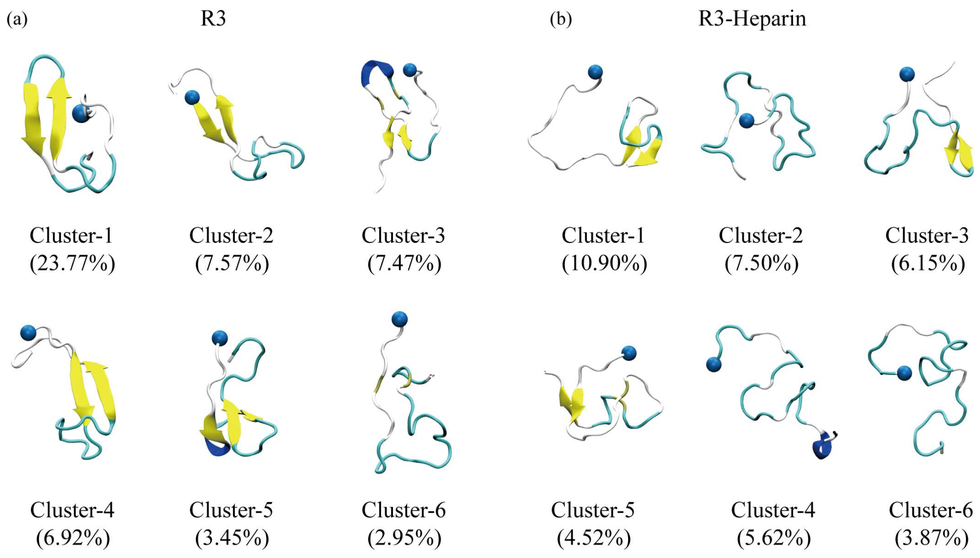


Figure 2. Representative conformations of the top six most-populated clusters of R3 monomer in R3 (a) and R3-heparin (b) systems.

3. Heparin extends the conformation of R3 monomer and reduces the number of hydrogen bonds in R3. As the R3-heparin contact number increases, the Rg of R3 increases, whereas the intra-peptide contact number decreases.

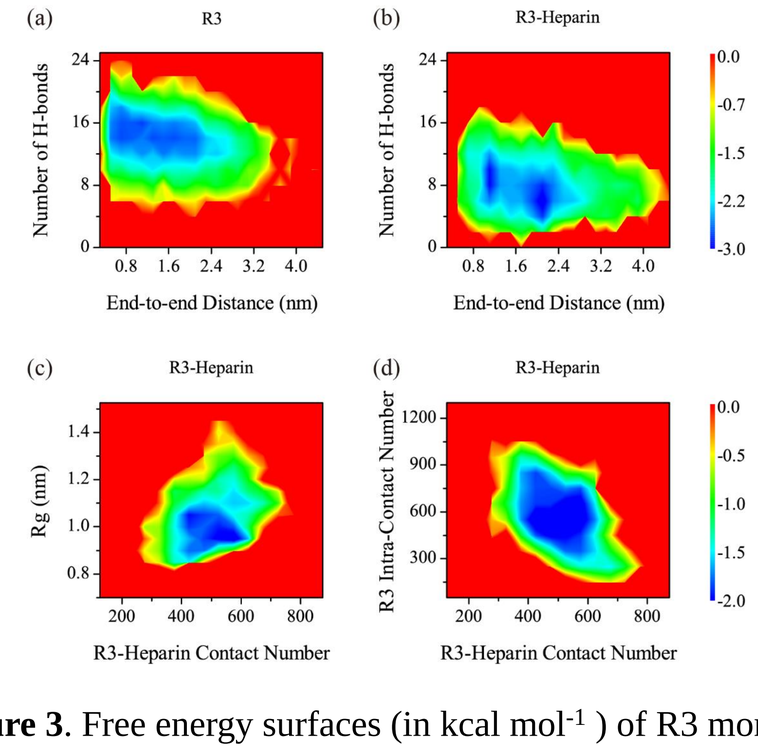


Figure 3. Free energy surfaces (in kcal mol^{-1}) of R3 monomer.

4. Heparin reduces the intra-peptide interaction. Positively charged residues Lys in R3 are the prominent interaction sites with the negatively charged heparin.

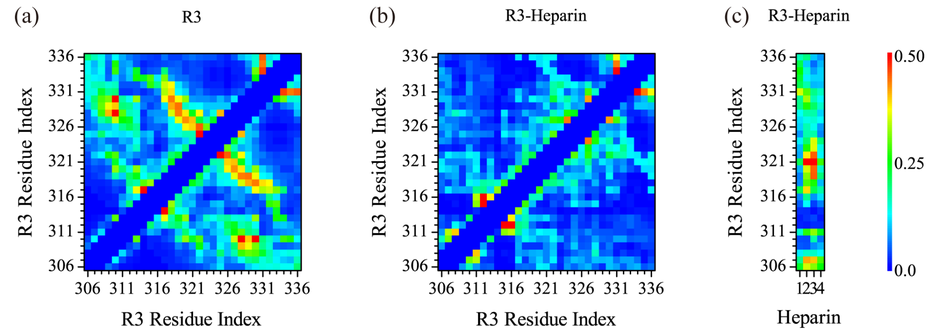


Figure 4. Contact probability maps.

5. Interaction of heparin with R3 inhibits the formation of salt-bridges in R3 and exposes the hydrophobic SASA of R3 around the core fibril nucleating motif.

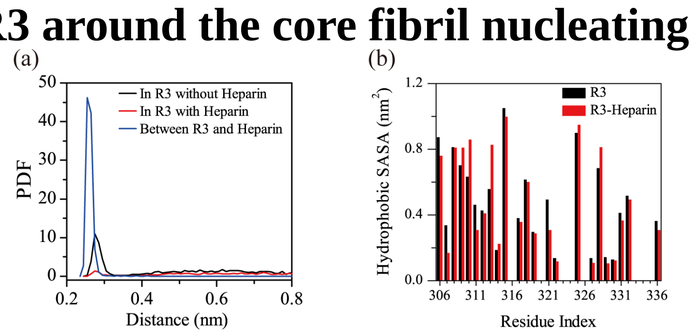


Figure 5. (a) PDF distribution of distance between positively and negatively charged residues. (b) Exposed surface areas of R3 monomer.

Conclusions

1. Isolated R3 monomer mainly adopts disordered coil conformations and a much lesser extent β-hairpin structures.
2. Heparin interacts strongly with residues Lys of R3 monomer, thus inhibits the formation of intra-peptide hydrogen bonds and salt-bridges.
3. Heparin extends the conformation of R3 monomer and exposes its fibril nucleating region, which facilitates R3-R3 interaction.

References

1. von Bergen, M. et al., PNAS 2000, 97 (10), 5129-34.
2. Montejo de Garcini, E., et al., Journal of Biochemistry 1987, 102 (6), 1415-21.
3. Goedert, M., et al., Nature 1996, 383 (6600), 550-3.