The binding process of BmKTX and BmKTX-D33H toward to Kv1.3 channel: a molecular dynamics simulation study

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Abstract

The potassium channel Kv1.3 is an important pharmacological target and the Kaliotoxin-type toxins (α-KTX-3 family) are its specific blockers. Here, we study the binding process of two kinds of Kaliotoxin-type toxins:BmKTX and its mutant (BmKTX-D33H) toward to Kv1.3 channel using MD simulation and umbrella sampling simulation, respectively. The calculated binding free energies are -27 kcal/mol and -34 kcal/mol for BmKTX and BmKTX-D33H, respectively, which are consistent with experimental results. The further analysis indicate that the characteristic of electrostatic potential of the α-KTX-3 have important effect on their binding modes with Kv1.3 channel; the residue 33 in BmKTX and BmKTX-D33H plays a key role in determine their binding orientations toward to Kv1.3 channel; when residue 33(or 34) has negative electrostatic potential, the anti-parallel β-sheet domain of α-KTX-3 toxin peptide will keep away from the filter region of Kv1.3 channel, as BmKTX; when residue 33(or 34) has positive electrostatic potential, the anti-parallel β-sheet domain of α-KTX-3 toxin peptide will interact with the filter region of Kv1.3 channel, as BmKTX-D33H. Above all, electrostatic potential differences on toxin surfaces and correlations motions within the toxins will determine the toxin-potassium channel interaction model. In addition, the hydrogen bond interaction is the pivotal factor for the Kv1.3- Kaliotoxin association. Understanding the binding mechanism of toxin–potassium channel will facilitate the rational development of new toxin analogue.

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