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An effective molecular blockers of ion channel of M2 protein as anti-influenza A drug

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Motivation:

Design of a drug molecule that can effectively bind to the M2 ion channel and block a diffusion of ions H^+ through and inhibit influenza A virus replication is an important task.

Methods

A new class of positively charged, +2, molecules is proposed to block diffusion of H^+ ion through the M2 channel. Several drug candidates, derivatives of a lead compound (diazabicyclooctane), is proposed and investigated. Molecular dynamics of thermal fluctuations of M2 protein structure and ionization-conformation coupling of all the ionizable residues were simulated at physiological pH via original methods [1]. The influence of the most probable mutations of key drug-binding amino acid residues in the M2 ion channel are investigated too.

Results

It is shown that the suggested blocker drug molecule has high binding affinity for the native and mutant M2 ion channel. There are two in-channel binding sites of high affinity for the native M2 protein, the first one demonstrates formation of two H-bonds with two of four serine residues Ser-31A (B) or Ser-31C(D), and the second one has H-bonds with two of four histidine residues His-37A (B), or His-37C(D). Six types of the most probable mutations of residues Ser-31A(B,C,D) are analyzed by the same computation protocol, as for the native M2 protein, and it is shown that the binding site with His-37A(B,C,D) residues is highly conservative with high binding affinity. Probability of double mutants, namely Ser-32 and His-37 is quite low and does not exceed 10^{-5}.The main advantages of the new drug molecule is the positive charge, +2, which creates a positive electrostatic potential barrier (in addition to a steric one) for a transfer of H^+ ion through M2 ion channel and may serve as an effective anti-influenza A virus drug.

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