Structural Basis for Anesthetic Binding on Voltage-gated Cation Channels
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Introduction: The microscopic modulation of voltage-gated ion channels by anesthetics is poorly understood. Previous experimental work showed that whereas K-Shaw2 is sensitive, the wild-type Kv1.2 channel is generally resistant to most general anesthetics. Interestingly, mutation of five residues in the Kv1.2 S4-S5 linker with the equivalent residues in K-Shaw2 converts the new construct (Kv1.2-FRAKT) into an anesthetic-responsive channel. Here, we employed the Molecular Docking technique allied with MD simulations to explore the structural basis that underlies the anesthetic sensitivity of Kv1.2-FRAKT.

Material and Methods: A MD-generated ensemble of membrane-equilibrated structures of K-Shaw2, Kv1.2 and Kv1.2-FRAKT, in the activated-open and resting-closed conformations, was subjected to docking calculations against a family of anesthetic chemotypes, composed by halothane, isoflurane, sevoflurane and propofol. Results and Discussion: Docking solutions were clustered into eight distinct binding sites according to their localization on the protein structure. In spite of similar affinities to distinct sites, the analysis shows that ligand binding to three specific spots is channel-conformation dependent. Specifically, “site 1” occurs exclusively in the activated-open structures of the anesthetic-sensitive isoforms, emerging thereby as one putative site accounting for the ligand action on these channels.

Conclusion: Taken together, our findings reveal binding sites that may underly channel-specific effects of general anesthetics providing thus new directions for further experimental investigation of this topic.

Palavras Chave: voltage-gated channel, anesthetic, molecular dynamics, docking
Patrocínio: FAP-DF, CNPq