Side Fenestrations Provide an "anchor" for a Stable Binding of A1899 to the Pore of TASK-1 Potassium Channels

Ramírez D.

Arévalo B.

Martínez G.

Rinné S.

Sepúlveda F.V.

Decher N.

González W.

A1899 is a potent and selective inhibitor of the two-pore domain potassium (K2P) channel TASK-1. It was previously reported that A1899 acts as an open-channel blocker and binds to residues of the P1 and P2 regions, the M2 and M4 segments, and the halothane response element. The recently described crystal structures of K2P channels together with the newly identified side fenestrations indicate that residues relevant for TASK-1 inhibition are not purely facing the central cavity as initially proposed. Accordingly, the TASK-1 binding site and the mechanism of inhibition might need a re-evaluation. We have used TASK-1 homology models based on recently crystallized K2P channels and molecular dynamics simulation to demonstrate that the highly potent TASK-1 blocker A1899 requires binding to residues located in the side fenestrations. Unexpectedly, most of the previously described residues that interfere with TASK-1 blockade by A1899 project their side chains toward the fenestration lumina, underlining the relevance of these structures for drug binding in K2P channels. Despite its hydrophobicity, A1899 does not seem to use the fenestrations to gain access to the central cavity from the lipid bilayer. In contrast, binding of A1899 to residues of the side fenestrations might provide a physical "anchor", reflecting an energetically favorable binding mode that after pore occlusion stabilizes the closed state of the channels.

A1899

drug-protein interaction

ion channels

molecular docking

molecular dynamics

TASK-1

monomer

n (2,4 difluorobenzyl) 2' [[[(4 methoxyphenyl)acetyl]amino]methyl]biphenyl 2 carboxamide

potassium channel

potassium channel TASK 1

tryptophan

unclassified drug

benzamide derivative

benzeneacetamide derivative

n (2,4 difluorobenzyl) 2' [[[(4 methoxyphenyl)acetyl]amino]methyl]biphenyl 2 carboxamide

nerve protein

potassium channel subfamily K member 3

tandem pore domain potassium channel

animal cell

Article

crystal structure

drug binding site

drug protein binding

female

hydrogen bond

lipid bilayer

molecular docking

molecular dynamics

nonhuman

oocyte

priority journal

Xenopus laevis

animal

antagonists and inhibitors

binding site

chemical phenomena

chemistry

human

metabolism

molecular dynamics

Animals

Benzamides

Benzeneacetamides

Binding Sites

Humans

Hydrophobic and Hydrophilic Interactions

Molecular Dynamics Simulation

Nerve Tissue Proteins

Potassium Channels, Tandem Pore Domain