Abstract: 125

Identification of the A293 (AVE1231) binding site in the cardiac two-pore-domain potassium channel TASK-1: a common low affinity antiarrhythmic drug binding site

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Background:
The two-pore-domain potassium channel TASK-1 regulates atrial action potential duration. Due to the atrium-specific expression of TASK-1 in the human heart and the functional upregulation of TASK-1 currents in atrial fibrillation (AF), TASK-1 represents a promising target for the treatment of AF. Therefore, detailed knowledge of the molecular determinants of TASK-1 inhibition may help to identify new drugs for the future therapy of AF.

Purpose:
In the current study, the molecular determinants of TASK-1 inhibition by the experimental antiarrhythmic compound A293 (AVE1231) were studied in detail.

Methods:
Alanine-scanning mutagenesis together with two-electrode voltage-clamp recordings were combined with in silico docking experiments.

Results:
Here, we have identified Q126 located in the M2 segment together with L239 and N240 of the M4 segment as amino acids essential for the A293-mediated inhibition of TASK-1. These data indicate a binding site which is different to that of A1899 for which also residues of the pore signature sequence and the late M4 segments are essential. Using in silico docking experiments, we propose a binding site at the lower end of the cytosolic pore, located at the entry to lateral side fenestrations of TASK-1. Strikingly, TASK-1 inhibition by the low affinity antiarrhythmic TASK-1 blockers propafenone, amiodarone and carvedilol was also strongly diminished by mutations at this novel binding site.

Conclusion:
We have identified the A293 binding site in the central cavity of TASK-1 and propose that this site might represent a conserved site of action for many low affinity antiarrhythmic TASK-1 blockers. Affinity blockers share one common drug binding site. Improved knowledge of the molecular determinants of TASK-1 inhibition may help to identify new compounds for AF therapy.
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