Panagiotis Xynogalos

Dr.med.

Class III- antiarrhythmic drug dronedarone inhibits Kir2.x inward rectifier potassium channels

Fach/Einrichtung: Innere Medizin

Doktorvater: Prov.-Doz. Dr. med. Edgar Zitron

Cardiac I_{K1} current is crucial for stabilizing the resting potential and for the terminal phase of cardiac repolarization. Drug effects on I_{K1} current have been associated with both anti-arrhythmic and pro-arrhythmic effects. In human cardiomyocytes the current is constituted by the potassium channel subunits Kir2.1, Kir2.2 and Kir2.3 which assemble to form heterotetramers.

Dronedarone is a novel amiodarone derivate that is clinically used for the treatment of atrial fibrillation. Its anti-arrhythmic properties are based on multi-channel effects which resemble those of amiodarone. After initially promising data from clinical trials, the use of dronedarone was restricted to patients without heart failure because of concerns with respect to proarrhythmia.

Dronedarone has been shown to cause a mild inhibitory effect on I_{K1} current in guinea pig cardiomyocytes. However, the molecular mechanisms underlying this effect have not been further investigated to date. The aim of this dissertation was to examine the pharmacological and molecular properties of dronedarone blockade of Kir2.1, Kir2.2 and Kir2.3 channels in an expression system.

Kir2.1, Kir2.2 and Kir2.3 were expressed in homomeric composition in Xenopus oocytes and experiments were performed with the two-microelectrode voltage clamp technique. Dronedarone induced an inhibition of homomeric Kir2.1 channels at high concentrations, but not of homomeric Kir2.2 or Kir2.3 channels. The inhibition was neither voltage dependent nor frequency dependent. Rectification properties of the channels were not altered. In order to further characterize the binding site of dronedarone, a set of mutated Kir2.1 channels was used in which pore residues that had already been linked to Kir2.1 drug binding had been mutated to alanine. Of those Kir2.1 mutants, only Kir2.1-E224A exhibited a loss of drug effect pointing to an essential function of E224 for binding of dronedarone. By contrast, in the other pore mutants the effect of dronedarone was not altered. In addition to drug binding in the channel pore, PIP_2 interference has been described as an alternative mechanism of Kir2.x

channel inhibition. In order to test a potential role of PIP_2 interference in the observed effects, the effect of dronedarone was examined in Kir2.1-K182Q mutants and no alteration in comparison to Kir2.1 wild type was found. Thus, overall these findings can be reconciled with a model of open channel block with an access of the drug from the intracellular side and binding in the channel pore. Finally, the effect of amiodarone was also tested under analogous conditions. Comparable to the effect of dronedarone, amiodarone also inhibited Kir2.1 channels at high concentrations without affecting Kir2.2 and Kir2.3.

These findings add to the mechanistic understanding of the inhibition of I_{K1} current by the new class III antiarrhythmic drug dronedarone. These effects may contribute to the anti-fibrillatory effectivity of dronedarone. However, they may also contribute to its proarrhythmic risk with respect to ectopic focal activity. Further studies are needed to evaluate the affinity and functional relevance of the effects of dronedarone on cardiac I_{K1} current in native cardiomyocytes and in vivo models.