UKE Paper of the Month Juli 2017

2′-Deoxyadenosine 5′-diphosphoribose is an endogenous TRPM2 superagonist

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ABSTRACT: Transient receptor potential melastatin 2 (TRPM2) is a ligand-gated Ca^{2+}-permeable nonselective cation channel. Whereas physiological stimuli, such as chemotactic agents, evoke controlled Ca^{2+} signals via TRPM2, pathophysiological stimuli such as reactive oxygen species and genotoxic stress result in prolonged TRPM2-mediated Ca^{2+} entry and, consequently, apoptosis. To date, adenosine 5′-diphosphoribose (ADPR) has been assumed to be the main agonist for TRPM2. Here we show that 2′-deoxy-ADPR was a significantly better TRPM2 agonist, inducing 10.4-fold higher whole-cell currents at saturation. Mechanistically, this increased activity was caused by a decreased rate of inactivation and higher average open probability. Using high-performance liquid chromatography (HPLC) and mass spectrometry, we detected endogenous 2′-deoxy-ADPR in Jurkat T lymphocytes. Consistently, cytosolic nicotinamide mononucleotide adenylyltransferase 2 (NMNAT-2) and nicotinamide adenine dinucleotide (NAD)-glycohydrolase CD38 sequentially catalyzed the synthesis of 2′-deoxy-ADPR from nicotinamide mononucleotide (NMN) and 2′-deoxy-ATP in vitro. Thus, 2′-deoxy-ADPR is an endogenous TRPM2 superagonist that may act as a cell signaling molecule.

STATEMENT:

The identification of 2'-deoxy-ADPR as an endogenous TRPM2 superagonist and potential novel second messenger is a major step towards understanding how channel activation is linked to physiological processes and disease.

BACKGROUND:

This work was performed at the Department of Biochemistry and Molecular Cell Biology in the group of Prof. Andreas H. Guse in collaboration with the groups of Prof. Barry Potter in the Department of Pharmacy & Pharmacology at the University of Bath and at Oxford University's Department of Pharmacology in the UK. The study was supported by the Deutsche Forschungsgemeinschaft (GU 360/16-1 to A.H.G.), the Wellcome Trust (Project Grant 084068 to B.V.L.P. and A.H.G.; Programme Grant 082837 to B.V.L.P.) and Landesforschungsforderung Hamburg (Research Group ReAd Me to A.H.G.).