Sudden death and ABCA1

M. TSUJITA^I, L. Alves da Silva^{II}, K. Nakasuka^{I,III}, Y. Seo^I, Z.H. Tseng^{IV}, R.C. Ford^V, T. Stockner^{VI}, S. Yokoyama^{VII}

^INagoya City University Graduate School of Medical Sciences, Nagoya, Japan, ^{II}Medical University of Vienna, Vienna, Austria, ^{III}Division of Cardiology, Department of Medicine, University of California, San Francisco, United States of America, ^{IV}Division of Cardiology, Department of Medicine, University of California, San Francisco, San Francisco, United States of America, ^VFaculty of Biology Medicine and Health, The University of Manchester, United Kingdom, ^{VI}Medical University of Vienna, Center for Physiology and Pharmacology, Vienna, Austria, ^{VII}Chubu University, Kasugai, Japan

Aim: We focused on one of the causes of sudden death, dyslipidaemia which leads to acute hypoglycaemia. Methods: The Abca1-null mice is a model of hypoalphalipoproteinemia. Probucol(prob) is an inhibitor of ABCA1. To visualise the drug function, we first investigated the docking pose of prob to ABCA1 using GOLD (Genetic Optimization for Ligand Docking), an in silico structural analysis application. The docking ability of cholesterol and POPC to the drug-ABCA1 complex was then investigated. Human ABCA1(PDB:5XJY) was used for the structure. To prepare the protein structure for docking calculations, all H₂O and other cofactors were removed and the hydrogen atoms were added using PyMOL. Energy minimisation was also performed to obtain optimised ligand-gometries. In the animal studies, WT and Abca1-null mice were treated with standard- or 0.2% prob-chow for 2 weeks. Plasma was collected for measurement of corticosterone(CORT) and ACTH. Results: The top-1 docking pose of prob to ABCA1 was found in the transmembrane helix pocket formed by TM7, 8 and 11. The hydroxyl groups at each end of prob were directed towards 11360 and V1768. No possible poses were found for cholesterol and POPC docking to prob-ABCA1 complex. Plasma CORT levels were 10-600 ng/ml plasma in WT. Abca1-null and prob-fed WT were between 0-80 and 5-210 ng/ml plasma, respectively. ATCH levels 30 min after CRF injection in WT and prob-fed WT were 0.5-0.7 and 0.8-2.8 ng/mL plasma, respectively. Conclusion: Genetic deletion of ABCA1 or its inhibition by prob, resulting in no docking of cholesterol and POPC, indicating no transport by this transporter, results in hypoalphalipoproteinemia. Plasma HDL cholesterol is the major source of cholesterol storage in the adrenal cortex of mice. Plasma glucose levels in these models dropped to dangerous levels during acute stress, leading to loss of consciousness, hypoglycaemic arrhythmias and sudden death, which we observed during anaesthesia and handling of these animals.