Sudden death and ABCA1

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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 H_2O 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 I1360 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.