Abstract

Reactive oxygen species (ROS) are thought to contribute substantially to the genesis and progression of atherosclerotic lesions. Therefore the antioxidative properties of antihypertensive drugs may play an important role beside their well known main mechanism of action. Moreover the lipophilic driven interaction with membranes may alter physicochemical membrane properties leading to 'feed-back' mechanisms of embedded enzymes.

The antioxidative effects of different dihydropyridine-calcium channel inhibitors (DHP; nisoldipine; BAY K 8644, nifedipine) in comparison to Angiotensin conversion enzyme inhibitors (ACE-Inh.: ramiprilate, enalapril, captopril) were investigated in an *'in vitro'* setting with superoxide ($^{\bullet}O_2^-$) generated radicals in aqueous solution and in the presence of multilamellar Dimyristoylphosphocholine (DMPC- MLV) vesicles. Furthermore influence of DHP and ACE-inhibitors on changes in membranous phase-transitions and -temperatures of MLV were calorimetrically studied. In a third experimental setup the membranous stabilities of 'giant unilamellar vesicles' (GUV) and intact trypsinised endothelial cells (EC) were analysed via 'pipette aspiration' against suction pressure in parameters of the area expansion modulus K_a. EC were investigated under control and conditions of enhanced ROS-formation ($c_{Glucose}$= 5 mmol/l and 30 mmol/l, respectively, here c_{drugs}=1 µmol/l).

The $^{\bullet}O_2^-$- formation was found to be diminished by the DHP and DMPC- MLV shifted this effect to nanomolar concentrations. In contrast the ACE-inhibitors have minor scavenging properties with no enhancement in the presence of lipids.

The calorimetric investigations revealed that the hydrophilic ACE-Inh. interact only with the polar headgroups of the lipid bilayer, while the DHP exhibited influence on the main phase- transition, indicating that these drugs interfere with the hydrocarbon core. This indicates that the lipophilic drugs soften the membranes but the pipette-aspiration assay showed that micromolar concentrations of DHP tended to increase the physical resistance of the GUV- membranes in contrast to the addition of ACE-Inh., identified by appropriate values of K_a. In EC ROS-induced cellular damage was indicated by destabilising of the cellular- membrane (from $K_{a,\ control}$ =701 mN/m to $K_{a,\ HG}$ =265 mN/m), which was attenuated in the presence of DHP (K_a =650 mN/m) and suppressed in part by ACE-Inh. (Ramiprilat: 60%).

Thus, in addition to the well known antioxidative effects of the DHP a membrane stabilising component may contribute to the pleiotropic mechanism of cell protection.