T2

Isolated bc_1 Complex as a Screening System for Potential Anti-Malaria Drugs

A. Müllebner[a], *T. Rosenau*[b], *A. Patel*[b], *L. Gille*[a]

[a]Research Institute of Biochemical Pharmacology and Toxicology, University of Veterinary Medicine Vienna,

[b]Department of Chemistry, University of Natural Resources and Applied Life Sciences, Vienna, Austria

Malaria is responsible for 1–2 million deaths per year. Therefore, the development of new and inexpensive anti-malaria drugs is required. The mitochondrial bc_1 complex in protozoa was identified as a suitable drug target for malaria antibiotics. The mechanism is based on a stronger inhibition of the bc_1 complex in plasmodia than in mammalian bc_1 complex. Aim of this study was to set up a model system for the screening of compounds with possible anti-malaria activity. Due to the sequence homology of the bc_1 complex in plasmodia and *Saccharomyces cerevisiae*, its bc_1 complex can be used as a model. Therefore, the membrane-bound bc_1 complex was isolated via a detergent-based solubilization and chromatographic purification from bovine heart mitochondria and from yeast mitochondria as models for mammals and plasmodia, respectively. The measurement of the quinol : cytochrome c oxidoreductase activity in both complexes gave turnover numbers of about 200 s^{-1} indicating a functional enzyme preparation. Titration of the enzymatic activity with stigmatellin revealed an IC_{50} of 2.15 ± 0.28 n*M* for bovine and 1.80 ± 0.19 n*M* for the yeast bc_1 complex indicating the non-selective toxicity of this compound. However, if the only available anti-malaria drug for this target atovaquone was used, an IC_{50} of 12.4 ± 1.08 µ*M* for bovine and 4.52 ± 0.35 µ*M* for yeast bc_1 complex was obtained. In contrast to stigmatellin, the drug atovaquone inhibits the yeast complex three times more than the mammalian bc_1 complex. These basic biochemical data indicate that the model consisting of isolated bovine and yeast bc_1 complex is suitable for the identification of new anti-malaria drugs.