DRUG-DRUG INTERACTIONS OF CYTOCHROME P450 3A4 STUDIED BY ELECTROCHEMISTRY

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Introduction Mammalian cytochrome P450s are the key enzymes involved in Phase I metabolism of clinically relevant drugs and contribute to the metabolism of a huge number of xenobiotics. Cytochrome P4503A4 (CYP3A4) is the major cytochrome P450 in human liver responsible for more than 60% of drug turn over. Whenever two drugs are administered together, the possibility of drug interactions exists if both drugs are metabolised by the same P450 enzyme. It is therefore very important to use in vitro screening methods to evaluate potential drug-drug interactions. Here we report the first such electrochemical interaction measurement for CYP3A4.

Methods Redox potential, drug metabolism and IC50 measurements were carried out using electrochemical techniques of cyclic voltammetry (under anaerobic conditions) and chronoamperometry.

Results The recombinant CYP3A4 was immobilised on glassy carbon electrode (GC) using a polyelectrolyte polymer (diallyldimethylammonium chloride) and cyclic voltammetry carried out under anaerobic conditions. The voltammograms showed a single redox couple with a midpoint potential of – 0.097 V (vs. NHE). The peak current was linear with scan rates up to 150 mV/s^{-1}, indicating that the protein was adsorbed on the electrode surface. Chronoamperometric experiments were then carried out in the presence of erythromycin as a substrate. Three different known inhibitors of CYP3A4 namely ketocanozole, cimetidine and diclofenac were then tested and their respective IC50s measured. The latter data are in good agreement with microsomal data.

Conclusion The findings constitute the first step towards the creation of an in vitro electrochemical platform for drug-drug interaction measurements.