Clozapine and levomepromazine induce the cytochrome P450 isoenzyme CYP3A4, but not CYP1A1/2, in human hepatocytes

P. Danek, A. Basinska-Ziobroni, W.A. Daniel, J. Wojcikowski
Institute of Pharmacology, Polish Academy of Sciences, Krakow, Poland

Introduction

CYP1A1/2 and CYP3A4 are jointly involved in the metabolism of ca. 70% of all the marked drugs. Induction of cytochrome P450 isoenzymes is one of the most common causes of undesired drug–drug interactions. In the case of therapeutic agents active in their parent form, induction increases their elimination rate and reduces the desired pharmacological effect, whereas as regards pro-drugs, the enhanced formation of their active metabolite(s) may produce an increased pharmacological effect. The aim of the present study was to ascertain whether the neuroleptics with different chemical structures and mechanisms of pharmacological action clozapine and levomepromazine may induce CYP1A1/2 and CYP3A4 in human liver.

Methods

Experiments were performed in vitro using inducible-qualified human cryopreserved hepatocytes from three different donors (Thermo Fisher Scientific, Walthman, MA, USA). For the treatment of cells, the neuroleptics were added to the culture medium at therapeutic concentrations of 0.25, 0.75 and 2.5 µM for levomepromazine and 1, 2.5 and 10 µM for clozapine. Each treatment lasted 72 h and was renewed every 24 h when the culture medium was changed. Afterwards, the culture medium was changed to a medium without the neuroleptics, but containing the CYP isoform-specific substrates, i.e. 1000 µM caffeine (CYP1A1/2) or 200 µM testosterone (CYP3A4). CYP isoenzyme activities were determined in the culture medium using the following CYP isoform-specific reactions: caffeine 3-N-demethylation (CYP1A1/2) and testosterone 6β-hydroxylation (CYP3A4). The concentrations of CYP-specific substrates and their metabolites formed in the culture medium were measured by the HPLC with UV detection. The levels of CYP1A1/2 and CYP3A4 proteins in hepatocytes were measured using human CYP1A1, CYP1A2 and CYP3A4 ELISA kits.

Fig. 1 The effect of levomepromazine and clozapine on CYP1A1/2 and CYP3A4 activities measured as the rates of specific reactions of caffeine and testosterone in a culture of human hepatocytes from different donors

Fig. 2 The effect of levomepromazine and clozapine on the CYP1A1, CYP1A2 and CYP3A4 protein levels in a culture of human hepatocytes

Results

1. Clozapine and levomepromazine at their highest concentrations significantly increased the activity and protein level of CYP3A4 in the cultures of human hepatocytes from three different donors.
2. Clozapine (10 µM) potently enhanced the activity and protein level of CYP3A4 up to 605% and 158% of the control value, respectively, while levomepromazine (2.5 µM) was weaker in that respect: it increased CYP3A4 activity and protein level up to 183% and 135% of the control value, respectively.
3. Lower concentrations of the drugs (levomepromazine 0.25 and 0.75 µM; clozapine 1 and 2.5 µM) did not produce any significant changes in the activity and protein level of CYP3A4.
4. The investigated neuroleptics at the tested concentrations exerted no statistically significant effect on the activity and protein level of CYP1A1/2.

Conclusions

By inducing CYP3A4, clozapine and levomepromazine may accelerate the metabolism of CYP3A4 substrates, i.e. the endogenous substrate testosterone and drugs (e.g. antidepressants, benzodiazepines, calcium channel antagonists, macrolide antibiotics). This, in turn, may lead to pharmacokinetic interactions, e.g. to a decrease in drug concentrations after their co-administration with clozapine or levomepromazine to patients.

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