INTRODUCTION

Cyclosporine A (CsA) is a powerful immunosuppressant drug widely used in transplantation procedures and in the treatment of several autoimmune diseases. However, its therapy is associated with numerous side-effects, especially dose-related cholestasis. Mechanism(s) underlying these effects remain(s) largely unknown. Tacrolimus (FK506), a macrolide immunosuppressant that possesses similar but more potent (10-100 folds) immunosuppressant properties compared to CsA, is considered as an alternative primary immunosuppressant to CsA in hepatic transplantation. The effect of FK506 on bile flow is at the moment unclear and little is known about its effect at the canalicular level. The aim of the present work was to perform a comparative study of FK506 and CsA on canalicular function using the well differentiated human HepaRG cell line, considering the great difference in the therapeutic doses of both drugs.

RESULTS

CsA inhibits canalicular efflux more potently than FK506

![Graph showing the effect of CsA and FK506 on canalicular efflux](image)

Data represent the means ± SEM

Effect of FK506 and CsA on NTCP

![Graph showing the effect of FK506 and CsA on NTCP](image)

Data represent the means ± SEM

Involvement of CpkC-P38 in CsA induced cholestasis

![Graph showing the involvement of CpkC-P38 in CsA induced cholestasis](image)

Generation of ROS and ER stress by CsA at high dose

![Graph showing the generation of ROS and ER stress by CsA at high dose](image)

SUMMARY

- CsA-dependent PKC-P38 is involved in CsA-induced cholestasis at low doses, however, at high doses CsA induces ROS generation and disruption of pericanalicular F-actin distribution.
- Our results support the conclusion that FK506 is not cholestatic at therapeutic doses.