cells, the MDR1 gene product P-glycoprotein (P-gp) operates as an ATP-driven efflux pump for lipophilic cationic compounds such as rhodamine 123 and doxorubicin; (2) the multispecific organic anion transport system (MOAT) mediates the canalicuar excretion of organic anions (bilirubin-glucuronide, sulfobromophthalein, glucuronides and glutathion-conjugates); (3) the bile salt export carriers. This study tests the effect of inhibitors of P-gp-mediated transport in tumor cells on their efficacy on the biliary secretory mechanisms taking advantage of a MOAT deficient rat strain (TR-rats) that lacks organic anion secretion. Cyclosporin A inhibits all these transport components and vesicular transport of fluid phase markers (horseradish peroxidase). In contrast low concentrations of PSC 833 (0.02 $\mu$M) and dexniguldipine (2 $\mu$M) exhibited a specific inhibitory effect on P-gp mediated transport only. Furthermore, cyclosporine A (1 $\mu$M) induced cholestasis, an effect not seen with PSC833 and dexniguldipin at the concentrations used. It is concluded that, in contrast to cyclosporin A, PSC 833 and dexniguldipin specifically inhibit P-gp mediated transport in liver. These different effects of PSC 833, dexniguldipin and cyclosporin A on hepatic transport could be of possible clinical relevance.

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## Differential inhibition by cyclosporins and dexniguldipine of ATP-dependent export carriers in the hepatocyte canalicular membrane

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Primary active ATP-dependent export carriers are recognized to play an important role in multidrug resistance of tumor cells and in the transport across the hepatocyte canalicular membrane. Inhibition of these carriers can restore the sensitivity of tumor cells to some chemotherapeutic drugs and may lead to cholestasis. The sensitivity of ATP-dependent transport of taurocholate, leukotriene $C_4$, and the anthracyclines daunorubicin and doxorubicin to inhibition by cyclosporin A, its non-immunosuppressive analog PSC 833 and dexniguldipine was studied in rat hepatocyte canalicular membrane vesicles. Cyclosporin A, PSC 833, and dexniguldipine inhibited the ATP-dependent taurocholate transport with $IC_{50}$ values of 1 $\mu$M, 1 $\mu$M, and 8 $\mu$M, respectively. ATP-dependent leukotriene $C_4$ transport was half-maximally inhibited by 6 $\mu$M cyclosporin A and 15 $\mu$M PSC 833; the corresponding $IC_{50}$ value for dexniguldipine was above 50 $\mu$M. ATP-dependent doxorubicin or daunorubicin transport was inhibited with $IC_{50}$ values of 4 $\mu$M, 0.8 $\mu$M and 0.3 $\mu$M for cyclosporin A, PSC 833 and dexniguldipine, respectively. The results allow for a functional distinction between these three ATP-dependent transport systems by means of the modulating agents dexniguldipine, cyclosporin A and PSC 833. Dexniguldipine was the most potent drug to inhibit ATP-dependent transport of the anthracyclines. Furthermore, this *in vitro* test system using hepatocyte canalicular plasma membrane vesicles is useful to detect inhibitory side effects which may lead to intrahepatic cholestasis. Inhibition of the ATP-dependent taurocholate export carrier in the canalicular membrane has been shown to induce cholestasis.

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## Effect of cyclosporine on serum cortisol levels in rabbits

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P-glycoprotein (P-gp) was found to be highly expressed in the adrenal cortex. The function of the P-gp in the adrenal cortex has not yet been defined. The aim of the present study was to determine whether the blockade of P-gp by cyclosporine (CsA), a known substrate for P-gp, alters the secretion of the cortisol in rabbits. Serum cortisol levels were measured at 8 am and 1 h and 8 h after ACTH stimulation test on day 1. The same procedure was repeated on day 7, after 6 days of CsA treatment. The ACTH stimulation test was performed by tetracosactide 0.5 mg i.m. at 8.30 am on days 1 and 7. The rabbits were treated by CsA 20–30 mg/kg/day s.c. from days 2–7. The whole blood CsA levels were measured on day 7, using commercially available fluorescein polarization immunoassay. Serum cortisol values were determined by radioimmunoassay adjusted for expected values. The mean whole blood CsA level in the first group of six rabbits treated by 20 mg/kg/day CsA was 1171 $\mu$g/l. This level was considered not to be optimal for P-gp blockade and the dose of CsA was increased to 30 mg/kg/day in the next group of three rabbits. In this group the mean whole blood CsA level was 2291 $\mu$g/l. The mean serum cortisol value at 8 am was found to be significantly higher on day 7, i.e. after CsA treatment, than on day 1, i.e. before CsA treatment (13.3 nmol/l (CI 95% 3.99–22.7) versus 1.67 mnol/l (CI 95% 1.28–2.05)). This difference was significant in the whole group of animals and in the group of six animals treated by 20 mg/kg/day of CsA, whereas in the group of three animals treated by 30 mg/kg/day CsA no difference was found in the two measurements. Mean serum cortisol value 1 h after ACTH stimulation was also found to be significantly higher on day 7 than on day 1 (72.3 nmol/l (CI 95% 56.4–88.2) versus 23.0 nmol/l (CI 95% 12.5–33.5)). No difference in these values was found in the groups treated by different doses of CsA; nor was any difference found between the mean