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Protein kinase C-dependent regulation of human hepatic drug transporter expression

Mayati, Abdullah ; Le Vee, Marc ; Moreau, Amélie ; Jouan, Elodie ; Bucher, Simon ; Stieger, Bruno ; Denizot, Claire ; Parmentier, Yannick ; Fardel, Olivier

Abstract: Hepatic drug transporters are now recognized as major actors of hepatobiliary elimination of drugs. Characterization of their regulatory pathways is therefore an important issue. In this context, the present study was designed to analyze the potential regulation of human hepatic transporter expression by protein kinase C (PKC) activation. Treatment by the reference PKC activator phorbol 12-myristate 13-acetate (PMA) for 48h was shown to decrease mRNA expression of various sinusoidal transporters, including OATP1B1, OATP2B1, NTCP, OCT1 and MRP3, but to increase that of OATP1B3, whereas mRNA expression of canalicular transporters was transiently enhanced (MDR1), decreased (BSEP and MRP2) or unchanged (BCRP) in human hepatoma HepaRG cells. The profile of hepatic transporter mRNA expression changes in PMA-treated HepaRG cells was correlated to that found in PMA-exposed primary human hepatocytes and was similarly observed in response to the PKC-activating marketed drug ingenol mebutate. It was associated with concomitant repression of OATP1B1 and OATP2B1 protein expression and reduction of OATP, OCT1, NTCP and MRP2 activity. The use of chemical PKC inhibitors further suggested a contribution of novel PKCs isoforms to PMA-mediated regulations of transporter mRNA expression. PMA was finally shown to cause epithelial-mesenchymal transition (EMT) in HepaRG cells and exposure to various additional EMT inducers, i.e., hepatocyte growth factor, tumor growth factor-1 or the HNF4 inhibitor BI6015, led to transporter expression alterations highly correlated to those triggered by PMA. Taken together, these data highlight PKC-dependent regulation of human hepatic drug transporter expression, which may be closely linked to EMT triggered by PKC activation.

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Fig. 1

A

B

Fig. 2

A

B

Fig. 3

A

B

Fig. 4

Fig. 5

□ - PMA ■ + PMA

Fig. 6

Fig. 7

Fig. 8

Fig. 9