S17-4 Development of therapeutic method against cholestasis by the regulation of cell-surface expression of Bile Salt Export Pump (BSEP/ABCB11)

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The efficient biliary excretion of bile acids is mediated by the bile salt export pump (BSEP/*ABCB11*), an ATP-binding cassette transmembrane transporter on the bile canalicular membrane. The functional repression of BSEP induces severe cholestasis. PFIC2 is a lethal hereditary disease caused by a mutation in BSEP gene. We have previously demonstrated that E297G and D482G BSEP, frequent mutations in European patients, result in impaired membrane trafficking, while both mutants retain their transport functions. Accordingly, restoration of the reduced cell-surface expression of these mutated BSEPs is an important task for achieving the therapeutic goal for PFIC2 patients with E297G and D482G mutations. Since 4-phenylbutyrate (4PBA), an FDA approved drug for urea cycle disorders, has been shown to restore the reduced cell-surface expression of mutated plasma membrane proteins, we investigated the effect of 4PBA treatment on E297G and D482G BSEP. Transcellular transport and cell-surface biotinylation studies using MDCK II cells demonstrated that 4PBA treatment increased the functional cell-surface expression of wild-type (WT), E297G, and D482G BSEP. The prolonged half-life of the cell-surface-resident BSEP produced by 4PBA treatment was responsible for this result. Moreover, treatment of SD rats with 4PBA resulted in an increase in Bsep expression at the canalicular membrane, which was accompanied by an increase in the biliary excretion of [^{3}H]taurocholic acid . In conclusion, 4PBA treatment with a clinically achievable concentration induces the functional cell-surface expression of WT, E297G, and D482G BSEP in MDCK II cells, and also induces functional Bsep expression at the canalicuar membrane in vivo. 4PBA is a potentially useful pharmacological agent for treating not only PFIC2 patients with E297G and D482G mutations but also other cholestatic patients, in whom the BSEP expression at the canalicular membrane is reduced. However, from the in vivo study using SD rats, a high dose is likely necessary for a satisfactory effect. To improve its clinical application, further studies are underway to identify more potent agents.