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**UNCONJUGATED BILIRUBIN MODULATES THE INTESTINAL EPITHELIAL
BARRIER FUNCTION IN A HUMAN-DERIVED, IN VITRO MODEL**

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Background and Aims. Unconjugated bilirubin (uBb) is known to promote intestinal secretion without affecting nutrient absorption or the enterocyte's digestive ability. In the current study, the effects of unconjugated bilirubin on the barrier function of the intestinal epithelium were investigated. **Methods.** Monolayers of human intestinal cell line CaCo-2 were challenged with unconjugated bilirubin at increasing concentrations or at different albumin/uBb ratio (Alb/uBb). Transepithelial electrical resistance and paracellular fluxes of 4kDa fluorescein isothiocyanate conjugate dextran were measured. Cell monolayer viability was studied using the MTT test. Enterocyte cytoskeletal actin organization was investigated with optic microscopy after phalloidin staining. **Results.** uBb induced a dose (50-400 μ M) and Alb/uBb-dependent decrease of transepithelial electrical resistance in CaCo-2 monolayers. This effect was maximal at 4-6 hours and tended to be reversed at 24 hours. Also, unconjugated bilirubin significantly increased fluorescent dextran paracellular passage. The cell viability was not affected by unconjugated bilirubin over the 50-500 μ M concentration range. Finally, uBb-treated monolayers clearly showed evidence of intracellular actin reorganization. **Conclusions.** In the studied model, unconjugated bilirubin modulates intestinal paracellular permeability probably via cytoskeletal actin rearrangement. This effect may be of particular relevance in the first days of life when intestinal permeability is a critical factor in exposure to food antigens and small bacterial products and increased unconjugated bilirubin concentrations are often present in the intestinal lumen. We also speculate that unconjugated bilirubin might affect the permeability of vascular endothelium, which is regulated similarly to epithelia.