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Neither SGLT-2 Specific Inhibitor nor SGLT-1 Specific Inhibitor, only Dual SGLT-2/1 Inhibitor can Reduce Glucose Absorption and Improve Ultrafiltration during Peritoneal Dialysis in Rats

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Objectives : We aimed to (i) explore whether both SGLT-1 and SGLT-2 are expressed, their respective anatomical localizations and proportions in human peritoneal biopsies; (ii) to elucidate whether only dual SGLT-1/SGLT-2 inhibition can reduce glucose absorption and improve ultrafiltration in uremia PD rats; (iii) to elucidate the underlying mechanisms.
Methods : The localizations and proportions of both SGLT-1 and SGLT-2 in human peritoneal biopsies were analyzed by immunohistochemistry and immunofluorescence. 48 male SD rats were then randomly were divided into six groups (each n=8): the sham group, uremia group, uremia PD group, empagliflozin-treated group (SGLT-2i), mizagliflozin-treated group(SGLT-1i) and sotagliflozin-treated group(dual SGLT-1/2i). We evaluated the structural and functional changes of peritoneum respectively.
Results : Both SGLT-1 and SGLT-2 were comparably expressed in human peritoneum, and they were prominently located in the endothelium and mesothelium. PD patients showed increased expressions of both SGLT-1 and SGLT-2 compared with healthy controls. In animal experiments, both SGLT-1 and SGLT-2 were also equally expressed in the peritoneal endothelium and mesothelium. Their expressions were both significantly increased by high-glucose PDF treatments but reversed by sotagliflozin-cotreatment. Compared to the sham controls, uremia rats were characterized by more glucose absorption, lower D/D_0 glucose ratio, higher D/P_{cre} ratio, higher D/P_{urea} ratio, and less net utrafiltration. After infusion of high-glucose PDF for 4 weeks, more marked changes were noted. Consistent with these functional changes, the uremia rats were characterized by more significant EMT process, significantly increased angiogenesis, significantly increased permeability of the peritoneal vasculature, accompanied by significantly increased levels of proinflammatory and profibrotic cytokines. Such changes were also further significantly enhanced in uremia PD rats, but markedly reversed by sotagliflozin co-treatment.
Conclusions : High-glucose PDF significantly increased the peritoneal expressions of both SGLT-1 and SGLT-2, which facilitate more glucose absorption, eventually leading to a vicious cycle. Only dual SGLT-2/SGLT-1 inhibiton can reduce glucose absorption and improve ultrafiltration during PD.