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5-HT2/5-HT2B receptor antagonism abrogates fibrotic potential of peritoneal fibroblasts by targeting STAT3 pathway in CAPD patients

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Objectives: Peritoneal fibrosis results in ultrafiltration failure in continuous ambulatory peritoneal dialysis (CAPD) patients. 5-hydroxytryptamine (5-HT; Serotonin) strongly induces extracellular matrix synthesis in peritoneal fibroblasts in a Transforming growth factor beta 1 (TGF-β1) dependent manner. We aimed to evaluate anti-fibrotic role of inhibitors of 5-HT and 5-HT (Terguride and SB204741), respectively in human peritoneal fibroblasts (HPFB) isolated from peritoneum of CAPD patients.

Methods: Peritoneal fibroblasts isolated from CAPD patients (n=6) and controls (n=8),were incubated with 5-HT (1μM)/TGF-β1 (10ng/ml) for 1 hour and later with 5-HT (1μM)/TGF-β1 (10ng/ml) and terguride or SB204741 (1μM, each) for 24 hours (Post-treatment strategy). In pre-treatment strategy, cells were pre-treated with terguride or SB204741 (1μM, each) for 1 hour and later with only 5-HT (1μM)/TGF-β1 (10ng/ml) for 24 hours. Real time PCR for pro-fibrotic (TGFB1, COL1A1, COL1A2, ACTA2, CTGF and FN1) and anti-fibrotic genes (MMP2/TIMP1) expression was performed. Type I collagen and α-SMA, phosphorylation status of Smad-3, ERK1/2, Src and STAT-3 was examined by western blotting.

Results: In 5-HT/TGF-β1 stimulated HPFB, upregulated pro-fibrotic gene expression was observed, which significantly reduced on co-culture with 5-HT /5-HT inhibitors, with no effect on anti-fibrotic genes mRNA expression. In 5-HT stimulated HPFB, treatment with both 5-HT inhibitors decreased type 1 collagen and α-SMA with reduced ERK1/2 phosphorylation, however, Smad-3 phosphorylation remain unaltered. In 5-HT/TGF-β1 simulated HPFB, 5-HT inhibitors decreased STAT3 phosphorylation, without affecting Src phosphorylation.

Conclusions: TGF-β1 mediated non-canonical pathways, ERK1/2 and STAT3 have been implicated in in the development of fibrosis. 5-HT receptor antagonists might reduce fibrotic potential of HPFB via suppression of TGF-β1 mediated non-canonical pathways.