CROSSTALK BETWEEN TOLL-LIKE RECEPTOR 4 AND DOPAMINE IN A MOUSE MODEL OF DEXTRAN SULFATE SODIUM-INDUCED COLITIS

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BACKGROUND: Changes in dopamine levels, deregulated dopaminergic machinery and altered Toll-like receptor 4 (TLR4) expression have been consistently associated with clinical and preclinical settings of IBD. In this study, we aimed to assess the crosstalk between the enteric dopaminergic system and TLR4 signaling in the enteric nervous system (ENS) of a mouse model of dextran sulfate sodium (DSS)-induced colitis.
METHODS: Male C57/Bl6 (WT) and TLR4-/- mice (8±1 weeks old; N=32 mice) received 1.5% DSS in drinking water for 5 days, switching thereafter to regular drinking water for 3 days. Small intestine inflammation was evaluated by measuring disease activity index and by histological analysis. Gastrointestinal transit was measured by nonabsorbable-FITC-labeled dextran distribution. Changes in ileal muscle tension were isometrically recorded following: i) cumulative addition of dopamine (0.1-300 μM); ii) electric field stimulation (EFS, 4 Hz) in presence of 30 μM dopamine with or without 10 μM SCH-23390 (D1R antagonist) or 10 μM sulpiride (D2R antagonist). Immunofluorescence distribution of the neuronal HuC/D or glial (GFAP and S100β) markers and dopamine β-hydroxylase (DBH) and dopamine transporter (DAT) were determined in longitudinal muscle myenteric plexus whole-mounts (LMMPs) preparations by confocal microscopy.
RESULTS: In WT mice, DSS treatment determined a delayed gastrointestinal transit, a reduction of dopamine-induced relaxation (-26%, N=5, P<0.05), reactive gliosis and 1.2-fold increase in DBH immunoreactivity. After DSS treatment TLR4-/- mice showed a significant increase in dopamine-induced relaxation (+30%, N=5, P<0.01) and a 2.3-fold increase in 4-Hz EFS-elicited contraction (N=5, P<0.001), which was sensitive to D1R and D2R activation. In DSS-treated TLR4-/- LMMPs, the ENS neurochemical coding was altered as evidenced by a reduced number of HuC/D+ neurons (-12%, N=5, P<0.05), a 1.4-fold increase of DBH immunoreactivity. No significant change was, however, observed in both GFAP and S100β staining.
CONCLUSIONS: In mice, TLR4 signaling influences the severity of small intestine inflammation as well as ENS activity and neurochemical coding, sustaining a dopaminergic-mediated control of the small intestine neuromuscular function.