

## SGLT2 inhibitors alleviate inflammatory bowel disease by downregulating NHE1 expression

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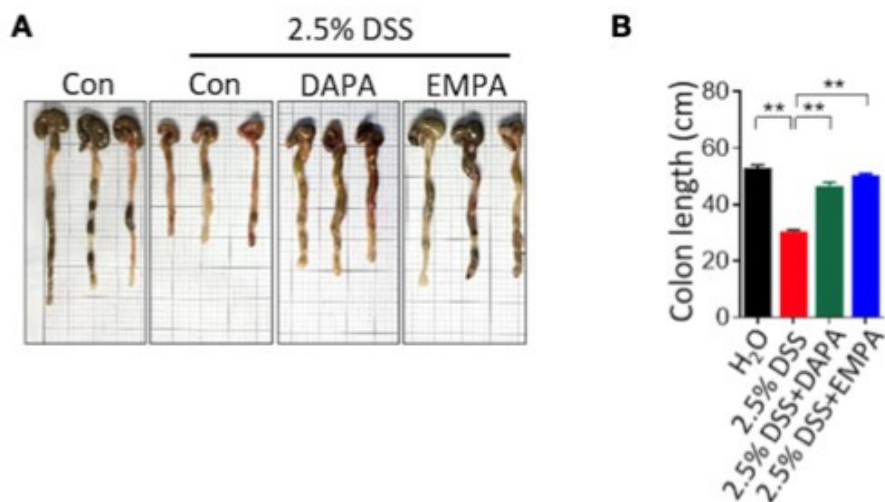
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**Background/Aims:** Classically M1 macrophages, characterized by aberrant glycolysis and secretion of inflammatory cytokines, play pivotal roles in inflammatory diseases, including inflammatory bowel disease (IBD). Recently, sodium-glucose co-transporter 2 (SGLT2) inhibitors were shown to suppress Na<sup>+</sup>/H<sup>+</sup> exchanger 1 (NHE1) and Na<sup>+</sup>/Ca<sup>2+</sup> exchanger 1 (NCX1) activity, regulating downstream intracellular Ca<sup>2+</sup> concentrations in cardiomyocytes. However, whether SGLT2 inhibitors regulate M1 macrophage polarization by downregulating NHE1 and NCX1 remains unknown.

**Methods:** We analyzed cellular responses to SGLT2 inhibitors using mouse bone marrow-derived macrophages and peritoneal macrophages treated with lipopolysaccharide (LPS). To induce IBD, we used dextran sulphate sodium salt (DSS)-induced colitis mouse model.

**Results:** We observed that NHE1 and NCX1 are overexpressed in LPS-treated macrophages, leading to M1 macrophage polarization. Mechanistically, NHE1 and NCX1-mediated Ca<sup>2+</sup> accumulation in the macrophage resulted in enhanced glycolysis by upregulating PI3K/AKT/mTORC1 signaling. SGLT2 inhibitors suppress both the levels and activities of NHE1 and NCX1, and consequently downregulate PI3K/AKT/mTORC1 signaling and glycolysis in LPS-treated macrophages. Inhibition of LPS-stimulated M1 polarization and cytokine production by SGLT2 inhibitors was observed in vivo, ex vivo, and in an IBD mouse model.

**Conclusions:** NHE1 promotes M1 macrophage polarization and SGLT2 inhibitor is a potentially novel strategy to treat M1 macrophage-mediated inflammatory diseases, including IBD.



**Fig. 1. SGLT2 inhibitors attenuate DSS-induced IBD in mice.** (A-B) Representative images (A) and length (B) of the colon of DSS-induced IBD mice treated with DAPA or EMPA. Data are expressed as means  $\pm$  SD of three independent experiments and are normalized against values measured in controls.  $p < 0.01$ , \*\*;  $p < 0.001$ , \*\*\*;  $p < 0.001$ . DAPA; dapagliflozin, EMPA; empagliflozin, DSS; dextran sodium sulfate, IBD; inflammatory bowel disease.