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Inhibition of soluble epoxide hydrolase attenuates high-sucrose diet-mediated gut barrier dysfunction

Jun-Yan Liu,[1] Ai-Zhi Lin,[2] Xian Fu,[2] Jiang Qing,[2] and Bruce Hammock[3]

[1]Chongqing Medical Univ; [2]Chongqing Medical University; and [3]Univ of California-Davis

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High sucrose is a typical feature of Western diet which has been reported as a causative factor for many morbidities. However, the associated underlying mechanisms remain largely unknown, and effective therapeutic strategies for high sucrose diet (HSD)-mediated organ injuries are an urgent need. Here we reported a soluble epoxide hydrolase (sEH) is a therapeutic target for HSD-mediated injuries to the gut barrier. Specifically, the mice fed with an HSD for 16 weeks resulted in gut barrier dysfunction including colon inflammation and tight junction impairment in a gut barrier. A target metabolomics analysis of murine colon tissue revealed that the reduced colon levels of epoxyeicosatrienoic acid caused by upregulation of its metabolic enzyme soluble epoxide hydrolase (sEH) contributed greatly to HSD-mediated gut barrier injuries. Next, administration of a chemical inhibitor of sEH to the mice fed on an HSD significantly attenuated HSD-mediated intestinal injuries by ablating HSD-mediated colon inflammation and improving the HSD-mediated impaired tight junction, which was further supported by the results from the mice with intestinal-specific knockout of the sEH fed on an HSD. Furthermore, *in vitro* studies revealed that treatment of EET significantly attenuated high sucrose-mediated intestinal epithelial inflammation and impaired tight junction but 5,6-dihydroxyeicosatrienoic acids, the product of EETs mediated by sEH, failed to do so. In addition, EETs but not DHETs, are anti-inflammatory and increases intestinal epithelial tight junction. This study provides insight into and therapeutic strategy for HSD-mediated gut barrier dysfunction.

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