Lack of transcriptionally active Nrf2 mitigates colon dysfunction in female mice – the role of estrogen receptors.

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The nuclear factor-erythroid-2-related factor 2 (Nrf2) is a key transcription factor regulating the cellular reduction-oxidation homeostasis and influencing the expression of numerous signaling pathways. We observed that Nrf2 transcriptional knockout (tKO) mice have inflammatory bowel diseases-like changes in the colon at basal condition. Additionally, these changes appear rather in females than males and lapse with age. However, those potentially harmful features do not influence mouse development and disease manifestation. Therefore, we aimed to verify how the lack of transcriptional activity of Nrf2 influences functionality of the intestines in young (3 m.o.) and older (6 m.o.) female mice with the functional Nrf2 (WT) or with the transcriptionally inactive form of Nrf2 (tKO). Moreover, to verify the role of estrogens in Nrf2 tKO females, some mice had implemented 17beta-estradiol-releasing (0.7-1.3 µg/day) or placebo implants (n=6 per group and test). Mice were subjected to functional tests of gastrointestinal track activity which included whole gastrointestinal transit, castor-oil induced diarrhea and colonic bead expulsion. After testing, mice were euthanized, venous blood was collected, and the intestines were dissected. The total macroscopic damage score was calculated for each animal and intestinal samples were preserved for histological staining and biochemical analysis of inflammation and estrogen receptors localization. The results indicated an age-dependent alterations in Nrf2 tKO females which included changed gastrointestinal tract function, microscopic alterations in the proximal colon, higher expression of estrogen receptor alpha as well as lower level of GPR30 receptors in the intestines. Additionally, treatment with 17beta estradiol influenced gastrointestinal tract functionality and estrogen receptors localization in Nrf2 tKO mice. Therefore, lack of transcriptionally active Nrf2 may influence function of gastrointestinal tracks in female mice and the estrogen receptor signaling may be implicated in those changes. (Study supported by the Sonata 14 program of the National Science Centre 2018/31/D/NZ4/00077 to APP).

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