Hyperhomocysteinemia decreases intestinal motility leading to constipation

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Abstract

Elevated levels of plasma homocysteine (Hcy) called hyperhomocysteinemia (HHcy) have been implicated in inflammation and remodeling in intestinal vasculature, and HHcy is also known to aggravate the pathogenesis of inflammatory bowel disease (IBD). Interestingly, colon is the pivotal site that regulates Hcy levels in the plasma. We hypothesize that HHcy decreases intestinal motility through matrix metalloproteinase-9 (MMP-9)-induced intestinal remodeling leading to constipation. To verify this hypothesis, we used C57BL/6J or wild-type (WT), cystathionine β-synthase ($CBS^{+/-}$), $MMP\text{-}9^{-/-}$, and $MMP\text{-}9^{-/-}$+ Hcy mice. Intestinal motility was assessed by barium meal studies and daily feces output. Plasma Hcy levels were measured by HPLC. Expression of ICAM-1, inducible nitric oxide synthase, MMP-9, and tissue inhibitors of MMPs was studied by Western blot and immunohistochemistry. Reactive oxygen species (ROS) including super oxide were measured by the Invitrogen molecular probe method. Tissue nitric oxide levels were assessed by a commercially available kit. Plasma Hcy levels in the treated MMP-9 group mice were comparable to $CBS^{+/-}$mice. Barium meal studies suggest that intestinal motility is significantly decreased in $CBS^{+/-}$ mice compared with other groups. Fecal output-to-body weight ratio was significantly reduced in $CBS^{+/-}$ mice compared with other groups. There was significant upregulation of MMP-9, iNOS, and ICAM-1 expression in the colon from $CBS^{+/-}$ mice compared with WT mice. Levels of ROS, superoxide, and inducible nitric oxide were elevated in the $CBS^{+/-}$ mice compared with other groups. Results suggest that HHcy decreases intestinal motility due to MMP-9-induced intestinal remodeling leading to constipation.