Ultra-low dose DPI is a cheap and effective potential therapeutic agent to prevent colitis-associated colorectal cancer

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Background: There are about 15-20% colorectal cancer developed from colitis. The most common forms of inflammatory bowel disease are Crohn's disease (CD) and ulcerative colitis (UC).The pathogenesis of UC and CD is various and including immunologic, environmental and genetic factors.Excessive reactive oxygen species (ROS) production has been observed in the inflamed mucosa of IBD patients. ROS is widely known as a negative factor on cancer initiation,progression and survival stage. NADPH oxidases (NOXs) are the main resource of ROS. Although diphenyleneiodonium (DPI) were assessed as inhibitors of both mitochondrial respiration and ROS synthesis and used in research for decades, few research using it as an potential drug in mice model.

Methods: We used male C57BL/6 mice were treated with 3.5% DSS and 2% DSS respectively for five days and seven days to make fatal enteritis and early stage colitis. After the DSS period, ultra-low dose DPI or control solvent was intraperitoneal injection everyday. Then, the survival rate and inflammatory level of intestinal tract in different groups were observed. Quantitative PCR and enzyme-linked immuno sorbent assay (ELISA) were applied to evaluate the inflammatory factors between experimental and control groups. Intracellular ROS were meatured by fuorescence microscopy using 2'7'-dichlorofluorescein diacetate(DCFH-DA). Htoxylin-eosin (H&E) staining assessed histological patterns of several organs in DPI group and control group. Disease activity index and histological activity index were assessed. Certain signal pathways were verified on protein level.

Results: In the fatal enteritis model, compared with control group, ultra-low dose DPI group has a better survival rate. In early stage colitis model, mice's weight and colon length are better than those in control group. The level of inflammatory factors--COX2, IL6 ,TNF-a and IL12 are lower than the control group. In RAW246.7 cell line, compared with other concentrations, ultra-low dose DPI group had a lower level of inflammatory factor, such as COX2, IL6, CCL5, IP10, TNF-a and MCP1.Utral-low dose DPI could inhibited NF-κB and MAPK pathway. Histological patterns of DPI and control groups had no significant differences.

Conclusion: Ultra-low dose DPI could prevent the progress of inflammatory bowl diseases and have no negative effect on other organs.This study will provide a new pharmacological evidence that ultra-low dose DPI has a positive significance for prevention of colitis-associated colorectal cancer.

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