Long term treatment with the dipeptidyl peptidase-4 inhibitor Sitagliptin, reduces carcinogenesis and reactive oxygen species in the colon of rats

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Subjects with type 2 Diabetes Mellitus (T2DM) and insulin resistance (IR) are at increased risk of developing colon cancer[1]. Anti-diabetic drugs stabilizing incretin hormones, such as inhibitors of dipeptidyl peptidase-4 activity (DPP4i) may affect colon carcinogenesis but the data present in the literature are controversial[2, 3]. Therefore, we studied whether long-term administration of the DPP4i Sitagliptin (SITA) affects 1,2-dimethylhdrazine (DMH)-induced colon carcinogenesis, a robust experimental model to identify drugs or dietary treatments with chemopreventive activity against colon cancer [4, 5]. Male F344 rats fed a high-fat (HF) diet promoting colon carcinogenesis and IR, were induced with DMH (100 mg/kg x 2 times). One week later, animals were allocated to two groups: one continuing with HF diet (Controls; n=8) or receiving SITA (n=8) mixed in the diet (260 ppm). Body weight, food consumption and glycemia were not affected by SITA. Fifteen weeks after DMH the number of the precancerous lesions Mucin Depleted Foci (MDF) was significantly lower in rats treated with SITA (MDF/colon: 9.5±0.9 and 6.4±0.9, in Controls(n=8) and SITA groups(n=8), respectively; means±SE, $P<0.05$). Reactive oxygen species (ROS) in the blood were also significantly lower in the SITA group (6.75±0.69 and 5.63±0.75 (H_2O_2 mM) in Controls (n=5) and SITA (n=6) respectively, means±SE $P<0.05$). DPP4 activity measured in the intestine was lower in rats treated with SITA, while the enzymatic activity in the plasma was not affected. Intestine growth morphometric parameters and colon proliferation, determined by Proliferating Cell Nuclear Antigen expression, were not affected by SITA. In conclusion, In conclusion, the results of this study show for the first time that SITA, a DPP4i with clinical effectiveness in the treatment of human T2DM, decreases colon carcinogenesis and blood ROS levels when administered to rats at a dosage similar to the human therapeutic setting. These results indicate a protective effect towards the carcinogenesis processes, which could be exploited in chemoprevention trials with patients at risk.

References:

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