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Preventive action of maleimide derivative 1-(4-Cl-benzil)-3-Cl-4-(CF_3-fenilamino)-1H-pyrrol-2,5-dion on rat's renal system in 1,2-dimethylhydrasine-induced colon carcinogenesis

Ochronne działanie pochodnej maleimidu 1-(4-Cl-benzyl)-3-Cl-4-(CF_3-fenylamino)-1H-pirolo-2,5-dionu na system nerkowy szczurów z karcinogenezą okrężnicy indukowanej 1,2-dimetylohydrazyną

INTRODUCTION

The development of target therapy makes patients' life quality and span better. Due to their selectivity, novel anticancer drugs target key molecules of signaling pathways in tumors such as tyrosine kinases not affecting normal tissues and cells [1, 7, 10, 11]. These compounds have different structures which requires accurate investigation. The novel maleimide derivative 1-(4-Cl-benzil)-3-Cl-4-(CF_3-fenilamino)-1H-pyrrol-2,5-dion (MI-1) has been synthesized using *in silico* design as a tyrosine kinases inhibitor [2]. MI-1 suppresses the proliferative activity of the transformed and tumor cell lines [9] and it does not affect normal fibroblasts and endotheliocytes [3, 5]. Low toxic effects of MI-1 were shown with respect to small intestine mucous membrane, pancreas, spermatogenic epithelium and liver of rats [3, 4]. The influence of MI-1 on the renal system deserves particular attention because of anti-cancer drugs nephrotoxicity.

The aim of this study is to evaluate the peculiarities of MI-1 action on the morpho-functional state of rat's kidneys in 1,2-dimethylhydrazine-induced colon carcinogenesis.

MATERIAL AND METHODS

The experimental model of colon carcinogenesis in adult white mail rats was induced by subcutaneous injections of 1,2-dimethylhydrazine (DMG, 20 mg/kg) one time per week during 20 weeks. Animals of the control group were injected 0.1 ml saline solution (control-saline). MI-1 in a dose 0.027 and 2.7 mg/kg was given *per os* to intact and 1,2-dimethylhydrazine-treated rats daily during the time. MI-1 was dissolved in 0.1 ml vegetable oil. Thus, there were other two control groups in the experiment: control-oil and control-oil+saline. All animals were examined for intestinal tumors.

The status of kidneys was evaluated after measurement of urea, creatinine and chlorides levels in blood serum using standard assay kit «PLIVA Lachema» (Chech Republic), histological examination and morphometry. Statistical analysis of significance was performed using a Student's *t* test.

RESULTS AND DISCUSSION

The number and size of intestinal tumors in both groups which were treated with MI-1 was lower than in a DMG-treated single group. The localization and morphology of tumors were different. In the MI-1 groups adenomas tumors were frequently located in the distal and proximal colon, whereas in the DMG-treated single group adenocarcinomas were located in the distal colon and rectum [8].

Biochemical investigation of blood serum and morphometrical investigation of renal tissues did not reveal significant changes in rats' kidneys after MI-1 daily administration during 20 weeks. But MI-1 in a dose 2.7 mg/kg caused an increased creatinine level by 35% versus control ($p \leq 0.1$) (Table 1) and some signs of vascular system damage and features of inflammation in the intersticium were observed. Both doses of MI-1 induced reduction of the tubular index by about 10% but epithelium thickness did not change significantly (Table 2). It indicates slight retention of initial urine, which might have been provoked by reabsorption disorders.

Table 1. The levels of creatinine, urea and chlorides in blood serum of rats in 1,2-dimethylhydrazine-induced colon carcinogenesis (M±m)

Group, dose, mg/kg	Creatinine, μM	Urea, mM	Chlorides, mM
Control-oil	73.69±9.11	7.71±0.71	107.81±4.34
MI-1, 0.027	77.81±10.56	8.64±0.54	107.7±2.91
MI-1, 2.7	99.82±10.56	7.31±0.48	105.61±1.08
Control-saline	56.18±5.6	7.49±0.37	110.56±4.15
DMG	61.4±5.34	6.71±0.37	105.53±1.97
Control-saline+oil	71.12±2.05	6.71±0.57	106.14±1.88
DMG+MI-1, 0.027	71.54±4.24	7.46±0.57	107.15±2.63
DMG+MI-1, 2.7	88.24±10.45	7.8±0.47	108.69±2.39

Injections of DMG were found to result in reduction of proximal tubules epithelial layer thickness by about nine per cent and increasing of lumen diameters by 17% in kidneys of rats with colon tumors. Thus, changes were revealed in the tubular index reduction by about 22% (Table 2). DMG invoked induction of distal tubules epithelial cells proliferate activity. Such a reaction was observed in rats with the most invasive tumors in colon [8]. The vast hemorrhages, thrombosis and stasis of small vessels were observed in kidney of DMG-treated rats.

Table 2. The influence of MI-1 on tubular apparatus of rats' renal system in 1,2-dimethylhydrazine-induced colon carcinogenesis (M±m)

Group, dose, mg/kg	Distal tubules			Proximal tubules		
	epithelium thickness, μm	lumen diameter, μm	tubular index	epithelium thickness, μm	lumen diameter, μm	tubular index
Control-oil	7.56±0.16	11.87±0.45	0.68±0.01	10.8±0.38	11.13±0.45	1.0±0.01
MI-1, 0.027	7.51±0.18	12.79±0.58	0.61±0.01*	10.95±0.28	10.95±0.46	1.03±0.04
MI-1, 2.7	7.44±0.15	12.15±0.26	0.62±0.02*	11.34±0.39	11.08±0.33	1.05±0.06
Control-saline	7.05±0.19	12.72±0.44	0.56±0.01	10.77±0.27	11.04±0.19	0.99±0.04
DMG, 20 mg/kg	6.98±0.19	12.36±0.29	0.58±0.02	9.85±0.3**	12.92±0.31**	0.77±0.02**
Control-saline+oil	7.11±0.13	12.64±0.16	0.56±0.01	11.3±0.17	11.73±0.59	0.99±0.06
DMG+MI-1, 0.027	6.97±0.13	12.25±0.31	0.58±0.02	10.18±0.19***	12.17±0.21	0.85±0.01
DMG+MI-1, 2.7	6.80±0.14	12.45±0.22	0.56±0.02	9.94±0.30***	11.31±0.59	0.90±0.04

* $p \leq 0.05$ versus control-oil ** $p \leq 0.05$ versus control-saline *** – $p \leq 0.05$ versus control-saline+oil

1,2-Dimethylhydrazine-induced colon carcinogenesis and its simultaneous administration with MI-1 did not disturb the levels of urea, creatinine and chlorides in blood serum (Table 1). It proved absence of functional disorders in the renal system. But vessels remained congested and leucocytic infiltration was observed in combined action conditions. MI-1 administration to DMG-treated rats was found to result in some preventive action on rats' renal system. Simultaneous administration of MI-1 and DMG did not induce the lumen increase of proximal tubules in contrast to that provoked by single 1,2-dimethylhydrazine action (Table 2). In addition, hyperplasia of distal tubules epithelial cells after combined administration was indicated only in one animal (MI-1 in dose 2.7 mg/kg) whereas for DMG-treated rats it was typical.

CONCLUSIONS

Thus, the novel maleimide derivative MI-1 reduces the frequency of preneoplastic changes in rats' kidney tubular epithelium in 1,2-dimethylhydrazine-induced colon carcinogenesis in spite of the functional disorders in kidneys after 10- and 30-days MI-1 administration, as it was shown in our previous research [6].

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SUMMARY

The novel maleimide derivative 1-(4-Cl-benzil)-3-Cl-4-(CF_3-fenilamino)-1H-pirol-2,5-dion does not cause significant structure-functional changes in rats' kidneys after 20 weeks' daily administration. The induction of proliferate activity of distal tubules epithelial cells and reduction of proximal tubules epithelial layer thickness in kidneys of rats with colon tumors in 1,2-dimethylhydrazine-induced colon carcinogenesis were observed. Maleimide derivative displays some preventive action to tubular apparatus of rats' kidney cortical nephrons and reduces the frequency of preneoplastic changes in tubules epithelial cells in experimental colon carcinogenesis conditions.

Key words: maleimide derivative, 1,2-dimethylhydrasine, renal system, colon carcinogenesis

STRESZCZENIE

Nowa pochodna maleimidu 1-(4-Cl-benzyl)-3-Cl-4-(CF_3-fenylamino)-1H-pirolo-2,5-dion nie powoduje istotnych zmian strukturalno-funkcjonalnych w nerkach szczurów po 20-tygodniowym podawaniu. Zaobserwowano indukcję aktywności proliferacyjnej komórek nabłonkowych kanalików dystalnych i spadek grubości warstwy nabłonkowej kanalików proksymalnych nerek szczurów z rakiem okrężnicy w przebiegu karcinogenezy indukowanej 1,2-dimetylohydrazyną. Pochodna maleimidu wykazywała pewien efekt ochronny na aparat kanalikowy nefronów korowych nerek szczurów i redukowała częstość zmian preneoplastycznych w komórkach nabłonkowych kanalików w warunkach doświadczalnej karcinogenezy okrężnicy.

Słowa kluczowe: pochodna maleimidu, 1,2-dimetylohydrazyna, system nerkowy, karcinogeneza okrężnicy