ONCOLOGY

A Weak Carcinogen Protects from a Potent Carcinogen Requiring No Metabolic Activation

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The weak carcinogen N-methyl-N'nitro-N-nitrosoguanidine injected 1 h before the potent carcinogen β-propiolactone decreased by half the incidence of induction and the number of tumors of the rumen in SWR mice. β-Propiolactone decreased the incidence of lung adenomas induced by weak carcinogen in these mice. Mutual effects of both compounds, which are inactivated in the body by a nonenzymatic route and requiring no metabolic activation for realization of their carcinogenic effects are probably realized through competition for targets.

Key Words: *N-methyl-N'nitro-N-nitrosoguanidine; β-propiolactone; anticarcinogenesis; tumors of the rumen*

1,2:3,4-Dibenzanthracene, a weak carcinogen, inhibits the carcinogenic effect of 7,12-dimethylbenzanthracene in mice [4]. The inhibitory effect was not due to inhibition of induced tumors because it was evaluated by the inducer activity of 7,12-dimethylbenzanthracene. It was suggested that the effect of 1,2:3,4-dibenzanthracene is realized through its effect on the activity of enzymatic systems, which detoxify the polycyclic carbohydrates in skin cells. 1,2:3,4-dibenzanthracene is an inductor of microsomal monooxygenases, but their activity increases under the effect of this agent no earlier than after 6 h, while carcinogenesis is inhibited if 1,2:3,4-dibenzanthracene is applied to the skin 5 min before the carcinogen [4]. 1,2:3,4-Dibenzanthracene may compete with 7,12-dimethylbenzanthracene for metabolically activating enzymes or for targets. Some compounds protect the animals from carcinogic effects of polycyclic carbohydrates, azo stains, and nitrosamines [6]. All these carcinogens require metabolic activation, and the protective agents as a rule affect the activity of xenobiotic metabolism enzymes, and therefore it is difficult to disclose the mechanism of their action on such chemical models.

SWR mice are highly sensitive to the gastric carcinogen β-propiolactone (PL) and weakly sensitive to N-methyl-N'nitro-N-nitrosoguanidine (MNNG) [2]. Both these carcinogens do not require metabolic activation, are water soluble, similarly exposed toward target cells inactivated in the stomach without enzymes, and their high or low carcinogenic activity in the cells they enter [5,7] is determined by the specific features of their effects on cell targets (or a common target). Therefore, mutual effects of these compounds on tumor induction are expected to be indicative of their competitive binding to targets. We tried to get experimental evidence of this an effect or its absence.

MATERIALS AND METHODS

Female SWR mice (Institute of Cytology and Genetics, Siberian Division of the Russian Academy of

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TABLE 1. Incidence and Multiplicity of Papillomas of the Rumen and Adenomas of the Lung in Mice Treated with MNNG and PL Alone or in Combination ($M \pm m$)

Group and exposure	Life time, days	Papillomas of the rumen		Adenomas of the lung	
		mice with tumors	tumors per mouse	mice with tumors	tumors per mouse
1: MNNG (n=18)	350±11.1	5 (27.8%)	1	12 (66.7%)	2.3±0.37
2: MNNG+PL (n=14)	338±15.3	7 (50%)*	1.6±0.3	5 (35.7%)	1.6±0.45
3: PL (n=12)	356±15.4	11 (91.9%)	2.9±0.85	2 (14.3%)	1

Note. *$p<0.05$ *vs.* group 3.

Sciences) were used. The animals were kept 7-10 per cage and fed natural fodder and water *ad libitum.* At the age of 6 months they were divided into 3 groups and administered (through intragastric tubes) 0.2 ml solutions containing 0.3 mg MNNG (group 1) or 2 mg PL (group 3) for 5 weeks. To group 2 animals, MNNG was administered like in group 1, and after 1 h PL, like in group 3. Basic solution of MNNG (Serva) in water was stored frozen; PL was synthesized from 2-iodopropionic acid at boiling temperature of 53-54°C/12 mm Hg (51-52°C/11 mm Hg according to the method of by Johanson). The doses of the carcinogen were $^1/_{20}$ LD_{50}. Mice were observed for 55 weeks. The animals that died during a 200-day period after the last administration of carcinogens were sacrificed at the end of experiment, and 1 ml 10% formalin was injected into the stomach *in situ.* The stomach and lungs were removed and immersed in formalin. For counting the tumors, the stomach was dissected along the minor and greater curvatures into 2 parts and examined with a magnifying glass. The adenomas in the lungs were counted. The significance of the differences in the incidence of tumors between experimental groups was evaluated using Fisher's arcsin transformation.

RESULTS

One-third of mice treated with MNNG and almost all (11 out of 12) mice injected PL developed gastric tumors: papillomas 0.5-5 mm in diameter, solitary in group 1 and generally multiple in group 3 (Table 1). By decreasing the number of administrations by half and the total dose of PL in comparison with the common dose [7], we created conditions for manifestation of the probable additive effect of carcinogens (group 2). However, the combination significantly decreased the incidence of gastric tumors and decreased it almost by half (Table 1).

In contrast to gastric tumors, the incidence of lung adenomas was higher in MNNG-treated mice (66.7%) than in PL-treated mice (14.3%). A clear-cut tendency to a lower incidence and a lesser number of adenomas was observed in group 2.

Thus, a weak carcinogen (MNNG for the rumen and PL for the lungs) administered before or soon after a potent carcinogen suppressed the tumor-inducing activity of the latter.

These data cannot be explained from a traditional viewpoint of the genotoxic mechanism of carcinogenic effects. There are many sites for potential reactions of the carcinogens with DNA and in the entire cell population of the rumen; the incidence of tumors and formation of adducts does not allow us to explain the protective effect of the weak carcinogen by its competition with the potent carcinogen for the same nucleotide in the same target cell. This effect might be explained by activation of the DNA reparation system which was damaged by the weak carcinogen. However, in our experiments, when the weak carcinogen was injected 1 h before or 1 h after the potent one, it could be expected to compete with this latter for the repair systems and therefore not attenuate, but potentiate its carcinogenic effect.

Our results suggest the presence of a target for carcinogens other than DNA. The probable targets are androgen and glucocorticoid receptors [3], other transcription factors, or some other regulatory molecules of target cells or the structures regulating them [1].

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