ACTION OF 7,8-BENZOFLAVONE ON INCIDENCE OF SKIN TUMORS INDUCED BY POLYCYCLIC HYDROCARBONS

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Tumors were induced in CBA mice or (C57BL × CBA)F_1 hybrids by application of benzo(a)pyrene (BP), 6-methyl-BP, 6-formyl-BP, or 7,12-dimethylbenz(a)anthracene (DMBA) to the dorsal skin. If 7,8-benzoflavone (BF) was mixed with the above compounds it reduced the carcinogenic action of the methyl-substituted hydrocarbons (DMBA and 6-methyl-BP) but did not affect the carcinogenic action of BP itself or of 6-formyl-BP. The inhibitory action of BF on carcinogenesis induced by methyl-substituted hydrocarbons is due, it can tentatively be suggested, to inhibition of oxidation of the methyl group.

KEY WORDS: carcinogenesis; carcinogens; 7,8-benzoflavone; antitumor action.

Numerous investigations have shown that for polycyclic aromatic hydrocarbons (PAH) to exhibit their carcinogenic action, they must first undergo preliminary enzymic activation. Modifiers of metabolism of the carcinogens therefore exert a strong influence on this process. The inhibitor of PAH metabolism 7,8-benzoflavone (BF) prevents carcinogenesis induced by 7,12-dimethylbenz(a)anthracene (DMBA) but does not affect the action of benzo(a)pyrene (BP) [1, 3]. This difference can perhaps be explained by the different individual properties of these carcinogens. However, a difference in principle between the pathways of activation of methyl-substituted and nonmethyl PAH to the "final" carcinogen cannot be ruled out. This difference could also be manifested during the action of an inhibitor of carcinogen metabolism such as BF.

To choose between these two possible explanations of the difference between the action of BF on carcinogenesis induced by BP and DMBA, in the investigation described below the action of this inhibitor was studied on carcinogenesis induced by DMBA, BP, 6-methyl-BP, and 6-formyl-BP. The last compound is a nonmethyl-substituted BP.

EXPERIMENTAL METHOD

BP and DMBA were obtained from Fluka, BF from Chemapol, and the 6-substituted BPs were synthesized in the Oncologic Scientific Center by Candidate of Chemical Sciences O. A. Pan'shin by the method described previously [2].

In the experiments of series I and II male CBA mice were used, and in the other series hybrid male (C57BL × CBA)F_1 mice. The animals were divided into nine groups, with 30 mice in each group, depending on the experimental conditions.

Altogether 20 applications each of two drops of a solution of the PAH in benzene or a mixture of the PAH with BF were made to the depilated skin of the interscapular region of all the animals once a week. In groups 1 and 2 1mM solutions of DMBA and BF and in groups 3-9 8 mM solutions of the PAH and BF were used. Each mouse in the first two groups received approximately 100 μg of the substance, and in all the other groups 800 μg. The animals of groups 1 and 2 remained under observation for 12 months and of the remaining groups for 15 months. At the end of the experiment all the surviving mice were killed and the skin tumors taken for histological examination. The differences in the doses and times of observation were due to the fact that DMBA has a more powerful carcinogenic action.

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TABLE 1. Effect of BF on Tumor Development in Mice

Group of mice	Substance	Number of mice						Time of appearance of first tumor in group (months of experiment)
		at beginning of experiment	at time of appearance of first tumor	with tumors				
				carcinoma		papilloma		
				abs.	%	abs.	%	
1	DMBA	30	28	21	75,0	1	5,6	3rd
2	DMBA + BF	30	30	4	13,3	1	3,6	7th
3	BP	30	27	24	80,0	2	6,6	3rd
4	BP + BF	30	30	22	73,3	5	16,6	4th
5	6-Methyl-BP	30	30	19	63,3	5	16,6	5th
6	6-Methyl- BP + BF	30	30	3	10,0	5	16,6	7th
7	6-Formyl BP	30	30	2	6,6	5	16,6	7th
8	6-Formyl-BP + BF	30	30	1	3,3	3	10,0	8th
9	BF	22	22	0	0	0	0	—

Legend. Observations on mice of groups 1 and 2 lasted 12 months, on mice of groups 3-9 15 months.

EXPERIMENTAL RESULTS

As Table 1 shows, BF considerably inhibited the carcinogenic action of both methyl derivatives of PAH used in the experiments. The first tumor appeared later in these groups treated with BF and the number of animals with skin tumors at the end of the experiment was significantly less than in the groups without BF. When BP and 6-formyl-BP were used as inducers of carcinogenesis, BF had virtually no inhibitory action and only a tendency toward a reduction in the incidence of tumors and their slightly later appearance were noted.

Comparison of the carcinogenic action of the PAH used (groups 1, 3, 5, and 7) showed that as regards the degree of carcinogenic activity they were arranged in the following order:

DMBA > BP > 6-methyl-BP > 6-formyl-BP.

It must not be forgotten that DMBA was used in a concentration only one-eighth that of BP and its derivatives, so that it caused tumors in a rather lower dose than BP.

The results thus showed that BF is an inhibitor of the carcinogenic action of methyl-substituted PAH but has a very weak effect on carcinogenesis induced by nonmethyl derivatives or unsubstituted compounds. Since BF *in vitro* is an inhibitor of the mono-oxygenase system, which is responsible for PAH metabolism, it can be postulated that the inhibition of carcinogenesis observed in these experiments was due to inhibition of one stage of conversion of methyl-substituted PAH which is absent during activation of unsubstituted PAH. This stage could perhaps be oxidation of the methyl group to hydroxymethyl. This stage is evidently essential for manifestation of the carcinogenic action of methyl-substituted PAH and is absent during the oxidation of unsubstituted PAH.

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