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ROLE OF VITAMIN A IN CHEMICAL CARCINOGENESIS OF THE MAMMARY GLAND

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The effect of feeding rats with large doses of vitamin A on the concentration of the polycyclic hydrocarbon 7,12-dimethylbenz(a)anthracene (DMBA) and its metabolites in various organs and in the blood and also on the rate of metabolism in the liver of rats after intravenous injection of the carcinogen were studied. In hypervitaminosis A the quantity of DMBA and its metabolites was found to be considerably reduced in all the organs tested and in the blood. The rate of DMBA metabolism in the liver of the animals increased with an increase in the dose of vitamin A.

KEY WORDS: hypervitaminosis A; 7,12-dimethylbenz(a)anthracene; metabolism; carcinogenesis of the mammary gland.

During the last decade the anticarcinogenic activity of vitamin A has been studied in many countries. It has been shown that vitamin A has a prophylactic action and, in some precancerous states, a therapeutic action also in experimental animals. Preliminary feeding with large doses of vitamin A protects animals against induction of cancer in them by various chemical carcinogens [2]. The anticarcinogenic action of vitamin A in such cases may be due to modification of metabolism of hydrocarbons in the body [9] and to a change in the level of the carcinogen or of its carcinogenic metabolite in the target organ. Some workers consider that the concentration of a carcinogen in the target organ is an important factor for the induction of tumors by polycyclic hydrocarbons [4].

The object of this investigation was to study the concentration of a carcinogen and its metabolites in certain organs and in the target organ during induction of mammary gland cancer in rats receiving large doses of vitamin A.

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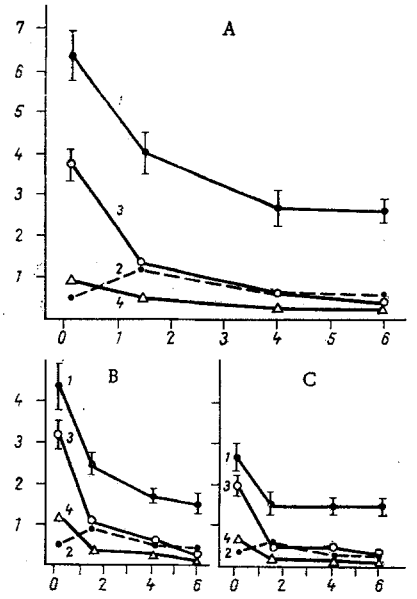

Fig. 1. Concentration of DMBA-^{3}H and its metabolites in organs and blood of rats after intravenous injection of 2 mg DMBA with an activity of 10 μCi. A) Control rats; B) rats receiving $150 \cdot 10^3$ i.u. of vitamin A; C) rats receiving $250 \cdot 10^3$ i.u. of vitamin A. 1) Liver; 2) mammary gland; 3) adrenals; 4) blood. Here and in Figs. 2 and 3: abscissa, time of investigation (in h); ordinate, radioactivity (in Figs. 1 and 2 – in counts/min $\cdot 10^5$/g tissue or/ml blood; in Fig. 3 – DMBA-^{3}H concentration expressed in relative units).

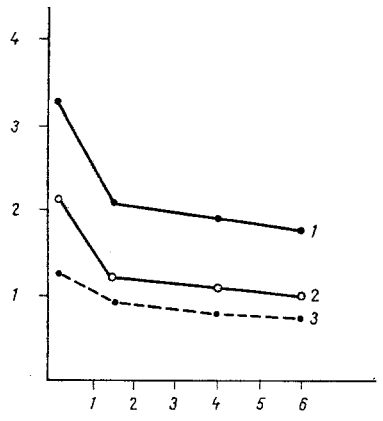

Fig. 2

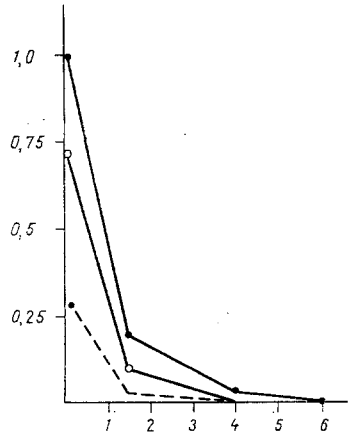

Fig. 3

Fig. 2. Concentration of DMBA-^{3}H and its metabolites in lipids of rat liver after intravenous injection of 2 mg DMBA with activity of 10 μCi. 1) Control rats; 2) rats receiving $150 \cdot 10^3$ i.u. of vitamin A daily for 3 days; 3) rats receiving $250 \cdot 10^3$ i.u. vitamin A daily for 5 days.

Fig. 3. Concentration of DMBA-^{3}H in rat liver after intravenous injection of 2 mg DMBA with activity of 10 μCi. Legend as in Fig. 2.

EXPERIMENTAL METHOD

Female Wistar rats weighing 100-110 g were used. The animals of the control group received 1.25 ml corn oil daily for 5 days before receiving the carcinogen; the animals of the two experimental groups received vitamin A acetate per os in a dose of $150 \cdot 10^3$ i.u. daily for 3 days and $250 \cdot 10^3$ i.u. daily for 5 days in 1.25 ml oil.

A lipid emulsion containing 7,12-dimethylbenz(a)anthracene (DMBA) was injected into the caudal vein in a dose of 2 mg per animal. The concentration of DMBA and its metabolites in different organs after injection of the carcinogen was studied by means of DMBA-^{3}H (Radiochemical Centre, Amersham, specific radioactivity 6.4 Ci/mmole), which was injected along with the unlabeled carcinogen in a dose of 10 μCi per animal. The rats were killed 10 min and 2, 4, and 6 h after the injection. Lipids were isolated by Folch's method [5]. The carcinogen and its metabolites were separated by thin-layer chromatography [10]. The content of radioactivity in the samples was measured on a liquid scintillation spectrometer.

EXPERIMENTAL RESULTS

The dynamics of the concentration of the carcinogen and its metabolites in the various organs and blood is illustrated in Fig. 1. Radioactivity was maximal after 10 min in the liver, followed (in diminishing order) by the adrenals, spleen, kidneys, blood, and mammary gland. With the passage of time the radioactivity decreased in all organs, but remained maximal in the mammary gland after 1.5 h. In the animals with hypervitaminosis A the radioactivity in all the organs and in the blood was considerably lower than in the control animals. An increase in the dose of vitamin A led to a decrease in the content of label in all the organs.

Measurement of the radioactive label of DMBA-^{3}H in the various organs reflected not only the quantity of unchanged DMBA, but also the quantity of various products formed during metabolism of the carcinogen (lipid-soluble products, water-soluble products, and also various complexes of the carcinogen or its metabolites with cell receptors). Investigation of the quantity of radioactivity in the lipids showed that feeding the animals with vitamin A led to a decrease in lipid-soluble metabolic products of DMBA, and in this case the changes were found to depend on the content of vitamin A in the animals' diet (compare Figs. 1 and 2).

With an increase in the content of vitamin A in the animals' diet the rate of metabolism of the carcinogen increased (Fig. 3).

Metabolism of polycyclic hydrocarbons is known to take place by means of a system of multipurpose oxidases, located mainly in the endoplasmic reticulum of the liver cells of animals. Polar metabolites are rapidly excreted with the urine or as conjugates with glucuronic and sulfuric acids they are excreted with the bile into the alimentary tract [8]. It has also been found that the formation of polar metabolites is directly dependent on the rate of metabolism of the carcinogen [8].

Experiments in vitro showed that vitamin A inhibits the binding of DMBA with macromolecules of rat liver microsomes [6], and accelerates the formation of water-soluble and retards the formation of lipid-soluble metabolic products of the carcinogen [1].

Microsomal enzymes of the liver and target organ are responsible for detoxication of several exogenous xenobiotics, including carcinogens [3]. A reduction of carcinogenicity of this sort has been observed for aromatic amines and polycyclic hydrocarbons [11]. Huggins et al. [7] found that preliminary administration of small quantities of polycyclic hydrocarbons to rats reduced the frequency of appearance of mammary gland tumors induced by DMBA. It was reported in 1968 [11] that intraperitoneal injection of 5,6-benzoflavine inhibited the formation of tumors induced by 3-methylcholanthrene in the lungs of rats. Later these same workers showed [12] that 5,6-benzoflavine is a powerful inducer of aryl-carbon hydroxylases in the liver, lungs, and small intestine of rats and mice.

It is possible that the protective effect of preliminary processing of the inducers is partly due to an increase in the rate of removal of the carcinogen from the body. Wheatley [13] suggested that the increase of tumor formation induced by DMBA in the mammary gland observed under the influence of 2-diethylaminoethyl-2,2-diphenylvalerate hydrochloride, an inhibitor of microsomal enzymes, is due to raising of the carcinogen level in the target organ. Dao et al. [4] consider that the concentrations of the carcinogen in the target organ is an important factor in the origin of a tumor.

The present investigation showed that the rate of metabolism of the carcinogen in the animal's liver is increased in hypervitaminosis A. The carcinogen is more rapidly excreted from the body as polar metabolites and its concentration in the target organ is substantially reduced.

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REACTIVITY OF THE LIVER TO GLUCOCORTICOIDS DURING CHEMICAL HEPATOCARCINOGENESIS

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Liver cells during chemical carcinogenesis (3'-methyldimethylaminoazobenzene) and cells of primary hepatomas retain the property of reacting to partial hepatectomy by increased incorporation of ^{3}H-thymidine into DNA, just as under normal conditions this process is inhibited by dexamethasone. The inducibility of tyrosine aminotransferase (EC 2.6.1.5) likewise remained unchanged, whereas induction of tryptophan pyrrolase (EC 1.13.11.11) in primary hepatomas was abolished. The adequacy of a model of chemical carcinogenesis of an organ if the heterogeneity of its cell populations is disregarded is discussed.

KEY WORDS: dexamethasone; hepatocarcinogenesis; enzymes; DNA.

It is now widely recognized that among the properties of neoplasms as a whole primary and secondary properties must be distinguished [2]. The primary properties, possessed by both benign and malignant tumors, include uncontrolled cell proliferation, whereas the secondary properties include systemic action of the tumor on the host arising in the course of its progression and characterizing only tissue which has undergone malignant change, ability to produce metastases, chromosomal anomalies, and absence of control over specific functions belonging to the homologous tissue. It is evident that during the investigation of uncontrolled cell proliferation characteristic of a neoplasm attention must be directed to concrete control mechanisms. The object of this investigation was to study the action of glucocorticoids, which inhibit DNA synthesis and cell division both in the liver, in which they induce the synthesis of various enzymes, notably tyrosine aminotransferase (TAT) and tryptophan pyrrolase (TP), and in the tissues in which they give a catabolic effect (lymphocytes, fibroblasts, etc.) [2, 11, 13]. It was hoped to elucidate changes in the regulation of DNA synthesis and induction of enzyme synthesis by glucocorticoids during chemical carcinogenesis.

EXPERIMENTAL METHOD

Male Wistar rats weighing 150-250 g, kept on an ordinary diet or on a special diet including 3'-methyldimethylaminoazobenzene (3'-MDAB) (diet No. 3 according to [9]), were used. Animals with Zajdela ascites

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