EFFECT OF COBALT ON INDUCED CARCINOGENESIS OF THE SKIN

M. A. Finogenova

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Cobalt in a dose of 10 μg, which stimulates the production of endogenous erythropoietin, activates the development of skin tumors induced in mice by 20-methylcholanthrene. Cobalt in a dose of 100 μg had no appreciable effect on cutaneous carcinogenesis.

The effect of cobalt on induced cutaneous carcinogenesis has been studied by Kasirsky [7] and by Thompson and Gautieri [13], who demonstrated its inhibitory action on the development of skin tumors induced by 20-methylcholanthrene in mice. Cobalt is known to stimulate the production of endogenous erythropoietin [4-6], which, as has recently been shown, is a nonspecific growth factor for malignant cells both in vivo [2, 8, 11] and in vitro [9, 10].

It was therefore decided to investigate whether the action of cobalt as a stimulator of endogenous erythropoietin production could be differentiated from the action of cobalt as an inhibitor of cutaneous carcinogenesis, as shown by Kasirsky [7].

EXPERIMENTAL METHOD

Experiments were carried out on female CBA × C57Bl mice weighing 20-22 g. A 0.5% solution of 20-methylcholanthrene (20-MC) in benzene was applied in a volume of 0.02 ml to a previously shaved area of skin in the interscapular region once a week until the end of the experiment.

The mice of group 1 (70 animals) received an intraperitoneal injection of 10 μg cobalt ($CoCl_2 \cdot 6H_2O$) in 0.1 ml physiological saline twice a week for 8 weeks. The mice of group 2 (72 animals) were kept under similar conditions but the dose of cobalt was increased tenfold. The first injection of cobalt coincided with the time of application of the carcinogen, the second was made on the 3rd day thereafter. The mice of group 3 (70 animals) acted as the control and they received an injection of 0.1 ml physiological saline under the same conditions.

The following indices were studied: the time of appearance of the first papillomas and the first carcinomas, and the mean latent period of development of the papillomas and malignant tumors.

EXPERIMENTAL RESULTS

The first papillomas appeared 8 weeks and the first carcinomas 17 weeks after the beginning of the experiment in the mice of group 1, after the 8th and 16th weeks respectively in the mice of group 2, and after 10 and 17 weeks respectively in the mice of group 3 (control). In both experimental groups the appearance of the first papillomas was thus accelerated by 2 weeks. So far as the time of appearance of the first carcinomas is concerned, slight acceleration (by 1 week) was observed only in the animals of group 2.

The mean latent period of appearance of papillomas in the mice of group 1 was 13.6 ± 0.29 weeks, in the mice of group 2 (tenfold increase in the dose of cobalt) it was 14.6 ± 0.21 weeks, and in the control group 15.0 ± 0.21 weeks, i.e., injection of cobalt in a dose of 10 μg shortened the mean latent period of appearance

Laboratory of Carcinogens, Institute of Nutrition, Academy of Medical Sciences of the USSR, Moscow.
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of the papillomas by 1.14 weeks ($P < 0.001$), whereas in the animals of group 2 the latent period was shortened by only 0.4 week, which is not statistically significant.

The mean latent period of appearance of carcinomas in the mice of group 1 was 21.7 ± 0.28 weeks, in group 2, 24.1 ± 0.30 weeks, and in the control group 23.6 ± 0.30 weeks. The difference observed by comparing the indices for the animals of group 1 and the control group was 1.9 weeks ($P < 0.001$), whereas in the mice of group 2 there was actually a slight increase of 0.5 week in the mean latent period, although this difference is not statistically significant.

Only when injected in a dose of 10 μg was cobalt thus found to have a definite stimulant action on cutaneous carcinogenesis in mice, and a tenfold increase in the dose of cobalt had no appreciable effect. The differences in the effects of different doses of cobalt on induction of tumors must probably be explained by differences in their mechanism of action. Many workers studying the action of cobalt have observed a disturbance of oxido-reduction processes in the body. The results of a study of the effect of cobalt on enzyme systems participating in oxido-reduction showed that cobalt inhibits the activity of succinate oxidase, choline, cytochrome oxidase, and catalase [1, 12, 14]. Depression of respiration and oxidative phosphorylation in several tissues by cobalt was discovered by Yastrebov [3] in his investigations, and with an increase in the concentration of cobalt this effect was intensified. It therefore seems likely that a small dose of cobalt (10 μg), by its indirect action as a stimulator of production of endogenous erythropoietin, may facilitate the development of papillomas and carcinomas whereas a large dose (100 μg) affects metabolic processes in the tissues without facilitating the development of cutaneous carcinogenesis or behaving antagonistically to the action of the increased level of erythropoietin.

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