ONCOLOGY

DISTINCTIVE FEATURES OF THE DEVELOPMENT OF M-1 TUMORS IN RATS DURING CHANGES IN THE FUNCTIONAL CONDITION OF THE NERVOUS SYSTEM

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Recently pathological physiologists and clinicians have been paying more and more attention to the importance of the functional condition of the central nervous system in the pathogenesis of tumors.

In this connection there is particular interest in the research into the role of functional trauma of the central nervous system in the development of tumors. In our laboratory, P. Ia. Novorasova [6] showed that preliminary, prolonged trauma to the higher divisions of the central nervous system in mice by means of an electric current accelerated the development of the ascitic form of adenocarcinoma. Conversely trauma of brief duration to mice by an electric current retarded growth of the tumors. A. N. Kursheva [3], in experiments on rats, also noted that growth of an inoculated M-1 tumor was dependent on the original condition of the central nervous system. In these investigations attention was drawn to the importance of the type of nervous activity. S. I. Lebedinskaia and A. A. Solov'ev [5] also demonstrated the importance of the type of nervous behavior of the animals. They found that in rats with a strong type of nervous system a tumor developed more slowly than in rats with a weak type, in which the weight of the tumor reached considerable magnitudes; a neurotic state of the rats intensified tumor growth. Similar results were obtained by F. M. Khaletskaia [11] in experiments on mice by overstraining the activity of the nervous system, and by E. I. Vodakova and O. A. Serdiukova [1] in experiments on rats of various ages with trauma to the nervous system.

The present investigation is devoted to the study of the growth of tumors in rats with different types of nervous behavior after injection of small and large doses of caffeine.

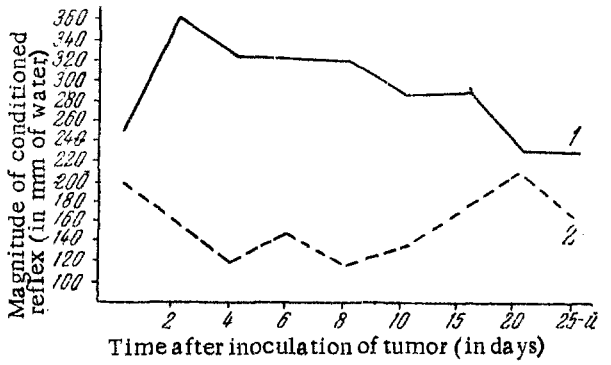
It was shown by the observations of I. P. Pavlov and his co-workers that caffeine increases the excitation of the cortical cells [2, 4 and others]. Later investigations showed that the injection of small doses of caffeine improves differentiation but large doses bring about limiting inhibition [8, 9, 10].

EXPERIMENTAL METHOD

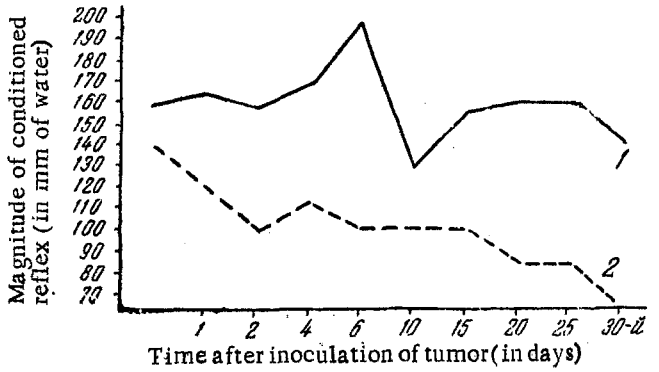
As a preliminary measure a system of conditioned reflexes was produced over a period of 4 months in 28 experimental rats by the motor-alimentary method of Kotliarevskii. After the establishment of a dynamic stereotype in the rats, in order to define more precisely the type of nervous activity, experiments were carried out in which the stereotype was changed (the rate of extinction and restoration of the conditioned reflexes was determined) and the caffeine test was applied. As a result, the type of nervous activity of the rats was subdivided into strong excited, strong inert and weak.

Of the 28 experimental animals 16 were included in the group of experiments to study the effect of small doses of caffeine on the development of M-1 tumors.

In order to study the effect of large doses of caffeine on the growth of tumors the other 12 rats were used. It was established that to increase the process of excitation in the nervous system of the rats, the small doses of caffeine used must differ according to the type of nervous behavior of the animal: for rats of a strong



a



b

Fig. 1. Curves showing the changes in the total magnitude of the conditioned reflexes in rats of strong (1) and weak (2) types of nervous activity, receiving small doses of caffeine, after inoculation of a tumor (a); control experiments (b).

and balanced type the dose should be 0.002 g, and for rats of a strong excited and weak type, 0.001 g (body weight 200-220 g). Using different doses of caffeine in all nine experimental rats (7 with a strong and 2 with a weak type of nervous system), we noted improvement of differential inhibition and high functional mobility of the nervous processes; 7 animals (5 with strong and 2 with weak types of nervous system) acted as controls (inoculation of the tumor without injection of caffeine).

The large doses of caffeine which were used also varied according to the type of nervous behavior of the animals: for rats of a strong balanced and strong excited type the dose was 0.05 g, and for rats of weak type – 0.01 g (body weight of the rats 200-220 g). During the injection of large doses of caffeine 2 rats with a strong inert type of nervous system died. In 3 rats of strong excited type and 2 rats of weak type of nervous system, severe disorders of conditioned reflex activity were observed. In this group 5 rats acted as controls (3 with a strong excited type and 2 a weak type of nervous system). Caffeine was injected subcutaneously in all the rats for a period of 10 days before inoculation of the tumor, and daily for 25 days after inoculation. Inoculation of the tumor in the first and second groups was carried out from different rats affected by tumors.

EXPERIMENTAL RESULTS

In rats of strong excited and strong inert types of nervous system, receiving small doses of caffeine, the tumor developed more slowly and did not reach a large size; in rats with a weak type of nervous activity the tumor developed more rapidly and attained a large size.

In animals with a strong type – both excited and inert – of nervous system, receiving small doses of caffeine, development of the tumor was observed on the 7th-9th day after transplantation; in the control group the tumor was already apparent on the 3rd-4th day. The average weight of the tumor in the rats with a strong

type of nervous system on the 25th day was 9 g, and in the control rats 17.2 g; in the rats of weak type of nervous activity it was 42 g.

On comparing the character of the changes in the total magnitude of the conditioned reflexes (the sums of the magnitudes of the motor reflexes of the rat throughout one session) in a rat with a strong type of nervous activity taking part in the experiment (Fig. 1, a) and in a control rat (Fig. 1, b) we observed that caffeine brought about an increase in the strength of the conditioned reflexes and maintained the strength of the excitatory processes, and it was this latter factor which restrained the development of the inoculated tumor. In rats with a weak type of nervous system, on both experimental (see Fig. 1, a) and control (see Fig. 1, b) groups the transplanted tumor was found to be too powerful a stimulus; this led to the development of limiting inhibition in the nervous system, to a fall in the magnitude of the conditioned reflex and, consequently, to a weakening of the defense mechanisms and to acceleration of the growth of the tumor.

Confirmation of this point of view is obtained from experiments in which large doses of caffeine were used. In all the rats receiving large doses of caffeine there were severe disorders of conditioned reflex activity. A weakening and dying away of the positive conditioned reflexes, together with disinhibition of differential inhibition were observed, which may account for the presence of phasic states in these animals.

Observation of the development of the tumor in rats receiving large doses of caffeine showed that the tumor appeared in these animals on the 3rd-4th day after inoculation, and it reached a large size; after 25 days the weight of the tumor varied between 67 and 100 g. In the control rats of this group the weight of the tumor averaged 49 g.

On the basis of the results obtained it may thus be postulated that small doses of caffeine, which normalize the functional condition of the nervous system in rats during the growth of a tumor, facilitate the appearance of protective mechanisms in the process of development of an inoculated tumor; large doses of caffeine lead to disturbance of the functional state of the nervous system and to the development of limiting inhibition.

Our findings are in agreement with those obtained by S. P. Sizenko [7] in experiments in which small doses of caffeine and bromide were used during x-ray therapy of experimental sarcomas in rats. In these experimental conditions this author observed an enhanced therapeutic effect.

SUMMARY

It was shown in experiments on rats that small doses of caffeine inhibit the development of the transplanted tumor (sarcoma M-1) by increasing the functional mobility of the nervous system. Large doses of caffeine accelerate the growth of the tumor in connection with the development of the limiting inhibition in the central nervous system.

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