THE INFLUENCE OF GLYCINE ON THE LIVER GLYCOGEN CONTENT IN HEALTHY MICE AND MICE SUFFERING FROM CANCER UNDER THE INFLUENCE OF MEDINAL

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Marked changes in metabolic processes are observed in the organism during the development of malignant neoplasms, and there are grounds for the hypothesis that the central nervous system plays a significant part in this, since a series of investigations has established the dependence of the rate of development of malignant tumors on the state of the nervous system in animals [1, 4, 6, 7, 8, 10, 11]. However, these investigations were not concerned with changes in metabolism. It is therefore interesting to obtain data on the influence of the central nervous system on metabolism in animals suffering from malignant tumors.

During the development of malignant neoplasms the most marked changes are observed in the carbohydrate metabolism [3, 5, 9, 12]. It is known that a series of amino acids, called "glucoplastic", influence the course of carbohydrate metabolism, and, in particular, alter the liver glycogen content in animals. The effect of these amino acids has not, however, been sufficiently studied in animals suffering from cancer. Moreover there are no data in the literature concerning the mechanism of the action of these amino acids on liver glycogen, and no data are given on the role of the central nervous system in these processes. Nonetheless the central nervous system definitely plays a significant part in the synthesis and breakdown of glycogen, and the action of any factors (including amino acids) is, evidently, mediated by the central nervous system. The aim of this work has therefore been the study of the effect of a glucoplastic amino acid—glycine—on glycogen formation in the liver of healthy mice and those suffering from cancer during different functional states of the central nervous system.

EXPERIMENTAL

The glycogen content of the liver was determined by the Pfluger method, as modified by A. M. Genkin [2]; mice with ascitic carcinoma of Ehrlich were used, awake and asleep. One group of mice received glycine, the other did not. A parallel investigation was carried out on healthy white mice, also asleep and awake. In this case also, some of the mice received glycine, while the remainder did not. Sleep was induced with medinal, introduced as 1% solution, 1.5 mg per 10 g body weight. Medinal solution was injected 4 times a day at 4 hourly intervals, which produced 18-20 hours of sleep with a 4-6 hour waking interval at night, when the animals were fed and watered.

20% solution of glycine was administered subcutaneously (into the back) in the dose of 2.5 mg per 1 g body weight once a day throughout the duration of the experiment (7 days).

Altogether 8 series of experiments were performed in 170 animals.

RESULTS

Analysis of the data obtained revealed that the liver glycogen content in mice with ascitic Ehrlich carcinoma fluctuated between 0.23 and 0.74% (average 0.38%) during the waking state, while in healthy animals (awake) the liver glycogen content was from 2.10 to 3.26% (average 2.50%). The amount of glycogen in the liver of mice with cancer was found to be, on the average, 1.43% with individual variations from 0.98 to 1.93% during medinal-induced sleep, while in healthy mice during sleep the average liver glycogen content was 4.72% with individual fluctuations from 3.55 to 5.23%.

The liver glycogen content in mice with cancer who were receiving glycine solution varied, during medinal-induced sleep, between 0.63 and 1.18% giving an average of 0.89%, while in healthy mice receiving the same amount of glycine the glycogen content varied from 4.07 to 4.65% giving an average of 4.40%.

The amount of glycogen in mice with cancer in the waking state and receiving glycine was on an average 2.12% with individual variations from 1.09 to 3.07%, and in healthy mice in the waking state also receiving glycine the amount of the polysaccharide varied from 3.27 to 5.09% giving an average of 4.00%.

The average data of these experiments are given in the figure.

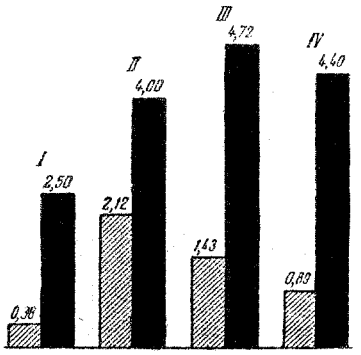

Fig. Liver glcogen content in healthy white mice and those suffering from cancer (in %): light columns -healthy mice, dark columns - mice with cancer.
I) Awake; II) Awake and receiving glycine; III) Asleep after medinal; IV) Asleep after medinal and receiving glycine.

The experimental results indicate the development of malignant neoplasm is associated with a sharp drop in liver glycogen content.

Subcutaneous administration of glycine to healthy mice (awake) increased the liver glycogen content by 1.5 times on an average.

Administration of the same amount of glycine to mice with cancer (awake) produced a 5.5-fold increase in their liver glycogen content, thus bringing it up to the lower limit of normal.

During the depression of the central nervous system with medinal the liver glycogen in healthy mice was 1.8 times higher, on an average, as compared with healthy mice in the waking state. In the case of mice with cancer the liver glycogen content increased 4 times during medinal-induced sleep as compared with the level in the waking state. However, in spite of this considerable rise in glycogen content it still did not reach the normal level, remaining on the average 1.7 times lower than in the case of healthy mice in the waking state.

Administration of glycine to healthy mice during medinal-induced sleep was associated with an average increase of glycogen of 1.7 times compared with the liver glycogen content of healthy mice in the waking state. However, this increase was within the same limits as the increase observed under the influence of medinal producing sleep.

The liver glycogen content of sleeping mice suffering from cancer, to whom glycine had been given, was 2.3 times higher (on an average) than in similarly afflicted mice in the waking state, but did not reach the level found in mice subjected to the action of medinal alone.

The findings reported indicate that the central nervous system participates in the processes of glycogen synthesis in the liver, since when it is depressed by the action of medinal administered to the experimental animals, glycine fails to produce the same glucoplastic effect as that observed in waking animals under the same experimental conditions. The influence of the central nervous system on processes of glycogen synthesis is apparent both in healthy animals and those suffering from cancer, but the degree of this influence is not the same in the two cases. Evidently when the central nervous system is under the depressive action of medinal and the animal is asleep, glycogen synthesis by the liver is enhanced as the result of diminished carbohydrate breakdown in the organism (compared to the waking state). This accummulation of glycogen in the liver is not equally pronounced in healthy animals and those with cancer, presumably because the development of malignant

neoplasms is associated with profound disturbances in the enzyme systems of the organism, including those involved in the synthesis and breakdown of glycogen in the liver. Nevertheless, the amount of glycogen in the liver increases during medinal-induced sleep in mice with cancer. When glycine is administered against this background of increased liver glycogen content, no glucoplastic effect is observed either in the healthy mice or those with cancer, such as occurs in animals in the waking state. Apparently glycine cannot be taken up by glycogen or the corresponding enzyme systems involved in its synthesis, without the participation of the fully functioning central nervous system. Or, it may be that the enzyme systems involved in glycogen synthesis are maximally used up at the time when the animal succumbs to sleep, and so are unable to increase further the liver glycogen content following the administration of glycine. Assuming the latter hypothesis, it may be said that the enzyme systems concerned with glycogen synthesis are "weaker" in animals with cancer, since on the administration of glycine the liver glycogen content not only does not increase, but shows a tendency to drop. This may be explained by the entry of glycine, not used in glycogen synthesis, into other metabolic processes in the organism; this metabolism may involve the inclusion of glycine in tissue proteins, since glycine is an amino acid. The possibility is not excluded that involvement of glycine in this sort of metabolic process may require additional energy resources, resulting in greater expenditure of glycogen synthesised in the liver, and so leading to some diminution in liver glycogen. Further experiments are needed to prove the above hypotheses. But there is no doubt that the glucoplastic effect of glycine, both in healthy mice and those with ascitic Ehrlich carcinoma, is mediated by the central nervous system as indicated by the organism's response to the administration of the amino acid to sleeping and waking animals.

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