METASTASIS FORMATION BY BROWN-PEARCE TUMOR IMPLANTED IN THE BRAIN

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In previous experiments in which tumors were implanted into certain animal organs (testis, metaphysis of the femur) we noticed that the tendency to preferential involvement of particular organs shown by the tumor metastases varied in relation to the site of implantation. Similar findings were obtained by other workers [8, 9 and others]. The susceptibility of some organs and the resistance of others, related to the site of implantation and to the subsequent growth of the tumor, led us to the hypothesis that the differential distribution of metastases among the organs is determined not only by neurotrophic disturbances arising by reflex pathways in the affected organs, but also by protective and adaptive processes arising at the same time and in the same way in unaffected organs [11, 10, 12].

The aim of our work was to investigate metastasis formation in relation to implantation in various areas of the brain.

In human clinical medicine we find primary malignant tumors of the brain of varying structure and localization, and also secondary tumors of the brain – metastases from tumors of certain internal organs.

In the literature on experimental oncology some writers include the brain among tissues showing high resistance to tumor development [13], while others attribute low resistance to it [1, 4].

Pearce and Brown, while studying the rabbit tumor which they described, observed that on implantation into the brain the tumor develops without formation of metastases.

We implanted a Brown-Pearce strain of tumor in some rabbits in the tissue of the superficial layer of the brain, and in others in the lateral ventricle. Injections of 0.3 and 0.5 ml respectively of a 25% suspension of finely shredded tumor in physiological saline were made into the brain under ether anesthesia through a burr-hole in the skull.

The implantation in the brain tissue was carried out at the junction of the anterior and middle thirds of the left hemisphere, and the tumor suspension was injected into the upper layer of tissue at the same level, which was achieved by introducing the needle with a mark on it always to the same depth.

For implantation in the lateral ventricle the tumor suspension was injected through a needle in the anterior horn of the lateral ventricle.

Altogether 119 animals were included in the experiment.

In a preliminary series of experiments the tumor was implanted in ten rabbits in brain tissue and in ten

rabbits in the left lateral ventricle. At the same time in three control rabbits the same tumor was implanted in the testis.

In all the control animals, which died on the 32nd-38th day, tumors had developed in the testis, together with numerous metastases disseminated throughout the internal organs.

Of the ten rabbits in which the tumor was implanted in the tissue of the left cerebral hemisphere, in seven a tumor the size of a pea to a pine kernel developed. Of these animals, two rabbits died on the 42nd-50th day and the rest were killed after 60 days. In no case were metastases present.

Of the ten rabbits with implantation in the left lateral ventricle of the brain, tumors developed at the site of implantation – in the cavity of the anterior horn – in eight animals. Of these rabbits three died on the 40th day, five on the 50th-53rd days and the rest were killed on the 60th day. In six rabbits a tumor had developed in one ventricle, and in two rabbits it had extended also into the second lateral ventricle. In no case were metastases found in the internal organs. In one rabbit with a tumor in both lateral ventricles, paralysis of both hind limbs was observed during the last three days of life.

In order to analyze the results obtained, and in particular to elucidate what was responsible for the absence of metastases after implantation of the tumor in the brain tissue or the lateral ventricle, new series of experiments were called for.

In these experiments, following the example of the previous investigation, an additional stimulus was applied in the form of a single injection into the left testis of 0.5 ml of a 1% solution of formalin five days after implantation of the tumor in the tissue or lateral ventricle of the brain. Two series of experiments on 42 animals were set up. The same number of rabbits constituted two control series: in these animals implantation of the tumor was made in the tissue of the brain or in the lateral ventricle without the additional feature. The rabbits in which implantation of the tumor was made into the left testis (12 animals) served as a control of the activity of the tumor suspension used in the two experiments. All the animals were killed 35 days after implantation. The results of the experiments are shown in the table.

EXPERIMENTAL RESULTS

In the experimental groups of animals with both forms of implantation and with the additional stimulus, tumor metastases were found in certain internal organs in 13 rabbits. In the corresponding control groups (i.e., without the additional stimulus) no metastases were found in the internal organs.

The lateral ventricles on transverse section of the brain of a rabbit (No. 1123). A large tumor is seen in the left lateral ventricle extending into the right ventricle.

With implantation of the tumor in the brain tissue of the left hemisphere, the primary tumor nodules varied in size from a grain of buckwheat to a pine kernel. There was no significant difference in the dimensions of the primary nodules in the experimental and control groups. In only one of the experimental animals had the tumor spread in the upper layer of brain tissue of almost the whole anterior third of the hemisphere.

With implantation in brain tissue metastasis formation took place only in the presence of a primary focus. In five rabbits metastases were situated in the liver – from one to three nodules in size from a millet seed to a pea. In one of these cases (two pea-size nodules) the kidney was affected in addition to the liver (in one kidney – three nodules the size of a millet seed in the cortical layer).

With development of the tumor in the lateral ventricle, tumor growth in the control animals was restricted to the cavity of one ventricle. In the group with an additional stimulus, in seven rabbits the tumors extended into the cavities of both ventricles (see figure). In six of these animals there were metastases also in internal organs. Metastasis formation was observed always only in the presence of a primary tumor focus, when there were metastases in the liver in seven rabbits, in three of them with simultaneous involvement of the kidneys. In one rabbit the kidneys alone were

affected. Metastases in the liver appeared as one to four nodules in size from a millet seed to a pea, in the kidneys – one to three nodules from a millet seed to a grain of buckwheat, situated in the cortical layer. In three animals the kidney lesions were bilateral.

In one animal with metastases a bilateral paralysis of the hind limbs was observed at the end of the experiment. Metastases in the spine were not found.

The results which we obtained in our experiments show (see table) that implantation of a tumor of the Brown-Pearce strain into the brain tissue or the lateral ventricle of the brain does not lead to metastasis formation in the internal organs. In not one of the 42 animals in which this implantation was performed were metastases found despite the growth of the tumor. It might be thought that by virtue of some reason the cells of the implanted tumor, despite growth of the tumor in the brain tissue, do not infiltrate the vessels and do not enter the general circulation.

Metastasis Formation by Brown-Pearce Tumors Implanted in the Brain With the Application of an Additional Stimulus

Nature of the experiment	Number of rabbits in the group	Number of rabbits		Number of organs with metastases
		with a tumor at the site of implantation	with metastases in internal organs	
First group of animals				
Implantation of tumor in brain tissue; 5 days later injection into the testis of 0.5 ml of 1% formalin solution.	20	18	5	6
Second group of animals				
Implantation of tumor into brain tissue (control)	20	16	0	0
Third group of animals				
Implantation of tumor in the lateral ventricle of the brain; 5 days later injection into the testis of 0.5 ml of 1% formalin solution.	22	19	8	11
Fourth group of animals				
Implantation of tumor in the lateral ventricle of the brain (control)	22	18	0	0
Fifth group of animals				
Implantation of tumor in the testis.	16	16	15	63

However, our experiments show also that the property of tumors growing in the brain not to form metastases in internal organs is disturbed in case of application of an additional stimulus to an organ so far removed from the brain as the testis. Hence it can be concluded that on implantation in the tissue or ventricle of the brain and with subsequent survival and growth of the transplantate, the tumor cells enter the general circulation and reach the organs, but they do not survive and metastases are not formed. Tumor cells reaching the organs probably meet tissues resistant to them. This resistance is lost after injection of a small quantity of formalin into the testis.

The results obtained from our investigation not only confirm our previous observations but also demonstrate

the importance of central mechanisms both in the appearance and maintenance of resistance to the tumor cell, and also in its disappearance.

The absence of metastasis formation on implantation of the tumor in the brain, and its survival in that organ may be due to the inclusion in the response of the brain to trauma of protective and adaptative reactions which are not confined to the area of the brain itself but which also extend to the other organs and tissues of the body. The action of formalin on the testis caused interference with the mechanism of these reactions which probably led to those trophic changes determining the survival of the tumor cells circulating in the blood stream in a particular organ. This procedure also affected the growth of the tumor implanted in the lateral ventricle – which extended to the opposite lateral ventricle, thereby demonstrating trophic changes and loss of resistance in the brain itself.

SUMMARY

When Brown-Pearce tumor is implanted into the tissue of the brain or its lateral ventricle, the cells of the tumor, conveyed to internal organs, do not ingrow and no metastases are formed. Additional stimulation of the testis by injection of a small amount of formalin (after implantation of the tumor into the brain) resulted in formation of metastases in certain internal organs. Experiments prove the significance of the central nervous mechanisms in resistance of the tissues to tumor cells, as well as in disturbance of this resistance.

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