Basic Aspects of Brain Tumor Localization by Radioactive Substances*

A Review of Current Concepts

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Most brain tumors accumulate various substances from the blood stream, such as vital dyes and various radioactive isotopes. The exchange of these substances between plasma and tumor tissue is much faster and freer than between plasma and normal brain tissue. Since the concentration of many radioactive compounds is greater in the tumor than in the surrounding brain tissue, a tumor-brain concentration ratio exists that can be measured for diagnostic purposes. This principle is the basis of radioactive brain scanning.

Frequently, the reason given for a positive brain scan is the regional absence or greatly increased permeability of the blood-brain barrier; however, very little effort has been made to clarify the physiological or biochemical factors involved in this phenomenon. The difficulty is that any explanation involves the entire concept of the blood-brain barrier; this is poorly understood even under normal conditions. At present, the blood-brain barrier is considered a hypothetical mechanism with considerable rate-limiting capacity; it is generally believed to consist of a multitude of membranes with a variety of enzyme actions rather than being a simple anatomical sieve. Pathological alterations of the barrier are assumed rather than known.

To determine the possible mechanism responsible for the uptake of substances by normal and neoplastic brain tissue, one has to consider many factors, including the differences in vascular permeability, the size of the extracellular space, and the metabolism involved. We have outlined these various factors in our present study.

Vascular Permeability

Brain tumors, particularly glioblastomas and metastatic tumors, contain abnormal blood vessels. Purely mechanical factors may be responsible for the irregularities of the vascular lumen. Locally increased blood pressure bearing upon a defective and consequently weak portion of an abnormal vessel wall could result in dilation, which in turn could easily cause a change in vascular permeability in terms of increased filtration. In addition, there seems to be a profound metabolic (anaplastic) change in the cellular components of the neoplastic vasculature, at least in malignant brain tumors. This is manifested by endothelial proliferation in the wall of arterioles, venules, and capillaries.

On electron microscopic examination, the blood vessels of glioblastomas show signs of increased metabolic processes in the endothelial cells (accumulation of mitochondria and vesicles) as well as vacuolization and marked variation in the width of the basement membrane. The possibility of increased permeability across the neoplastic capillary wall by heightened active transport, in contrast with increased diffusion through a structurally deficient vessel, must therefore be seriously considered also.

Nyström pointed out that the vascular changes were much less pronounced in the gliomas of lesser malignancy. The ultrastructure of the blood vessels of astrocytomas and oligodendrogliomas did not differ essentially from that of normal vessels. This, of course, might be one of the reasons why radioactive brain scan is sometimes "negative" in these gliomas. However, an adequate electron microscopic study of the capillaries involved in tumor formation has not been made, and further investigations are needed. According to Torack, capillary changes vary depending on the involvement of the tissue in the pathological process.
Although a parallel between embryonic and neoplastic blood vessels is frequently drawn, connoting increased permeability of their walls, a definite conclusion is lacking. As far as their ultrastructure is concerned, embryonic capillaries have a poorly developed basement membrane which might explain their leakiness. However, tumor vessels have many additional features, such as the increased metabolic activity of their endothelial cells and perivascular astrocytes, or the close attachment of tumor cells to the basement membrane, as well as the enlarged extracellular space in the vicinity of the blood vessels; any of these structural peculiarities or a combination of them could be responsible for the increased exchange of material between plasma and tumor tissue.

Tumoral and Peritumoral Edema

Some gliomas are edematous compared with normal brain tissue. This is manifested by increased water and sodium content and an increased Na/K ratio.

The uptake of radioactive substances by brain tissue adjacent to tumor is frequently much greater than that of distant brain and often equal to that of the tumor itself. However, it is not known how much the surrounding edema contributes to the detection of the tumor on the scan. Since peritumoral edema usually consists of a proteinaceous plasma exudate, experience gained in similar traumatic edemas suggests that the edematous tissue immediately adjacent to the neoplasm is relatively freely accessible not only to small but also to large molecules circulating in the plasma.

Experiments by Kotsilimas, et al., with Hg\textsuperscript{200} chloromerodrin suggest increased vascular permeability at the boundary between neoplastic and normal tissue.

Blood Content of Tumor Tissue

There is considerable variation in the volume of blood per unit of tumor tissue as well as in the speed of its circulation. Although it may seem arbitrary to distinguish between the labeled substance still contained in the vascular lumen and that which has egressed into the surrounding tissue, the amount pooled in the blood is important in vascular tumors. Long, et al., emphasized that those substances which produce a high tumor-brain concentration ratio are protein-bound in plasma; this statement implies that a significant portion of these tracers remain in the blood stream. Nevertheless, it seems to me that the idea that radioactive blood contained in the tumor is the main source of some positive brain scans has been overemphasized. The tumors used in the experiments of Matthews and Molinaro\textsuperscript{21} had a residual blood volume of 4.6%. This is less than double that of the normal gray matter and could hardly be held responsible for the disproportionately high concentration of various isotopes in these tumors.

Pinocytosis

It is worth considering what may be the mechanism for the uptake by tumor of substances with large molecular weight. Some of these compounds are very valuable in radioactive brain scanning and in the study of altered barrier permeability. It is also known that they are transferred into the neoplastic tissue from the blood stream by other means than simple diffusion.

The mechanism responsible for the uptake of large molecules might be pinocytosis. The exact chemical action responsible for pinocytosis is not known, but it is assumed that the particles engaged by the cell surface membrane and incorporated in vesicles become part of the cytoplasm after an enzymatic breakdown of the isolated membrane. This mechanism serves as an instrument in the uptake by the cells of high-molecular substances without a breakup of the molecules.

Raimondi\textsuperscript{22} attempted to localize RISA in human brain tumors at the electron microscopic level. In his opinion, serum albumin is transferred into the capillary endothelium and beyond by pinocytosis. This conclusion is supported by the observation that the number and size of pinocytotic vesicles is increased in neoplastic and abnormal nervous tissue, an observation which is also shared by Klatzo and Miquell\textsuperscript{17} and by Bakay and Lee. Although pinocytosis is obviously operational in the bulk transport of such large molecules as albumin or chloromerodrin, its relative importance in the uptake of these compounds by tumor tissue awaits further clarification. Since pinocytosis is a relatively slow, gradual process, it fails to explain completely the increased barrier permeability.