Permeability in brain tumors

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The factors governing permeation of exogenous substances into tumors may be arbitrarily divided into two groups: those related to the characteristics of the tumor and those related to the properties of the substance. The tumor factors are vascularity, capillary permeability, the size of the interstitial space of tumors, the metabolism of tumor cells, and the presence of pathological processes such as cyst formation and necrosis. The tracer characteristics that may influence permeability are molecular weight, binding to plasma proteins, lipid solubility, and rate of clearance from the blood.

Tumor Factors

Permeation of radioactive tracers into brain tumors is affected by the degree of vascularity of the tumor. With soluble tracers, intravascular radioactivity may constitute a considerable proportion of the tumor's radioactivity. With particulate tracers, fine capillaries can act as a filter. 

Primary and secondary brain tumors contain a large interstitial space as compared with normal brain. It has been shown by autoradiography that there is a high uptake of some tracers such as RIHSA into this interstitial space. On the basis of tracer dilution techniques, many other substances such as bromide and sulfate ions are believed to be entirely extracellular in their distribution, and their high permeation into brain tumors as compared with brain is thought to reflect a relatively large interstitial compartment in tumors. However, these results require verification by other techniques such as autoradiography and ultracentrifugation.

For example, a recent autoradiographic study showed that the concentration of sulfate in neuron perikarya was 15% of the blood level, indicating that the classical extracellular tracers may indeed penetrate into cells to an appreciable extent. Autoradiographs of mouse ependymoblastoma show that at 10 minutes after the intravenous injection of RIHSA this tracer is largely intravascular. Extravascular RIHSA slowly increases to a maximum at 24 hours at which time 59% of the tumor radioactivity is within tumor cells.

Scintillation counting at various times after injection shows that tumor radioactivity slowly increases despite falling brain and plasma levels. This is consistent with intracellular uptake as shown by autoradiography. In comparison to RIHSA, serial scintillation counting of several tissues in mice after the injection of chloromerodrin-mercury-203 demonstrates tumor levels of radioactivity to be more dependent on plasma levels. This suggests that a significant part of tumor radioactivity is freely diffusible. Zonal centrifugation has confirmed this and has shown that about one third of the total radioactivity in the tumor is intracellular. No autoradiographic methods suitable for localizing diffusible compounds have been applied to the study of chloromerodrin.

Scintillation counting of ependymoblastomas in mice after the intravenous injection of technetium-99m-pertechnetate reveals that the tumor level of radioactivity is entirely dependent on the blood concentration. This suggests that virtually all the tracer is diffusible and that little is fixed in cells. Here again, zonal centrifugation confirms the diffusibility, and in addition, shows that about
Permeability in brain tumors

one fifth of the total radioactivity in the tumor is intracellular.4

Specimens from 24 patients undergoing craniotomy for tumor were assayed for radioactivity within 3 hours of injection. Meningiomas were most radioactive, slow-growing astrocytomomas least radioactive, and malignant glial tumors and metastatic tumors intermediate in their permeability to pertechnetate.7

In summary, of the diagnostic tracers considered, RIHSA permeates brain tumor cells to the greatest extent and pertechnetate to the least. However, none is specific in its affinity for tumor cells and each is present in some other tissue or tissues in greater concentration than in tumor.14

A technique of high resolution autoradiography suitable for localizing diffusible substances15 was used to study the permeation of tritiated hydrocortisone into the mouse ependymoblastoma.8 Autoradiographs were made at varying time intervals from 1½ minutes to 1 hour after the intravenous injection of hydrocortisone. All tissue was frozen within 15 seconds of interruption of the blood supply. In the tumor the drug left the blood vessels in significant quantity within 1½ minutes after injection. It coursed through tumor cells immediately adjacent to blood vessels with no apparent respect for anatomical boundaries, and reached high concentrations in the interstitial space within 10 minutes. However, at this time there were some unequivocally labeled tumor cells. The stroma of the tumor, which is well seen when the tumor is implanted subcutaneously, was considerably more radioactive than the tumor parenchyma. Finally, by 1 hour after injection, most of the radioactivity had disappeared from the tumor.

Most of the tracers used for brain tumor detection, including RIHSA, chloromerodrin, and pertechnetate, do not appear to be used by the tumors for energy metabolism or synthesis of structural components. However, some tracers such as fatty acids10 and phosphate9 permeate into brain tumors and are used metabolically. To date, attempts to exploit the metabolic peculiarities of brain tumors in enhancing uptake have been unsuccessful.

Pathological processes such as cyst formation and necrosis have effects on permeability that vary from tumor to tumor and from tracer to tracer. With RIHSA, cyst fluid was usually more radioactive than solid parts of the human brain tumors studied, especially at long time intervals.12 With pertechnetate, at the shorter time intervals studied, solid tumor was more radioactive than cyst fluid.7 Necrotic tumor was generally more permeable to RIHSA than was viable tumor,12 while with pertechnetate, permeation into necrotic tissue was variable.7

Tracer Factors

Unfortunately, very little is known about the ways in which physical and chemical properties of tracers may affect their permeation into brain tumors. Large molecules such as RIHSA or iodinated PVP reach maximum concentration in tumors later after injection than do smaller molecules.11 There are insufficient data available to evaluate the effect on permeation of other factors such as the degree of binding to plasma proteins, lipid solubility, and rate of clearance from the blood stream.

References

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Round Table Discussion: neurochemistry of brain tumors