In summary, the significant reduction of IMT uptake in normal brain tissue and in gliomas during AA load proves that IMT utilizes one of the amino acid carrier systems. Therefore, IMT can be used as a tracer of amino acid transport in SPECT studies. The spatial resolution is limited, but it may be improved with new generations of SPECT systems. Thus, SPECT studies with IMT may offer clinical potentials similar to that of PET studies using ^{11}C-labeled amino acids.

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EDITORIAL

Saturation of Amino Acid Uptake by Human Brain Tumor Demonstrated by SPECT

Saturation of human blood-brain barrier (BBB) transport of positron-labeled amino acids has been demonstrated by PET. In this issue, Langen et al. examines saturation of amino acid BBB transport in several types of tumors using SPECT to image a single-photon analog of tyrosine. It is alpha-methyltyrosine labeled in the 3 position of the ring with ^{123}I and is referred to as IMT. The importance of this report is that it represents, to my knowledge, the first SPECT examination of human BBB amino acid uptake saturation in several types of brain tumors.

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An intravenous preload of a commercial parenteral nutritional supplement containing the 20 common amino acids was given before, during, and after the labeled IMT was given intravenously.

Ten patients were studied: five with gliomas; two with meningiomas; two with pituitary adenomas; and one with metastases. The two pituitary adenomas could not be seen by SPECT, so no tumor data are presented in these two cases, but normal brain was measured. The patients were fasted for 12 hr, scanned, and tumor and brain uptake of IMT was measured. One week later they were scanned with the amino acid preload, the infusion being given intravenously prior to and during the scan.

The results of this paper suggest that amino acid competition can be demonstrated in non-neoplastic brain and in gliomas. These findings are compatible with the hypothesis suggested by Davson and Oldendorf that glial cells, through some humoral mechanism, cause brain capillaries to become structurally, functionally, and chemically altered to create the BBB (*1*). Recent studies in tissue culture support this hypothesis (*2*).

Since almost any major disruption of brain cellular integrity results in loss of the BBB, it may well be shown that loss of BBB represents very abnormal or dead astrocytes in the region. One might speculate that in metastatic tumors and meningiomas there are no astrocytes present. Capillaries in these lesions are permeable to all small molecules,

and no BBB carrier systems are needed nor can saturation of carrier-mediated transport be measured. As astrocytic ability to maintain the BBB is lost, the capillary reverts to the structure and general permeability characteristics of non-neural capillaries. This hypothesis could be supported by extending the studies of Langen et al. and including a larger number of patients. The healthy BBB is selectively permeable, showing a wide range of permeabilities based on chemical structure and not on molecular size. For example, D-glucose and nicotine permeability are very high, but for L-glucose and methotrexate, the permeability of the healthy BBB is nearly zero.

Langen et al. used a commercial mixture of amino acids to estimate capillary saturation. There are probably three amino acid carrier mechanisms in BBB. These carrier mechanisms require the alpha-amino zwitterion acid configuration found in all of these amino acids. However, the methyl group on the alpha carbon of alpha-methyldopa does not abolish BBB carrier affinity. Although I am unaware of studies of BBB carrier affinity of alpha-amino tyrosine, affinity for the large neutral carrier has been demonstrated for alpha-methyldopa (*3*). Depending on the electrical change (+, 0, or −) of the R-group, a particular amino acid develops an affinity for one of these three carriers. The large, neutral amino acids cross-compete with each other for BBB transport as do the basic amino acids.

Since IMT has a neutral R-group, one would expect neutral amino acids in the preload to compete with it. This could be substantiated by using a cold phenylalanine preload before injecting IMT. Phenylalanine has the highest affinity for the neutral carrier. In separate studies, a basic amino acid, such as arginine, which has no affinity for the neutral carrier, could be used to measure basic amino acid carrier system affinity for IMT.

Although alpha-methyltyrosine does not enter into protein synthesis, it is not free of biologic activity since it inhibits tyrosine hydroxylase. It remains to be demonstrated whether IMT inhibits tyrosine hydroxylase. Although this could not produce any toxic effects in the trace amounts used for scanning, one might expect some different binding effects in regions of high concentrations of tyrosine hydroxylase.

At present, one objective of PET research is to suggest analogous single-photon studies that might be studied by the simpler, and more widely available, SPECT.

Although several examples of cross-inhibition and self-inhibition of BBB carrier systems have been shown by PET, this paper by Langen et al. may be the first SPECT study of human BBB carrier saturation. Although we have measured the ability of phenylalanine to cross-inhibit uptake of ^{75}Se-selenomethionine in vivo in phenylketonuria, only whole brain was counted and no imaging was attempted (*4*).

This paper by Langen et al. is pioneering in that it may lead to further in vivo "fingerprinting" of tumors shown by CT and MRI. Such nonsurgical characterization may well simplify the decision whether or not to surgically biopsy a known lesion. Since only about 10% of cases with brain tumors have any chance of a long-term benefit from surgery, it is especially important to clearly define the nature of brain tumor. Most patients with brain tumors die in the first postoperative year and many in the first three postoperative months. Medical and radiation therapies could be started early with greater histologic certainty.

There is a vast body of literature on selective BBB permeability in rats. It would be valuable to discover whether the human and rat BBB are, as I suspect, identical. This SPECT paper opens a new field of human brain and brain tumor selective transport carriers. The authors should continue from this most encouraging start.

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