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EDITORIAL

Carbon-11-Putrescine: Back to the Drawing Board

The oft-stated aim of PET neuro-oncologists is to exploit metabolic differences between tumor tissue and surrounding normal brain in order to improve tumor localization and permit non-invasive determinations of tumor histology and growth rate that can be used to assess histological grade and response to therapy (*1*). As the article by Hiesiger et al. in the current issue of *The Journal of Nuclear Medicine* demonstrates, this laudable aim remains elusive: [^{11}C]putrescine, the high-profile PET brain-tumor tracer of the 1980s (*2,3*) has proved to be a disappointment in the 1990s. What lessons can be learned from the putrescine experience?

At first glance, the rationale for synthesizing ^{11}C-labeled putrescine seems unusually attractive. Endogenous putrescine, the immediate precursor of spermidine and spermine, is synthesized from ornithine by ornithine decarboxylase (ODC), the rate-limiting enzyme in polyamine synthesis (*4,5*). A second decarboxylase, S-adenosyl-L-methionine decarboxylase (SAMDC) catalyzes the formation of S-adenosyl-S-methylhomocysteamine, from which an aminopropyl moiety is transferred to putrescine to form spermidine, and to spermidine to form spermine (*4*). Whereas ODC activity and putrescine concentration are low in normal brain (*1,4,6*), elevated concentrations of di- and polyamines and their biosynthetic and catabolic enzymes have been reported in a wide variety of rapidly growing tissues, including primary and metastatic brain tumors (*4–8*). Finally, and perhaps most to the point, ODC activity, putrescine concentration and SAMDC activity in biopsy specimens of rat and human tumors, including gliomas, have been correlated with histopathological criteria of malignancy (*5,6,9–11*).

Although exogenously administered putrescine does not readily cross the intact blood-brain barrier (BBB), it rapidly traverses the more permeable blood-tumor barrier (*2,3,12*). Preliminary [^{14}C]putrescine autoradiographic studies in T9-gliosarcoma-bearing rats indicated that target-to-background (i.e., tumor-to-contralateral brain) concentration ratios as high as 35:1 were achievable and suggested that ^{11}C-labeled putrescine might serve as a "near ideal" PET tracer for the metabolic imaging of human brain tumors and, within the context of an appropriate pharmacodynamic model, as a marker for tumor growth rate (*2*). These high hopes were bolstered in 1987 by Hiesiger et al. (*3*), who reported in this journal that [^{11}C]putrescine PET studies of primary and metastatic brain tumors provided a better signal-to-noise ratio than glucose metabolic rate measurements obtained with [^{11}C]2-deoxyglucose (^{11}CDG); Hiesiger et al. also anticipated that [^{11}C]putrescine would prove useful for locating small glycolytically hypometabolic lesions and would provide a quantitative index of degree of malignancy.

But doubts began to emerge, even as new claims for [^{11}C]putrescine were being made. In their 1987 *Journal of Nuclear Medicine* article, Hiesiger et al. grappled with the possibility that some or all of the observed tumor uptake of plasma ^{11}C radioactivity ([^{11}C]putrescine, $^{11}CO_2$ and nonvolatile ^{11}C-labeled putrescine metabolites) was due to deficiency of the BBB, and that uptake of *exogenous* putrescine did not necessarily reflect the rate of tumor polyamine biosynthesis. In 1988, Warnick et al. reported surprisingly low in vivo rates of [exogenous] putrescine conversion to spermidine and spermine in T9 rat gliosarcoma

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and U-87 MG human glioblastoma (*1*). In order to explain these results, which seemed to contradict the findings of previous studies describing enhanced polyamine metabolism in rat and human gliomas, the authors conjectured that polyamine metabolism might vary with tumor growth fraction, and they discussed the importance of alternative pathways of putrescine metabolism (*1,4,13*) and the existence of multiple endogenous polyamine pools. In their current paper, Hiesiger et al. conclude that [^{11}C]putrescine uptake relates primarily to BBB breakdown rather than to tumor polyamine metabolism or mitotic activity and, therefore, "appears to have more limited diagnostic utility than ^{18}FDG or ^{11}CDG."

In retrospect, it is not difficult to see where things went wrong. First, the lack of a comprehensive biophysical/biochemical model for [^{11}C]putrescine uptake, based on accepted in vitro and in vivo biochemical data and taking into account BBB transport, extra- and intracellular compartmentalization and tracer metabolism to polyamines, nonpolyamine metabolites and CO_2, led to ambiguous or uninterpretable PET results. Second, the graphical evidence of irreversible tumor uptake of [^{11}C]putrescine, presented by Hiesiger et al. in their 1987 paper, was ultimately based on a *single* 50-min patient study in which, at 20 min after tracer injection, only 9% of the plasma ^{11}C radioactivity was identified by HPLC as putrescine—the remaining 91% was characterized as "[^{11}C]O_2 and nonvolatile metabolites." Third, the difficulties in interpretation occasioned by tumor heterogeneity (both histological and metabolic) and volume averaging, and the limitations of data analytic strategies relying on average regional (region of interest) or peak values were not fully appreciated (*14*). Finally, insufficient attention was paid to the mechanism of putrescine uptake, the limitations of experimental brain-tumor models, and the relative merits of other nonglucose ^{11}C and ^{18}F PET tracers employed for brain-tumor imaging (*15–17*).

In conclusion, the lessons learned from the [^{11}C]putrescine experience—the importance of tracer kinetic modeling, the need for complete radiochemical characterization of the arterial input function, and the constraints imposed by in vivo tumor biology—need not be re-learned during the evaluation of each new brain-tumor radiotracer. Claims of diagnostic and prognostic utility for novel PET tracers must be evaluated within the context of the bedside neurological examination and the results of CT/MRI scanning and standard neurodiagnostic tests. Given the biologic and metabolic diversity of human brain tumors—which extends to individual metastatic deposits—multidimensional prospective clinical trials will be required to establish meaningful estimates of in vivo sensitivity and specificity.

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Correction

In the November 1991 issue of the *Journal,* the author line for "Noninvasive Delineation of the Effects of Moderate Aging on Myocardial Perfusion", by Senneff et al (pages 2037–2042) was printed incorrectly. It should read: Martha J. Senneff, Edward M. Geltman, and Steven R. Bergmann, with the technical assistance of Judy Hartman.