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Introduction

The unnatural amino acid 1-amino-cyclopentane-1-carboxylic acid (ACPC) has been reported to inhibit the growth of several types of tumors in experimental animals.[1] Studies on the metabolism of ACPC have shown that ACPC is itself the active inhibitor since it is not metabolized by normal or neoplastic tissues.[2] The lack of metabolism of ACPC has also been observed by Berlinguet et al.[3] and Christensen et al.[4] Using autoradiographic techniques with the ^{14}C-labeled compound, Berlinguet et al.[3] showed that there was a selective uptake of ACPC by tumor tissue. Tumor detection with ^{11}C-ACPC proved that this amino acid had a high affinity for malignant tumors.[5-7] However, quantitative evaluation of ^{11}C-ACPC uptake in neoplastic lesions was not yet reported. We studied the kinetics of intravenously injected ^{11}C-ACPC in a rabbit VX-2 tumor using positron emission tomography (PET).

Materials and Methods

The synthesis of ^{11}C-ACPC was reported elsewhere.[8] The rabbit (3kg) was fasted for 12 h prior to the experiment and anesthetized by pentobarbital sodium 20mg/kg. After transmission scanning, 2 mCi of ^{11}C-ACPC was injected as a bolus into an ear vein. Serial 3 min scans were performed at the slice level of the tumor. Arterial blood samples were withdrawn from a femoral artery at given times. The samples were centrifuged, and plasma counting was performed in an NaI auto-well counter. Scans were finished 60 min after injection. The spatial resolution was 1.2 cm FWHM at high resolution mode. The scans were corrected for decay and attenuation. Region of interest was carefully determined in order to include the pixel of maximum count in the tumor.

Results

The time course of ^{11}C activity in plasma and tumor is presented in Figure 1. ^{11}C-ACPC in plasma decreased rapidly after injection, whereas its activity in the tumor was increased with time up to 60 min. Tumor

radioactivity exceeded that of plasma within 6 min of ^{11}C-ACPC administration. Because of technical reasons, the measured radioactivity was not corrected for residual ^{11}C-ACPC within the vascular compartment of tumor tissue.

The kinetic evaluation of ACPC uptake into the tumor was attempted using unidirectional transport model developed Patlak et al.[9] and Blasberg et al.[10] The method involves plotting the ratio of the total tissue activity at time T[Ct(T)] and the concentration of a test substance in the plasma [Cp(T)] versus the time integral of the plasma activity at time T divided by Cp(T). The slope of such a plot, if linear, is equal to blood-to-tumor transfer constant (Ki). Figure 2 illustrates this approach applied to the ROI data of the tumor. The original imaging and blood sample times differed and interpolated values of Cp(T) were used in the calculation. A linear relationship was established from 20 min after injection to 60 min which indicated that the transport was unidirectional. Approximating the slope with a least-squares analysis yielded a value of Ki (0.0173 ml/g/min) and showed that 20 min was needed for ^{11}C-ACPC to achieve a steady state between blood and its rapidly exchangeable distribution volume.

Discussion

Tumor scanning by PET with ^{11}C-ACPC showed that this unnatural amino acid had a high affinity for malignant tumors. At the present time, existing limitations of spatial resolution with PET scanner make it unlikely that PET would contribute to the early diagnosis of neoplasms. However, the physiologic tumor-localizing agents may provide a unique approach to quantitative in vivo analysis of tumor metabolism. ACPC has been used in the past as a nonmetabolizable model for amino acid transport studies in both normal and tumor systems. This amono acid has been shown to be highly reactive with amino acid Transport Systems A and L.[11] Like ^{18}F-FDG, ^{11}C-ACPC may have the ability to mimic natural substances and be influenced by the same transport processes. The preliminary result presented here may form the basis for the quantitative analysis of the in vivo distribution of ^{11}C-labeled ACPC in tumor.

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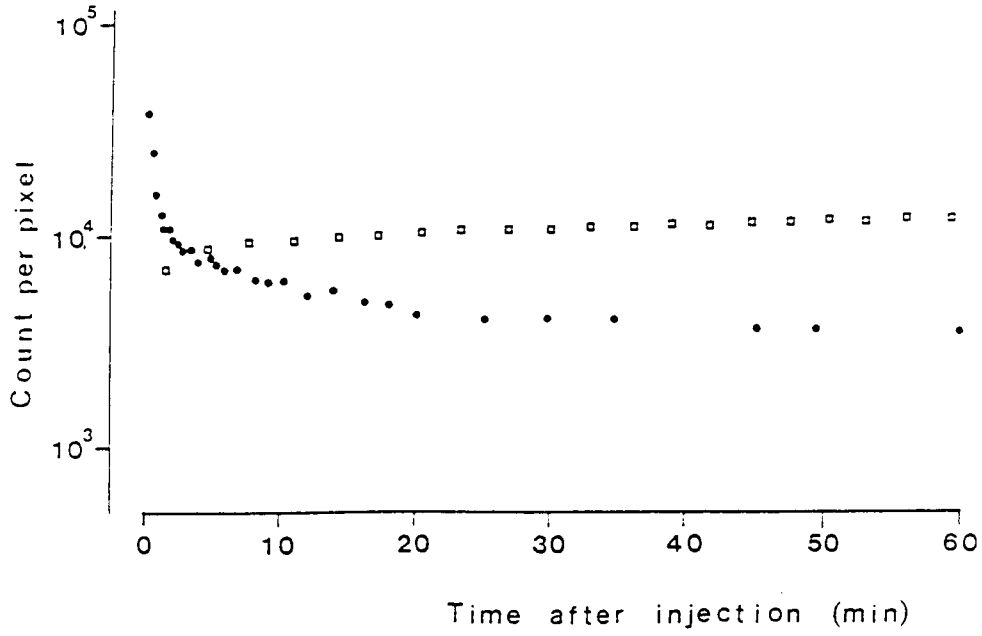

Fig. 1. Time course of ^{11}C activity in arterial plasma (filled circles) and VX-2 tumor (open circles) after bolus intravenous administration of 2 mCi of ^{11}C-ACPC in the rabbit.

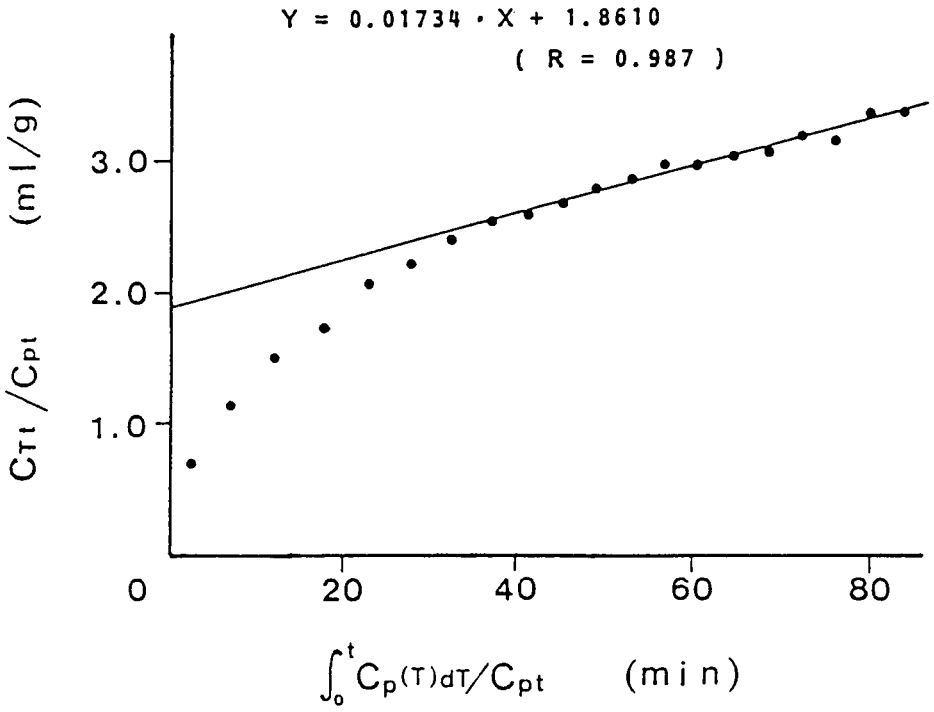

Fig. 2. Graphical analysis of the tumor in the rabbit over a time course of 3 to 60 min. A plot of tumor ^{11}C-ACPC activity / final plasma radioactivity (ordinate) versus the plasma arterial radioactivity integral / final plasma radioactivity (abscissa) is shown. The solid line represents the best linear fit by a least-squares analysis of the PET data points from 20 to 60 min.