45Ti-DTPA and Blood-Brain Barrier

III. 10 ^{45}Ti-DTPA and Blood-Brain Barrier

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Titanium-45, one of the positron emitting tracers, has a short half life of 3.09 hr. Ishiwata and Ido prepared ^{45}Ti-diethylenetriaminepentaacetic acid (DTPA) and investigated its in vivo behavioral characteristics in aminals.[1] And we have recently reported the possible usefulness of ^{45}Ti-DTPA as a Blood-Brain Barrier (BBB) indicator on positron emission computed tomography by using the autoradiographic technique.[2] The purpose of this study is to make further evaluation of ^{45}Ti-DTPA as a BBB indicator in comparison with ^{14}C-AIB - a widely used autoradiographic tracer for demonstrating BBB breakdown - by multiple labeled autoradiograpic technique recently we have reported.[3]

Materials and Method

1) Hypertonic mannitol solution (1.4 mol) 2.5 ml was infused through the external carotid artery into the internal carotid artery of anesthetized Wistar rats so as the destroy BBB according to the method of Pappius et al.[4] Then ^{45}Ti-DTPA (3-5 mCi), ^{14}C-AIB (100 μCi/kg) and 2% Evans Blue (2 ml/kg) were injected into the femoral vein simultaneously.

Thirty minutes after the injection, animals were decapitated. Brains were frozen in powdered dryice and sectioned 30 μm thickness in a cryostat with taking photograph of the Evans Blue stained brain. The sections were exposed to a X-ray film for the first six hours to obtain the image of ^{45}Ti. Forty-eight hours later, the second exposure was done for 10 days to get the image of ^{14}C.

2) C6 rat glioma cells were implanted into the brains of Wistar rats according to the method we had already reported elsewhere.[5] About three weeks later, ^{45}Ti-DTPA (3-5 mCi) and ^{14}C-AIB (100 μCi/kg) were injected into anesthetized tumor bearing rats intravenously. Autoradiographic images were processed as mentioned above. The sections used for autoradiography were subsequently stained by hematoxylin eosin and compared with the autoradiographic images.

Results

1) In all five animals showing destruction of BBB, the autoradiographic image of ^{45}Ti-DTPA was almost identical to that of Evans Blue, however, ^{14}C-AIB autoradiographic image was somewhat different from other two images (Fig. 1).

2) In all three brain tumor bearing animals, ^{45}Ti-DTPA autoradiography represented the brain tumor image clearly. However, ^{14}C-AIB image was much blurred (Fig. 2).

Discussion

^{45}Ti has a short half life of 3.09 hr and low energy as same as ^{11}C has in a series of positron emitting radionucleides, therefore, ^{45}Ti-labeled tracers are expected to have the better resolusion on positron emission computed tomography. Our previous study[2] showed that the ^{45}Ti-DTPA combined with serum albumin and extravasated where BBB was destroyed, the same as Evans Blue did.[6] Consequently the image of ^{45}Ti-DTPA autoradiography looked similar to that of Evans Blue as seen in this experiment. However, it was different from the autoradiographic image obtained by ^{14}C-AIB - one of the established tracers for manifesting BBB impairment. The ^{45}Ti-DTPA demonstrated the clear image of BBB breakdown in spite of its much higher energy than ^{14}C, whereas the autoradiographic image of ^{14}C-AIB was blurred.

There seems to be several reasons responsible to the different images between the two tracers. The molecular weight of AIB, one of neutral aminoacids, is small (1×10^2), while that of ^{45}Ti-albumin complex is much larger (5×10^4). And it is a natural result that a smaller molucule tends to spread more quickly in brain extracellular space. Blasberg et al.[7] stated that the initial distribution volume of AIB in brain tissue was several-fold greater than that of DTPA. This different pharmacokinetics between the two tracers could be due to the rapid transport of AIB into brain endothelial cells in addition to the relatively rapid uptake by choroidal, meningeal and ependymal associated tissues. These characteristic features of AIB probably resulted in the blurred autoradiographic image.

Our results obtained in this experiment clearly demonstrate the different properties between ^{45}Ti-DTPA and ^{14}C-AIB, which will give us a important clue for understanding the nature of BBB. Also the clear autoradiographic image of ^{45}Ti-DTPA seems suitable for evaluating the BBB function more precisely with the aid of quantitative positron autoradiography rather than using ^{14}C-AIB with blurred autoradiographic image.

Acknowledgement

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Reference

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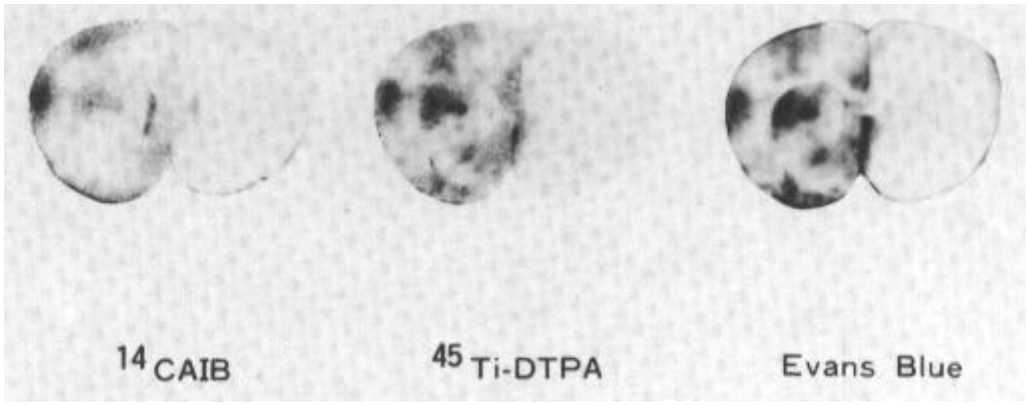

Fig. 1. The images obtained by ^{45}Ti-DTPA and Evans Blue looked similar each other, but the ^{14}C-AIB image seemed different.

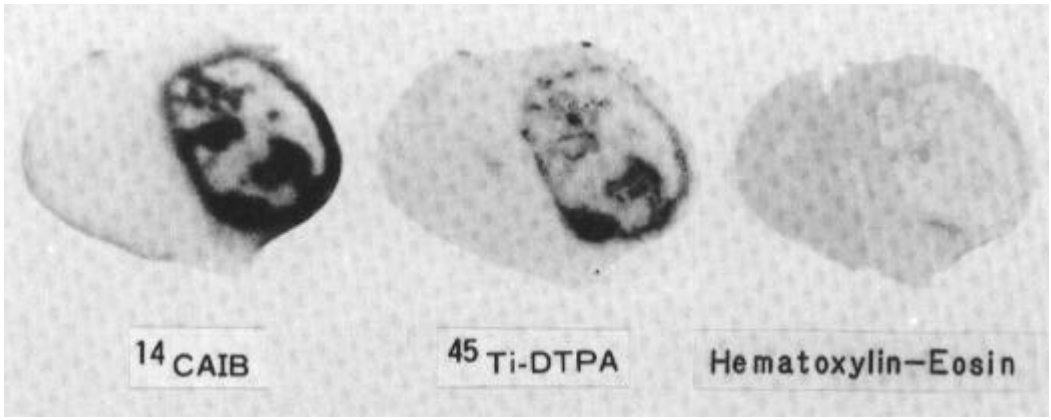

Fig. 2. ^{45}Ti-DTPA autoradiography demonstrated clear and sharp brain tumor image, while ^{14}C-AIB image was blurred.