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journal or publication title	CYRIC annual report
volume	1984
page range	185-192
year	1984
URL	http://hdl.handle.net/10097/49243

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Abstract

The metabolic rate of ^{18}F-2-deoxy-2-fluoro-D-glucose(^{18}FDG) in the rat brain microvessels(Fig. 1) was determined and compared with the rate in the whole brain as a function of time(Fig. 4)(Table 1). The radioactivity of ^{18}FDG-6-P in the microvessels showed the rapid accumulation within 3 min and gradually increased during 30 min after the intravenous injection. On the other hand, the radioactivity of ^{18}FDG-6-P in the whole brain showed the gradual increase from the first time. The contribution rates of microvessels to the whole brain were 27-58 % at first(10 sec), and rapidly decreased to 0.17-0.36 %(30 min). The uptake of β-methyl-[1-^{11}C]heptadecanoic acid(BMHDA) in the microvessels showed the higher value than that in the whole brain.

The result clearly demonstrated that the phosphorylated ^{18}FDG in the rat brain microvessels was the negligible factor in the whole brain, and this indicates the optical density of ^{18}FDG autoradiogram and the image on positron emission tomography(PET) at 30 min after injection show that the image will be made by nerve cells and glial cells without microvessels. And brain microvessels may mainly consume free fatty acid as an energy source.

Results and Discussions

Local cerebral glucose utilization(LCGU) effects greatly to the brain function. Though many experimental and clinical studies are performed by autoradiography and positron emission tomography(PET), often we have taken no notice of important problems, that is, which is the main compartment to contribute to the total brain metabolism. We usually say brain microvessels are negligible to LCGU because their volume is too little(2.1-4.5 %).[1,2] However, if other compartment such as glial cell is compared as volume, its volume is much larger than nerve cell volume, at that time, we definitely don't say LCGU shows the glial cell metabolism. All answers to justify this consideration, which LCGU shows nerve cell metabolism, is an assumption. Because the in vivo study of each compartment metabolism is very difficult at the present time.

Fortunately, setting a limit to the study of brain microvessels, they are able to be isolated safely, and their metabolism is maintained in usual condition.

In this study, at first, we determined the isolated microvessels behaved naturally on glucose metabolism(Fig. 2), and at least, membrane of microvessels is correctly intact after the isolation method was used. In isolated microvessels, phosphorylation of glucose and its analogue is said to start more rapidly than in vivo condition by Pasteur effect. Fig. 3 shows the radioactivity of ^{18}F didn't decrease and remained in the microvessels' pellet after contrifugation(50,000 rpm) and yet after 10 times rinses. This radioactivity is considered to be from ^{18}FDG-6-P, and indicates that phosphorylated ^{18}FDG didn't flow out(efflux) through the membrane. At least on ^{18}FDG metabolism in microvessels, we can practice brain compartment analysis.

As previously denoted, the volume of each compartment definitely doesn't show its metabolism. However, the result we could represent was very simple, which ^{18}FDG metabolism in microvessels was negligible to compare with total brain metabolism, as expected.

On the other hand, the results also indicated some interesting findings as follows

1) Radioactivity in microvessels showed the rapid accumulation within 3 min after injection.
2) The values of ^{18}FDG-6-P in microvessels were little(below 0.1%dose/g tissue).

Gjedde and his colleague showed the abilities of glucose transport on both luminal and abluminal membranes of capillary endothelium are equal.[3] Assuming both transport systems are carrier mediated, except that the concentrations of endogenous glucose in microvessels and parenchyma are different, transport rate constants of these membranes are considered to be simular value(k_1 and k_5, k_2 and k_4 in Fig. 5; possible model on glucose transport). For the purpose to expect that the function of phosphorylated ^{18}FDG will show the rapid accumulation, simulating functions were calculated (see appendix). Assuming that $k_1 = k_5$, $k_2 = k_4$ and k_6 was used as equal as the value of phosphorylating constant on whole brain as previously determined in this study, the function of phosphorylated ^{18}FDG in microvessels was evaluated. As the phosphorylating constant k_3 cannot be determined, Fig. 6 shows as arbitrary unit. This function also showed rapid accumulation, however, it showed relatively less rate in rapid phase than that we estimated. Further more, even if assuming the unphosphorylated ^{18}FDG in microvessels is simular with the function of ^{18}FDG in serum, the ratio of rapid accumulation to slow increase which we determined was found to be higher, that is, the addition to the true value of phosphorylated FDG in rapid phase, which was found in measured value. As a reason of the result, we considered the rapid phosphorylation may occur in microvessels during brain perfusion. Though, we

intended to rapidly perfuse as we can, the point was not able to deny. In all cases, it can deny that the rapid accumulation can not be found, because the properties of both membranes were same.

The function of phosphorylated ^{18}FDG was found to behave as it were integral value of monoexponential decay curve. So we can suppose that the unphosphorylated ^{18}FDG in microvessels will decrease in early time after injection. That indicates the function of unphosphorylated ^{18}FDG doesn't maintain same concentration as a function of time, and if long time will spend to accumulate the radioactivity in brain, not only phosphorylated but also unphosphorylated ^{18}FDG in microvessels will be negligible in total radioactivity.

In vitro studies, we determined the microvessels consume a lot of glucose than the heart muscles(Fig. 2). However, the value in vivo was very little. As a reason, Goldstein et al supposed that brain microvessels consumed many materials such as free fatty acid or ketone bodies as same as glucose in vivo[4), and our result on ^{18}FDG metabolism also suggested that assumption. Furthermore, our preliminaly study on accumulation of beta-methyl-[1-^{11}C]heptadecanoic acid as a metabolic trapped agent on beta oxydation in microvessels showed the higher value than whole brain(2.23%dose/g microvessels, and 0.25%dose/g brain; 10 min after injection).

Brain microvessels may consume free fatty acid, and endogenous glucose will freely pass through microvessels without consumption. On the other hand, brain consumes a lot of glucose and little free fatty acid. That is to say, the mutual-aid metabolism in heterogeneous tissue. According to use this kind of radiopharmaceutical, let us add the true microvessels' metabolism may be studied.

In conclusion, if we study heterogeneously consisted tissue such as brain, compartment analysis is much important to make its metabolism clear, and we believe this kind of study greatly contribute to positron emission tomography.

Appendix

Assuming the glucose transport through luminal and abluminal membranes of brain microvessel are carrier-mediated[4)], and hydrolysis of ^{18}FDG-6-P is little, the differential functions of both unphosphorylated and phosphorylated ^{18}FDG in microvessels and parenchyma are as follows:(Fig. 5)

$$df(t)/dt = k_1 y(t) + k_5 h(t) - (k_2+k_3+k_4) f(t)$$
$$dg(t)/dt = k_3 f(t)$$
$$dh(t)/dt = k_4 f(t) - (k_5+k_6) h(t)$$
$$dj(t)/dt = k_6 h(t)$$

According to calculate these equations, the phosphorylated ^{18}FDG in microvessels $g(t)$ can be written to

$$g(T) = k_3 \int_0^T \left(\frac{k_1{*}\ e^{-(k_5+k_6)t}}{\alpha - \beta} [\alpha e^{\alpha t} \int_0^t y(t){*}e^{(k_5+k_6-\alpha)t} dt - \beta e^{\beta t} \int_0^t y(t){*}e^{(k_5+k_6-\beta)t} dt] \right) dT$$

Where

$$\alpha,\ \beta = \frac{-(k_2+k_3+k_4-k_5-k_6) \quad \sqrt{(k_2+k_3+k_4-k_5-k_6)^2+4k_4k_5}}{2}$$

$y(t)$; serum ^{18}FDG concentration as a function of time

References

1) Rackl A., Pawlic G., Bing R. J., Cerebral microcirculation and metabolism Vol. 1 (1981) pp17-21.
2) Blasberg R. G., Fenstermacher J. D., Patlak C. S., J. Cereb. Blood Flow Metabol. 3 (1983) 8-32.
3) Gjedde A., Christensen O., J. Cereb. Blood Flow Metabol. 4 (1984) 241-249.
4) Goldstein G. W., Betz A. L., Ann. Neurol. 14 (1983) 389-395.

Table 1. ^{18}FDG-6-P in microvessels and whole brain.

	WHOLE BRAIN	MICROVESSELS	
% VOLUME	100%	2.1 - 4.5% *	CONTRIBUTION RATE
10 sec	0.001 ± 0	0.016 ± 0.010	27.3 - 58.6 (%)
1 min	0.026 ± 0.004	0.026 ± 0.016	2.1 - 4.4
3 min	0.134 ± 0.016	0.042 ± 0.015	0.7 - 1.4
10 min	0.496 ± 0.030	0.052 ± 0.020	0.2 - 0.5
30 min	1.037 ± 0.039	0.082 ± 0.011	0.2 - 0.4
	(n = 3)	(n = 2)	

Values are mean ± SD (%dose/g tissue)

*; Microvessels' % volumes were quoted from Rackl et al and Blasberg et al.

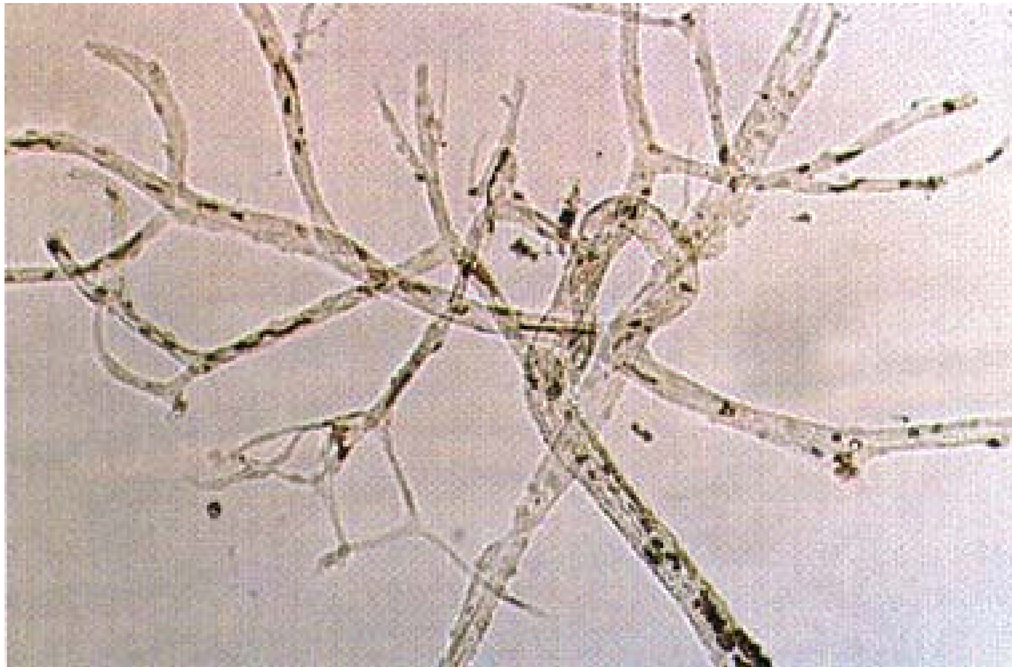

Fig. 1. Light microscopic appearance of isolated rat brain microvessels.

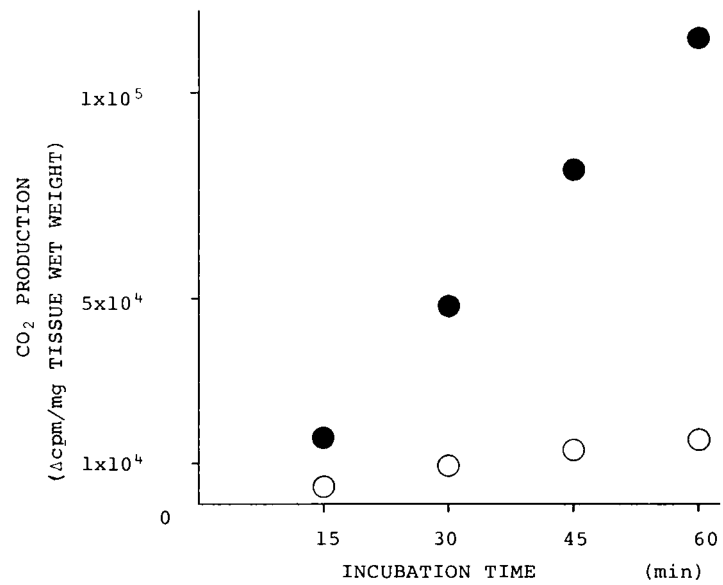

Fig. 2. Effect of incubation time on $^{11}CO_2$ production from ^{11}C-glucose in rat brain microvessels(●) and heart muscles(o).

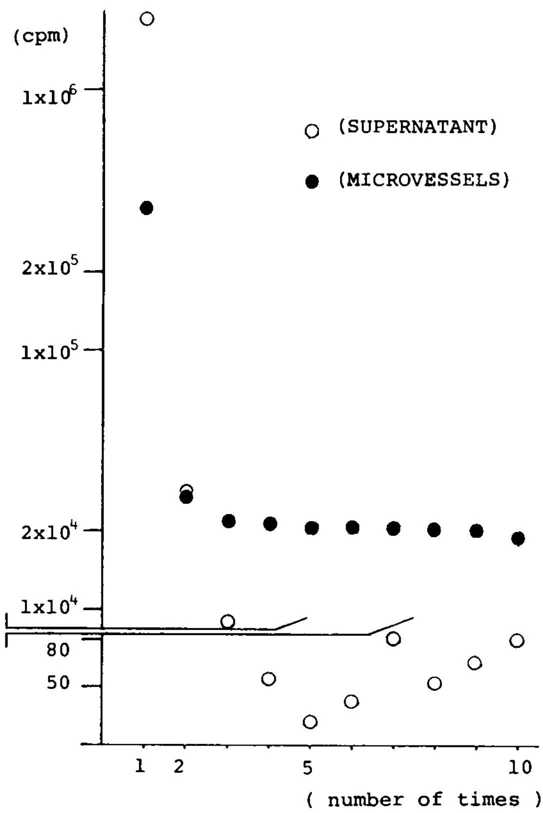

Fig. 3. Radioactivity of both microvessels and supernatant.

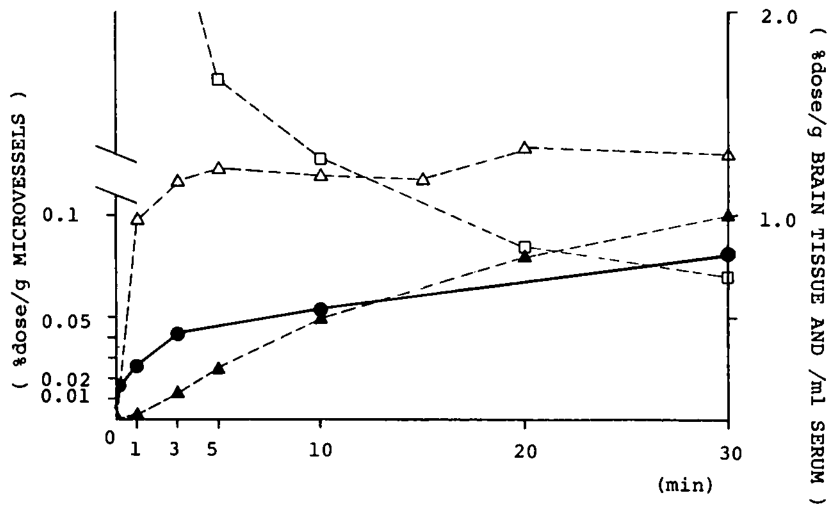

Fig. 4. Metabolic rate of both microvessels and whole brain as a function of time. (□) = serum ^{18}FDG, (△) = whole brain ^{18}FDG and ^{18}FDG-6-P, (▲) = whole brain ^{18}FDG-6-P, (●) = microvessels ^{18}FDG-6-P.

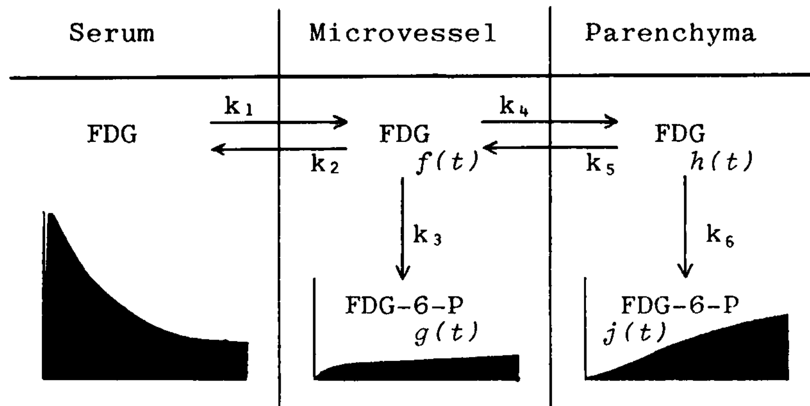

Fig. 5. Schematic drawing of possible model on ^{18}FDG transport in brain. k_1 to k_6 ; rate constants. $f(t)$, $g(t)$, $h(t)$, and $j(t)$ are the concentrations of unphosphorylated and phosphorylated ^{18}FDG in microvessels and parenchyma, respectively.

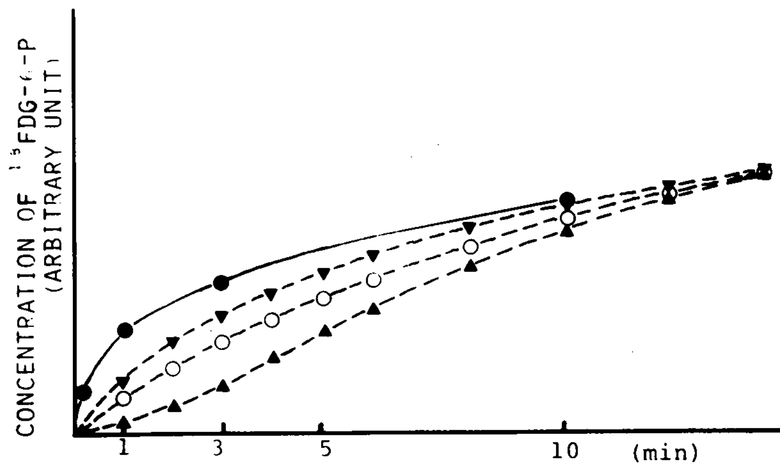

Fig. 6. Simulated functions of phosphorylated ^{18}FDG-6-P in microvessels.
(●) = measured data.
(▲) = rate limiting step in luminal membrane.
(▼) = rate limiting step in abluminal membrane.
(o) = inlet and outlet rate constants of both luminal and abluminal membranes are equal.