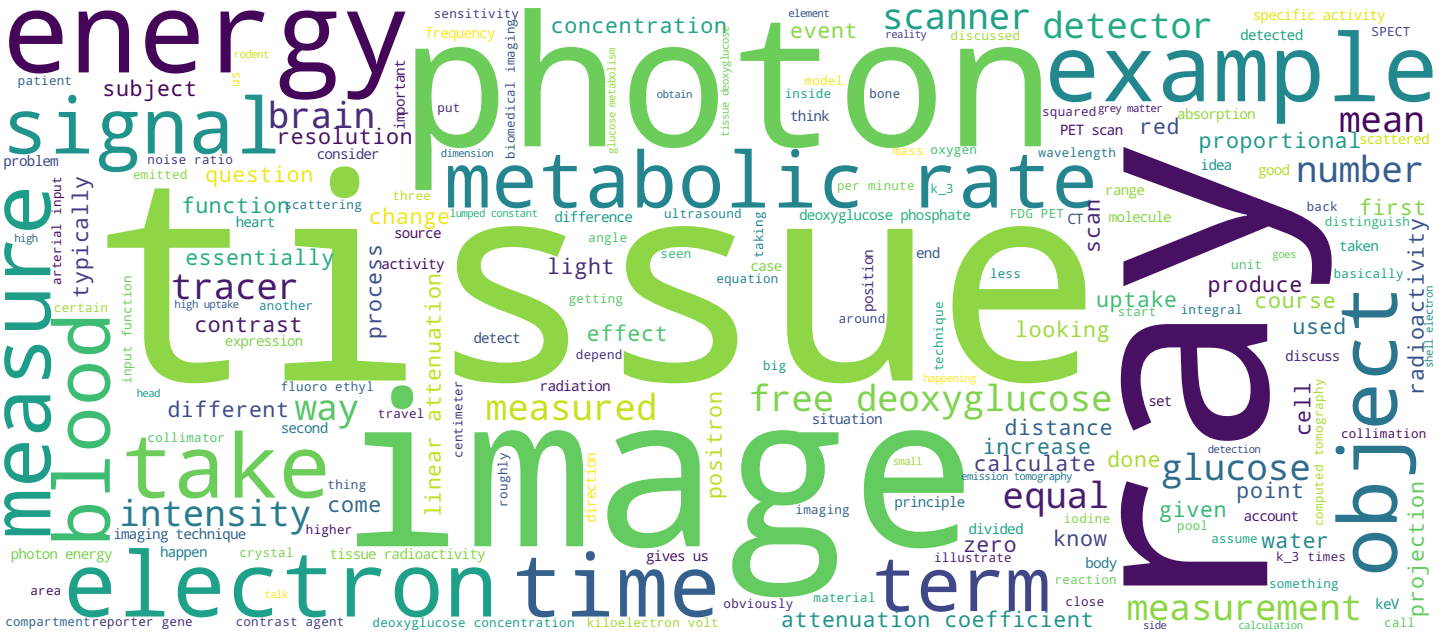
7.3 Metabolism measured by deoxyglucose

Fundamentals of Biomedical Imaging

Prof. Rolf Gruetter



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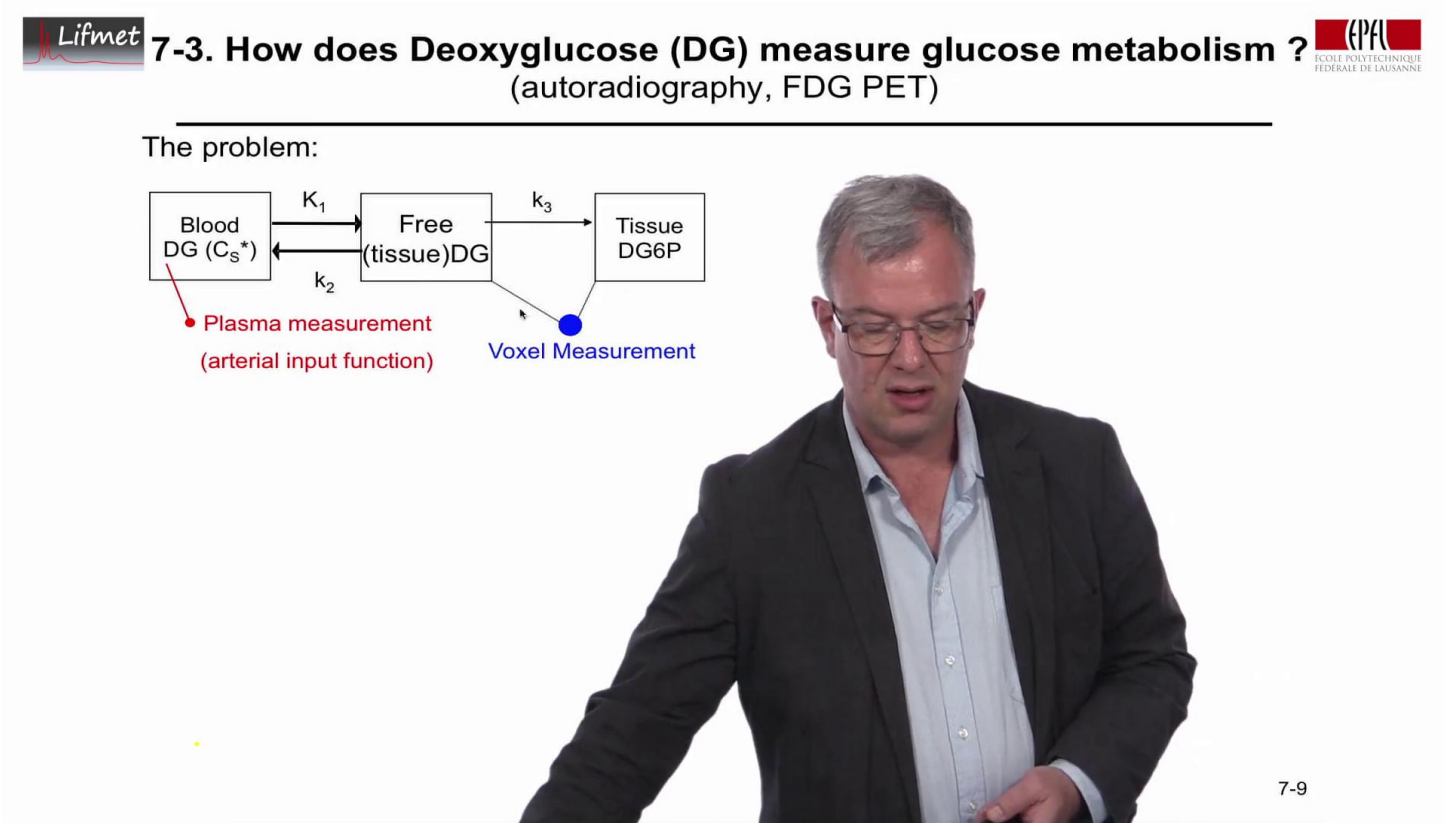
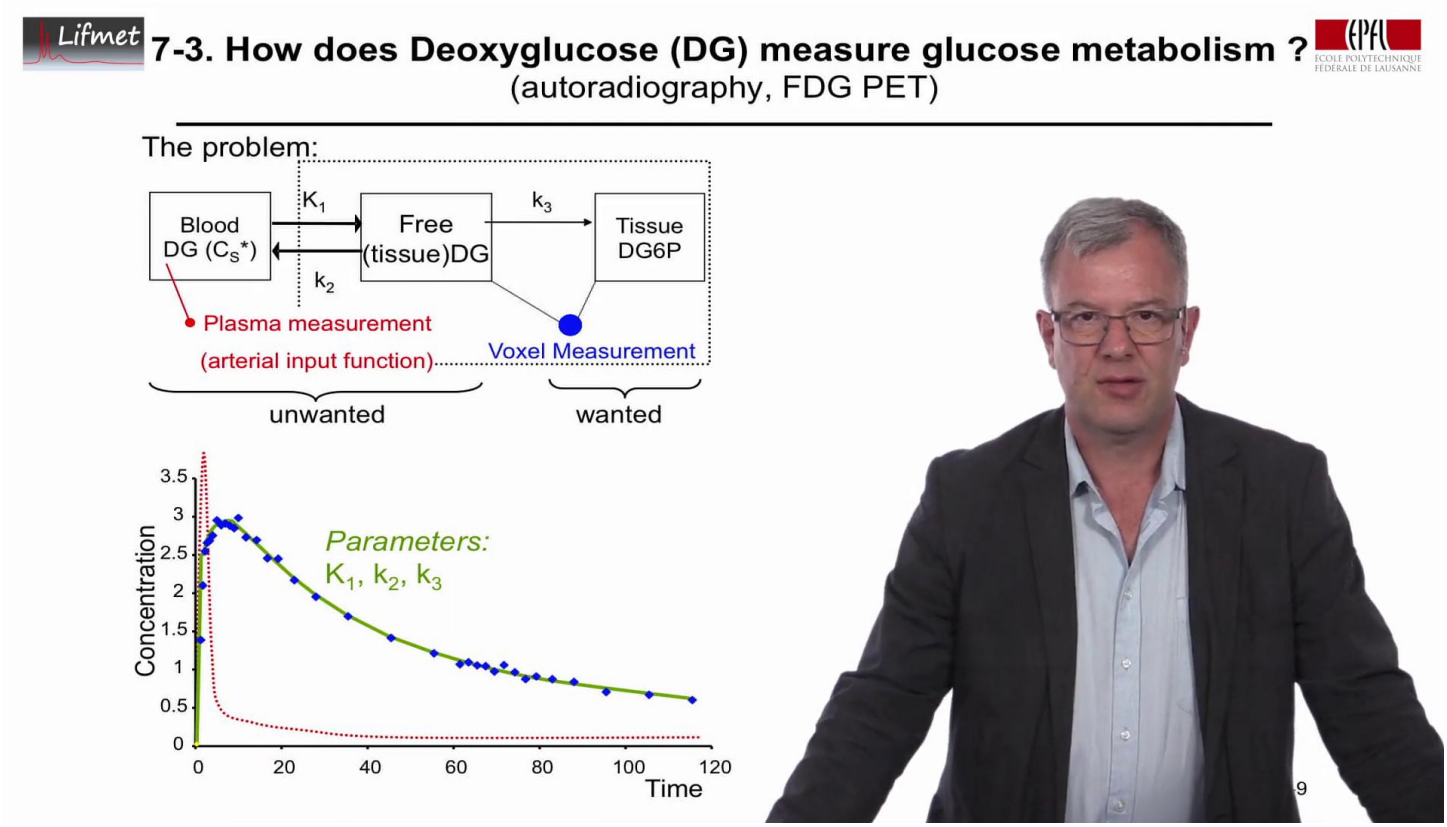


So to come back, how does deoxyglucose measure glucose metabolism? And here, I want to stay specifically with the term deoxyglucose because it's not just FDG PET fluorodeoxyglucose, it's 2-deoxyglucose paired with C11 label that would be also a PET technique or C14, or H3 tritium. So it's the same process here. And the question is: how do we in the end measure with deoxyglucose glucose metabolism? There is a problem here, and I want to state this first. We have deoxyglucose in the blood. That's our C_s *. This is what we can measure by taking blood samples and we can measure the arterial input function like we just discussed, so that we can measure. Then, two transport processes describe the reaction constants K_1 and k_2. We have the uptake of the free deoxyglucose that is, into the tissue, that's tissue deoxyglucose. And finally we have the metabolic rate. The metabolic rate of glucose consumption that produces in the tissue the deoxyglucose-6-phosphate. And this is what we measure with the imaging techniques, largely. With PET [inaudible] FDG. In our voxel measurement, and this is, here, the problem is this is what we are essentially measuring.

Notes

Summary

0m 04s



So, what we don't want to be able to measure what we don't want to have as a measurement is the enrichment of the deoxyglucose in the blood. We don't want that activity, or the free deoxyglucose. We really just want to measure the buildup of the deoxyglucose-6-phosphate. That's what is wanted. And so, in the measurement principle of FGD PET this has to be taken into account, and as you shall see as we shall see, this actually has a specific consequence on how the scans are being performed. So if look at over time, we have the concentration of the tracer on the y-axis, time on the horizontal axis. Here's the concentration, so it's some arbitrary units. And this is what is measured, let's say, with the imaging technique. It's a blue curve. And what we have measured in the blood the arterial input function, that is in red. One can take now, as I said, with Laplace transform or other mathematical means one can take now the differential equation that we've established. We know the red curve, we have measured the blue points and we can now fit our model. Taking into account the above transformations one can fit this model and obtain K_1, k_2 and k_3 to the data.

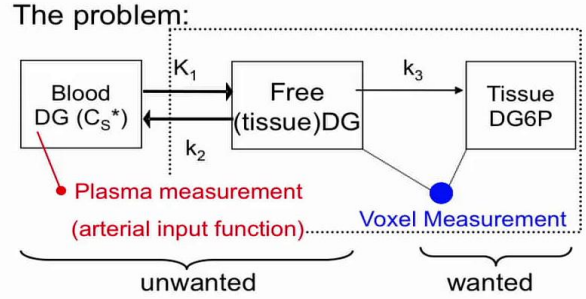
Notes

Summary

1m 30s

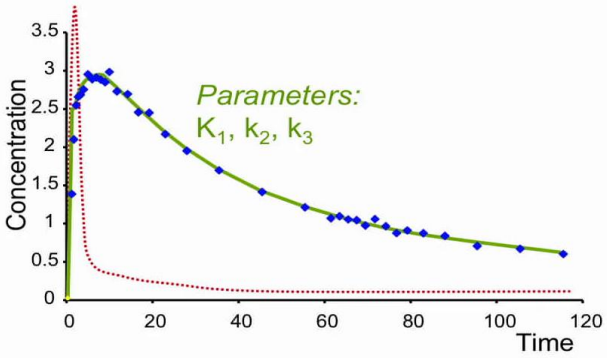
7-3. How does Deoxyglucose (DG) measure glucose metabolism ?
(autoradiography, FDG PET)

The problem:



$$\frac{dC^*_{free}(t)}{dt} = K_1 C^*_S(t) - (k_2 + k_3) C^*_{free}(t)$$

$$\frac{dC^*_T(t)}{dt} = k_3 C^*_{free}(t) \qquad C^*_T(T) = k_3 \int_0^T C^*_{free}(t)dt$$



7-9

This is fairly mathematically involved and I want to show here a simple approach which also illustrates how we do the measurement. in practice. So let's look at the free deoxyglucose here this pool here, this compartment. This compartment, the buidup so this is one reaction in, two reactions going out, this is the flow of the tracer in K_1 times C_s *, that's the blood, minus k_2 times C_3, the free deoxyglucose, that's what's going by backward transfer, out of the tissue, minus (k_3 times C_3), that's the consumption rate of the free deoxyglucose. As to the tissue, in this model, the way it's set up here we have the tissue radioactivity, the deoxyglucose-6-phosphate that's equal to k_3 times the specific activity of the free deoxyglucose. But we have no idea of how this develops. We can solve this differential equation here if we know the free tissue deoxyglucose concentration then the radioactivity in the tissue is given times k_3 times the integral of the free deoxyglucose concentration over time. Now we can make here the assumption, and for many tissues this is a good assumption, that we have fairly rapid glucose transport so that is the specific activity of free glucose in the tissue.

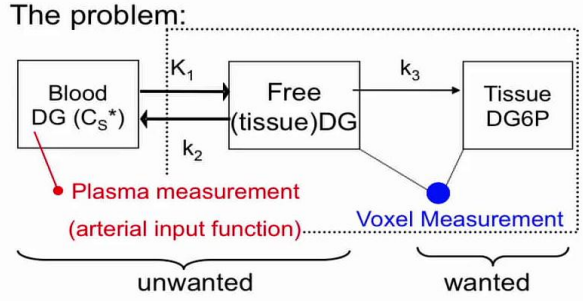
Notes

Summary

2m 52s

7-3. How does Deoxyglucose (DG) measure glucose metabolism ?
(autoradiography, FDG PET)

The problem:



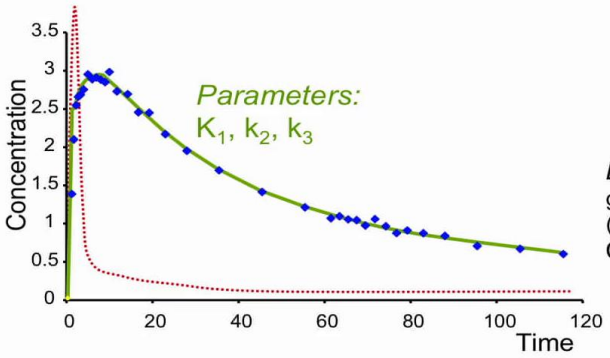
$$\frac{dC^*_{free}(t)}{dt} = K_1 C^*_S(t) - (k_2 + k_3) C^*_{free}(t)$$

$$\frac{dC^*_T(t)}{dt} = k_3 C^*_{free}(t) \qquad C^*_T(T) = k_3 \int_0^T C^*_{free}(t)dt$$

Rapid glucose transport : C_S*(t)≅C_{free}*(t)

$MR_{Glc} \propto k_3$ $\quad k_3 = \dfrac{C^*_T(T)}{\int_0^T C^*_S(t)dt}$

$$MR_{Glc} = \frac{C_S}{LC} \frac{C^*_T(T)}{\int_0^T C^*_S(t)dt}$$



Lumped constant (LC): differences between glucose and DG
(affinities for transporters and hexokinase)
C_S: blood glucose concentration

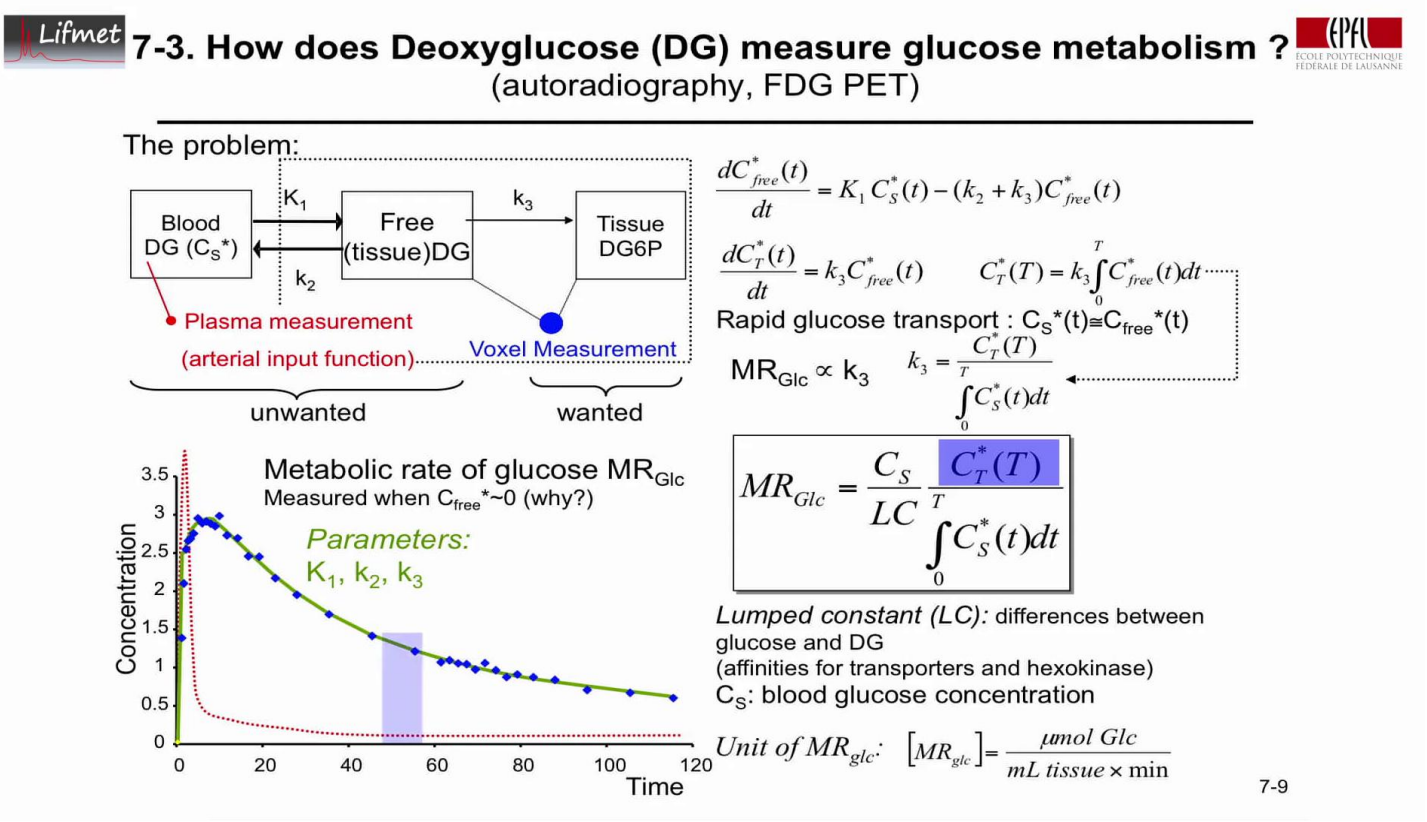
7-9

Free deoxyglucose is pretty much mimicking the specific activity of the free deoxyglucose in the blood, all of the deoxyglucose in the blood. So we'll set here the free deoxyglucose concentration in the tissue equals to the concentration that we have in the blood. The specific activity. And then, we can take this expression here, we can calculate k_3, we'll have the integral of what's happening in the blood from zero to big T. The time integral times the concentration of the tissue radioactivity at time big T. This gives us the rate constant k_3. And k_3 is essentially proportional to the metabolic rate of glucose. Actually, in reality, the metabolic rate of glucose this is proportional, so here's the k_3, that's this term here is written as the blood concentation of glucose divided by a term called lumped constant. This lumped constant is a term that takes into account the difference in affinity of deoxyglucose relative to glucose for the process of transport and the metabolic rate, so this is glucose transporters and hexokinase. C_s is the blood glucose concentration here. So, this lumped constant can be measured.

Notes

Summary

4m 21s



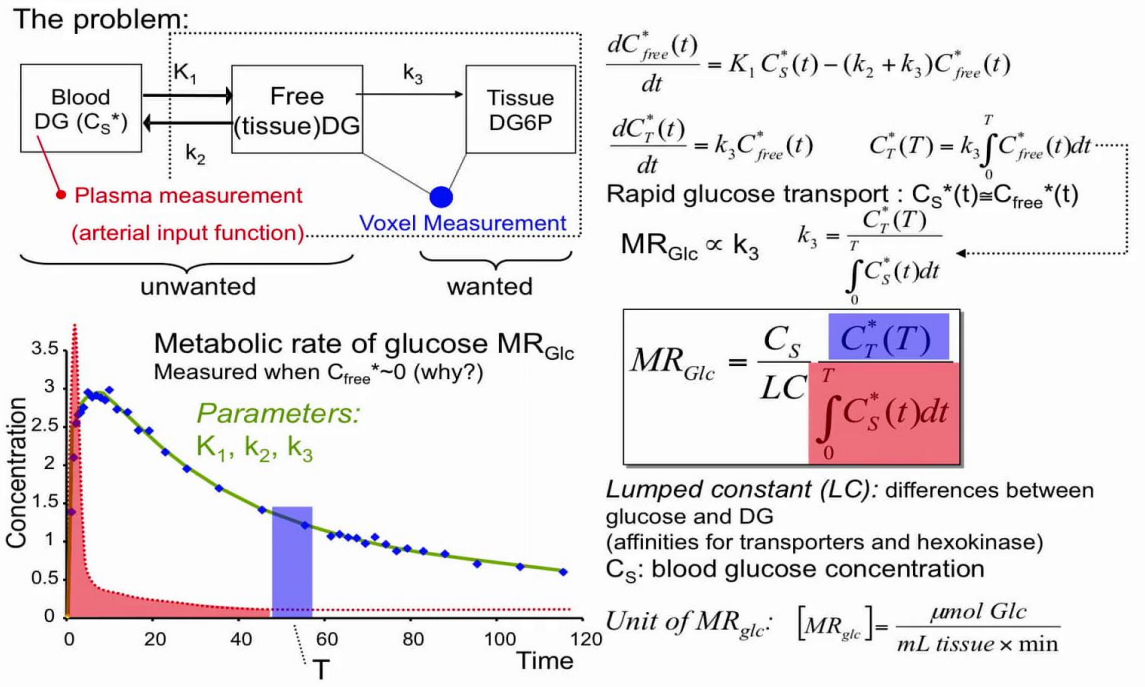
It is generally just assumed to be a certain value and so we then have the metabolic rate of glucose is proportional to k_3, and here's the proportionality constant. Just as a side point, the unit of MR glucose is micromol of glucose molecules per millimeter tissue per minute. Typically it's reported as micromols per gram per minute, its equivalent, because the specific weight, the density of our soft tissues is essentially 1, so it's 1 gram per milliliter so this is very close. So, the metabolic rate of glucose should be measured when the tissue, specific activity of free deoxyglucose is essentially negligible. Why is this so? Well, here we're coming back to the problem. We, in the imaging technique, even if this is zero, and this is not zero we will not be able with the tracer techniques to distinguish between these two pools. We won't see the difference, the radioactivity that we measure is independent of the chemistry, so we have this factor contributing. So ideally, we would want to just measure that, so that's why we would want to measure at a time point where the tissue deoxyglucose concentration is negligible. And so, we're doing...

Notes

Summary

5m 53s

7-3. How does Deoxyglucose (DG) measure glucose metabolism ?
(autoradiography, FDG PET)



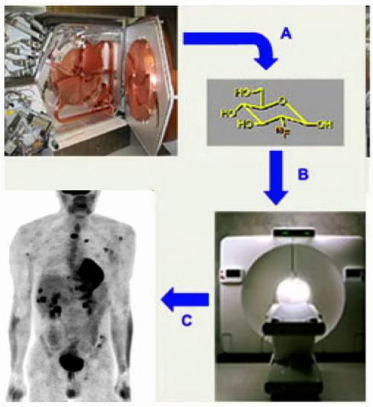
typically this experiment is typically done at around 45 to 60 minutes after the injection, bolus injection of the deoxyglucose at this time point. So this is our big T here, the measurement that we're doing so that's this term here, that's what we've measured here and now we have to evaluate this integral and that's just taking the integral of the arterial input function. And there we go, voila, we have the calculation of the metabolic rate of glucose that can be done in this way. This explains that's when the patient goes for a PET scan to measure the metabolic rate of glucose you have the uptake phase so we will wait a certain amount of time typically 45 to 60 minutes. This is to get the uptake of the tracer into the tissue and to have minimal tracer in the blood at that point so that the image represents what's in the tissue and not in the blood.

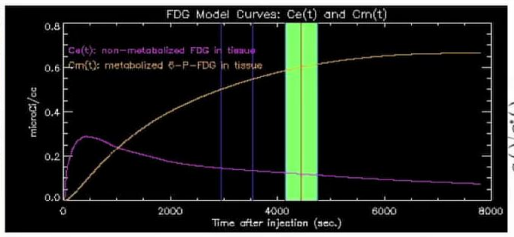
Notes

Summary

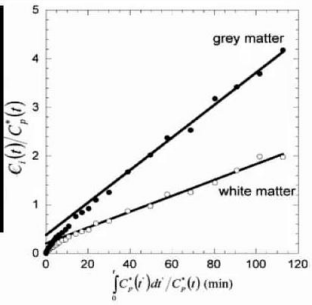
7m 12s

Ex. Typical FDG PET scan





45 min uptake phase (minimal tissue FDG)
then scan FDG-6P



7-10

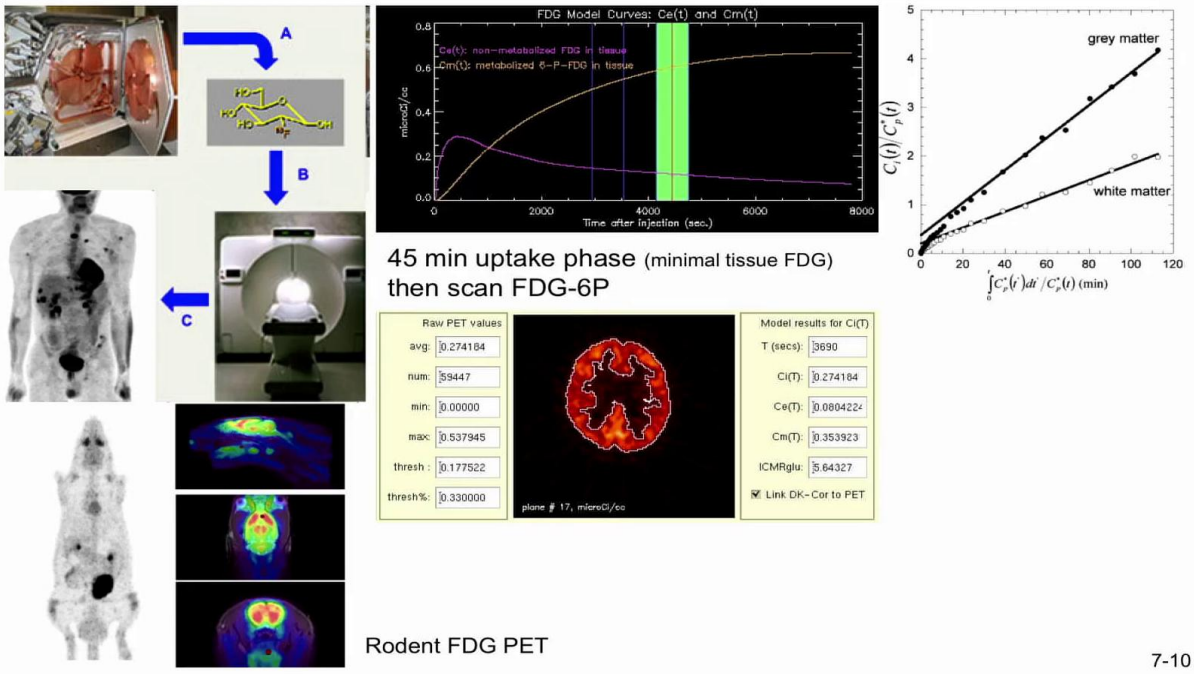
So how is a typical FDG PET scan being performed? Well, first we need to produce the FDG, this is done in a cyclotron. The production of F18, then with radiochemistry it's attached to a glucose molecule. The person is placed into the scanner. Here's the scanner, and we obtain the image here. This is a typical FDG scan, high uptake in the heart in the brain up here, and we have also a lot of activity in the bladder as it is being secreted by the urinary system. And here's an image of a patient not so lucky with metastases in the body, and these metastases are clearly visible. So, if we look at the uptake, we have the uptake-- the measurement is done roughly here. We have the metabolized FDG, deoxyglucose-6-phosphate non-metabolized FDG here in this model curve. So, we have the 45-minute uptake phase, so we do the injection, we wait 45 minutes, put the subject into the scanner and then we measure essentially the distribution of fluoro-deoxyglucose-6-phosphate. And this is here by plotting the tissue concentration to the plasma concentration, and here, this is a reformulation of the expression I showed on the previous slide.

Notes

Summary

8m 09s

Ex. Typical FDG PET scan



7-10

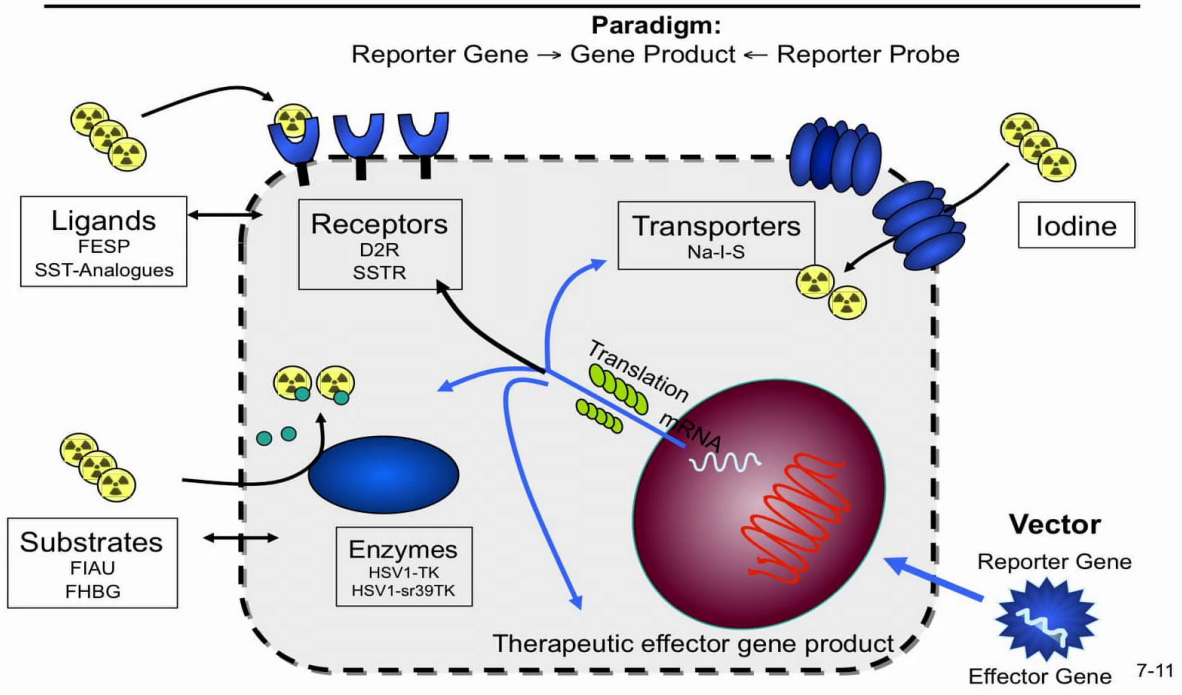
This linearizes in these tac-tac plots linearizes the different times big T the measurement and we can see here that there is an increase in tissue radioactivity in white matter that is less than in grey matter and that's a direct experimental demonstration of higher metabolic rate of glucose here in the brain for grey matter, grey matter being where the neurons are, the electrical firing white matter the connections between the neurons. And so, if we look at the PET scan, we get the raw values that are obtained with the modeling, such as the modeling that's done here or that I showed on the previous slide, one can calculate in the end the local metabolic rate, cerebral metabolic rate of glucose. This is the brain here, L stands for local, so this is basically a way of saying that an image has been taken. If we look at the FDG scans of a rodent this is a whole body scan and here is from the brain in red, this is color coded in red shows high uptake of the deoxyglucose and phosphorylation. So, this is the essential principle here for FDG PET scanning.

Notes

Summary

9m 35s

Ex. PET Reporter Gene Imaging

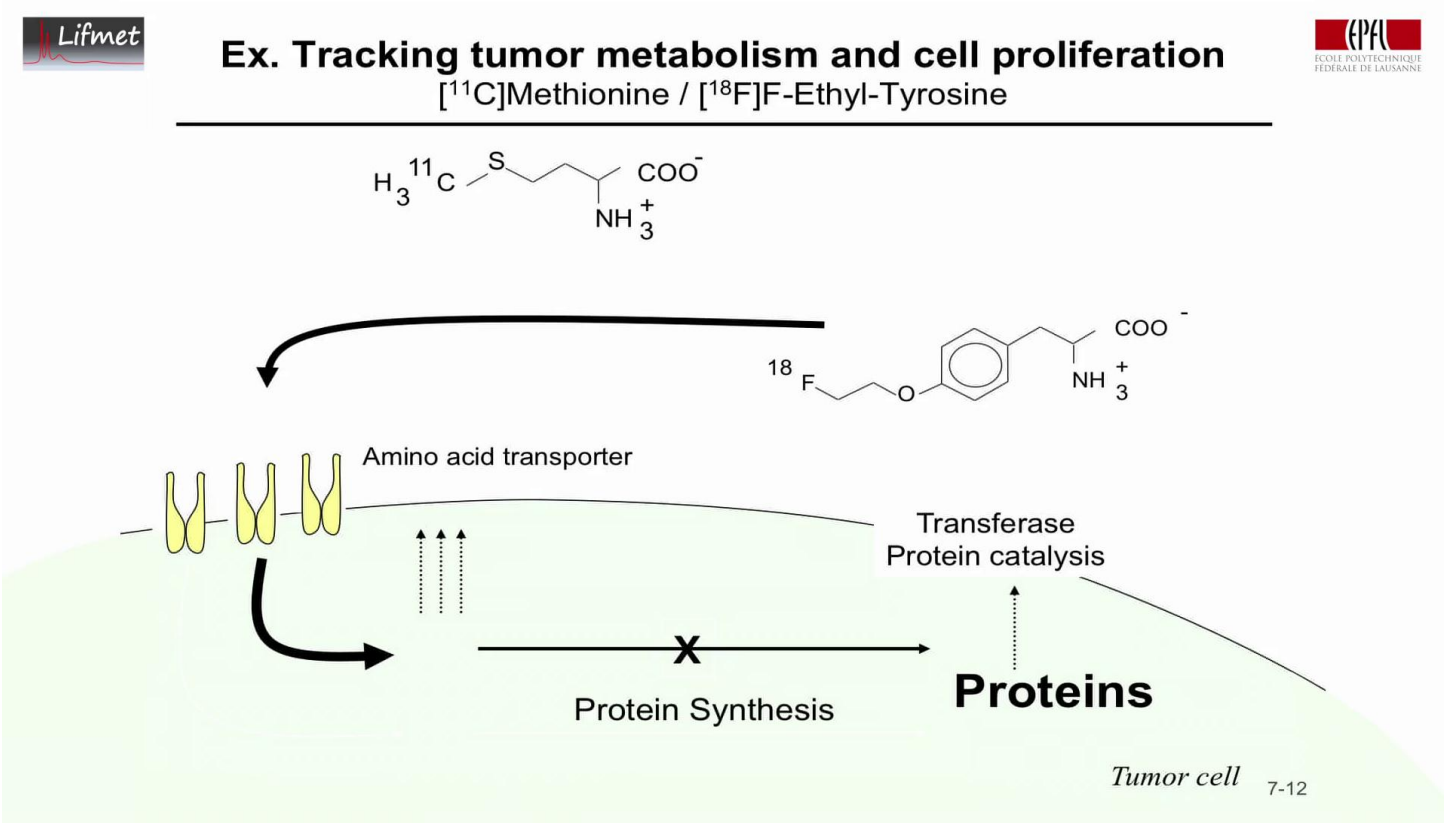


I'll just briefly mention a few other ways of using tracers with for example with PET for gene imaging. So here's a reporter gene that interacts with a gene product and then you have a reported probe. So here's actually a CT contrast, so this is iodine that is being transported. We have ligands with fluorinated ligands that bind to receptors. We have substrates with fluorine contrast agents that are binding to these molecules. These are the reporter genes here, the Herpes Simplex virus family of reporter genes. And so with the binding of a specific ligand to that reporter gene, that reports the activation of another gene, gene expression can be imaged or the effect of therapy can be measured.

Notes

Summary

10m 54s



Let's look briefly at another example, that's tumor metabolism and cell proliferation. The two examples I want to give you C11 Methionine and Fluoro-Ethyl-Tyrosine. So methionine is a neutral amino-acid, it's transported by the large neutral amino-acid transporter molecule. With C11 it is measurable by PET, enters the tissue, and through protein synthesis, is incorporated into proteins. So this is a way to measure protein synthesis. So fluoro-ethyl-tyrosine goes through the same transporter and is then entered into the cell, but because it is complex with fluoro-ethyl, it's chemically modified, it will, just like fluorodeoxyglucose be stuck in the cells and stay. What we can image here is the uptake of fluoro-ethyl-thyrosine and that's been found to be a good marker of cell proliferation.

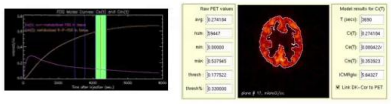
Notes

Summary

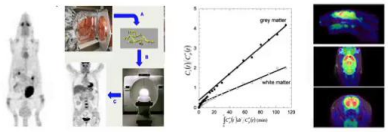
12m 00s

Credits

FDG-PET for Metastatic Melanoma, Case of the Month—February 2005
http://www.nepetimaging.com/pdf/feb_05.pdf



"Tomographic measurement of local cerebral glucose metabolic rate in humans with (F-18)2-fluoro-2-deoxy-D-glucose: Validation of method"
Phelps ME, Huang SC, Hoffman EJ, Selin C, Sokoloff L, Kuhl DE, Ann Neurol 6:371-388, 1979.



Unidentifiable source *(from the Internet)*

Notes

Summary

12m 54s