Intra and Intercellular Molecular Transport

During winter quarter 1973 while enrolled in Physical Biochemistry 206 at the University of California, Berkeley, I developed a model for molecular transport through biological membranes at discrete pore sites consisting of proteins in helical configuration spanning the membrane. Molecules from the exterior of the cell enter the cell by traversing the long axis of the protein approximately 100 Angstroms in length. I have worked on the consequences of this model to the present.
Questions to be answered are:
1. After entering the cell, how do the molecules find their way to the correct target molecule?
2. How is the pore selective?
3. What is the propulsive mechanism for molecules entering the cell?

Answer to 1.

The accepted answer to 1 is by diffusion, which means that the number of molecules it takes to find their way to the correct target molecule is proportional to r^2 where r is the distance from the entry site in the membrane to the target molecule. For example if r=100Å and the target has a cross section of 4Å^2, then for every molecule that strikes the target area, $[4\pi r^2]/4=\pi 10^4=(3.1)10^4$ molecules do not reach the target site. If the molecule in question is O, it takes $(3.1)10^4$ Oxygen molecules that do not reach the target site for every O molecule that does. This limits the rate at which an animal can move and if a way to target molecules existed, the cells with this ability would have a selective advantage over those who do not. For example, those animals with the ability to target O, would be able to move faster than those that do not have the ability to target O. It was this idea that led to the search for a possible way that a cell could target molecules.
The hypothesis is made that the protein pore spanning the cell wall continues into the cell as a hollow protein tube connecting the pore to a specific site on an organelle within the cell. A unique molecular tag on the end of the tube and the complement of the tag on the organelle insures that the proper tube connects to the proper organelle.

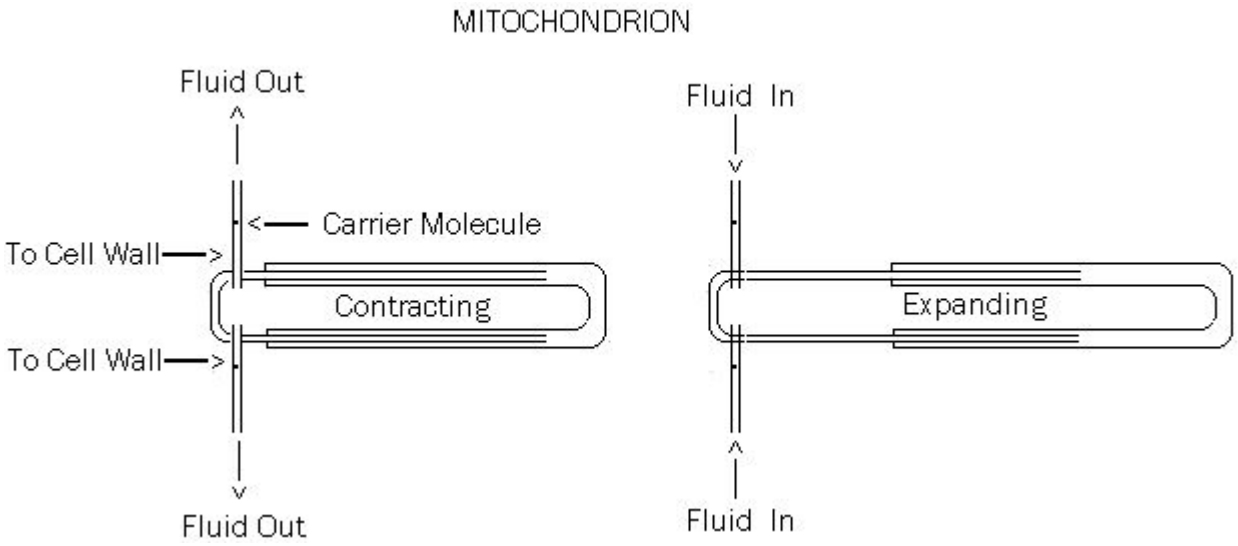
Answer to 2.
It is hypothesized that each tube contains a carrier molecule that shuttles back and forth through the tube from the cell surface to the target site and back. On each trip to the surface the carrier molecule chemically combines with a specific molecule on the outside of the cell that is then carried into the interior of the cell and to the target site where the carried molecule then combines with a specific molecule at the target site. For example, in humans it is hypothesized that myoglobin is the carrier molecule for O, shuttling back and forth from the surface of the cell through a tube to a target site in a mitochondrion. Each cell in the resting human body needs approximately 10^4 oxygen molecules per second. Supposing that the carrier molecule travels at a typical cellular diffusion speed of $1cm/10^2$ sec $=10^{-2}$cm/sec= 10^6Å/ sec. and assuming each tube is $(0.5)10^5$Å long, with each tube containing

one myoglobin molecule shuttling back and forth through the cell wall membrane bringing in one oxygen molecule on every trip with a round trip time for the myoglobin molecule of 0.1 sec, means that each cell needs 10^3 tubes.

Answer to 3

As regards the propulsive mechanism to drive the carrier molecules back and forth inside their respective tubes. It is proposed that in addition to the oxidation of glucose the mitochondria also act as contractile vacuoles expanding and contracting thereby forcing intracellular fluid (icf) in and out of the tubes (Hypothesized to be) attached to the mitochondria. The back and forth motion of the icf provides the propelling mechanism moving the carrier molecule back and forth.
If the mitochondrial skeleton consists of a closed system of circumferential tubes in which the icf is alternately heated by oxidation of glucose and cooled by the blood, (Figure 1), then the volume of the mitochondria would alternately expand and

FIGURE 1



contract alternately drawing fluid in the attached tubes (Labeled "To Cell Wall") into and out of the mitochondria and alternately drawing the carrier molecule (Myoglobin) in the attached tubes back and forth from the cell wall to the mitochondria. This model is proposed to replace the untenable kinesin cytoskeletal motor model for molecular transport within cells.

The energy source for the proposed expansion and contraction of mitochondria is oxidation of glucose. This poses a problem as do all chemical reactions involving the use of enzymes to lower the energy threshold at which the reaction occurs. While accepting the fact that enzymes can increase reaction rates by orders of magnitude, the accepted explanation involves quantum mechanical tunneling which is not correct. The quantum mechanical atom to which Schrödinger's Equation is applied

has a positively charged nucleus which is held together by a binding energy mass defect BE=- (Δm)c^2. The derivation of BE=- (Δm)c^2 depends on the validity of the absolute constancy of the speed of electromagnetic radiation. However the speed of electromagnetic radiation is not an absolute constant as is evident by the measured speed of radar waves being some 2 orders of magnitude smaller than the speed of light from a tungsten filament source. This necessitates the creation of a new atom which is the subject of my book "Principia Mathematica Physica Atomica".
In the case of mitochondrial oxidation of glucose, it is proposed that the energy of activation is provided by electrical energy transported by the central nervous system to the peripheral nervous system and by hypothesis through nerve fibrils (Similar to the nerve fibrils found in the axons of nerve cells) extending from the PNS nerve fibers external to the cell, to the mitochondria internal to the cell.
The brain generates 25W of electrical power as determined by measuring oxygen and glucose concentration in a carotid artery and oxygen and glucose concentration in a jugular vein. The 25W are conducted down the spinal cord and act as the excitation energy for the oxidation of glucose with an energy yield of ~3 to 1. This means that if all of the 25W are used as excitation energy, 75W of power would be liberated by the oxidation of glucose and 75W is one's basal metabolic rate.
This raises the interesting possibility that muscle contraction is due to mitochondrial expansion, figure 1, at right angles to the direction of muscle contraction and under control of the CNS. The mitochondrial expansion draws icf from between the sarcomeres through tubes and into the mitochondria. This pulls the sarcomeres together causing muscle contraction and increases the cross sectional area of the muscle so that the volume of the contracting muscle remains constant at all times. Voluntary muscles act in pairs so that a contracted bicep muscle is pulled back into its resting length by a contracting triceps.

What is the source of the excitation energy for the 25W liberated by the brain? Non-dividing nerve cells (As well as dividing nerve cells) have a constant stream of proteins traveling down their axons. Where do they go, what do they do? The degradation of protein in the brain along with the liver are the two major sources of urea in the blood. I hypothesize that the energy of activation for the oxidation of glucose in NERVE CELL mitochondria is due to the degradation of proteins in the axons of nerve cells and that the liberated energy provides the excitation energy for the oxidation of glucose and that the oxidation of glucose in NERVE CELL mitochondria provides the energy for the action potential.

The brain, unlike the vast majority of non nerve cells, does not require insulin in order for glucose to enter nerve cells. Insulin is not found in non nerve cells and I hypothesize it is found in nerve cells and that the degradation of protein in nerve cells is metabolically controlled by insulin in the nerve cell axon. Further the energy of activation for the proposed insulin + protein degradation is hypothesized to come from the Maxwell-Boltzmann distribution of molecular translational kinetic energy. That is, those insulin molecules with kinetic energy 1.5KT+nKT where n is some number between 0<n<2 provide the energy of activation for the proposed insulin + protein degradation.

My hypothesis is that the energy of activation for the oxidation of glucose in mitochondria has two sources. For all mitochondria in non-nerve cells, the energy of activation is provided by electrical energy (Action potentials) generated by the nerve cells of the brain. For all mitochondria in nerve cells, the energy of activation is provided by the degradation of protein and the degradation of protein is metabolically controlled by insulin in the nerve cell axon.
I therefore hypothesize that insulin is a necessary catalyst for the degradation of protein in human axons and that degradation of protein in axons of the brain provides 8W of excitation energy per second for the oxidation of glucose in the axons of the human brain which is the energy source for the 25W of electrical energy per second coursing its way down the spinal cord which provides the energy of excitation for the oxidation of glucose in the mitochondria of the cells of the body which provide the heat energy for the expansion of mitochondria which draws icf into the mitochondria, (Figure 1) which draws carrier+carried molecules (myoglobin+oxygen, glucose+carrier molecule, etc.) towards the mitochondria. Cooling of the fluid in the circumferential mitochondrial tubes by the blood, causes the mitochondria to contract which pushes the icf in the tubes to the cell surface (Figure 1) which pushes carrier molecules toward and through the cell surface membrane.
The consequences of the model are:
1. Insulin must exist in the axons of the brain for this model to be correct. This can be experimentally verified using tritiated insulin if indeed it has not already been experimentally verified..
2. ~50gm of protein/day are degraded in the axons of the brain using ~(2)10^-3gm of insulin per day. A 150lb human degrades for energy ~65gm of protein/day (Ganong): So the brain is degrading a sizeable % of the total protein degraded by the body. The total amount of protein degraded by the brain can be measured by measuring the urea concentration in the carotid and the urea concentration in the jugular assuming all protein degradation in the axons results in urea.

The implications for diabetes are profound. Lack of insulin results in decreased electrical wattage flowing down the spinal column (This is experimentally testable) which decreases the flow of excitation energy to the mitochondria which decreases the rate at which glucose+carrier molecules (As well as all other carrier+carried molecules) are brought into nonnerve cells which decreases the rate at which glucose is oxidized. This raises the possibility that the effects of diabetes might be alleviated by externally providing a source of electrical energy using a battery pack to bring the electrical power in the spinal cord back up to 25W.

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