TranscribeMe!

Transcription details:

Date: 08-Feb-2016

Input sound file: 191_Huffines_Sports_Med_NeuferHD5

Transcription results:

S1 00:00 From East Carolina University, we have Dr. Darrell Neufer. Please join me in welcoming him.

S2 00:15 In 1814, a young 16-year-old girl was travelling through Europe with three companions of hers. Like many teenagers of the day, they were interested in the paranomal. One of their favorite topics was the topic known as galvanism. Galvanism derives from a scientist named Luigi Galvani who had discovered about 20 years earlier in the 1780s and 90s that if you applied an electrical impulse to a frog corpse, that the legs would contract. Now, this actually where scientists represents the beginning of electrophysiology and neuroscience. But to the young teenagers, this represented sort of a cult idea and bringing to life organisms using electricity. Now, the four companions - late one night - decided they were going to have a competition to see who could write the best horror story.

S2 01:18 Mary Shelley set about her task of writing a horror story. It took her about a year and a half. By the time she was 18, she submitted it anonymously and by the time she was 20, it was published. The story was Frankenstein. I'm sure you all are familiar with it. It was based on a young doctor who brought inanimate human to using electricity and of course it's been adapted into a number of movies. Most recent I think is coming out in a couple of weeks.

S2 01:49 What I want you to consider today is that life actually does emanate from the flow of electricity and then metabolic diseases arise from disruptions in the flow of that electricity. To put some context into it, I want you to think or consider a cell that has all of the parts that are needed to make that cell alive. But what does it need to transfer into something that is living? Most of you are aware I'm sure that there are what it would need would be energy charge, including some form of energy that the cell can use as well as an electrical charge.

S2 02:30 Our story begins today and on this planet with the molecule oxygen. Oxygen sits at number eight on the periodic table which means and I also want to point out that what's below it - sulfur. Keep that in mind because that will come up later in the presentation. Now, oxygen has atomic number eight which means it has eight protons and eight electrons orbiting that nucleus. Now, those electrons, if you remember back to high school chemistry, they circle and are organized in orbitals which are much more difficult to draw than my artistic capabilities, but they're represented there and each electron has a spin of its own called a spin resonance. The way the electrons like to organize themselves in the orbitals is to have two electrons with opposite spins organized in progressively increasing orbitals away from the nucleus. You'll see, that the first orbital has two electrons. The two s-orbital is filled and then you get to the two p-orbital and there are two unpaired electrons with the same spin residence.

S2 03:42 Now, on this planet, you can't generate a more molecule that has more of an attraction for electrons. It is always looking for more electrons. Now, an oxygen atom doesn't exist on the planet because it's not stable as such and so the easiest thing for nature to do is simply combine two oxygen atoms to form an oxygen molecule where they are sharing those unpaired electrons. The other easy thing to do is to take hydrogen atomic number one and put two hydrogens there, they share the electrons and presto, you have water. All of metabolism is built on this very basic chemistry.

S2 04:26 Galvanism can be redefine as the induction of electrical current between two chemicals differing with electronegativity. What does that mean? Well, we all intuitively understand and then if you move a stronger magnet closer to a weaker magnet, it will attract the piece of iron. We could also classify those as a stronger donor and a weaker donor. If the weaker magnet has the piece of iron attached to it and we've assigned units to these magnets, then we have a difference in potential energy of nine units. Why is that important? Well, because we can get work, we can do work out of that potential energy difference. With molecules or chemicals, we talk in terms of couples whether the molecule or atom has the electron associated with it or if it doesn't.

S2 05:20 What we really want to know as biochemists, can we assign a number, can we assign a magnetic strength to that molecule? These were experiments were done by biochemists in the 1950s and whether it create a reaction with the simplest redox couple - which is the hydrogen ion redox couple - and compare that with oxygen connecting with the water. When you do that, oxygen pulls electrons from the hydrogen and it registers with the volt meter about 816 millivolts, very positive, very attractive. Another redox couple that's common in biology is in NAD/NADH redux couple and you'll see that it is less attractive for electrons than the hydrogen. Hydrogen actually takes electrons away from the NADH/NAD redox couple.

S2 06:11 Well, let's jump forward a little bit. If we consider the oxidation of a simple sugar molecule

and we send it through the factories that the cell has to metabolize it through glycolysis TCA cycle, by the time we get through all those chemical reactions, six molecules of CO_2 have been produced which you exhale and a little bit of energy has been generated. What's left over is 16 hydrogen molecules which the easy thing for nature to have done would be they simply combine those with oxygen to form water.

S2 06:42 But the ingenious thing that's done is that the hydrogens are combined and captured by NADH and carried to the mitochondria where there's an electrical current that is set up. The advantage of this is that it represents between NADH and oxygen over a volt of potential energy that the mitochondria is going to use to generate about 26 to 30 more ATP molecules. We'll focus a little bit on this inter-mitochondrial membrane. It's a membrane that is composed of various different proteins. The electron transport system as it's known transports electrons by default. Why is that? Because it's simply a series of magnets each progressing to a stronger magnet with oxygen sitting at the end, the ultimate electron magnet. Electron flow is always towards oxygen.

S2 07:38 The second point to make before we start this process is that electon flow cannot occcur wihthout proton pumping and proton pumping cannot occur without electron flow. If we were starting from scratch and we added fuel which is the NADH, what happens? Well, electrons start pumping. protons or hydrogen ions start being-- or electrons start flowing, protons start pumping, oxygen starts being consumed and you can imagine that as the protons begin to build up on the outer surface that membrane, it creates a back pressure on the pumps. Eventually, the system reaches the point where the back pressure is so high that it completely opposes further actions of the pump. The system at this point is not broken, it's simply reached a static head. We can - in the lab - actually measure that static head which up in the upper right is a potentiometer showing the membrane potential at its maximum and electron flow at its lowest point. Mitochondria never do this in vivo because they are slightly leaky. The membrane is slightly leaky to protons.

S2 08:45 Now, recognize what that means. It means that now, electrons can start flowing, it means that the membrane potential has dropped a little bit, it means that oxygen can start being consumed again. Basically, it's the way to get the system going again. If there's another protein inserted into the membrane that allows protons to flow through back into the matrix like the ATP synthase, then this system starts running faster. But the point in going through this is to demonstrate that this system is primed, ready to respond to demand.

S2 09:22 Now, we need to cover one more thing. If we were starting from scratch with a cell that has low ATP levels and we want to bring ATP levels up, you can imagine that ATP would start climbing, and climbing, and climbing, but that will also create a back pressure on the ATP synthase. As the system continues to climb, the membrane potential starts to rise, electron flow starts to decrease, and oxygen consumption starts to decrease until the system reaches another static head. At this point, there's a ratio of about a thousand to one of ATP to ADP. This is how energetically the cell brings itself to life. This ATP to ADP gradient is used by all of the systems that are listed there to support a cell energetically.

S2 10:20 By now, you should be recognizing that there are a couple of regulators on this system. What's one? One is the rate of ATP utilization, because that determines the rate at which protons are coming through the ATP synthase. The second regulator is the membrane potential, because that's regulating the rate at which electrons are flowing through the system and therefore, the rate at which electrons are being pulled through the pathways of metabolism. The key to the whole system is the fact that oxygen is always yanking on electrons, always wanting it. This would be an open circuit except for the fact that it has these two regulators associated with it. But really, what we're talking about is a biological electrical circuit extending all the way back up to the food that we eat, the electrons flowing through all those pathways and eventually flowing through this system.

S2 11:17 Now, this is a pressurized system. Meaning that when the system is working at its lowest, that's when there is the most electrons within the system because there's oxygen always around, those electrons have the potential to leak to oxygen prematurely to form super oxide - the parent molecule of all reactive oxygen species - and that's converted to H202 which we'll talk about in a second. The point being that mitochondria are always idling or consuming energy, it takes fuel the way the system is supposed work is in between meals. We tap into fuel, those fuel reserves and then we eat to replenish those reserves. The problem is that we're now in a society where people are eating and the reserves are already replete and it puts a nutritional overload on the system, the result is that too much H2O2 is being released and it signals to the cell to decrease insulin sensitivity.

S2 12:18 Another way to view this is shown here. What I've done is put the mitochondrial membrane potential on the left Y axis. The dotted line is the membrane potential which electrons will start to leak an H2O2 start to be produced. A sedentery person that wakes up in the middle-- or wakes up, has donuts, goes to work, sits in front of their computer, has big lunch, goes back to their computer, goes home, eats dinner, they spend the entire day under pressure and above the dotted line. You contrast that with a person that is in caloric balance, gets a little bit of exercise and activity during the day and they spent most of the day below the dotted line.

S2 13:02 This is the classic figure of the energy cycle of life. In fact to paraphrase the great Mufasa, this completes the metabolic circle of life. But there's one more component that we are going to talk about. That takes us back to the mitochondrial inner membrane and a protein known as Nicotinamide Nucleotide Transhydrogenase which uses the membrane potential to drive the production of any DPH, again, generating an extremely high level. That ratio of NADPH to NADP serves as a generator to distribute electrons. Where are those electrons going? Well, our prodium inside the cell contains 22,000 of these redox-sensitive sulfur residues. They can exist either as an oxidized or a reduced species.

S2 13:53 Because we're living on a planet where oxygen is the default state and oxidation is the default state, to bring a cell to life requires the generation of electrical circuit to reduce those redox-sensitive thiols. In fact, the cell moves, if you're starting from scratch from a 100% reduced or oxidized to 90% reduced. It's like turning on a light bulb inside the cell. In fact, it's like turning on thousands and thousands of light bulbs. Although we didn't know it at the time when George Bush talked about a thousand points of light, this is exactly what he was talking about.

S2 14:34 Now, the redox circuit completes around to regenerate NADP. The interesting thing is that the H202 coming out of the mitochondria is a regulator of this circuit because it is buffered by the same system, it short circuits the system. If there's nutrition overload and the battery then senses that overload, it produces more H2O2, more short circuiting of the circuit, dimming of light bulbs and this is associated with the progression of various diseases. In fact, this system is going to be the topic of research for the next 50 to 100 years.

S2 15:12 Your take home points are that oxygen is the yanker of electrons from the food we eat. It generates a membrane potential which is used to generate an energy charge and an electrical charge that brings the human being to life. H2O2 regulates that electrical charge, but this presents for oxygen the remarkable yin-yang of oxygen. First, we all understand that oxygen is essential for life, but it's ironic that also oxidation is our ultimate demise on this planet and life for cells is all about avoiding becoming oxidized. Thank you.

S1 15:56 Great job. Great job Dr. Neufer. Thank you. Starting this off so well. We've got a couple questions here. Mike R. from the University of Tennessee what's to know. "Is a molecule considered oxidized if there is a great difference in polarity?"

S2 16:16 Only if it's subjective to reversible oxidation. Molecules can have polarity and not change their redox state, but polarity can come about by other means.

S1 16:28 How does this change-- it's interesting that you and I been this business for awhile and very rarely do we talk about electrical potential when we talked about metabolic flux. How does this change the conversation around mitochondrial biogenesis and things like obesity and probably about the things that deal with mitochondrial dysfunction.

S2 16:48 Yes. I know this is a sports medicine meeting or Sports Medicine Institute. It should be obvious from this that how do you take the pressure off the system. The easiest way is to step on the the gas. Even just a little bit will take complete pressure off the mitochondria because you're accelerating those protons in the rate at which they come back in, you completely remove the H202 production. That's why we think excercise is so healthy because it takes the pressure off the system if the person has put themselves under pressure. Don't eat too many electrons and make sure your protons are flowing.

S1 17:25 Look for the electronic content of your food.

S2 17:28 Yeah well.

S1 17:31 Join me in thanking Dr. Neufer for his talk.