

Dear Dr.Francis,

I hope this e-mail finds you well. I have some questions regarding the lecture you gave this morning.

1) You mention that actin binds to dense bodies, but in Dr.Siddiqui's lecture he mentions that it is intermediate filaments that bind to dense bodies. Is it both?

Yes

2) I am not sure I completely understand caveolae in terms of Ca^{2+} regulation. It says in the lecture that they have Ca^{++} ATPase that is Mg^{++} dependent. And that it is in close association with underlying SR. What is it that they do exactly? I think they have voltage gated Ca^{++} channels which when activated will cause more calcium to be secreted from the SR. Is that true? What do we need to know about $InsP_3$ Ca^{++} channels?

They act like T-Tubules in this regard and the info is in the lecture and the notes as far as what you need to know. The IP_3 channels on the SR let Ca^{++} out...

3) The activated MLCK leads to phosphorylation of P-light chain? I thought there were only an Essential light chain (ELC) and Regulatory Light Chain (RLC)? Do you mean the RLC?

MLCK phosphorylates the light chains that's all you need to know. The P- stands for a phosphorylation

4) Can you explain the purpose of the additional ATP in cross bridge cycling? Is it to "reset" or "cock" the myosin head back to its ready to fire position like in skeletal muscle?

The first ATP is needed to phosphorylate the regulatory light chains on the myosin. The second ATP is like that used for skeletal muscle. Recall that Myosin phosphatase is taking Ps off of the light chains at some rate, thus there is a battle between MP and MLCK, and every time MP takes off a P MLCK must use one ATP to put a P back on just so that myosin can go back into cross bridge cycling, which uses another ATP...

5) I'm not sure I understand what I need to know about Latch state. All I know is that its a result of tonic contraction which I assume means repetitive contraction? Is there anything mechanistically I should know about it?

From the slide If myosin light chains are dephosphorylated myosin ATPase activity

decreases. This means that it is more difficult to release myosin heads from actin which requires ATP hydrolysis. The myosin heads that stay attached can hold force at the muscle ends. (Think of this latch state as analogous to rigor in striated muscle.) This allows the smooth muscle to hold shape with very little ATP usage.

6) In lecture you didn't speak much about all the different ion channels (Cl,K,Na). Is that something we need to know in detail?

Not for my questions.

1) You mentioned that its the hydrolysis of ATP that releases the Actin and Myosin head from each other. I thought it was the addition of ATP that released both heads. At least that is what I remember from our musculoskeletal block regarding to skeletal muscle. In either case, what exactly do we need to know about the latch state? I'll quickly tell you what I understand. It's analogous to rigor mortis in skeletal muscle in that there is no ATP available so it cannot release the actin and myosin. Is there anything else that's important to know about it?

No, other than there can be little ATP doesn't have to be none...

2) There is a slide about SM contraction with little or no change in potential or intracellular calcium and then --> cAMP/cGMP relaxation and PLC contraction. The slide also says something about pharmacomechanic coupling. Are these all mechanisms part of pharmacomechanical coupling? I thought PM coupling related only to contraction. In simple terms, I'm trying to organize the material in such a way so I can better understand where everything belongs and I'm a little confused about how to think about pharmacomechanical coupling.

They are all pharmacomechanical coupling as far as I'm concerned as long as the binding dose not lead to a direct change in membrane potential, which would then be electromechanical coupling.

3) Is the G-protein mechanism for getting Ca²⁺ out of the SR the same thing as PM coupling?

Yes

1. I understand the examples of pharmacomechanical coupling that you gave in class, but what about electromechanical coupling? Is the increased sensitivity to Ca in a smooth muscle cell after a Rho/ROK signaling cascade (due to MP inhibition) an example of regulation through electromechanical coupling? How about adaptation?

Nerve stimulation in smooth muscle causes membrane depolarization, like in skeletal muscle. Excitation, the electrochemical event occurring at the membrane is followed by the mechanical event, contraction. In the case of smooth muscle, this excitation-contraction coupling is termed electromechanical coupling; the link for the coupling is Ca²⁺ that permeates from the extracellular space into the intracellular water of smooth muscle. There is another excitation mechanism in smooth muscle, which is independent of the membrane potential change; it is based on receptor activation by drugs or hormones followed by muscle contraction. This is termed pharmacomechanical coupling.

> 2. What is the purpose of forming a lot of adenosine in tissue that has recently used much ATP? I was thinking that if a tissue is using ATP, it is very active and will probably need O₂ and have many waste products. In order to bring needed O₂ and take away the waste, we would need more blood passing through that tissue. Could that be why we would want to form much adenosine and, thus, vasodilate in tissues that are using much ATP?

Adenosine is formed from cellular AMP acted upon by 5'-nucleotidase. The AMP is derived from hydrolysis of intracellular ATP and ADP. Adenosine formation increases during hypoxia and increased oxygen consumption, especially if the latter is accompanied by inadequate oxygen delivery. This leads to Adenosine in the extracellular space, which reaches the smooth muscle of the vessels that then relax and open up allowing more O₂ to perfuse that area...

3. If we are saying that the osmotic pressure in the blood is colloid pressure and that much of that pressure is caused by the negatively charged albumin in the blood, then does that mean that albumin does not dissolve in blood, but is actually suspended?

Yes

If so, why not? It is negatively charged, so I would think it would dissolve with ease.

If you have a negatively charged rock, does that mean it will dissolve? Also, if colloid (osmotic) pressure deals with suspended substances, shouldn't we still have a separate osmotic force due to dissolved substances?

Sure, but most of the small dissolved substances can pass to the interstitial side to set up an equilibrium, the albumin is more or less restricted to the capillary lumen, thus it cannot move to the interstitial side to reach an equilibrium, thus something else must move...

4. Also, I'm a little confused about what causes fibrosis during edema. You said that more proteins are being produced. I'm assuming those proteins get into the extracellular fluid and make it hard, but I don't get why they'd be produced and how they'd get into the extracellular fluid.

the edema is in the interstitial space, which means it is pushing apart tissue. The fibrosis is in response to this tissue damage...

5. I understand the purpose of an AV shunt, but I misunderstood what you were saying in class about vasoconstriction during extreme cold. Do AV shunts constrict like arterioles in extreme cold?

Yes they do, the AV shunts are open when you wish to move more blood through that area to let off heat.