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Science Signaling Podcast for 24 January 2017: Tissue-specific regulation of L-type calcium channels

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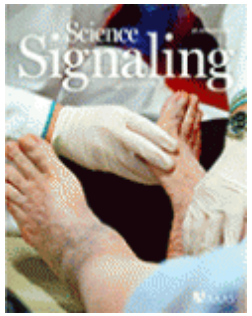

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Abstract

This Podcast features an interview with Johannes Hell and Manuel Navedo, senior authors of two Research Articles that appear in the 24 January 2017 issue of *Science Signaling*, about tissue-specific regulation of the L-type calcium channel $Ca_V1.2$. This channel is present in many tissues, including the heart, vasculature, and brain, and allows calcium to flow into cells when it is activated. Signaling through the β-adrenergic receptor (βAR) stimulates $Ca_V1.2$ activity in heart cells and neurons to accelerate heart rate and increase neuronal excitability, respectively. Using mouse models, Qian *et al*. found that βAR-mediated enhancement of $Ca_V1.2$ activity in the brain required phosphorylation of Ser^{1928}, whereas βAR-mediated enhancement of $Ca_V1.2$ activity in the heart did not require phosphorylation of this residue. In a related study, Nystoriak *et al*. demonstrated that phosphorylation of Ser^{1928} in arterial myocytes was required for vasoconstriction during acute hyperglycemia and in diabetic mice. These findings demonstrate tissue-specific differences in $Ca_V1.2$ regulation and suggest that it may be possible to design therapies to target this channel in specific tissues.

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Host – Annalisa VanHook
*Welcome to the Science Signaling Podcast for January 24th, 2017. I'm Annalisa VanHook, and today I'll be talking with Johannes Hell and Manuel Navedo about tissue-specific regulation of L-type calcium channels (**1**, **2**).*

L-type $Ca_V1.2$ channels—or L-type calcium channels—are present in cardiac and smooth muscle cells. Activation of these channels allows calcium to flow into the cell, which causes the cell to contract. The contractions of cardiac muscle cells enable the heart to pump, and the contractions of vascular smooth muscle cells controls the diameter of the blood vessels. L-type calcium channels are also present in neurons, where they control the excitability of these cells. In two related papers published in this week's issue of Science Signaling, groups from Manuel Navedo and Johannes Hell's labs report on how L-type calcium channel activity is regulated differently in different tissues. They also show how hyperglycemia stimulates L-type calcium channel activity in arterial smooth muscle cells, which contributes to some of the vascular complications of diabetes. Navedo and Hell spoke to me from the University of California, Davis.

Interviewer – Annalisa VanHook
Hello, Dr. Navedo and Dr. Hell. Welcome to the Science Signaling Podcast.

Ser^{1928} phosphorylation by PKA stimulates the L-type Ca^{2+} channel $Ca_V1.2$ and vasoconstriction during acute hyperglycemia and diabetes

Research Article

Phosphorylation of Ser^{1928} mediates the enhanced activity of the L-type Ca^{2+} channel $Ca_v1.2$ by the β_2-adrenergic receptor in neurons

Perspective

β-Adrenergic Regulation of the L-Type Ca^{2+} Channel $Ca_V1.2$ by PKA Rekindles Excitement

Research Article

Essential roles for $Ca_v\beta2$ and Ca_v1 channels in thymocyte development and T cell homeostasis

Research Resource

In Vivo Phosphoproteomics Analysis Reveals the Cardiac Targets of β-Adrenergic Receptor Signaling

Perspective

How Ca^{2+}-permeable AMPA receptors, the kinase PKA, and the phosphatase PP2B are intertwined in synaptic LTP and LTD

Interviewee – Manuel Navedo
Hi, I'm glad to be here.

Interviewee – Johannes Hell
Hello, Annalisa.

Interviewer – Annalisa VanHook
*In the first paper from your groups, you looked at how the activity of L-type calcium channels is controlled differently in neurons and cardiac cells (**1**). First of all, how do L-type calcium channels contribute to neuronal and cardiac cell functions?*

Interviewee – Johannes Hell
In the heart—and this is what the channel is most known for—the L-type calcium channel, $Ca_V1.2$, triggers every single [one] of our heartbeats. It also regulates gene expression in the heart. In the nervous system, it is equally important for its regulation of gene expression, but in addition it also controls the excitability of individual neurons, and it regulates the strength with which individual neurons communicate with each other.

Interviewer – Annalisa VanHook
You found that phosphorylation of a specific serine residue in L-type calcium channels controls their activity in neurons. How is that phosphorylation event controlled?

Interviewee – Johannes Hell
So, when we get excited about things like maybe an exciting paper, like ours maybe, or when we are in a fearful situation,

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like in a car accident, we trigger our stress response. And the stress response basically leads to a release of norepinephrine both in the brain and in the blood circulation. And in the brain, this norepinephrine actually augments our alertness, and it also allows us to better memorize details of the situation so we can avoid it in the future maybe. So in the brain, the norepinephrine, in turn, activates a receptor in the cell surface plasma membrane in neurons, and this receptor, called the β adrenergic receptor, in turn, activates protein kinase A. And, as you mentioned, what we found is that protein kinase A in neurons phosphorylates a specific residual in the calcium channel, and basically—to cut to the chase—the phosphorylation of this residue augments the channel activity, the calcium influx through the L-type calcium channel.

Interviewer – Annalisa VanHook
But you found that that same phosphorylation event on the L-type calcium channel wasn't relevant in cardiac cells.

Interviewee – Johannes Hell
Yes. So this is quite surprising. About 25 years ago, Dr. William Catterall, at University of Washington, Seattle, identified this specific residue known as Ser^{1928} as perhaps the main phosphorylation site for protein kinase A in this channel. It was, therefore, quite a big surprise when later our colleague, Dr. Franz Hofmann at the Technical University in Munich, made a knock-in mouse in which he basically eliminated this residue. And to everybody's surprise, in these mice, the regulation of the calcium channel in the heart was perfectly normal. So I

NAVIGATE THIS ARTICLE

should probably emphasize that the regulation of the calcium channel in the heart—also by norepinephrine—is physiologically extremely important because it causes the fight or flight response. So it was very surprising that this response was completely present in these mutant mice. That argues that this phosphorylation site, this Ser^{1928}, is not at all important for the upregulation of the calcium channel by protein kinase A in the heart. And for years, people believed that this is true everywhere for the channel, and we were left still in the dark about how protein kinase A regulates this so-important channel.

So, my lab studies the regulation of the calcium channel by various kinases in neurons. A couple of years ago we decided to look into more detail into the function of Ser^{1928} in neurons. We had no expectation that this phosphorylation would actually augment calcium channel activity, so we were very surprised when we found that stimulation of this β adrenergic receptor in neurons had no effect on the activity of the calcium channel in Dr. Hofmann's Ser^{1928} alanine knock-in mice. So this is completely different from the original results published by Dr. Hofmann in the heart. Apparently, we have the very same channel in the heart, in neurons, and, as you will hear from Manuel, my colleague here, in smooth muscle cells, yet the channels are completely differently regulated by the very same kinase in the different tissues. And, as far as we know, this is pretty much unprecedented, at least in terms of how extreme the effect is, which is pretty much an all-or-none effect.

> *Interviewer – Annalisa VanHook*
> *Do you know why these different tissues respond differently to the same phosphorylation event in the same channel?*

> *Interviewee – Johannes Hell*
> *Truth be told, we are puzzled, and we have no idea at this point. Apparently there must be additional factors which allow in the heart to regulate the channel perfectly normal. And those additional factors could be alternative phosphorylation sites. Dr. Catterall had described a few years ago another site, Ser^{1700}, which contributes to the increase in calcium channel activity in the heart upon stimulation of protein kinase A. It doesn't seem to be the whole story there either, so we are definitely missing a piece in the puzzle here; a very important piece, obviously. In the neurons, it is apparently sufficient, and I could not speculate how that could happen.*

> *Interviewer – Annalisa VanHook*
> *In the second paper, your groups looked at how hyperglycemia stimulates L-type calcium channel activity in arterial myocytes, which are the smooth muscle cells that line arteries (**2**). Hyperglycemia is a hallmark of diabetes, which is often associated with vascular complications such as hypertension, retinal degeneration, and an increased risk for stroke and heart disease. What these complications have in common is that they're linked to increased activity of L-type calcium channels, which in turn, increases the contractility of these cells. Manuel, how does high blood glucose stimulate L-type calcium channels?*

Interviewee – Manuel Navedo

Similar to cardiac cells and neurons, L-type calcium channels play a key role in vascular smooth muscle. They are the main source of calcium entry pathways in these cells, which regulate numerous physiological processes, including contraction and gene expression. We used, as a model, native murine vascular smooth muscle cells from small diameter cerebral arteries and native human mesenteric vascular smooth muscle cells from nondiabetic and diabetic patients. And what we found in our study using multiple genetically modified animals and a high-fat diet model of diabetes was that L-type calcium channels was potentiated through a mechanism that required PKA activity in response to an increasing extracellular glucose similar to hyperglycemia and in diabetes. This PKA-mediated potentiation of L-type calcium channels was surprisingly dependent on increased phosphorylation of the L-type calcium channel $Ca_V1.2$ subunit at Ser^{1928}. And this contributed to enhanced vasoconstriction during hyperglycemia and in diabetes. In fact, a single point mutation in which Ser^{1928} is replaced by an alanine to prevent phosphorylation of this site was sufficient to restore normal L-type calcium channel activity and vascular tone in diabetic mice. These are two very unexpected and remarkable findings, as a role for Ser^{1928} in PKA-mediated regulation of L-type calcium channels wasn't clear given results in the cardiac field, and were completely unknown in vascular smooth muscle, and the fact that PKA activity play[s] a well-established role in arterial relaxation in response to endogenous and exogenous vasodilatory agents.

> *Here we provide insight into this latter paradox by demonstrating that compartmentalization of PKA by the scaffold protein AKAP150, which bind[s] to L-type calcium channels and coordinate[s] a multienzyme complex that include[s] PKA to facilitate signaling to the channel was required for PKA-mediated increase in Ser^{1928} phosphorylation, L-type calcium channel potentiation, increased global calcium, and vasoconstriction during hyperglycemic conditions and in diabetes. Thus, targeting of PKA to L-type calcium channels by AKAP150 may provide a means for selective phosphorylation of the channel to promote increased global calcium and vasoconstriction rather than activation of vasodilatory pathways. A very exciting outcome of our study was the observation that changes in Ser^{1928} phosphorylation, L-type calcium channel activity, and global calcium in our murine model were recapitulated in native human cells and arteries from nondiabetic and diabetic subjects. This highlights the translational relevance of the work.*

> *Interviewer – Annalisa VanHook*
> *And so, what's the connection between PKA-mediated regulation of L-type calcium channels and hyperglycemia?*

> *Interviewee – Manuel Navedo*
> *This is a very important question. The upstream mechanisms by which an elevation in extracellular glucose leads to activation of AKAP150-anchored PKA in arterial myocytes is unclear. Research from several groups suggest that glucose*

> *might stimulate a $G_{\alpha s}$ signaling; this will activate adenylyl cyclase to produce cyclic AMP, which leads to cyclic AMP-dependent activation of PKA. Although the identity of the G protein that stimulate the $G_{\alpha s}$ signal or a role for AKAP150 in the aforementioned pathways are unknown, this type of arrangement may allow the scaffold to coordinate the clustering of specialized G protein–coupled receptors to serve as decoders with high specificity in response to high glucose or different stimulus.*

> *Interviewer – Annalisa VanHook*
> *In arterial myocytes, it looks like the scaffolding protein AKAP150 is what confers tissue specificity to L-type calcium channel phosphorylation in those cells. What about in other tissues?*

> *Interviewee – Manuel Navedo*
> *Potential mechanisms may include the expression of tissue-specific splice variants, which at least account for differences in L-type calcium channel activation kinetics between cardiac and vascular smooth muscle cells. There is a possibility for distinct and prominent tissue-specific phosphorylation sites, such as Ser^{1700}, which seems to play a prominent role in β adrenergic regulation of L-type calcium channels in the heart versus Ser^{1928}, which seems to be playing a key role in vascular smooth muscle as well as in neurons. One can also envision tissue-specific modulation of L-type calcium channels through interaction and regulation of signaling proteins with different AKAPs. The level of expression and different regulatory*

> *properties of distinct AKAPs may determine how L-type calcium channels will be modulated in different tissues.*

> *Interviewer – Annalisa VanHook*
> *Why are L-type calcium channels regulated differently in different tissues? Now that you know that they are, where do you go from here? Why is understanding this differential regulation important?*

> *Interviewee – Manuel Navedo*
> *This difference may have evolved as a regulatory mechanisms to match L-type calcium channel activity to organ and tissue function. For example, in contrast to cardiac L-type calcium channels, which are activated by an action potential with every heartbeat, smooth muscle L-type calcium channels are activated by graded membrane depolarization and have been shown to activate at more negative voltages, which may facilitate regulation of myogenic response. From a basic science and translational standpoint, it is important to understand key molecular mechanisms underlying L-type calcium channel activity in different tissues during physiological conditions such as diabetes. This may be used for development of rational therapies that could target unique features of channel regulation, such as channel phosphorylation, in different tissues, thus impacting calcium channel–based therapeutics.*
>
> *And so where do we go from here? It will be important to comprehensively examine how L-type calcium channel activity*

> *is distinctly regulated in different cells. It's also important to define upstream mechanisms medicating PKA activation in response to elevated glucose and in diabetes, as mentioned before, and to determine whether the proposed signaling pathways and effects in vascular reactivity observed in this study are conserved in smooth muscles from other vascular beds.*

> *Interviewee – Johannes Hell*
> *Part of the function of the L-type channel is to regulate the strength of synaptic transmission between neurons. Changes in the strengths of this transmission actually is how most people in the field of learning and memory believe we encode information. So when we learn certain places or how to get around somewhere or even maybe some new facts about calcium channels, we change the transmission between different neurons. And we have evidence that certain mechanisms depend on this very L-type calcium channel and especially on its stimulation by adrenergic signaling and Ser^{1928}. We have this invaluable tool, which we obtained from Dr. Hofmann in Munich—that is, the Ser^{17928} alanine knock-in mouse—which we now systemically will test for deficits in learning and memory. If we can pinpoint what exactly the deficits are, for example, in animal models of post-traumatic stress disorder, we actually may be able to inform clinicians how to better treat conditions like that.*

> *Interviewer – Annalisa VanHook*
> *Johannes and Manuel, thanks for speaking with me.*

> *Interviewee – Johannes Hell*
> *Yeah, thank you so much, Annalisa, for having us. We really appreciate it.*

> *Interviewee – Manuel Navedo*
> *Thank you for having us.*

> *Host – Annalisa VanHook*
> *That was Manuel Navedo and Johannes Hell discussing two papers published in the January 24th issue of Science Signaling. Those papers are by Nystoriak and colleagues and Qian and colleagues (**1**). You can read them online at stke.sciencemag.org.*
>
> *music*
>
> *The Science Signaling Podcast is a production of Science Signaling and the American Association for the Advancement of Science—Advancing Science, Serving Society. If you have any comments or questions, you can write to us at sciencesignalingeditors@aaas.org. I'm Annalisa VanHook, and on behalf of Science Signaling and AAAS, thanks for listening.*

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Intended Educational Use: Learn, teach

Discipline: Biochemistry, cell biology, human biology, neuroscience, physiology

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