Exploring the dominant role of Cav1 channels in signalling to the nucleus

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Synopsis
Calcium is important in controlling nuclear gene expression through the activation of multiple signal-transduction pathways in neurons. Compared with other voltage-gated calcium channels, CaV1 channels demonstrate a considerable advantage in signalling to the nucleus. In this review, we summarize the recent progress in elucidating the mechanisms involved. CaV1 channels, already advantaged in their responsiveness to depolarization, trigger communication with the nucleus by attracting colocalized clusters of activated CaMKII (Ca2+/calmodulin-dependent protein kinase II). CaV2 channels lack this ability, but must work at a distance of >1 μm from the CaV1-CaMKII co-clusters, which hampers their relative efficiency for a given rise in bulk [Ca2+]i. (intracellular [Ca2+]i). Moreover, Ca2+ influx from CaV2 channels is preferentially buffered by the ER (endoplasmic reticulum) and mitochondria, further attenuating their effectiveness in signalling to the nucleus.

Key words: calcium channel, Ca2+/calmodulin-dependent protein kinase II (CaMKII), cAMP response element-binding (CREB), endoplasmic reticulum (ER), gene transcription, mitochondrion

INTRODUCTION
Excitation–transcription (E–T) coupling is a process that converts the electrical or chemical activation of a cell to a signal that is conveyed to the nucleus and controls gene transcription. In this way, the expression of genes can be controlled in an activity-dependent manner. The neuronal remodelling that results is recognized to be necessary and important for long-term adaptive changes during neuronal development, learning and memory and drug addiction. The most scrutinized example of E–T coupling is calcium signalling to the transcription factor CREB (cAMP response element-binding) protein via phosphorylation at Ser133 [1,2]. As an important source of calcium influx, voltage-gated calcium channels have been well studied for their biophysical and biochemical properties [3–5]. Interestingly, in E–T coupling, it seems that calcium influxes through different calcium channels can engage different signalling pathways to the nucleus. For example, CaV1 (also called L-type) channels enjoy a big advantage in such signalling over CaV2 channels, even though CaV1 channels contribute only a minority of the overall Ca2+ entry in neurons [6–9]. The organization of signalling between Ca2+ entry and regulation of gene expression remains a matter of persistent debate [10–13]. Examining the fundamental aspects of E–T coupling would help answer many questions regarding how and when different Ca2+ channels couple to diverse signalling mechanisms.

Wheeler et al. [17] systemically compared the different E–T coupling efficiencies of CaV1 and CaV2 channels in both peripheral and central neurons. The results suggest that Cav1 channels enjoy three specific advantages in signalling to the nucleus, and highlight the possibility of a 'private line' by which local CaMKII (Ca2+/calmodulin-dependent protein kinase II) aggregation near CaV1 channels triggers signalling to the nucleus. CaV2 channels can tap into this line, but with far less effectiveness.

Abbreviations used: BAPTA, 1,2-bis(o-aminophenoxy)ethane-N,N,N′,N′-tetra-acetic acid; CaM, calmodulin; CaMKII, Ca2+/calmodulin-dependent protein kinase II; CREB, cAMP response element-binding; ER, endoplasmic reticulum; E–S, excitation-secretion; E–T, excitation–transcription; pCaMKII, autophosphorylated CaMKII; SCG, superior cervical ganglia; SERCA, sarco(endo)plasmic reticulum Ca2+ ATPase.

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E–T coupling has been extensively examined in hippocampal neurons because of their critical role in synaptic plasticity, learning and memory. Great progress has been achieved over the past 20 years to delineate the mechanisms involved, including the delineation of several important signalling pathways and identification of some key molecular players [1,14,15]. However, Wheeler et al. [16,17] chose to begin their study of E–T coupling in SCG neurons instead of hippocampal neurons for several reasons. First, SCG neurons contain a relatively simple Ca2+ channel repertoire with well-understood electrophysiological properties. This has been a great asset in studies of neuronal E–S (excitation–secretion) coupling, and makes them suitable for studying the excitation step of E–T coupling [15,18–23]. Secondly, the homogeneity of SCG neuronal cultures obviates the complications resulting from the mixture of different cell types that exists in preparations of hippocampal cultures. Thirdly, the relatively large soma and readily delineated nucleus of SCG neurons are of advantage for clear detection of nuclear signalling changes following stimulation (Figure 1). Finally, a robust viral expression in SCG neurons enabled the authors to manipulate easily and accurately some candidate molecules involved in E–T coupling [16,17,24].

Wheeler et al. [16] examined the fundamental aspects of E–T coupling in SCG neurons. Importantly, they found that CaM (calmodulin)/CaMKII may serve as a local Ca2+ sensor to help Cav1 channels decode external inputs. Specifically, the aggregation of pCaMKII (autophosphorylated CaMKII) on the membrane surface is a critical early step for signalling to the nucleus. However, there are some important questions that need to be addressed. How does pCaMKII aggregation trigger E–T coupling?

Is this process responsible for the differences in the signalling efficiency of Cav1 and Cav2 channels?

**CAV1 CHANNELS’ GATING ADVANTAGE**

Consistent with previous studies [8,25,26], Wheeler et al. [17] found that a mild 10 Hz stimulation or 40 mM K+ depolarization can trigger a nuclear pCREB response, which is prevented by the addition of the specific Cav1 blocker. Interestingly, upon intense stimuli of 100 Hz or 90 mM K+, the authors found that Cav2 channels can also contribute to the signal to pCREB (phospho-CREB). This is reminiscent of an uneven activation of the various calcium channel types [27,28], that could in principle be responsible for differing effectiveness of channels in signalling to the nucleus.

To test this, the relative degree of channel activation was measured at varying voltages. At more negative voltages, Cav1 channels contribute the majority of Ca2+ influx, while Cav2 channels contribute a progressively larger share as the membrane is further depolarized. Furthermore, the authors used Fura-2 ratiometric Ca2+ imaging to determine the relative contributions of Cav1 and Cav2 channels to [Ca2+]i (intracellular [Ca2+]). Again, Cav1 channels are responsible for a larger fraction of Ca2+ influx following mild stimulation, whereas the contribution of Cav2 channels predominated with more intense stimuli. This suggests a Cav1 channel ‘gating advantage’ over Cav2 channels [17].

**SPATIAL ADVANTAGE OF CAV1 CHANNELS**

Can this ‘gating advantage’ account for the entire Cav1 advantage in signalling to the nucleus? To address this question and bypass the differences in Cav1 and Cav2 voltage dependence, the authors plotted nuclear signal strength as a function of bulk [Ca2+]i elevation. Interestingly, the signalling events initiated by Cav1 and Cav2 channels do not respond in the same way to bulk [Ca2+]i rise. Instead, Ca2+ elevations resulting from Cav1 channels appear to signal to CREB ~10 times more efficiently than Ca2+ from Cav2 channels, independent of the gating advantage described previously. This finding suggests an appreciable difference in the cell-signalling mechanisms downstream of Ca2+ influx that determines the impact of Ca2+ ions from different calcium channels. Importantly, the authors found that while CaMKII activation is a common downstream signal of both Cav1 and Cav2 channels, activated CaMKII molecules were only recruited to the location near Cav1 channels, even when the calcium signal came from Cav2 channels. Can the differences in signalling potency be attributed to the distance or route that Ca2+ must traverse to activate CaMKII? To test this hypothesis, the spatial characteristics of...
CaV1 and CaV2 signalling were dissected using BAPTA (1,2-bis-(o-aminophenoxo)ethane-N,N,N′,N′-tetra-acetic acid) and EGTA, Ca2+ chelators with different buffering effects on Ca2+ levels close to a Ca2+ source [29–33]. CaV1-mediated signalling to CaMKII and pCREB were completely blocked by buffering local and global Ca2+ with BAPTA but not with EGTA, which largely spares local Ca2+ increases. In sharp contrast, both EGTA and BAPTA fully inhibited signalling through CaV2 channels. These data suggest that to elicit a pCREB response, Ca2+ entering through CaV2 channels must act at a considerably greater distance from the site of Ca2+ entry (∼1 μm), while CaV1 channels signal via recruiting locally activated CaMKII [29].

**ORGANELLAR DISADVANTAGE OF CaV2 CHANNELS**

If calcium entering through CaV2 channels must travel ∼1 μm to activate CaMKII near CaV1 channels and trigger a pCREB response, it follows that the factors controlling cytosolic Ca2+ buffering might impact CaV2 signalling to the nucleus. Mitochondrial calcium uptake is known to attenuate depolarization-induced [Ca2+], elevations in neurons and neuron-like cells [34–37]. Additionally, mitochondrial buffering is more pronounced with stronger depolarizations [35]. This evidence raised the possibility that mitochondria may preferentially buffer Ca2+ entering through the more positively activating CaV2 channels. In order to test this, mitochondrial calcium levels were measured in response to a purified calcium signal from CaV1 or CaV2 channels. The results suggested that mitochondria preferentially intercept Ca2+ entering through CaV2 channels rather than CaV1. Consistent with this, a characteristic hump or plateau in the intracellular Ca2+ decay phase following stimulation, the hallmark of mitochondrial Ca2+ buffering [35,36,38,39], was specifically prevented by blocking CaV2 but not CaV1 channels. To test this idea more rigorously, mitochondrial Ca2+ was measured during near-equil peaks of cytosolic Ca2+ arising from different sources. Using 20 mM K+ with the CaV1-selective agonist FPL 64176, flux through CaV1 channels alone produced only a modest rise in mitochondrial calcium. In contrast, equivalent Ca2+ fluxes produced jointly through CaV1 and CaV2 channels, evoked by 60 mM K+ stimulation, resulted in a ∼3-fold greater response. This directly verified that mitochondria take up Ca2+ entering through CaV2 channels in preference to that emanating from CaV1 channels. Furthermore, CaV2-mediated Ca2+ influx and signalling to pCREB was specifically unmasked by reduction of the driving force for mitochondrial Ca2+ uptake with the proton ionophore FCCP (carbonyl cyanide p-trifluoromethoxyphenylhydrazone). Taken together, the published evidence suggested that mitochondria buffer the calcium influx from CaV2 but not CaV1 channels and attenuate CaV2 signalling to the nucleus.

How is CaV2-mediated Ca2+ entry preferentially linked to mitochondrial Ca2+ uptake? While there is no direct evidence to support a CaV2-mitochondria apposition, previous work has shown that the ER (endoplasmic reticulum) may operate as a way-station for calcium en route to mitochondria [40–43]. Could the ER preferentially couple to CaV2 over CaV1 channels to create a CaV2-mitochondria preference? To test this hypothesis, SERCA (sarcoplasmic reticulum Ca2+ ATPases) were blocked with thapsigargin to prevent ER Ca2+ uptake. Thapsigargin increased the CaV2-mediated Ca2+ transient in response to 100 Hz >2-fold, but only augmented the CaV1 response to 10 Hz by ∼26%. This duplicated the pattern previously found for mitochondrial Ca2+ uptake when dissected with FCCP. Furthermore, regions of concentration of SERCA pumps often coincided with clusters of CaV2 channels, but not CaV1 channels. Together, this supports the notion that CaV2 signalling is preferentially attenuated by mitochondrial calcium buffering through an apposition of ER and CaV2 channels [17].

**CAV1 AND CAV2 SIGNALLING TO THE NUCLEUS IN HIPPOCAMPAL NEURONS**

Although SCG neurons offer their own unique advantages as a model cell system to study E–T coupling, understanding E–T coupling in central neurons is important for appreciating its relevance to synaptic plasticity and learning and memory. Therefore the authors further asked whether the distinct mechanisms employed by CaV1 and CaV2 channels to signal to CREB in SCG neurons generalized to other types of neurons. Indeed, the basic features of CaV1 and CaV2 signalling can be recapitulated in cultured hippocampal neurons. Just as in SCG neurons, depolarization with 40 mM K+ triggered CREB phosphorylation in hippocampal neurons that was completely inhibited by the CaV1 blocker nimodipine. Depolarizing neurons with 90 mM K+ in the presence of nimodipine produced a rise in pCREB that was abrogated by the CaV2 blockers. Finally, the authors investigated whether mitochondrial buffering led to the restriction of CaV2-mediated induction of pCREB in hippocampal neurons, as it does in SCG neurons. Hippocampal neurons were depolarized with 40 mM K+ in the presence of nimodipine to prevent CaV1 signalling. Remarkably, blocking mitochondrial buffering with FCCP triggered CREB phosphorylation mediated by CaV2 channels. Collectively, these results demonstrate that the differences in CaV1 against CaV2 signalling to CREB observed in SCG neurons extend to CNS (central nervous system) neurons, and once again highlight the usefulness of SCG neurons as a model cell system for studying E–T coupling.

**DISCUSSION**

Coupling between membrane depolarization and gene expression is important for synaptic plasticity and learning and memory, yet much remains unclear about how activation of nuclear transcription factors is regulated by Ca2+ channels and Ca2+.
translocation? Is E–T coupling dependent only on calcium, or CaV1 channels compared with CaV2 channels in signalling to the nucleus triggered by multiple calcium aggregation near CaV1 channels? If a molecule such as calmodulin translocates to the nucleus to trigger the pCREB response selectively buffer Ca2+ near CaV1 channels, not CaV2 channels, allowing CaMKII to act as a cell surface beacon to control the strength of signalling to CREB. (3) An ‘organellar disadvantage’ applies to Ca2+ entering through CaV2 channels, which is preferentially intercepted by Ca2+ sequestration by the ER and mitochondria. Operation of the ER/mitochondrial system limits the CaV2-dependent increase in [Ca2+]i, attenuates CaMKII aggregation, and consequent signalling to CREB. This Figure was reprinted from Cell 149, Wheeler, D.G., Groth, R.D., Ma, H., Barnett, C.F., Owen, S.F., Saha, P and Tsien, R.W., CaV1 and CaV2 channels engage distinct mechanisms of the initiation of E–T coupling have been revealed by Wheeler et al. [16,17]. First, CaMKII is identified as a key molecule in signalling to the nucleus triggered by multiple calcium sources. Secondly, CaV1 channels are shown to have an intrinsic gating advantage when the membrane is moderately depolarized compared with CaV2 channels. Thirdly, CaV2 channels activate CaMKII via Ca2+ elevations over a greater distance (>1 μm), whereas CaV1 channels have a nanodomain access to locally recruited CaMKII. Finally, the ER and mitochondria potentely and selectively buffer Ca2+ entering through CaV2 channels, putting CaV2 channels at an organellar disadvantage relative to CaV1 (Figure 2). All of these factors support a marked advantage of CaV1 channels compared with CaV2 channels in signalling to the nucleus during steady depolarizations or action potential firing at moderate frequencies. Although we now understand more clearly why CaV1 channels dominate the signalling to the nucleus, there are still many questions left to address. For example, how do CaV1 channels signal to the nucleus? What is the functional significance of CaMKII aggregation near CaV1 channels? If a molecule such as calmodulin translocates to the nucleus to trigger the pCREB response [16,29,44–46], what is the molecular mechanism controlling its translocation? Is E–T coupling dependent only on calcium, or might there be some dependence on membrane depolarization, above and beyond the downstream gating of calcium entry? To gain insight into these questions, a simple yet useful system such as cultured SCG neurons will be very helpful, although further work will be necessary to examine whether the mechanisms elucidated in cultured neurons are applicable in in vivo systems.

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