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Membrane Receptor Neighborhoods: Snuggling up to the Nucleus

Donald M. Bers
Department of Pharmacology, University of California, Davis, Davis, CA

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A provocative new study in this issue of *Circulation Research* by Ibarra *et al.*[1] suggests that the insulin-like growth factor 1 receptors (IGF-1R), exist in plasma membrane invaginations that come in very close proximity to (or even invade) the nuclear membrane in cardiac myocytes to selectively raise local nuclear $[Ca^{2+}]$ ($[Ca^{2+}]_{Nuc}$). This paper raises an intriguing and novel mechanism by which plasma membrane receptors may have preferential local access to nuclear signaling, even ventricular myocytes which are large cells with central nuclei.

The IGF-1R is a tyrosine kinase growth factor receptor that connects with many downstream signaling cascades.[2] The two best known pathways are Ras-Raf-mitogen-activated protein kinase and phosphatidylinositide 3 kinase (PI3K)-protein kinase B (PKB/Akt). However, Ibarra *et al.*[1] focus on a less well studied pathway in which IGF-1induces G_i-dependent phospholipase C (PLC) activation[3] and 1,4,5-inositol tris-phosphate ($InsP_3$) that can release Ca^{2+} from intracellular $InsP_3$ receptor ($InsP_3R$) stores.[4] They show that in cardiac myocytes IGF-1 triggers nuclear Ca^{2+} transients that precede cytosolic Ca^{2+} transients, and that blocking the nuclear Ca^{2+} transient prevents the cytosolic Ca^{2+} transient, but not vice-versa. Their data are consistent with the idea that a substantial fraction of plasma membrane IGF-R1 are in patches of plasma membrane invaginations that are extremely close to the nucleus, potentially as extensions of the transverse tubule (T-tubule) system. Further, they infer that these IGF-1R are G_i-coupled and that upon activation they produce PLC and $InsP_3$-dependent nuclear Ca^{2+} transients that contributes to Ca-dependent regulation of gene transcription (Fig 1B).

While many plasma membrane receptors signal to the nucleus, there are numerous potential pathways for this signaling. Even if we constrain ourselves to a narrow field involving $InsP_3$-dependent nuclear Ca^{2+} signaling,[5] which has been most extensively studied for G_q-coupled receptors (e.g. endothelin-1 (ET-1), α-adrenergic and angiotensin II receptors), there may be three different organizations to consider (Fig 1). In what might now be considered the classical or traditional model (Fig 1A), we showed that ET-1 triggered a rise in cytosolic $[InsP_3]$ in adult ventricular myocytes that precedes the rise of $[InsP_3]$ in the nucleus (using a FRET-based $InsP_3$ sensor)[6] and that most of the $InsP_3R$ in these myocytes is the type 2 $InsP_3R$ that is largely localized to the nuclear envelope and complexed with Ca-Calmodulin dependent protein kinase II (CaMKII).[7] We showed evidence for the hypothesis

Address for Correspondence: Donald M. Bers, Ph.D., Department of Pharmacology, University of California, Davis, 451 Health Sciences Drive, Davis, CA 95616, Phone: (530) 752-3200, FAX: (530) 752-7710, dmbers@ucdavis.edu.

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(Fig 1A) that ET-1 activation produces $InsP_3$ at the membrane which diffuses to nuclear $InsP_3R$, elevating local [Ca^{2+}] there to effectively activate CaMKII (and PKD) dependent phosphorylation of histone deacetylase 5 (HDAC5) to trigger HDAC5 nuclear export and de-repression of MEF2-dependent hypertrophic signaling.[5] It was known already that $InsP_3$ is better than Ca^{2+} at long-distance signaling in cells[8] and that CaMKII and PKD are HDAC kinases which could drive HDAC nuclear export and thus activate MEF2-dependent transcription.[9] Moreover, the high local [Ca] at the mouth of the $InsP_3R$ channel would facilitate CaMKII activation (which requires high local [Ca^{2+}]) in the nuclear environment. This working model nicely connects G_q-coupled receptor activation to an important role for $InsP_3/Ca^{2+}$ signaling in cardiac myocytes aside from E-C coupling, and connects nuclear $InsP_3R$ and CaMKII to transcriptional regulation in the heart downstream of G_q-coupled receptor activation. Indeed, this allows Ca-dependent local signaling (around the $InsP_3R$) to work in parallel to but independent of the global Ca^{2+} transients associated with regular E-C coupling.[5]

Ibarra *et al.*[1] suggest an important extension to this concept (Fig 1B). They show evidence that an entire receptor (in this case IGF-1R), G-protein, PLC and $InsP_3$ production complex is situated at the nucleus due to plasma membrane infoldings in direct apposition to the nuclear envelope. This would have the tremendous advantage of producing the $InsP_3$ very close to the $InsP_3R$ at the nucleus. It would greatly reduce the amount of $InsP_3$ production required to activate the local nuclear Ca transients. It also explains their observations of a faster rise in IGF-1-induced Ca transients in the nucleus vs. cytosol that was most apparent in cultured neonatal rat ventricular myocytes. Their nuclear vs. cytosolic difference in kinetics was not as clear in adult ventricular myocytes, but Ca^{2+} transients induced by IGF-1 were larger in the nucleus than cytosol, and that was opposite to what was seen with normal E-C coupling Ca^{2+} transients. Thus, IGF-1 and $InsP_3$-driven transients initiate first and strongest in the nucleus, whereas the normal beat-to-beat Ca^{2+} transients initiate and are stronger in the cytosol. That is consistent with data suggesting that $InsP_3R$ activation promotes relatively stronger nuclear Ca^{2+} signals,[10–12] although Ca^{2+} indicator calibrations in nucleus may differ from that in the cytosol.[13] While it would be worthwhile to further test the model proposed by Ibarra, especially in adult ventricular myocytes, this is an intriguing structural organization.

There is also convincing evidence of a third organization of G-protein coupled receptor to $InsP_3/Ca^{2+}$ signaling in the nucleus (Fig 1C). That is, some fraction of G_q-coupled receptors appear to be functional, intracellular and localized at or near the nucleus.[14–18] Indeed, there is evidence that many of the key molecules (G proteins, PLC and $InsP_3$ metabolizing proteins) are also at the nuclear membrane. Since the SR/ER network throughout ventricular myocytes is continuous with the nuclear envelope membranes,[19] the receptors and key signaling molecules could translocate to the nuclear envelope from ER without necessarily leaving that membrane. One issue for this organization is how the ligand (e.g. norepinephrine or Ang II) gets across the plasma membrane to gain access to the internal receptor. In some cases that might be mediated by membrane transporters (e.g. norepinephrine via extraneuronal monoamine transporter, EMT/OCT3),[14] while in other cases it might represent an intracellular autocrine signaling pathway (e.g. in response to myocyte produced Ang II).[15]

It is quite plausible that all three of these receptor complex organizations coexist in cardiac myocytes, and maybe even for the same type of receptors. There are certainly details about each of these working models that need to be better worked out and validated. However, these models also raise intriguing questions regarding which pathway might be most important for *a)* a given receptor type, *b)* different types of signaling contexts, c) cross-talk with different signaling networks and d) different pathophysiological conditions or

pharmacological responses. So, as in real estate, location again matters and receptor complexes may take up residence in different neighborhoods for reasons that we will still have to figure out.

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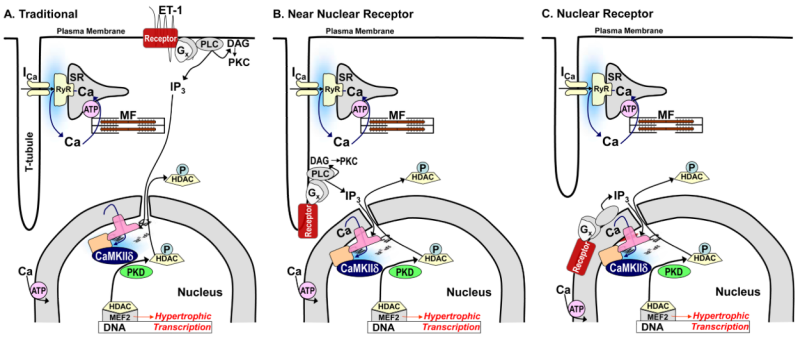

Figure 1. Three models of membrane receptor signaling to InsP3 dependent Ca^{2+} signals

A) in the traditional model receptors (as for ET-1 in this example) activate $InsP_3$ production at the cell periphery (or throughout the plasma membrane). But the $InsP_3$ must diffuse a potentially long way to the nuclear $InsP_3R$ to cause local nuclear [Ca^{2+}] elevation by release from the Ca^{2+} store in the nuclear envelope. **B**) The model shown by Ibarra *et al.*[1] indicating the IGF-1R complex in plasma membrane invaginations, reducing the diffusional distance for $InsP_3$ to reach the nucleus. **C**) A third model where functional G-protein coupled receptors can exist near or on the nuclear envelope. RyR, ryanodine receptor, I_{Ca}, Ca current, ATP, SR/ER Ca-ATPase; MF, myofilaments; P, phosphorylation, Cam, calmodulin, G_x, G-protein, DAG, diacylglycerol.