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Ryanodine Receptor

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Gene symbols: RYR1, RYR2, RYR3

1. General Information

1.1 Size and Evolution

The ryanodine receptor (RyR) is a selective Ca^{2+} release channel that is localized to the endoplasmic reticulum (ER) in both excitable and non-excitable cells. The RyR owes its name to the plant alkaloid and high affinity ligand ryanodine. The functional RyR exists as a tetramer composed of a single unit of approximately 565kDa. To date, it is the largest known ion channel. In mammals, there are three RyR isoforms that share approximately 70% homology and several biophysical properties (26). RyR1 is the dominant Ca^{2+} release channel present on sarcoplasmic reticulum (SR) in skeletal muscles (104, 127), RyR2 is predominant in cardiac muscle (73), and in brain there is more general expression of all three isoforms (29, 36, 67, 73, 126).

Based on phylogenetic analysis, it is likely that all three RyR isoforms evolved from a single ancestor. In addition, there is evidence to suggest that the RyR as well as another intracellular Ca^{2+} channel the inositol 1,4,5-trisphosphate receptor (IP3R) evolved from a common ancestral gene (107). Sequence analysis reveals a high degree of similarity in the channel pore region (107), supporting the common ancestor theory. This structural homology is also present between the pore-forming region of RyRs and other ion channels, which include voltage gated ion channels, cyclic nucleotide gated channels, and the transient receptor potential channels (TRP) (41). Phylogenetic studies also reveal that certain RyR domains are highly conserved from worms to humans. For instance, there is 35-40% homology at the amino acid level between *C. elegans* and vertebrates, and the functional domains including the leucine/isoleucine zipper, the pore region, and the transmembrane domains are highly conserved in all three RyR isoforms. Mutations in these domains alter channel functions such as caffeine-induced Ca^{2+} release, ryanodine binding, single channel conductance, and cation selectivity (31, 122).

1.2 The RyR genes

The organization of the phylogenetic tree supports the model than an expansion of the vertebrate gene family was associated with an initial duplication of the RyR1 gene, since only one RyR gene is found in invertebrates. Non-mammalian vertebrates express two RyR genes (80). Further, it appears that a second duplication occurred in mammals, which distinguishes them from other vertebrates. In mammals, three RyR isoforms are transcribed from three separate genes. In humans the gene for RYR1 is located on chromosome 19q13.2 and spans 104 exons. The RYR2 gene is located on chromosome 1q43 and spans 102 exons, and the RYR3 gene is located on chromosome 15q13.3-14 and spans 103 exons. An additional means of generating diversity in RyR channels is through alternative splicing (30, 73, 106, 107, 114). Although there are reports that splice variants, for example, of RyR3 exhibit reduced caffeine sensitivity (49), relatively little is known about the functional properties of alternatively spliced RyR channels.

1.3 Three-dimensional structure and ligand binding

Three-dimensional (3D) structural information is essential to an understanding of the functional properties of RyRs. While there are no published full length crystal structures of the RyR, there are several crystal structures of the N-terminal domain, and they reveal structural similarities with the IP3R (62, 92). Cryo-electron microscopy (EM) generated 3D reconstructions of RyR reveal a highly conserved structure, having the overall shape of a mushroom and consisting of two major components: a large, square prism-shaped cytoplasmic assembly composed of at least 10 distinct domains, and a differentiated small transmembrane assembly **(Figure 1)**. Sequence analysis (104, 106) and biochemical studies (20, 37) demonstrate that the N-terminus (~4000-4500 amino acid residues) contains the large cytoplasmic assembly, while the C-terminus (~500-1000 amino acid residues) comprises the transmembrane regions **(Figure 2)**. The precise number of transmembrane segments per single monomer unit is controversial; four-, six-, and ten-segment models have been proposed (20). However, a developing consensus supports that six transmembrane segments exist per monomer, in a fashion similar to that of IP3R (88).

RyRs are regulated by numerous natural ligands. Most of these ligands modulate specific sites on the large cytoplasmic portion of the channel. Ligands that activate RyR opening include cytosolic Ca^{2+}, which is the most potent activator, calmodulin (during low Ca^{2+} concentrations) (110), cyclic ADP ribose (cADPR; primarily an activator of RyR2) (58, 71), ATP (91), and the dihydropyridine receptor (DHPR; for RyR1) (11). Ligand interactions that inhibit the RyR include magnesium (68), FK506 binding protein 12 (FKBP12; for RyR1), and FKBP12.6 (for RyR2) (48). The role of NAADP as a direct allosteric activator of the RyR (versus a two pore channel or a transient receptor potential channel) is still a matter of controversy (13, 28, 56). A list of RyR activators and inhibitors is provided in **Table 1**.

In addition, protein-protein interactions via three leucine/isoleucine zipper motifs on the RyR2 allow binding of the adaptor proteins spinophilin, PR130, mAKAP, protein phosphatases PP1 and PP2A, and protein kinase A (PKA) to the channel complex **(Figure 3)** (66).

1.4 Post-translational modifications

In addition to regulation by ligand binding, RyR opening is controlled by post-translational modifications that include covalent phosphorylation, nitrosylation, and redox potential (oxidation/reduction of cysteine sulfhydryl moieties). Three major phosphorylation sites exist on the RyR and physiologically regulate RyR conductance. They include serine (S)2814, S2030, and S2808. S2814 and S2030 are phosphorylated by CaMKII and PKA, respectively. It is not yet resolved which of the kinases--CaMKII, PKA, or PKG-- phosphorylates S2808 on RyR2.

Increasing evidence supports the redox modulation of RyR channels (44, 84, 112). A

small number of hyper-reactive sulfhydryls on RyR are susceptible to oxidation (40), S-nitrosylation (5, 22), and S-glutathionylation (3) by a number of endogenous redox-active agents. Typically, exposure of RyR to these agents increases its sensitivity towards activators or decreases its sensitivity towards inhibitors (3, 75).

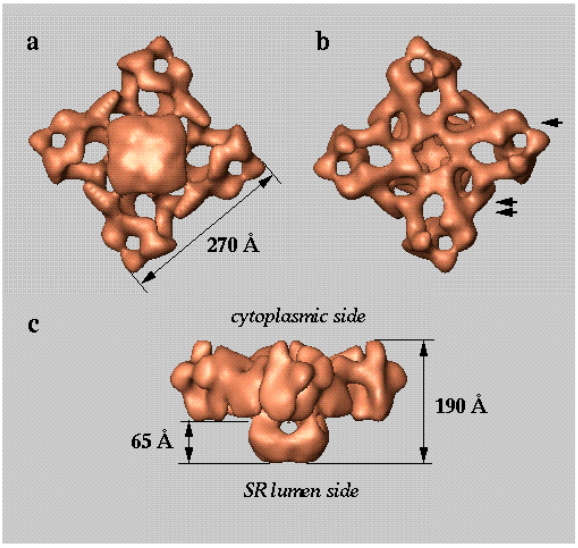

Figure 1. Three-dimensional reconstruction of the RyR1 from skeletal muscle by cryo-electron microscopy. Ryanodine receptors were purified from skeletal muscle membrane fractions and cryo-electron microscopy (EM) was performed as previously described (1). (A) “Bottom” view of the surface facing the ER lumen. (B) “Top” view of the cytoplasmic surface. Single arrow represents a cluster of domains that form the cytoplasmic assembly, termed “clamps.” Double arrows represent the largest cytoplasmic assembly domains, which connect the “clamps”, termed “handles.” (C) “Side” view of the transmembrane assembly. *Reprinted with permission from Macmillan Publishers Ltd: Nature Structural Biololgy, (93).*

1.5 The RyR pore

The RyR pore is the region which provides a pathway for ions to cross the dielectric barrier of the ER membrane and shares much of its architecture with K^+ channels. The putative membrane-spanning regions, which make up the RyR pore, have been identified within the last 1000 residues of the C-terminus (20, 104, 127). The ion handling properties of the RyR pore have also been examined in detailed (111). Although the RyR effectively excludes anions, it does not discriminate between cations as well. RyR channels are permeable to a wide range of divalent and monovalent inorganic cations and some organic monovalent cations. The rate of cation translocation through the RyR pore is higher than those of other ion channels (111). Because the RyR behaves as a single ion channel, the most likely explanation is that the RyR pore contains a short, wide, selectivity filter.

1.6 Ca^{2+}-induced Ca^{2+} release

In skeletal muscle, physical coupling of RyR1 with the DHPR causes RyR opening. However, in cardiac, smooth muscle, and non-excitable cells, RyR Ca^{2+} release is due to exposure of the RyR to cytosolic Ca^{2+}. This phenomenon is known as Ca^{2+}-induced Ca^{2+} release (CICR). The RyR is, in fact, a prototypic CICR channel. This triggering Ca^{2+} signal can arise from several different sources, including extracellular Ca^{2+} influx through the plasma membrane or intracellular Ca^{2+} released from neighboring IP3Rs. Regardless of the source, the effectiveness of the Ca^{2+} signal is dependent on both its speed and amplitude. Work by Fabiato and colleagues demonstrated that SR Ca^{2+} release is directly proportional to the amplitude and duration of the initial Ca^{2+} trigger. CICR subsequently undergoes feedback inhibition through binding of Ca^{2+} to low affinity Ca^{2+} binding sites on the RyR that are inactivating (8, 23).

1.7 RyR-associated pathologies

Over 300 RyR mutations have been associated with disorders (54), including the RyR myopathies malignant hyperthermia (69, 72), central core disease (63), multiminicore disease (25), atypical periodic paralyses (125), catecholaminergic polymorphic ventricular tachycardia, and arrhythmogenic right ventricular dysplasia type 2 (64, 87, 120). The RyR has also been indirectly linked to acquired pathologies such as heart failure (95) and over-exercise muscle fatigue (4). The following references provide a more comprehensive review of RyR structure and function (26, 39, 54, 90, 118, 126).

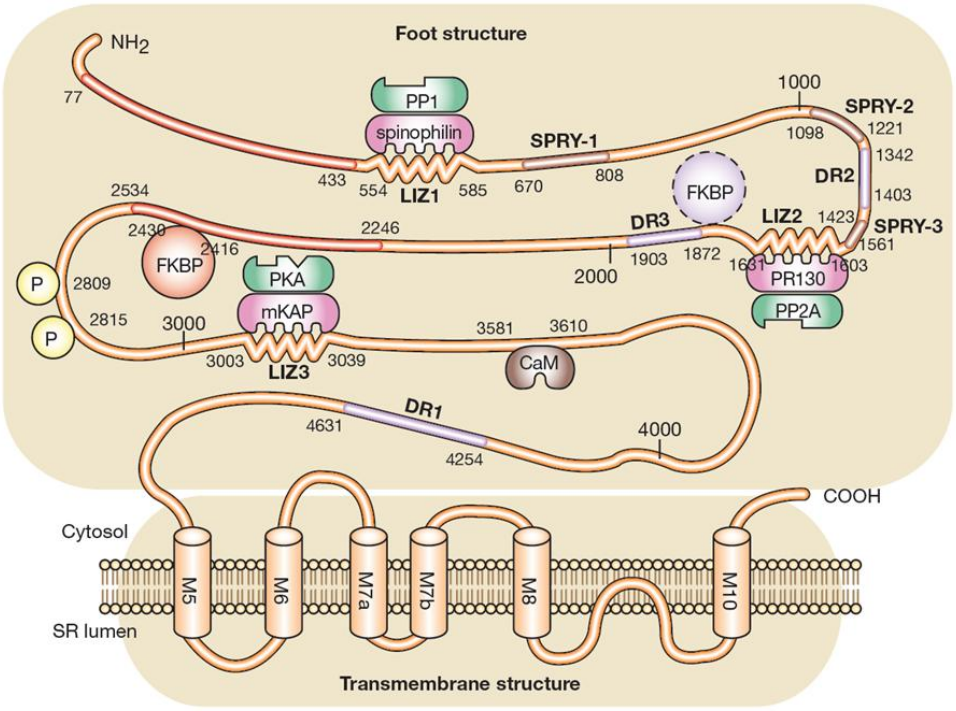

Figure 2. Structural domains and accessory proteins of the RyR2. The primary structure of the RyR and binding domains of protein phosphatases 1 and 2A (PP1, PP2A), protein kinase A (PKA), calmodulin, and FKBP12.6 are shown. PP1 and PP2A and PKA bind to the RyR via their specific adaptor proteins. Six transmembrane segments are shown as previously described (20). CaM, calmodulin; DR, divergent region; FKBP, calstabin-2; LIZ, leucine–isoleucine zipper; SR, sarcoplasmic reticulum. *Reprinted with permission from Macmillan Publishers Ltd: Nature Clinical Practice Cardiovascular Medicine, (116).*

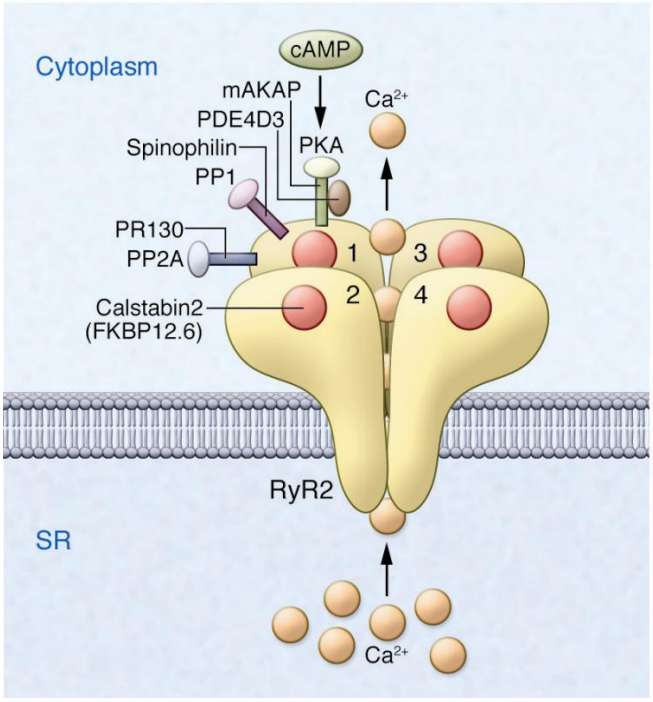

Figure 3. Diagram of the yR2 macromolecular complex with accessory proteins. The RyR2 macromolecular complex includes four identical RyR2 subunits (numerals 1-4). Each RyR2 subunit binds one calstabin2 (also known as FKBP12.6) as well as mAKAP, to which PKA catalytic and regulatory subunits and PDE4D3 are bound; PP2A and its targeting protein PR130; and PP1 and its targeting protein spinophilin (accessory molecules are only shown for one of the four RyR2 subunits, except calstabin2, which is shown for all four RyR2 subunits). The β-adrenergic signaling pathway can activate PKA through the second messenger cAMP. *Reprinted with permission from the American Society for Clinical Investigation: Journal of Clinical Investigation, (65).*

2. Pancreatic Information

2.1 RyR expression in the pancreas

Several groups have examined RyR isoforms in both acinar cells and islets. Muallem and colleagues failed to see expression of RyRs in rat pancreatic acini by immunofluorescence (IF) (57). Later, however, Nathanson and colleagues demonstrated expression of RyR2 by PCR and western blotting (59). By IF, they saw a non-apical pattern of labeling. A similar distribution of the RyR signal was observed by several labs including those of Yule (using BODIPY-ryanodine) (100) and Pandol (27). The latter found that all three isoforms were expressed. Our lab has further confirmed the presence of RyR in rat **(Figure 4)** (46, 94), mouse **(Figure 5)** (78), and in human acinar cells (unpublished).

The presence of RyR in pancreatic islets has been a subject of recent interest. Investigators first considered the possibility that β-cells possess RyR channels after discovering that IP3 caused release of only ~50% of the ER Ca^{2+} pool (98). Intracellular Ca^{2+} release is critical for physiologic regulation of insulin secretion by glucose and incretin hormones in pancreatic β-cells (47). Therefore, it was hypothesized that the β-cell ER may be equipped with RyR channels to help regulate this process. Initial studies utilized the RyR activator thimerosal to show intracellular release of Ca^{2+} from the IP3-insensitive pool (41, 122). The release was potentiated by caffeine, suggesting that RyRs are present. Subsequent studies demonstrated that low dose ryanodine-induced Ca^{2+} release from islet microsomes (31) and caffeine-induced Ca^{2+} release from the ER of intact β-cells (80). Work by Johnson et. al. first demonstrated the predominance of RyR2 in mouse islets (6, 47, 50). These studies were recently complemented with the interesting finding that a novel RyR2 splice variant exists in mouse pancreatic islets (107). The protein product is present in both mouse and human islets and remains fully functional. Lastly, Wehrens and colleagues confirmed the original findings that RyR2 is the predominant isoform, with the addition that RyR3 is also expressed at low levels (6).

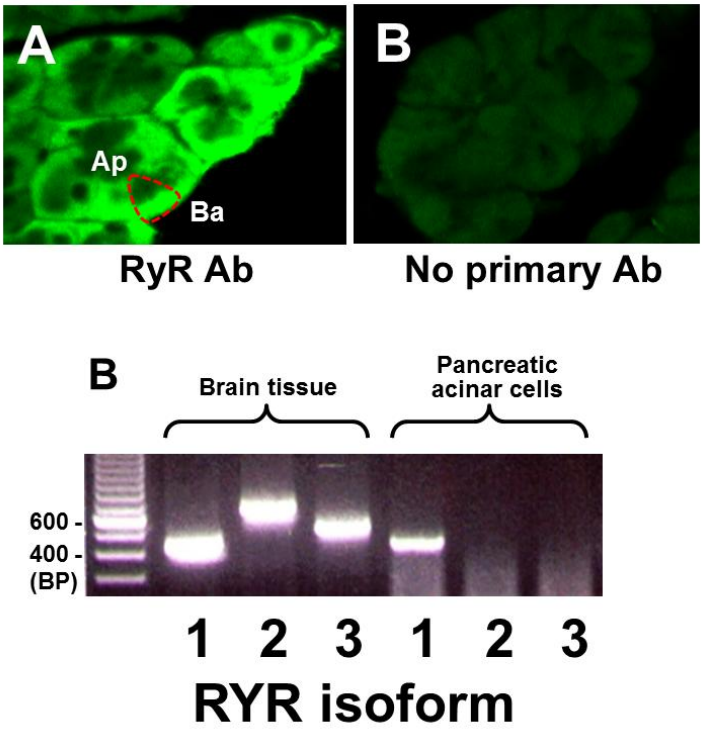

Figure 4. In mouse pancreatic acinar cells the ryanodine receptor (RYR) is localized to the basolateral region, and RYR1 is expressed. (A) *Left*: RYR is distributed in the basolateral region (Ba) of the acinar cell but excluded from the apical region (Ap). *Right*: control section without primary antibody but same laser confocal microscopy setting as at *left*. (B) PCR for RYR isoforms from brain tissue (positive control) and acinar cells. *Reprinted with permission from the American Physiological Society: American Journal of Physiology: Gastrointestinal and Liver Physiology, (78).*

2.2 RyR Ca^{2+} release in the acinar cell

RyR Ca^{2+} release in pancreatic acinar cells was first implicated with the use of caffeine (109). In these early studies, Petersen and colleagues described the globalization of acinar cell Ca^{2+} signals in the presence of 1 mM caffeine. These results suggested the presence of a RyR releasable Ca^{2+} pool that is triggered by IP3R-Ca^{2+} release. Later, Thorn et. al. described a primary role for the RyR in the generation of Ca^{2+} spikes (105). Even though RyRs appear to be concentrated in the non-apical region of acinar cells (as mentioned earlier), there is some controversy, over whether they can shape apical

Ca^{2+} signals or whether they primarily influence apical to basal Ca^{2+} waves. Evidence for both sides will be briefly presented below.
Thorn et. al. demonstrated that intracellular injection of the putative RyR ligand cADPR via a patch pipette induced apical Ca^{2+} spikes (105). This and other works suggested the presence of RyRs within acidic, non-ER, Ca^{2+} pools along the apical pole (35, 86). Leite et. al., however, showed that local uncaging of cADPR in the apical region failed to induce a Ca^{2+} transient, as opposed to uncaging into the basal region (58). RyRs have been implicated as crucial factors in the generation of agonist-induced apical to basal Ca^{2+} waves. Ryanodine at micromolar concentrations that inhibit CICR markedly reduced the speed of the Ca^{2+} wave (74, 100). In summary, RyRs are concentrated in the non-apical region, and they amplify Ca^{2+} signals that are initiated by apical IP3Rs.

2.3 The RyR in pancreas pathology

Whereas physiologic stimuli provoke low amplitude, oscillatory Ca^{2+} signals in acinar cells, pathologic insults (which cause pancreatic injury and pancreatitis *in vivo*) induce high amplitude, non-oscillatory Ca^{2+} signals. These latter aberrant Ca^{2+} signals are associated with acinar pathology such as intra-acinar protease activation (53, 89), vacuole formation (97), mitochondrial depolarization (89), and acinar cell leakage (45). Husain et. al. reported that RyRs modulate CCK- and carbachol-induced protease activation (46). Dantrolene, the RyR inhibitor used in this study, appeared to selectively reduce basal Ca^{2+} signals. Notably, neither dantrolene nor micromolar ryanodine (the latter from a previous study (74)) affected enzyme secretion. The findings implicate the RyR as a potential therapeutic for pancreatitis without the side-effect of perturbing pancreatic function (46, 78).
Ethanol, a major etiology of pancreatitis, given at concentrations that are achievable during intoxication (100 mM) accelerated the apical to basal Ca^{2+} wave generated by carbachol (79). Ethanol also enhanced intra-acinar protease activation and acinar cell injury. These changes were dependent on the RyR **(Figure 6)**. Another study confirmed that RyR inhibition (using ruthenium red) modulated pathological Ca^{2+} release and protease activation due to ethanol exposure in permeabilized acinar cells (33). Although the mechanism by which ethanol sensitizes RyRs is still unclear, a potential target is post-translational modifications by PKA phosphorylation (94).
Ethanol is readily converted by the pancreas to its non-oxidative metabolites in the presence of fatty acids to fatty acid ethyl esters (55). Whereas the oxidative metabolites induce mild Ca^{2+} signals, several of the non-oxidative metabolites including palmitoleic acid ethyl ester (POAEE) and ethyl palmitate both induce strong Ca^{2+} signals and convert oscillatory signals with physiological stimuli to that of a pathologic peak-plateau pattern (16, 17, 19). The Ca^{2+} signals with POAEE were partially dependent on the RyR (34). Bile acid exposure of acinar cells may constitute an important mechanism of biliary pancreatitis (82, 83). The bile acid taurolithocholic acid 3-sulfate (TLCS) induces robust peak-plateau Ca^{2+} signals (32, 108) and acinar cell injury that are dependent upon the RyR (45). Further, *in vivo* pancreatitis due to infusion of bile acids (TLCS or taurocholic acid; TC) can be prevented and, importantly, treated with the RyR inhibitor dantrolene (45). These data do not negate the potential involvement of IP3Rs that are concentrated in the apical region but also sparsely distributed along the ER in the basal region of the acinar cell. Overall, however, the findings provide potential for the use of RyR modulators as an adjunctive therapy for pancreatitis.
Recent studies have also examined the importance of the RyR in pancreatic islets. It has previously been established that the RyR serves an important function in regulating Ca^{2+} handling, insulin secretion, and glucose tolerance in pancreatic islets (6, 50).

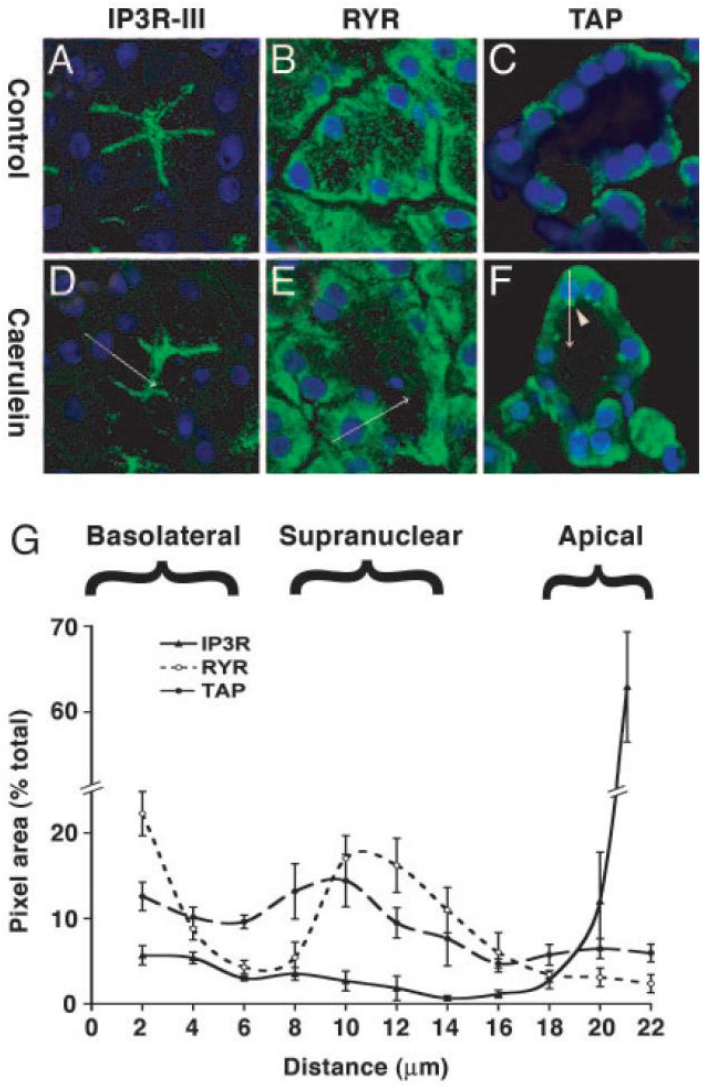

Figure 5. The distribution of Trypsin Activation Peptide (TAP) overlaps with RYR but not with IP3R. Confocal microscopy images of pancreas sections after 30 min of normal saline (*A*–*C*) or caerulein hyperstimulation (*D*–*F*) *in vivo* were labeled for IP3R-III (*A* and *D*), RYR (*B* and *E*), or TAP (*C* and *F*); nuclei were stained blue with TOPRO-3. Basal-to-apical line scans (see arrows in *D*–*F*) show that IP3R labeling is apical; RYR is distributed in the basolateral region, concentrated in the supranuclear region but excluded from the apical region. TAP appears as discrete supranuclear structures (arrowhead). (*G*) Overlap between TAP and RYR, but not IP3R, in the supranuclear region is quantified in five line scans from each section, relative to the distance from the basolateral membrane with the nucleus as a reference point. *Reprinted with permission from the United States National Academy of Sciences: Proceedings of the National Academy of Sciences, (46).*

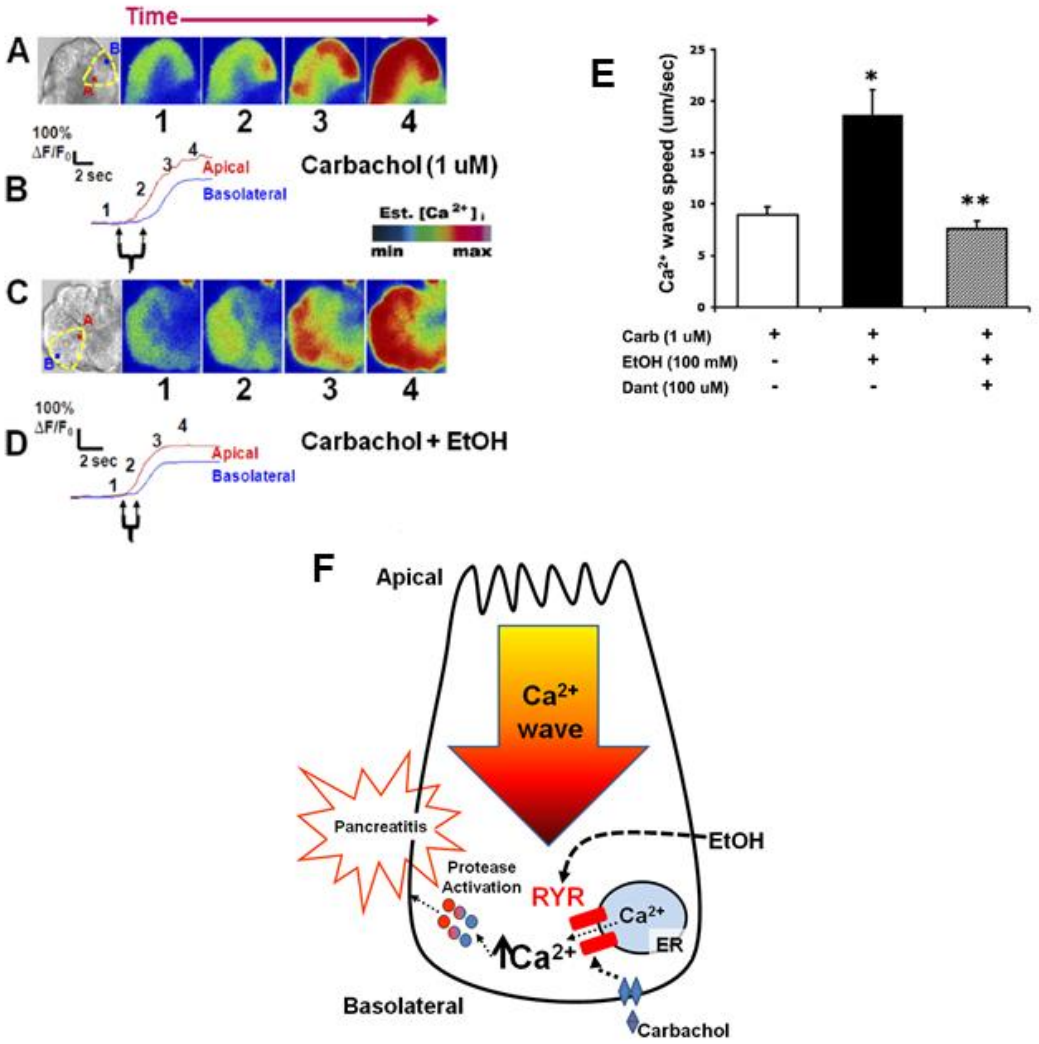

Figure 6. Ethanol accelerates the physiologic carbachol-stimulated Ca^{2+} wave. (A) Acinar cells were treated with or without ethanol (100 mM) for 30min prior to carbachol (1 uM) stimulation. From *left* to *right*, bright field view of an acinus labeled at the apical (*A*) and basolateral (*B*) regions of interest from an acinar cell. Cells were loaded with the Ca^{2+} indicator fluo-4 (5 uM). Upon stimulation with physiologic carbachol (1 uM), subsequent images show the initiation of the Ca^{2+} signal in the apical region followed by propagation to the basal region. (B) Each paneled image (*1– 4*), corresponds to a frame along a representative tracing of change in fluorescence over time for each region of interest. *Left* and *right arrows* show time of first Ca^{2+} rise in the apical and basal regions, respectively. *Est.* [Ca^{2+}]*i*, estimated [Ca^{2+}]*i*; *min*, minimum; *max*, maximum. (C-D) Cells were pretreated with ethanol (100 mM) for 30 min. (E) Quantitation of difference in Ca^{2+} wave speed with carbachol $\pm$ ethanol in the presence or absence of dantrolene (*Dant*, 100 uM). (*n* =13 cells in each). *, $p<0.005$. (F) Proposed mechanism by which ethanol evokes pathological effects on the pancreatic acinar cell. *Reprinted with permission from the American Society for Biochemistry and Molecular Biology: Journal of Biological Chemistry, (79).*

3. Tools for Study

3.1 Antibodies
A list of RyR antibodies and their applications are provided in **Table 2**.

3.2 Expression vectors
RyR1 and RyR2 have been overexpressed in HEK293 cells by Chen and colleagues (49). These constructs have proven useful for examining the role of various mutations on RyR Ca^{2+} release.

3.3 Animal models
The RyR1 (102) and RyR2 (103) knockout mice do not survive beyond neonatal life, while RyR3 deficient mice live to adulthood (7). Currently, there are no floxed conditional knockouts. There is, however, a knockout of CD38, the enzyme that synthesizes the putative RyR activator cADPR (77, 117). There are also knockins of the phosphomimetic and phosphoresistant mutations at S2808 and S2814 on RyR2 (95, 96). A certain strain of pig has a higher incidence of RyR mutations that predispose them to malignant hyperthermia (99). A knockin mouse model of malignant hyperthermia has also been established (24). .

3.4 Ligand binding
Ryanodine binding studies are useful to examine (1) the presence of RyRs and (2) the density of RyRs in cells or tissues of interest and (3) to indirectly determine RyR open state. A detailed methods protocol for performing tritiated ryanodine binding is provided by Meissner and colleagues (21)

3.4 Activators and inhibitors
A list of RyR activators and inhibitors are in **Table 1.**

3.5 Pull-down
Pull-down of RyR is achieved with high affinity using a FKBP12 or FKBP12.6 GST fusion protein (51, 61).

Table 1. RyR activators and inhibitors.

RyR Activators	Concentratio	References	Comments
Caffeine	**2 mM**	**(15, 46, 109)**	Also inhibits IP3Rs, phospholipase C, and phosphodiesterase (14).
Cyclic ADP ribose (cADPR)	**100 uM**	**(76, 77, 124)**	Can increase SERCA activity, leading to increased ER/SR Ca^{2+} content, and could thereby increase Ca^{2+} release (12, 115).
Cyclic inosine diphosphoribose ether (cIDPRE)	**200 uM**	**(38, 117)**	Synthetic, membrane permeant analogue of cADPR (38, 117).
4-chloro-m-cresol (4-CMC)	**1 mM**	**(42, 43)**	RyR1-specific agonist (10, 42, 43) .
Ryanodine	**10 nM**	**(9, 46)**	Nanomolar concentrations lock the RyR in an open subconductance state (85).
RyR Inhibitors	**Concentratio**	**References**	**Comments**
Ryanodine	**100 uM**	**(45, 74, 105)**	Micromolar concentrations inhibit the channel (85).
Dantrolene	**100 uM**	**(45, 46, 52, 78, 81)**	The only drug targeting RyRs to be used clinically (113, 128). Has poor water solubility.
Azumolene	**100 uM**	**(121, 123)**	Structurally similar, equipotent analog of dantrolene, with a ~30-fold greater water-solubility (2, 60). Also known as EU 4093.

Table 2. RyR antibodies.

Antibody	Vendor (cat #)	Host Species	Application	Target isoform	References
34C	**Iowa Hybridoma (34C)**	**Mouse**	**WB, IHC, IF, IP**	**RyR 1-3**	**(70, 94)**
C3-33	**Abcam (ab2827)**	**Mouse**	**WB, IHC, IF, IP, Flow Cyt, ICC, ELISA**	**RyR2**	**(18, 59, 101)**
H-300	**Santa Cruz (sc-13942)**	**Rabbit**	**WB, IHC, IF, IP, siRNA**	**RyR1-3**	**(119)**
XA7B6	**Santa Cruz (sc-73607)**	**Mouse**	**WB, IP**	**RyR1**	**(27)**

WB, western blotting; IHC, immunohistochemistry; IF, immunofluorescence; IP, immunoprecipitation; Flow Cyt, flow

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