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Signaling epicenters: The role of caveolae and caveolins in volatile anesthetic induced cardiac protection

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Abstract

Caveolae are flask-like invaginations of the cell surface that have been identified as signaling epicenters. Within these microdomains, caveolins are structural proteins of caveolae, which are able to interact with numerous signaling molecules affecting temporal and spatial dimensions required in cardiac protection. This complex moiety is essential to the mechanisms involved in volatile anesthetics. In this review, we will outline a general overview of caveolae and caveolins and their role in protective signaling, with a focus on the effects of volatile anesthetics. These recent developments have allowed us to better understand the mechanistic effect of volatile anesthetics and their potential in cardiac protection.

Keywords

caveolae; caveolin; lipid raft; volatile anesthetics; cardiac protection

Introduction

Cardiac disease remains the largest cause of mortality within the USA.[1] As a result, many have investigated the role of cardioprotective agents and interventions including opioids,[2] sub-lethal ischemia,[3] and volatile anesthetics.[4] Exploring the mechanisms of action of these agents has produced possible pharmaceutical targets to help prevent cardiac disease, yet none have been clinically trasnlated. In an effort to further understand cardiac protective signaling, caveolae, invaginations within the cell membrane and their structural components caveolins, have been shown to be essential to these mechanisms. This review will highlight a series of investigations that elucidate the multifaceted role of caveolae and caveolins

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within cardiac protection by altering temporal and spatial recruitment and organization of molecular signaling.

Caveolae and Caveolins

The “fluid-mosaic model” suggested by Singer and Nicolson [5] described the membrane as a fluid bilayer with a homogeneous lipid distribution. In recent years this model has been refined as the plasma membrane has been shown to consist of defined lipid rich regions interspersed with more fluidic membrane regions resulting in a much more complex view of the membrane than originally hypothesized. Caveolae are subcellular structures that were first described using electron microscopy in 1953 by George Palade.[6] Initially, these invaginations were identified as *plasmalemmal vesicles*. Two years later, similar structures were reported in the gall bladder epithelium,[7] and were described as *caveolae intracellulares* due to their cave-like, invaginated appearance. Since their initial discovery, caveolae have been found in almost all cell types,[8] with certain exceptions (e.g. erythrocytes, lymphocytes, and neurons[9–11]). Recent studies have shown that caveolar microdomains are more than lipid enriched invaginations of the plasma membrane.[6, 7] Caveolae play an important role in physiological functions such as cell surface signaling,[12–16] endocytosis,[17] calcium homeostasis,[18–20] adrenergic receptor regulation,[21] and intracellular cholesterol transport (Figure 1).[22, 23] The lipid composition of caveolae includes cholesterol,[22, 24] sphingolipids (such as sphingomyelin, ceramide and gangliosides),[25–27] glycosphingolipids[28] and fatty acids.[29]

Caveolins, structural proteins essential for caveolae formation, are present in three isoforms (Cav-1, -2, and -3). Cav-1 was the first member of the caveolin family to be identified as a phosphorylated protein in *v-Src* transformed cells.[30] Cloning of the Cav-1 complementary DNA (cDNA) revealed that it was identical to another protein, VIP21which was a component of trans-Golgi-derived vesicles.[31, 32] Cav-1 is a 22-kDa phosphoprotein and has two isoforms.[33, 34] Cav-1 is phosphorylated on Tyr14 by the tyrosine kinase Src[35] and contains three residues (Cys133, Cys143, and Cys156)[36] that are palmitoylated, stabilizing the protein at the membrane.. Cav-2 and Cav-3 were identified in 1996. Cav-2 was identified by microsequencing of a 20-kDa protein co-purified with adipocyte-derived caveolar membranes,[37] and Cav-3 was discovered through cDNA library screening in an attempt to find Cav-1 homologs.[38] Cav-2 has three known isoforms (α, β, and γ) and is phosphorylated on Tyr19 by Src and Ser23 and Ser36 by casein kinase II,[39, 40] whereas Cav-3 is not known to be phosphorylated.

Cav-1 and Cav-2 have similar tissue distribution being expressed in most cell types, while Cav-3 exists primarily in muscle cells.[41–43] Ablation of Cav-1 (i.e., Cav-1 KO mice) results in complete loss of caveolar invaginations in endothelial cells, adipocytes, fibroblasts, and pneumocytes, while caveolae were still present in muscle and cardiac cells.[44–46] Similarly, Cav-3 KO mice do not have any invaginated formations resembling caveolae (Figure 2) in muscle cells; however, caveolar structures are present in other cell types.[47, 48] Interestingly, overexpression of Cav-3 in cardiac myocytes dramatically increases the number of caveolae (Figure 1).[49] Moreover, in Cav-2 KO mice, caveolae remained unchanged.[50] These data suggest when both Cav-1 and Cav-3 are expressed,

such as in cardiac muscle, Cav-3 is the dominant protein necessary for caveolae formation; [51] however, there may be a significant but as of yet not clearly understood role for Cav-1 in cardiac physiology.

All three caveolins have an invariant structural motif.[36, 38, 42, 52, 53] Additionally, Cav-1 and Cav-2 can hetero-oligomerize in most cell types, whereas Cav-3 forms homo-oligomeric complexes in striated myocytes.[38, 54] Caveolins can form hetero- or homo-oligomer complexes composed of 14–16 monomers.[53, 55] Human Cav-3 recently has been shown to form a disc-shaped nonamer.[56]

Cholesterol is essential for caveolae formation through its ability to bind caveolins and regulate caveolin transcription.[22, 57] Caveolin binds to phospholipid liposomes only upon cholesterol incorporation, and this caveolin-cholesterol interaction promotes caveolin oligomerization,[22, 24] suggesting a dependence on cholesterol for protein oligomerization and insertion into membranes. Cells treated with agents that remove cholesterol (e.g. filipin, methyl-β-cyclodextrin, or nystatin) lose caveolin and caveolae, resulting in flattened plasma membranes as visualized by electron microscopy.[58–60]

Molecular trafficking via caveolae and caveolins

Caveolin contains a scaffolding domain (CSD) that is largely responsible for many of the functions of caveolins.[12, 61] Components involved in G-protein-coupled receptor (GPCR) signaling, (*e.g.* G-proteins and G-protein regulated effectors) have been shown to localize in association with the CSD while GPCRs are found in caveolae.[13, 62–65] Numerous signaling components, including tyrosine kinases,[35, 66] phospatidylinositol-3-kinase/ protein kinase B (PI3K/Akt),[67, 68] protein kinase C (PKC),[69, 70] mitogen activated protein kinases (MAPK) including extracellular-signal regulated kinase (ERK) and p38 MAPK,[71, 72] nitric oxide synthase (NOS),[73, 74] and adenylyl cyclase[14, 15, 75, 76] interact with the CSD of caveolins (Figure 1). Recently, it has also been suggested that caveolins directly interact with organelles such as the sarcoplasmic reticulum[56]and mitochondria[77] facilitating and regulating cellular processes and metabolism. These data suggest that caveolins function as scaffolds to support compartmentalization of signaling molecules in caveolae providing a mechanism for temporal and spatial regulation of signal transduction and cross-talk among signaling molecules.[8]

GPCRs are seven-transmembrane-domain receptors that comprise a large superfamily of signaling receptors involved in numerous cellular processes. Compartmentalization of these receptors and other proteins in microdomains located within the plasma membrane, such as in caveolae, may lead to optimal signaling and intracellular regulation.[78] Beta 2-adrenergic receptors have recently been identified to be negatively regulated via caveolae within cardiac myocytes.[21] Not only are GPCRs (*e.g.*, endothelin, bradykinin, serotonin, angiotensin-1, opioid, adenosine, adrenergic) found in caveolae, but G proteins can also interact directly with caveolins via their CSD.[79, 80] Furthermore, inactive Gα subunits have been observed to concentrate in caveolae and activation of the subunit causes Gα to move out of caveolae.[65, 81] Additionally, caveolae play a role in endocytosis of ligand bound GPCRs, which likely initiates, terminates, or maintains a signal.[82, 83] However, the

molecular mechanisms of ligand-induced movement out of caveolae, receptor-caveolae endocytosis, or the importance of caveolin in these processes are currently not well understood.

A myriad of protein kinases have been identified that can interact with caveolins via the CSD and alter cellular processes. Tyrosine kinases (Src, Lck, Fyn, and Lyn) are thought to be enriched in caveolae and interact with Cav-1, *via* the CSD. [35] Phosphorylation of caveolins via Src kinase can influence shape changes, muscle degeneration, inflammatory gene expression, transcytosis of albumin, the development of cancer, cardiac, and neurological protection from ischemia-reperfusion injury and cardiac failure.[84–88] MAPKs are also found within caveolae. Regulation of MAPK via caveolins has been identified in numerous cellular interactions including: lung fibrosis,[89] cellular proliferation,[90] cardiac hypertrophy,[91] and angiogenesis.[92] Sheer, mechanical, and osmotic stress have been shown to induce tyrosine phosphorylation, MAPK activation, and caveolae formation.[84, 93, 94] Furthermore, increased ERK activity downregulates Cav-1 mRNA and protein and overexpression of Cav-1 inhibits the MAPK/ERK signaling pathways, an inhibition that is dependent on the CSD.[71] Consistent with these results, both Cav-1 knockout (KO) mice and Cav-3 KO mice show increased activation of p42/44 MAPK.[95, 96] PI3K/Akt are essential cellular survival and proliferation kinases. PI3K and Akt have both been shown to interact with caveolins and localize to caveolae. [97, 98] Additionally, Akt and caveolins are vital to insulin signaling, which can be altered by insulin resistance.[99–102] Furthermore, isoforms of protein kinase C (PKC) can target to caveolae enhancing the regulation of caveolar-localized proteins.[69] This is observed with ceramides, which can recruit and activate PKC and Akt into caveolae where activation of PKC not only stabilizes the kinase complex but also enhances its ability to negatively regulate Akt.[70, 103]

Subcellular compartmentalization of ion channels facilitates and regulates signaling. Ca, K, Na, and Cl channels are concentrated and targeted to caveolae and can associate with caveolins.[104, 105] Among them, voltage-dependent potassium (Kv) channels were reported first within cardiac lipid-microdomains.[106, 107] In pancreatic β-cells, lipid raft disruption inactivates Kv2.1.[108] Adenosine triphosphate-sensitive potassium (K_{ATP}) channels, which are important for the regulation of vascular tone and cardiac protection from ischemia,[109–111] forms a complex with adenylyl cyclase in caveolae, allowing for sustained activation by protein kinase A.[112] Additionally, angiotensin II-activated PKC targets to caveolae to inhibit aortic K_{ATP} channels.[113] Recent investigations have also suggested that hyperpolarization-activated cyclic nucleotide-gated channel (HCN) 4 is closely regulated by Cav-3 during development[114] and for daily pacemaking.[115] Furthermore, Cav-3 can also negatively regulate Ca-activated potassium channels in transfected cells, facilitating channel trafficking.[116]

Cardiac Effects of Caveolae/Caveolin

Several investigators have generated Cav-1 and Cav-3 KO mice where either one or both genes are deleted and Cav-3 transgenic mice.[44, 45, 95, 117, 118] The regulation of cardiac physiology by caveolins may depend on cell specific expression and compartmentalization

of signaling complexes. As previously studied, all caveolin null mice have cardiovascular dysfunction. Cav-3 is mainly expressed within cardiac and skeletal muscle and is regulated in cardiac hypertrophy.[119] Conversely, Cav-3 KO mice, which lack morphologically caveolae, develop cardiomyopathy characterized by cardiac hypertrophy, dilation and reduced contractility as well.[95] Additionally, Cav-3 gene ablation leads to increased activity of the MAPK cascade in cardiac myocytes.[95] Park *et al*.[117] reported that Cav-1/3 double KO mice, which are deficient in all three caveolin proteins, have cardiac hypertrophy with cardiomyopathy and decreased contractility. Supporting these data, adenovirus-mediated overexpression of Cav-3 in neonatal cardiac myocytes decreases the ability of the adrenergic agonist phenylephrine or endothelin-1 to increase cell size, suggesting Cav-3 behaves as a negative regulator of hypertrophic responses.[91] However, global overexpression of Cav-3 results in Duchenne-like muscular dystrophy phenotype resulting in cardiac degeneration, fibrosis and reduced cardiac NOS activity and cardiac function.[118] By utilizing the alpha myosin heavy chain promoter our laboratory generated a cardiac-specific Cav-3 overexpressing mouse (Cav-3 OE) that was strikingly different.[49] These mice did not resemble a Duchenne's phenotype nor did they develop cardiomyopathy as they aged, in fact these mice where protected against cardiac failure.[88]

Myocardial ischemia/reperfusion injury and subsequent myocardial infarction remains a leading cause of morbidity and mortality. However, there are many beneficial experimental interventions that produce cardiac protection. Interstingly, perhaps the most effective is produced following brief (as short as 5 mins) ischemic exposure to the myocardium. This cardiac protection is termed ischemic preconditioning (IPC).[3] IPC has been described as a biphasic event where there is an acute phase, which occurs immediately after the IPC stimulus and lasts approximately 1–3 h and is transient.[120] The delayed phase of protection is observed 12–24 h after the initial stimulus and lasts up to 72 h.[121] Clinically relevant cardiac protection can be induced at the time of reperfusion and has been termed postconditioning.[122] Preconditioning and postconditioning are mediated via three parallel signaling pathways including GPCR and natriuretic peptide induced nitric oxide signaling, the reperfusion injury salvage kinase (RISK) pathway, and the survival activating factor enhancement (SAFE) pathway.[123, 124] Many of the molecules involved in these signaling pathways interact with caveolae and caveolins, including (GPCRs), receptor tyrosine kinases, TNF receptors, Src kinases, G-proteins, H-Ras, nitric oxide synthases, protein kinase C (PKC), phosphatidylinositol 3-kinase (PI3K), and MEK/ERK kinases.[97, 125] Interestingly, infusion of the caveolin scaffolding domain peptide of Cav-1 into ischemic/reperfused hearts increased the recovery of cardiac function where the effects were largely attributed to regulation of endothelial cell function.[126] Subsequently, it was shown that cardiac injury activated mitogen-activated protein kinases, and regulated Cav-3, and Cav-1, limiting the eNOS production suggesting a potential role of NO in IPC.[72, 127] Others have shown that IPC can modulate the microenvironment within caveolae to enrich cardioprotective proteins, including eNOS and the glucose transporter (GLUT-4).[128] Recently, an integral role for caveolae in IPC induced nitrosylation of mitochondrial proteins has been proposed.[129]

Intralipid, a commercially available lipid emulsification that has traditionally been used in parenteral nutrition, has been shown to reduce myocardial damage after a lethal hypoxic insult by inhibiting mitochondrial permeability transition pore and activating the cardio-protective GSK-3β pathway.[130, 131] This suggests a possible clinical treatment to decrease myocardial damage that may relate to lipid loading as a therapeutic endpoint. Further work needs to be undertaken to define the caveolin versus lipid enrichment component of this protective mechanism. It is possible that introduction of lipids to the membrane protects this vital structure from injury and maintains cellular integrity during stress, whether this effect is caveolin dependent or independent is not clear.

Caveolae/Caveolin in Anesthetic Effects

Volatile anesthetics were first used over 150 years ago, but their exact mechanism of action remains unknown. Volatile anesthetics are short chain halogenated alkanes and ethers that interact with cell membrane lipids and directly or indirectly interact with membrane bound proteins to produce a number of cellular effects. Thus, volatile anesthetics likely affect lipid microdomains, such as caveolae. Interestingly, emulsified volatile anesthetics were successfully used for anesthesia and enhanced preconditioning-induced cardiac protection, [132–135] suggesting that halogenated ethers dissolved in the lipid phase of micelles interact directly with caveolae.[136]

Many studies have shown that volatile anesthetics[4, 137] can exert cardiac protection similar to IPC and that anesthetic induced preconditioning (APC) is mediated by many of the same signal transduction elements involved in IPC.[138–153] APC is a biphasic event as well.[120, 121, 154–157] Within the first 1–2 hours, an acute phase is observed immediately after the preconditioning stimulus that involves pre-existing proteins, ion channel modifications, post-translational changes, and reactive oxygen species.[4, 150, 158] Approximately, 12–24 hours after the preconditioning stimulus a delayed phase is observed that involves *de novo* synthesis of proteins and translocation of molecules.[51, 155, 159] Additionally, subsequent work has shown the cardiac protective mechanisms include putative triggers (GPCRs, RTKs, G-proteins), mediators (protein kinases), and end-effectors (K_{ATP} channel and Glut4).[160–163]

APC-induced cardiac protection involves many different signaling mechanisms that have been shown to localize and interact with caveolin and caveolae including: GPCRs (opioid and adenosine receptors)[62, 64, 164, 165] and signaling mediators such as the Gα subunit of heterotrimeric G-proteins, Src kinases, PI3K, eNOS, PKC isoforms and ERK kinase.[35, 66–74] Furthermore, K_{ATP} channels, a possible end-effector involved in APC, are thought to be concentrated within caveolae.[112, 146]

Utilizing *in vitro* and *in vivo* experimental mouse models, we have shown that isoflurane increases the total number of caveolae at the sarcolemmal surface (Figure 2). We identified the importance of temporal signaling in Cav-1 activation involved in APC. Although, Src kinase is essential to phosphorylation of Cav-1, just as importantly we observed that inactivation of Src via C-terminal Src kinase (CSK) was necessary in order maintain acute APC (Figure 3).[86] Additionally, our laboratory reported that Cav-3 KO mice lacking

caveolae but expressing Cav-1 were resistant to acute APC. Pharmacological disruption of caveolae also prevented acute APC-induced cardiac protection, indicating that the presence of caveolae and the expression of Cav-3 were essential.[60] To further test the importance of Cav-3 in the heart, adult rat cardiac myocytes were isolated and infected with Cav-3 virus, which increased the number of surface caveolae and upregulated protective signaling pathways.[49] Likewise, cardiac specific overexpression of Cav-3 in mice resulted in innate cardiac protection from ischemia/reperfusion injury via down regulation of pro-apoptotic genes and upregulation of survival kinases.[49] Collectively, these data implicate a role for both Cav-1 and Cav-3 and the presence of caveolae in the acute phase of cardiac protection from ischemia-reperfusion injury.

More recently, we observed Cav-1 deficient mice still exhibited delayed cardiac protection from ischemia-reperfusion injury, whereas, Cav-3 KO mice completely lacked this ability.[51] Unlike acute APC, delayed APC has been suggested to require *de* novo gene and protein expression, which can ultimately lead to increased protein synthesis. Cav-1 KO mice still expressed Cav-3 and had caveolae. Pharmacological disruption of caveolae at the time of the protective stimulus had no effect on delayed APC, although, later disruption inhibited any protective effects. As a result, we hypothesized that Cav-3 was responsible for translocation of Glut4 to caveolae. We observed that both WT and Cav-1 KO mice were able to co-localize and translocate Cav-3 with the glucose transporter 4 (GLUT4) to caveolae following delayed APC stimulation, indicating that delayed cardioprotective effects are dependent on caveolae, Cav-3 and GLUT4 translocation (Figure 3).[51] A recent study looking at human Cav-3 has identified direct interaction sites with ryanodine receptors found on sarcoplasmic reticulum,[56] whereas our laboratory has recently identified caveolae directly interacting with mitochondria[77] suggesting an integral role for caveolins in cellular organelle regulation.

Anesthetic Pulmonary Effects

Plasma albumin is transported across the endothelium by transcytosis, a process regulated by the trafficking of vesicles.[166–168] The binding of albumin to the 60-kDa albumin-binding protein, gp60, in endothelial cell surface activates albumin transport *via* caveolae.[169–171] Additionally, MβCD, a cholesterol-binding agent that disrupts caveolae, inhibited transcellular albumin transport, suggesting that caveolae are responsible for transcytosis. Studies in Cav-1 KO mice suggest that the absence of caveolae can inhibit albumin uptake.[172]

Hu *et al*.[173] reported in an *ex vivo* rat lung that isoflurane, not sevoflurane, increased pulmonary endothelial albumin permeability. Furthermore, cultured endothelial cells, when exposed to high dose isoflurane resulted in a fourfold increase in fluorescent ^{125}I-albumin uptake in rat lung microvascular endothelial cells *via* Src activation as well as phosphorylation of Cav-1. These data suggest that higher doses of isoflurane may cause pulmonary edema as a result of increased albumin permeability secondary to increased caveolin levels.

Questions for the Future

Caveolae and caveolins serve complex roles in cell structure and biology. Caveolae and caveolins are vital to cellular signaling and function via modulation of temporal and spatial signaling components. Several studies have now identified a critical role for caveolae and caveolins in cardiac protection against I/R injury and heart failure. Both caveolae and caveolins serve integral roles in IPC, APC, and cardiac remodeling. However, the question remains whether it is the lipid rich caveolar environment or caveolins themselves that are critical for protection. Unfortunately, isolating caveolins from caveolae or other lipid rich microenvironments is difficult, though more focused work in knockout mice with lipid directed therapies may be a means to address such questions. Furthermore, it is not clear how caveolins are regulated. Recent reports have shown that caveolins can enhance mitochondrial function and that cellular caveolae interact directly with mitochondria.[77, 174] This suggests that caveolins may not only be structural proteins but active regulators of cellular signaling between the cell and its resident organelles. Future investigations will be necessary to identify how caveolins migrate from the cell membrane to the mitochondria and also whether similar mechanisms are involved in APC.

Caveolins are relatively small proteins yet seemingly can target organelles, coordinate cellular function and modulate signaling, suggesting a much more complex cellular distribution pattern than originally defined. Exactly how caveolins can perform these varied functions that are not classically explained by their plasma membrane enrichment in caveolae is unknown. Perhaps, caveolins undergo post-translational modifications such as phosphorylation,[175, 176] glycosylation,[177] or sumoylation,[178] or perhaps certain interactions with other resident proteins alter protein-protein interactions and targeting.

Recent studies have shown that neurons express all three caveolins[179, 180] but lack structural caveolae.[181, 182] These studies suggest that caveolins can still be functional regardless of the caveolar structure, perhaps by serving as scaffolds for signaling complexes involved in neuronal transmission and plasticity. Recent work revealed a key relationship between N-Methyl-D-aspartate (NMDA) receptor signaling and Cav-1 in primary neurons.[87] Interestingly, NMDA receptors have been known targets for anesthesia. Furthermore, Cav-1 has been implicated in enhancing arborization[183] or primary neurons and loss of caveolin-1 presents with an Alzheimer's like condition[184]. These data together, suggest that caveolins are vital to neuronal proliferation and signaling. Defining a role for caveolin in terminally differentiated cells such as cardiac myocytes and neurons may have larger implication to adaptation from stressors such as diabetes, aging, neurodegeneration, and other cardiovascular disorders.

Although caveolin expression in cardiac myocytes is protective, it is important to note that oncogenic cells also express caveolins. During the early phase of tumor development, Cav-1 can act as a tumor suppressor gene; however, Cav-1 has been shown to be up-regulated in numerous multi-drug resistant and metastatic cell lines as well as in human cancer cell types.[185–187] Recently, we have shown that caveolin-1 expression can prevent chemotherapy-induced apoptosis in the presence of volatile anesthetics.[188] These data suggest that the same mechanisms which protect the heart from a lethal ischemic stress, may also protect

oncologic cells against traditional chemotherapeutic strategies, which increase cell death. Furthermore, these data suggest that the use of volatile anesthetics prior to chemotherapies (such as during tumor resection) may actually be detrimental to overall outcome. In the future, perhaps targeting caveolins will be a possible therapy or adjuvant for decreasing the morbidity and mortality of many of these cancers.

Within the past decade, many new scientific discoveries have been made regarding caveolae and caveolins especially within cardiac protection. We now know that caveolins are not merely structural proteins but key components in pro-survival and many other cellular regulatory pathways. Given that caveolins have been shown to greatly enhance resistance to ischemic injury and cardiac remodeling, caveolins maybe an ideal target for future therapeutic agents though validation studies in large animal models and humans need to be performed.

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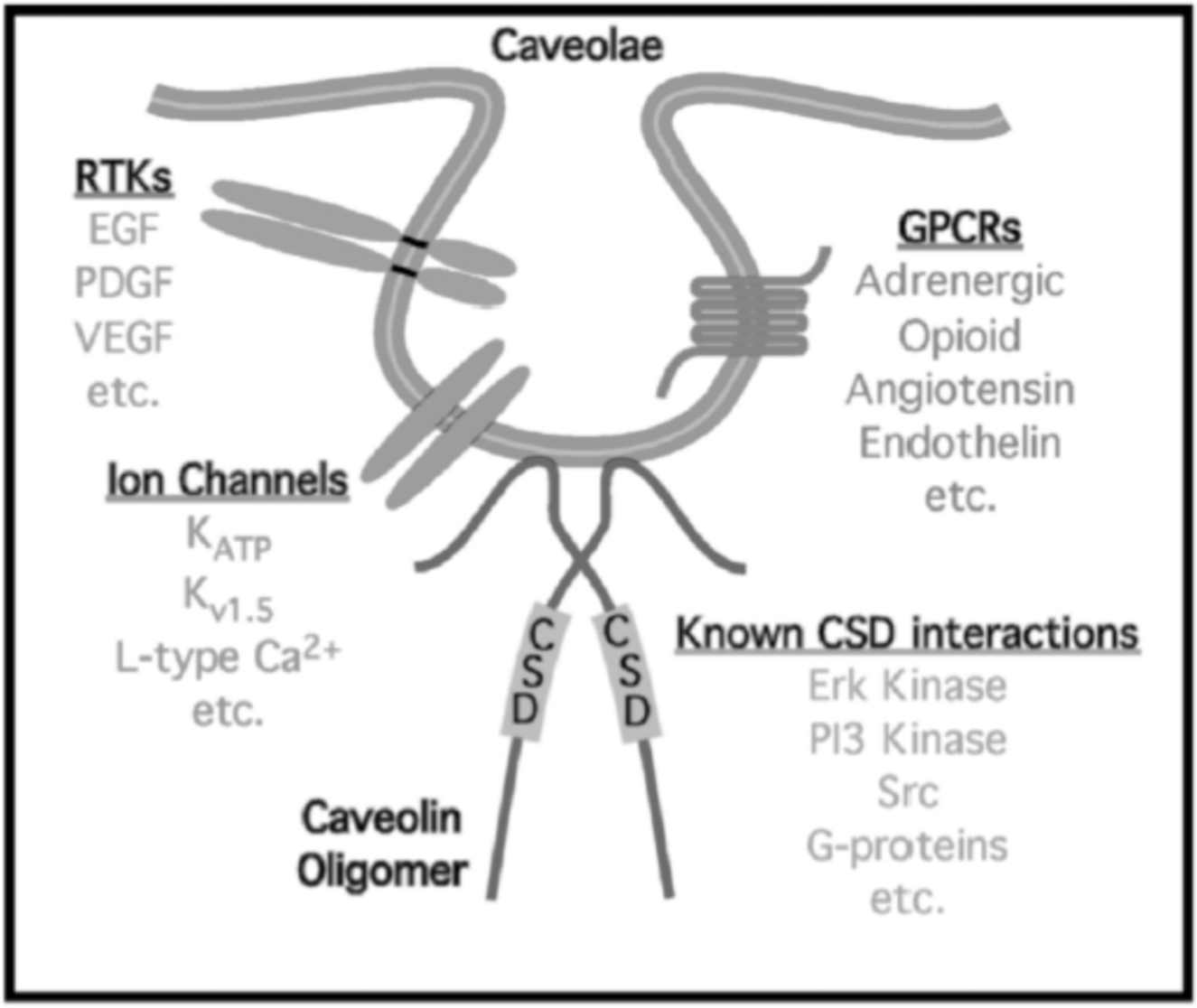

Figure 1. Caveolae are signaling epicenters

Caveolae are known to concentrate various signaling receptors (receptor tyrosine kinases, RTK; G-protein coupled receptors, GPCRs; caveolin scaffolding domains, CSD) as well as caveolins which can interact with many protein kinase.

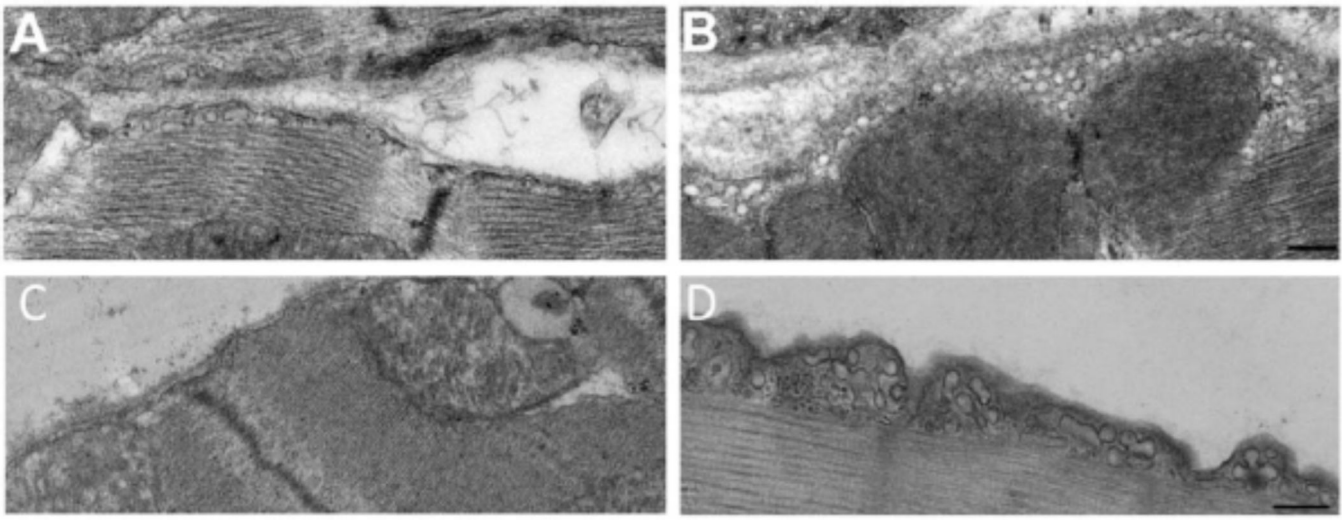

Figure 2. Electron microscopy of caveolae

A) Untreated cardiac myocyte; **B)** Caveolin-3 overexpressing cardiac myocyte have an abundance of caveolae; **C)** Caveolin-3.knockout cardiac myocyte lack caveolae; **D)** Isoflurane induces caveolae formation in cardiac myocytes; scale bar 200nm

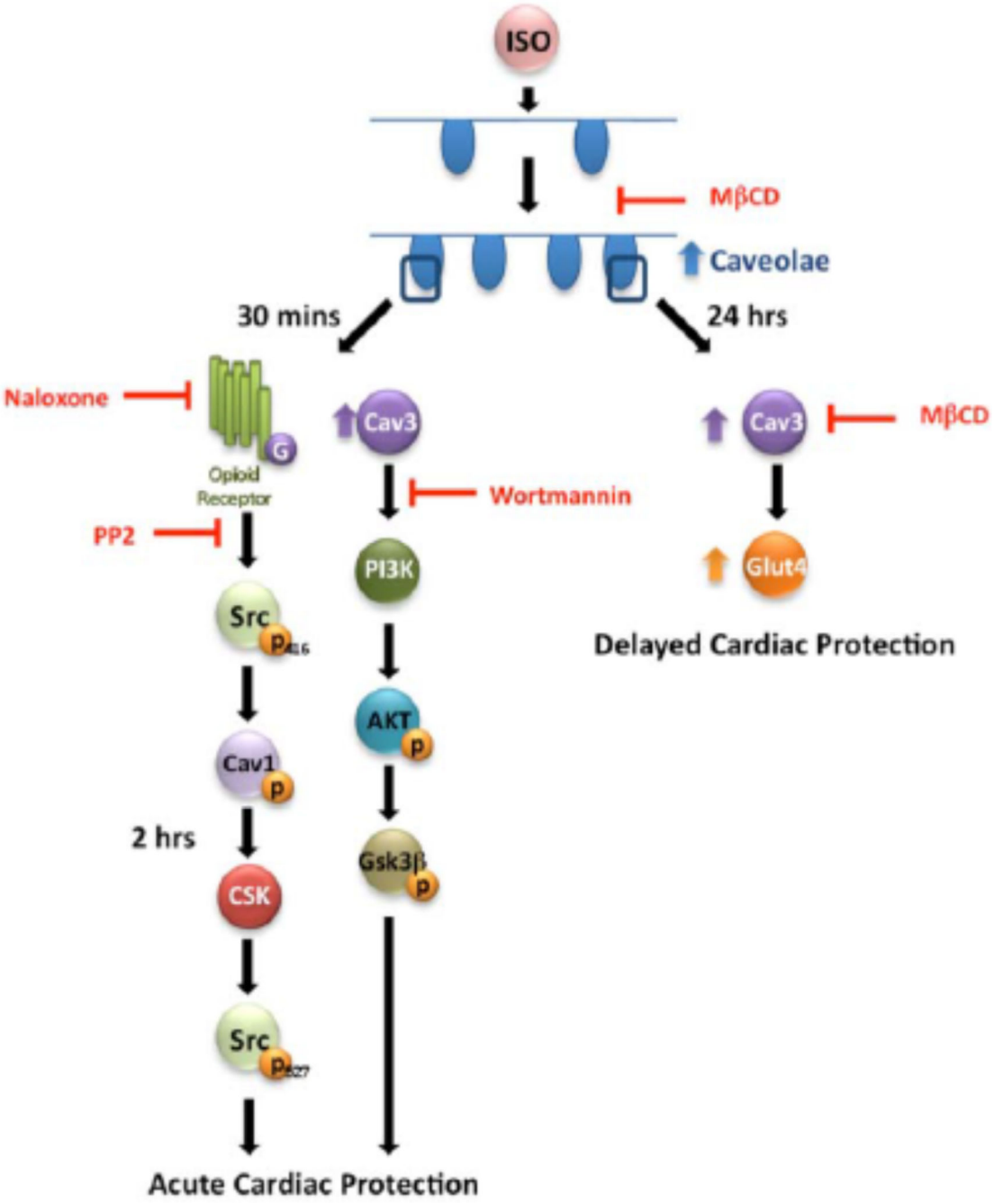

Figure 3. The role of caveolae and caveolins in anesthetic induced cardiac protection

Isoflurane increases caveolae formation at the cell surface Acute preconditioning requires both caveolin-1 and -3 and activates both Src kinase and PI3K/AKT/GSK pathway, whereas delayed cardiac protection increases caveolin-3 and increases GLUT 4 expression.