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THE INOSITOL TRISPHOSPHATE/CALCIUM SIGNALING PATHWAY IN HEALTH AND DISEASE

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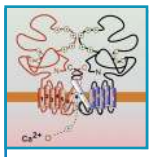

Berridge, MJ. The Inositol Trisphosphate/Calcium Signaling Pathway in Health and Disease. *Physiol Rev* 96: 1261–1296, 2016. Published August 10, 2016; doi:10.1152/physrev.00006.2016.—Many cellular functions are regulated by calcium (Ca^{2+}) signals that are generated by different signaling pathways. One of these is the inositol 1,4,5-trisphosphate/calcium ($InsP_3/Ca^{2+}$) signaling pathway that operates through either primary or modulatory mechanisms. In its primary role, it generates the Ca^{2+} that acts directly to control processes such as metabolism, secretion, fertilization, proliferation, and smooth muscle contraction. Its modulatory role occurs in excitable cells where it modulates the primary Ca^{2+} signal generated by the entry of Ca^{2+} through voltage-operated channels that releases Ca^{2+} from ryanodine receptors (RYRs) on the internal stores. In carrying out this modulatory role, the $InsP_3/Ca^{2+}$ signaling pathway induces subtle changes in the generation and function of the voltage-dependent primary Ca^{2+} signal. Changes in the nature of both the primary and modulatory roles of $InsP_3/Ca^{2+}$ signaling are a contributory factor responsible for the onset of a large number human diseases.

I. INTRODUCTION

The inositol 1,4,5-trisphosphate/calcium ($InsP_3/Ca^{2+}$) signaling pathway, which controls many different cellular processes, operates through either a primary or a modulatory mode **(FIGURE 1)**. Its primary role is evident in nonexcitable cells where it generates the Ca^{2+} signals to control processes as diverse as metabolism, secretion, fertilization, proliferation, and smooth muscle contraction (34, 38, 39, 249). In excitable cells, the primary Ca^{2+} signal depends on the entry of Ca^{2+} through voltage-operated channels, which can be enhanced by the release of Ca^{2+} by ryanodine receptors (RYRs) on the internal stores. This primary Ca^{2+} pathway regulates processes such as contraction in muscle cells, memory formation in neurons, and insulin secretion from beta cells. In these cases, the $InsP_3/Ca^{2+}$ signaling pathway has a modulatory role in that it can induce subtle changes in the generation and function of this primary Ca^{2+} signal. In this review, I describe how this $InsP_3/Ca^{2+}$ signaling pathway plays a role in multiple cellular processes and how subtle changes in the nature of both its primary and modulatory roles contribute to the onset of a large number human diseases such as Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), asthma, atrial arrhythmias, autism spectrum disorder (ASD), bipolar disorder, cancer, congestive heart failure (CHF), diabetes, Duchenne muscular dystrophy (DMD), epilepsy, Huntington disease (HD), hypertension, liver cholestasis, nephrolithiasis, osteoarthritis, pancreatitis, rheumatoid arthritis, schizophrenia, Sjögren's syndrome (SS), and spinocerebellar ataxias (SCAs).

II. $InsP_3$ FORMATION, ACTION, AND REGULATION

A. Formation of $InsP_3$

External stimuli, such as neurotransmitters, hormones, and growth factors, stimulate the formation of $InsP_3$ by activating either the G protein-coupled receptors (GPCRs) or the protein tyrosine kinase-linked receptors (PTKRs) that are coupled to different phospholipase C (PLC) isoforms **(FIGURE 2)**. The GPCRs are coupled to PLCβ isoforms, whereas the RTKs are linked to the PLCγ isoforms (79). The activated PLC hydrolyzes the precursor lipid phosphatidylinositol 4,5-bisphosphate ($PtdIns4,5P_2$) to form both diacylglycerol (DAG) and $InsP_3$. The $InsP_3$ functions by binding to the $InsP_3$ receptors ($InsP_3Rs$) to release Ca^{2+} from the endoplasmic reticulum (ER).

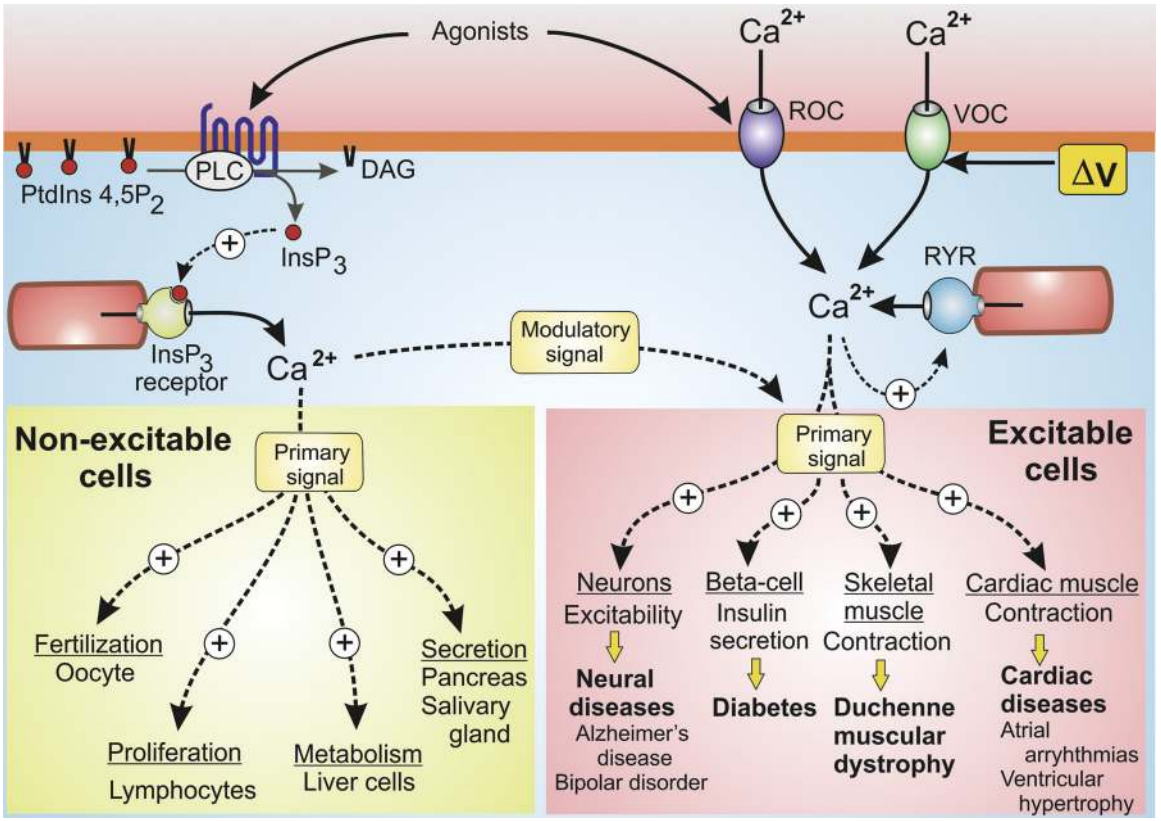

FIGURE 1. In response to agonists, activated receptors stimulate phospholipase C (PLC) that hydrolyzes phosphatidylinositol 4,5-bisphosphate (PtdIns4,5P_2) to form diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (InsP_3). The InsP_3 diffuses into the cell where it interacts with the InsP_3 receptor to release Ca^{2+}, which acts as a primary signal to activate processes such as fertilization, proliferation, metabolism, and secretion. In excitable cells, the primary Ca^{2+} signal is generated by receptor-operated channels (ROCs) or voltage-operated channels (VOCS) that promote the entry of external Ca^{2+}. This primary signal can be augmented by Ca^{2+} stimulating ryanodine receptors (RYRs) to release Ca^{2+} from internal stores. The InsP_3/Ca^{2+} signaling pathway can modulate this primary signal that functions to control processes such as neuronal excitability, beta-cell insulin secretion, and contraction of skeletal and cardiac cells.

B. InsP_3 Metabolism

The Ca^{2+}-mobilizing function of InsP_3 is terminated through its metabolism by either an InsP_3 3-kinase or an inositol polyphosphate 5-phosphatase **(FIGURE 2)** (80, 168). This inositol phosphate metabolism generates the inositol that is necessary to synthesize the phosphatidylinositol (PtdIns) that is required to maintain the signaling pathway. It also functions to generate a number of new inositol phosphates that operate in the inositol polyphosphate signaling pathways. The Ins1,4,5P_3 is either phosphorylated to Ins1,3,4,5P_4 by InsP_3 3-kinase or it is dephosphorylated by type I inositol polyphosphate 5-phosphatase to release Ins1,4P_2. The two products of these pathways are then sequentially dephosphorylated by a number of inositol phosphatases to form free inositol. A key component of this metabolic pathway is the inositol monophosphatase (IMPase) that hydrolyzes InsP_1 to free inositol that is one of the precursors used for the synthesis of PtdIns on the ER. The PtdIns is then transported to the plasma membrane where it functions as the precursor for the formation of PtdIns4,5P_2. A loss of function mutation in the *IMPA1* gene, which encodes the IMPase, results in severe intellectual disability (112). Lithium (Li^+) inhibits the IMPase resulting in a decline in the supply of inositol. This reduction of inositol by Li^+, which is the basis of the inositol depletion hypothesis (46, 48), may explain its action in controlling various neurodegenerative diseases such as bipolar disorder (BPD), Alzheimer's disease (AD), and HD. Li^+ can also delay the progression of ALS (116). The inositol depletion hypothesis thus provides further evidence that these diseases may be caused by an excessive elevation of the neuronal phosphoinositide signaling pathway as described later. The fact that Li^+ can improve non-rapid-eye-movement (NREM) sleep (122, 281) also supports the possibility that the InsP_3/Ca^{2+} signaling pathway is an important component of the tonic excitatory drive that regulates brain rhythms as described later (42).

Mutations in the *OCRL1* gene, which encodes inositol polyphosphate-5-phosphatase that converts inositol 1,4,5-trisphosphate to inositol 1,4-bisphosphate and inositol

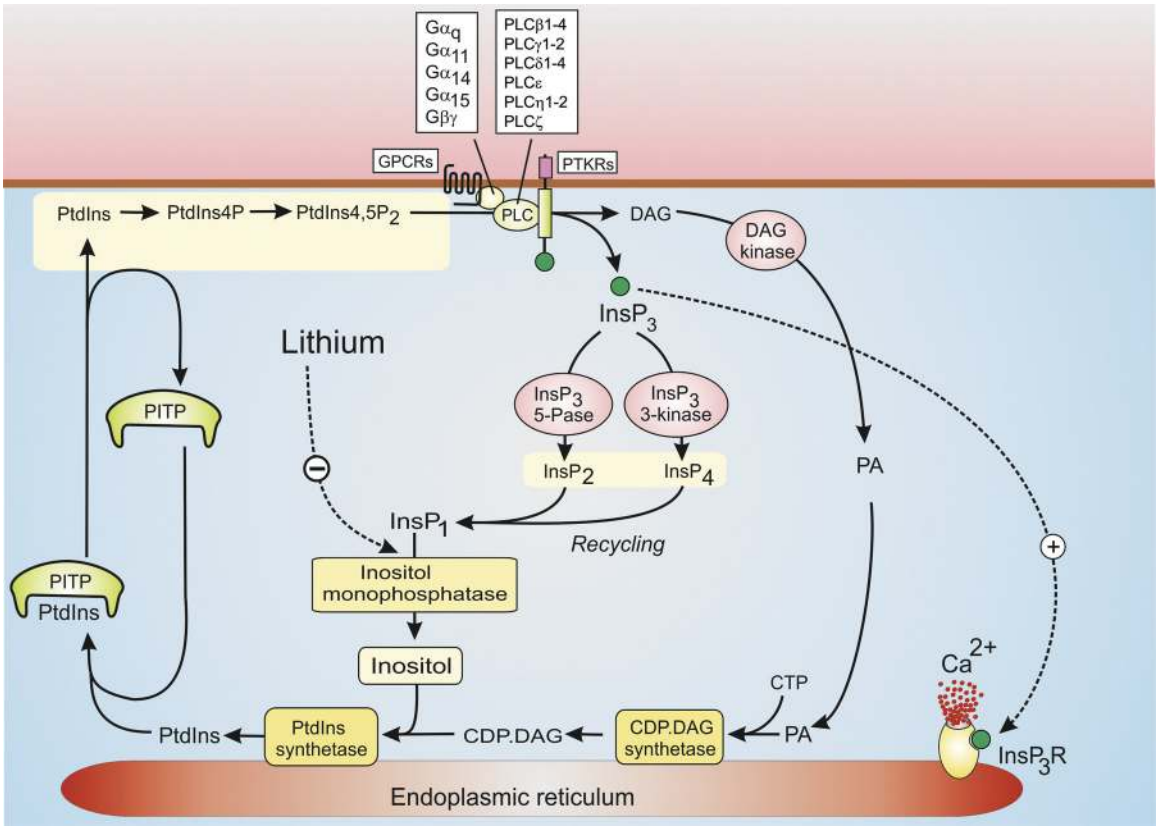

FIGURE 2. The cell-surface receptors responsible for $InsP_3$ formation belong to two main classes, the G protein-coupled receptors (GPCRs) and the protein tyrosine kinase-linked receptors (PTKRs) that are coupled to different phospholipase C (PLC) isoforms. The the GPCRs use the PLCβ isoforms, whereas the receptor tyrosine kinases (RTKs) are coupled to the PLC-γ isoforms. During the transduction process, the precursor lipid $PtdIns4,5P_2$ is hydrolyzed by PLC to produce both $InsP_3$ and diacylglycerol (DAG). The $InsP_3$ released from the membrane diffuses into the cytosol where it engages the $InsP_3$ receptors ($InsP_3Rs$) to release Ca^{2+} from the endoplasmic reticulum. The Ca^{2+}-mobilizing function of $InsP_3$ is terminated through its metabolism by either $InsP_3$ 3-kinase or $InsP_3$ 5-phosphatase. The resulting $InsP_2$ and $InsP_4$ enter an inositol phosphate metabolic pathway and are recycled back to free inositol. The DAG is recycled back to the precursor CDP-DAG, which then combines with inositol to reform the phosphatidylinositol (PtdIns) that is returned to the plasma membrane to be phosphorylated to the $PtdIns4,5P_2$ precursor to maintain the $InsP_3$ signaling pathway. A key component of this metabolic pathway is the inositol monophosphatase (IMPase) that hydrolyzes $InsP_1$ to free inositol. This IMPase is inhibited by lithium (Li^+), which thus acts to reduce the supply of inositol resulting in a decline in the activity of the $InsP_3/Ca^{2+}$ signaling pathway.

1,3,4,5-tetrakisphosphate to inositol 1,3,4-trisphosphate, causes Oculocerebrorenal syndrome of Lowe (OCRL) that is an *X*-linked disorder characterized by congenital cataracts and mental retardation (221).

C. $InsP_3R$ Activation by $InsP_3$ and Ca^{2+}

The primary mode of action of $InsP_3$ is to bind to $InsP_3Rs$ to release Ca^{2+} from the ER (106, 119, 229, 248, 249, 370, 371, 387). The $InsP_3R$ consists of four subunits that form a tetrameric channel that is embedded in the ER and in the nuclear envelope (NE) **(FIGURE 3)** (370). The $InsP_3Rs$ consist of three isoforms: $InsP_3R1$, $InsP_3R2$, and $InsP_3R3$ that have similar primary structures, but different physiological properties. Cells exploit these different properties to create Ca^{2+} signals with different spatial and temporal characteristics to control many different cellular functions. The structure of individual subunits consists of three main domains (370, 371). The receptor is embedded in the ER by six transmembrane domains (TM), and there is a pore (P) loop that connects TM5 to TM6. The loops that extend into the lumen of the ER are glycosylated. An $InsP_3R$-binding domain is located at the end of the long NH_2-terminal cytoplasmic region and is connected to TM1 by the modulatory domain. The conformational change induced by the binding of $InsP_3$ and Ca^{2+} is transmitted down to the transmembrane region to open the pore. Many regulators of $InsP_3Rs$ act on the modulatory domain to control the release of Ca^{2+} **(FIGURE 4)**.

The Ca^{2+}-mobilizing second messenger $InsP_3$ and Ca^{2+} are the primary regulators of the $InsP_3R$ (119, 229, 387). Acti-

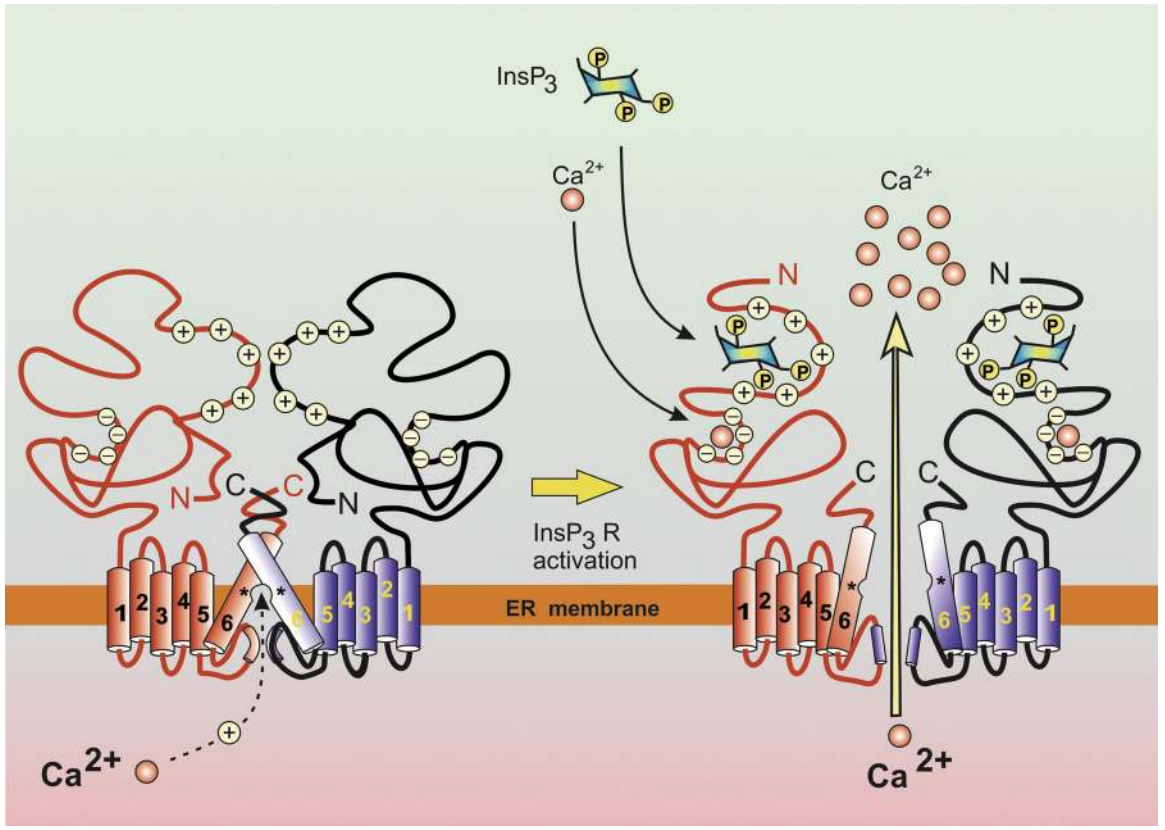

FIGURE 3. The $InsP_3R$ consists of four subunits, two of which are illustrated here. There are six transmembrane domains, with the pore loop located between TM5 and TM6. There is a long NH_2-terminal region that extends into the cytoplasm. The $InsP_3$ and Ca^{2+} bind to sites near the NH_2-terminal region and induce a conformation change that is transmitted down to the transmembrane region to open the pore to allow Ca^{2+} to enter the cytoplasm. This drawing is based on information contained in Taylor et al. (370).

vation of release begins when $InsP_3$ binds to the $InsP_3$-binding domain. Before the channel opens, $InsP_3$ has to bind to each of the four subunits (6). Once $InsP_3$ has occupied all four monomers, it induces a conformational change, which sensitizes the Ca^{2+}-binding site. When Ca^{2+} binds to this site, the channel opens and Ca^{2+} is released into the cytoplasm **(FIGURE 3)**. The action of Ca^{2+} is bimodal in that it stimulates release at low levels, but when Ca^{2+} rises above 300 nM, it becomes inhibitory. This dual control of the $InsP_3R$ by both $InsP_3$ and Ca^{2+} is central to its multiple functions in cell signaling.

D. $InsP_3$-Induced Ca^{2+} Oscillations

A characteristic feature of the $InsP_3$ signaling pathway is that it usually acts to release Ca^{2+} as brief transients. If signaling has to occur over a longer period, such spikes are repeated to give oscillations (33, 37, 111). Oscillations have been described in multiple cell types such as the insect salivary gland (311), hepatocytes (319, 403), osteoclasts (367), astrocytes (95), renal epithelial cells (2), mesoepithelial cells (293), pancreatic acinar cells (124, 296), oocytes (72, 84), and endothelial cells (258). A characteristic feature of these oscillations is that their frequency depends on the level of stimulus intensity (36, 47). Many functions such as salivary gland secretion, liver metabolism, smooth muscle contractility, and differential gene transcription, especially in developing systems, are controlled by such frequency coding. Gene expression is initiated more effectively using Ca^{2+} spikes rather than the same average Ca^{2+} concentration maintained at a steady level (209). The transcription factor NFκB is activated by low frequency spikes, whereas NF-AT activation requires higher frequencies (99). Changes in Ca^{2+} oscillation frequency can also regulate the activity of the protein kinase CaM kinase II (91).

Just how these oscillations are generated is still a matter of considerable debate. In some of the earliest models, it was suggested that the oscillator was based on a periodic sensitization of the $InsP_3R$ brought about by recharging of the intracellular store through the entry of external Ca^{2+} (37). In some cells, such entry is not necessary because much of the Ca^{2+} released during each transient is taken back into the ER. More recent studies have indicated that the oscillatory mechanism is more complicated as there are indications that the level of $InsP_3$ can oscillate together with the Ca^{2+} (301). The current concept is that oscillations may

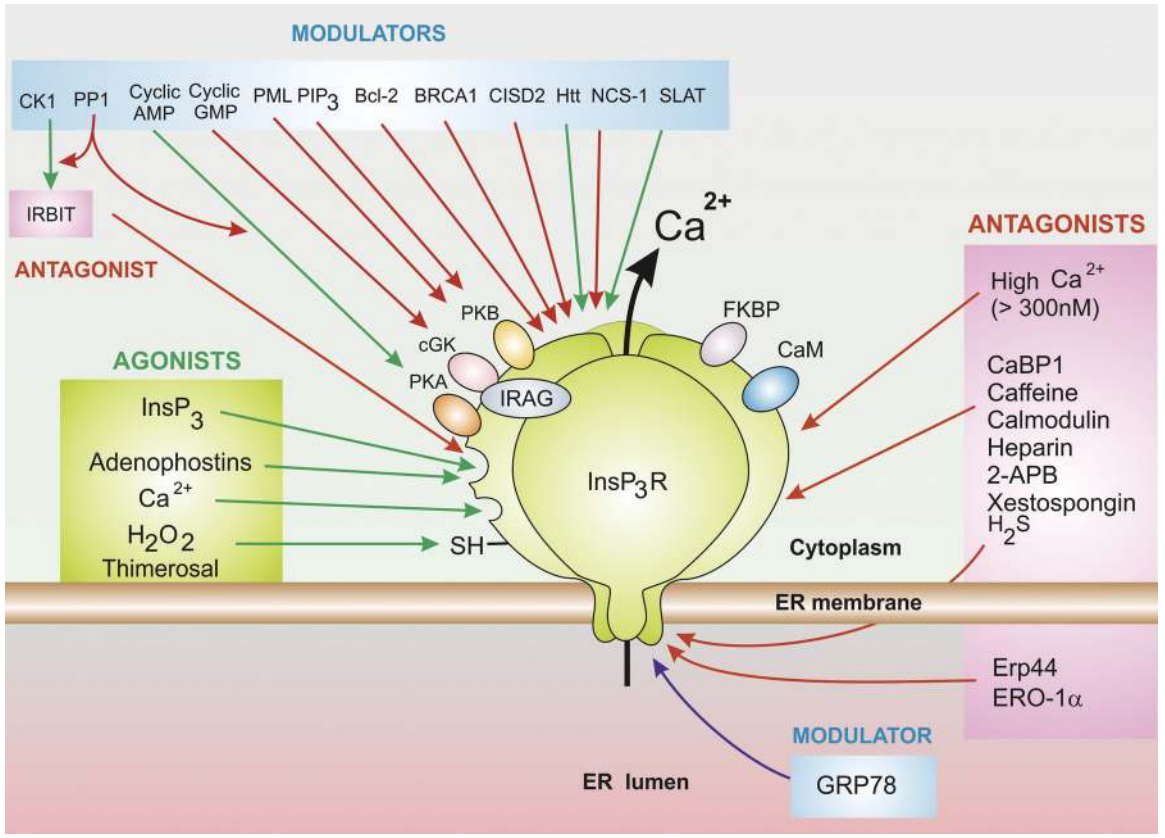

FIGURE 4. The $InsP_3R$ functions as a signaling hub in that it can be regulated by a large number of factors such as agonists, antagonists, and modulators. The primary agonists are Ca^{2+} and $InsP_3$. Adenophostin mimics the action of $InsP_3$. The receptor is also sensitive to reactive oxygen species (ROS) such as hydrogen peroxide (H_2O_2), and this action can be mimicked by thimerosal. A number of modulators can influence activity either positively (green arrows) or negatively (red arrows). Channel activity is modulated by phosphorylation through various signaling pathways using messengers such as cAMP, cGMP, and PtdIns3,4,5P_3 (PIP_3). Some of these phosphorylations are reversed by protein phosphatase 1 (PP1). High levels of Ca^{2+} inhibit the receptor. There also are a range of pharmacological agents that have been used to inhibit release of Ca^{2+} by the $InsP_3R$.

be driven by complex feedback interactions operating between $InsP_3$ and Ca^{2+} (129, 144, 301, 421).

E. $InsP_3R$ Regulation

A large number of stimulators and inhibitors function to regulate $InsP_3R$ activity (119, 170, 249, 292, 305, 387) **(FIGURE 4)**. Such protein-protein interactions indicate that the $InsP_3/Ca^{2+}$ signaling pathway is integrated with many other signaling pathways to control a number of different cellular processes (249). Proteins that have EF-hand Ca^{2+}-binding motifs, such as calmodulin, NCS-1, and Ca^{2+}-binding protein 1 (CaBP1), can regulate the activity of the $InsP_3Rs$. In neurons, the CaBP1 acts to inhibit the $InsP_3Rs$ by stabilizing the closed state of the channel in a Ca^{2+}-dependent manner (170, 211). Caffeine is an important inhibitor of Ca^{2+} release by the $InsP_3Rs$ (54, 164, 291, 322). Caffeine inhibits both the type 1 ($InsP_3R1$) (322) and type 3 ($InsP_3R3$) (180) release channels. Such inhibition of $InsP_3$-induced Ca^{2+} release may explain the observation that caffeine reduces the onset of AD (18, 287,361) and can also reduce the symptoms of acute pancreatitis (164).

Another group of proteins that interact with the $InsP_3Rs$ are some of the protooncogenes and tumor suppressors such as Bcl-2, BRCA1, PTEN, and PML. In general, the protooncogenes reduce $InsP_3R$ activity, whereas tumor suppressors tend to enhance $InsP_3R$ function resulting in apoptotic cell death. For example, the breast cancer 1 (BRCA1) protein binds to the $InsP_3R$ to enhance Ca^{2+} release that then induces apoptosis (149). Conversely, Bcl-2 acts to inhibit the $InsP_3R$ to reduce Ca^{2+} release (73, 318) with important implications for human diseases such as AD, BPD, cancer and HD (98, 140). Another important regulator that has implications for neural diseases is carbonic anhydrase-8 (Car8), which is an allosteric inhibitor of $InsP_3R1$ (156, 157, 425). Alterations in this regulation of the $InsP_3/Ca^{2+}$ signaling pathway by Car8 has been implicated in chronic inflammatory pain (425).

The activity of the $InsP_3Rs$ is regulated by a cycle of phosphorylation and dephosphorylation operated by a number of protein kinases and phosphatases (383, 418). For example, the cAMP-dependent protein kinase (PKA) phosphorylates $InsP_3R$ resulting in an increase in Ca^{2+} release (96). Phosphorylation events are also responsible for regulating the activity of IRBIT ($InsP_3R$-binding protein released with $InsP_3$) that acts to control Ca^{2+} release by the $InsP_3Rs$ (14, 15, 249). Once IRBIT is phosphorylated, it binds to the $InsP_3R$ to prevent the binding of $InsP_3$, thereby reducing the release of Ca^{2+}.

The redox state of the cell is also an important regulator of $InsP_3Rs$ (24, 55, 62, 253). In normal cells the cytoplasm is highly reduced, which is critical for normal cell function and survival. Any shift from a reduced to an oxidized state leads to oxidative stress and dysfunction of multiple cellular processes. Superoxide ($O_2^{\cdot -}$), hydrogen peroxide (H_2O_2), and peroxynitrite ($ONOO^-$) are typical reactive oxygen species (ROS) that can oxidize the $InsP_3R$ to markedly increase its sensitivity. Such dysregulation of the $InsP_3/Ca^{2+}$ signaling pathway plays a role in both aging and in many of the diseases linked to vitamin D deficiency (44, 45).

The $InsP_3/Ca^{2+}$ signaling pathway is also regulated by varying the cellular level of the $InsP_3Rs$, which depends on the balance between the synthesis of these receptors through transcription and expression and its removal by the endoplasmic reticulum-associated degradation (ERAD) pathway (see below). A number of mechanisms, many of which act through Ca^{2+}, regulate $InsP_3R$ transcription (132, 138, 256, 257). These studies reveal that L-type voltage-gated channels, NMDARs, nicotinic acetylcholine receptors (nAChR), and D1 dopamine receptors all act by increasing intracellular levels of Ca^{2+} responsible for triggering expression of $InsP_3Rs$. Transcription of $InsP_3Rs$ is also regulated in a Ca^{2+}-independent manner by factors such as tumor necrosis factor-α (TNF-α) acting through the specificity protein 1 (SP-1) (289, 408). The nuclear factor, erythroid 2-Like 2 (NRF2) transcription factor acts to reduce transcription of the type 3 $InsP_3R$ ($InsP_3R3$) (397). Finally, various drugs such as psychostimulants, morphine, cocaine, methamphetamine, and nicotine increase the transcription of $InsP_3R1$, and this might be relevant to their addictive behavior (201, 202, 257).

The subsequent expression of the $InsP_3R$ mRNAs can be regulated by microRNAs (miRs), which function as post-transcriptional regulators. In cardiomyoctes, miR-133a acts to inhibit the expression of $InsP_3R2$ (100, 387). Down-regulation of miR-133a accounts for an increase in the level of the $InsP_3R2s$, and this is a major contributory factor for the onset of cardiac hypertrophy. The expression of $InsP_3R3$ in cholangiocytes, which function in bile secretion, is suppressed by miR-506 (13). As described later, this decline in $InsP_3R3$ expression is responsible for a number of cholestatic disorders such as bile duct obstruction, biliary atresia, and biliary cholangitis/cirrhosis.

These transcription and expression mechanisms responsible for the synthesis of $InsP_3Rs$ are balanced by a pathway that removes the functional receptors through the ERAD pathway (222, 405). This ERAD mechanism depends on the ubiquitin-proteasome pathway (UPP) that degrades the $InsP_3Rs$ while they are functioning in the ER. The $InsP_3Rs$ are polyubiquitinated and are then recognized and degraded by the proteasomes. This ubiquitination is carried out by RNF170, which is a RING domain-containing protein ligase that resides on the ER, where it recognizes and associates with activated $InsP_3Rs$ (222, 405). Mutations in RNF170, which has been linked to autosomal dominant cerebellar ataxia (ADCA), interfere with this ubiquitination process and result in a decline in Ca^{2+} signaling via the $InsP_3Rs$ and is likely to be the cause of ADCA (405).

F. $InsP_3/Ca^{2+}$ Signaling and Autophagy

A large number of metabolic signaling pathways contribute to the regulation of autophagy (126). One of the first indication that Ca^{2+} may play a role emerged from studies showing that autophagy could be induced by Ca^{2+} released from the ER (162). Subsequent studies revealed that the $InsP_3/Ca^{2+}$ signaling pathway plays a prominent role in regulating autophagy (69, 90, 147). The action of Ca^{2+} is complicated because it can both stimulate and inhibit autophagy. This contradictory action of Ca^{2+} may depend on either the concentration or the location of Ca^{2+} signals (90). Low local levels of Ca^{2+} may be inhibitory, whereas autophagy may be stimulated by higher global levels of Ca^{2+}. A constitutive Ca^{2+} release by the $InsP_3R$ may create a local elevation of Ca^{2+} within the narrow gap between the ER and the mitochondria where it activates mitochondrial energy metabolism to maintain the formation of ATP that then acts to prevent autophagy by reducing the activity of AMP-activated protein kinase (AMPK). This Ca^{2+} signaling operates within the ER/mitochondrial shuttle, which means that this highly localized Ca^{2+} signal is hidden away from the other cytosolic Ca^{2+}-sensitive processes.

Elevation in various pathological aggregates such as amyloid, tau, α-synucleins and mutant Huntington fragments, which contribute to neurodegenerative disease such as AD, Parkinson's disease, and HD, may accumulate because of a decline in autophagy. These diseases are also associated with abnormal elevations in the $InsP_3/Ca^{2+}$ signaling pathway that may act to reduce autophagy. Such a mechanism may explain the observation that Li^+ can induce autophagy in some of these diseases through inhibition of the IMPase **(FIGURE 2)** resulting in inositol depletion and a subsequent reduction in the $InsP_3$-induced flux of Ca^{2+} that acts to reduce autophagy (115, 262, 325, 326, 327).

III. $InsP_3/Ca^{2+}$ SIGNALING AND DISEASE

The $InsP_3/Ca^{2+}$ signaling pathway is a major component of the highly versatile and dynamic cellular Ca^{2+} signaling system that regulates many different cellular processes (49, 50, 118, 249). One of the striking features of $InsP_3/Ca^{2+}$ signaling is its role in the development of multiple human diseases **(TABLE 1)** (40, 52, 53, 118, 249). When considering this pathological role, it is important to consider how vitamin D deficiency may act to enhance the alterations in the $InsP_3/Ca^{2+}$ signaling pathway. Vitamin D may act by maintaining the phenotypic stability of both the Ca^{2+} and the redox signaling pathways (44, 45). During Vitamin D deficiency, an increase in the resting state of these pathways would greatly enhance the activity of the $InsP_3/Ca^{2+}$ signaling pathway. In the following sections, the role of $InsP_3/Ca^{2+}$ signaling in different cell types will be described to illustrate how alterations in this signaling pathway contributes to different disease states.

IV. CELL PROLIFERATION

One of the important signals responsible for inducing cell proliferation is an increase in Ca^{2+} (35, 300, 313). For example, histone-induced proliferation of cholangiocytes is driven by the $InsP_3/Ca^{2+}$ signaling pathway (120, 121) through a mechanism that can be suppressed by miR-506, which is known to act by reducing $InsP_3R$ expression (13). One of the actions of $InsP_3$ is to generate a nucleoplasmic Ca^{2+} signal that is responsible for activating proliferation (314). In liver regeneration, $InsP_3/Ca^{2+}$ signaling triggers hepatocyte proliferation to create the new liver cells to restore liver function (276). The following examples illustrate further how the $InsP_3/Ca^{2+}$ signaling pathway has a prominent role in generating the Ca^{2+} signals that drive cell proliferation and how alterations in this signaling pathway contribute to acute lymphoblastic leukemia, asthma, cancer, infertility, and severe combined immune deficiency (SCID).

A. Fertilization

Before sperm can fertilize the oocyte, they have to become hyperactive to enable them both to pass through the mucous layer within the oviduct and to penetrate the zona pellucida to react with the oocyte plasma membrane. This hyperactivity is driven by an increase in Ca^{2+} released by $InsP_3Rs$ located in the redundant nuclear envelope (RNE) that surrounds the sperm axoneme (158). This hyperactive state is triggered by vitamin D acting in a nongenomic mechanism to activate the formation of the $InsP_3$ responsible for the release of Ca^{2+} (60, 61).

At fertilization, the sperm fuses with the oocyte and injects phospholipase Cζ (PLCζ), which is unique to sperm, where it hydrolyzes $PtdIns4,5P_2$ to form $InsP_3$ that acts through the $InsP_3Rs$ to trigger the Ca^{2+} oscillations that activates the egg to begin its development (272, 362, 390). During each spontaneous oscillatory Ca^{2+} transient, which occurs approximately every few minutes, there is a rapid decline in the ER luminal Ca^{2+} concentration. The level of Ca^{2+} is gradually replenished through store-operated Ca^{2+} entry that depends on both STIM1 and Orai1. The buildup of Ca^{2+} within the lumen of the ER may be an important feature of the oscillatory mechanism in that it sensitizes the $InsP_3Rs$ resulting in the activation of the next transient. These sperm-induced Ca^{2+} transients induce chromosome separation and the cell proliferation that occurs during early development.

Mutations in PLCζ are responsible for some cases of male infertility (11, 272).

B. Lymphocyte Proliferation

Foreign substances are recognized by the sophisticated chemical surveillance system that is operated by the immune system. The thymus-derived cells (T cells) and the bone marrow-derived cells (B cells) are the main lymphocytes responsible for immune responses. T cells deal with intracellular pathogens (cell-mediated immunity). On the other hand, extracellular pathogens are dealt with by the B cells (humoral immunity). This role of the T and B cells is a good example of how cells are induced to proliferate in response to specific stimuli.

Activation of B cells is driven by the B-cell antigen receptor (BCR), which assembles a hetero-oligomeric complex made up of two Igα and Igβ signaling proteins that are associated with the antigen-binding immunoglobulin IgM receptor that consists of two heavy chains and two light chains. When antigen binds to the IgM, it activates Lyn that is a non-receptor tyrosine kinase that phosphorylates tyrosine residues located on the immunoreceptor tyrosine-based activation motifs (ITAMs) in the cytoplasmic regions of Igα and Igβ. The phosphorylated ITAMs recruit and activate various transducing components such as phospholipase Cγ2 (PLCγ2). Following activation of PLCγ2, $PtdIns4,5P_2$ is hydrolyzed to form $InsP_3$ and DAG that contribute to the activation of proliferation (155, 392). To activate proliferation, $InsP_3$ must generate a Ca^{2+} signal that lasts for a long period. This prolonged signal is achieved by activating both the release of internal Ca^{2+} and the entry of external Ca^{2+}. The first step is for $InsP_3$ to releases Ca^{2+} from the ER by binding to the $InsP_3Rs$. Once the ER is depleted, the stromal interaction molecule 1 (STIM1) activates Orai1 to induce the entry of external Ca^{2+} (20, 155). This gives rise to a prolonged Ca^{2+} signal, which is encoded in the form of repetitive Ca^{2+} oscillations (255), that activates NFAT resulting in B-cell activation characterized by proliferation and differentiation (19, 329).

Table 1. *Alterations in the activity of the $InsP_3/Ca^{2+}$ signaling pathway contributes to the onset of multiple human diseases*

Disease	Modification of the $InsP_3/Ca^{2+}$ Signaling Pathway	Reference Nos.
Alzheimer's disease (AD)	Enhanced $InsP_3/Ca^{2+}$ signaling in neurons activates memory loss	94, 108, 171, 360
Anhydrosis	Reduced $InsP_3/Ca^{2+}$ signaling in sweat glands	191
Amytrophic lateral sclerosis (ALS)	Enhanced $InsP_3/Ca^{2+}$ signaling in motor neurons	189, 366
Asthma	$InsP_3/Ca^{2+}$ signaling pathway drives excessive pulmonary smooth muscle cell contraction	56, 145, 294
Atrial arrhythmias	Enhanced $InsP_3/Ca^{2+}$ signaling leads to the development of atrial arrhythmias	159, 210, 227, 426
Autism spectrum disorder (ASD)	Decline of $InsP_3/Ca^{2+}$ signaling contributes to the onset of ASD	135, 225, 333
Biopolar disorder (BPD)	Excessive $InsP_3/Ca^{2+}$ signaling may drive the neuronal excitatory-inhibitory imbalance	103, 332
Cancer	Hyperactivity of the $InsP_3/Ca^{2+}$ signaling pathway contributes to the excessive Ca^{2+} signals that drive the onset and progression of cancer	76, 86, 396
Congestive heart failure	Nuclear $InsP_3/Ca^{2+}$ signaling drives ventricular cardiac hypertrophy	148, 154, 214, 218, 267, 406, 427
Diabetes	$InsP_3/Ca^{2+}$ signaling acts synergistically with glucose to control insulin release from pancreatic β-cells	25
Duchenne muscular dystrophy (DMD)	Enhanced $InsP_3/Ca^{2+}$ signaling contributes to skeletal muscle degeneration	23, 81, 212, 259
Epilepsy	An increase in the $InsP_3/Ca^{2+}$ signaling pathway contributes to the excitation-inhibition imbalance	93, 265, 286
Hypertension	Enhanced $InsP_3/Ca^{2+}$ signaling contributes to the increased smooth muscle tone	1, 4
Huntington's disease	Enhanced $InsP_3/Ca^{2+}$ signaling contributes to the selective loss of striatal neurons	29, 52, 53, 106, 118, 368
Infertility	Mutations in phospholipase Cζ (PLCζ) result in reduced $InsP_3$ and a decline in fertilization	11, 272
Kashin-Beck disease	Enhanced $InsP_3/Ca^{2+}$ signaling contributes to chondrocyte necrosis	59, 363, 423
Kawasaki disease	$InsP_3/Ca^{2+}$ signaling acts in T cells to contribute to the inflammatory response	200, 277, 416
Liver cholestasis	A decline in $InsP_3/Ca^{2+}$ signaling reduces bile secretion by cholangiocytes	8, 27, 342
Lymphoblastic leukemia	Alterations in the $InsP_3/Ca^{2+}$ signaling pathway drives enhanced proliferation	282
Nephroliasis	Increased $InsP_3/Ca^{2+}$ signaling contributes to the formation of kidney stones	177
Osteoarthritis	Enhanced $InsP_3/Ca^{2+}$ signaling contributes to cartilage destruction by the chondrocytes	304, 419
Pancreatitis	Enhanced $InsP_3/Ca^{2+}$ signaling contributes to pancreatic cell necrosis	134, 164, 279
Rheumatoid arthritis (RA)	Enhanced $InsP_3/Ca^{2+}$ signaling contributes to osteoclast proliferation and differentiation	408
Schizophrenia	A decline in $InsP_3/Ca^{2+}$ signaling in GABAergic inhibitory neurons	290
Sjogren's syndrome (SS)	A decline in $InsP_3/Ca^{2+}$ signaling causes the decrease in salivary gland fluid secretion	372
Spinocerebellar ataxias	Dysregulation of the $InsP_3/Ca^{2+}$ signaling pathway leads to degeneration of the Purkinje neurons	53, 66, 106, 335

See text for further details.

In T cells, proliferation and cytokine production depend on a sustained Ca^{2+} signal that results from the activation of the $InsP_3/Ca^{2+}$ signaling system in a manner similar to that just described for the B cells (109, 160, 275). The major histocompatibility complex II (MHCII), which detects the antigen, binds to the large T-cell receptor (TCR) complex that activates transducers to generate the signals to induce the transcriptional events that initiate DNA synthesis. A major pathway for lymphocyte activation depends on the stimulation of PLCγ1 that hydrolyzes PtdIns4,5P_2 to form $InsP_3$ to release Ca^{2+} from the internal store. During T-cell receptor (TCR) Ca^{2+} signaling, the SWAP-70-like adaptor of T cells (SLAT) protein binds to the $InsP_3$R1 through its EF-hand and PH domains and has an important role in generating the Ca^{2+} signal that drives T-cell proliferation (117). One of the actions of the anti-apoptotic protein Bcl-2 is to inhibit this release of Ca^{2+} by the $InsP_3$Rs (140, 318). One of the primary functions of this $InsP_3/Ca^{2+}$ signal is to initiate chromatin decondensation that induces the gene transcriptional cascade responsible for T-cell activation (207).

When the ER empties, the STIM1 protein activates the plasma membrane Orai1 channels responsible for the influx of external Ca^{2+} (109). This influx of Ca^{2+} acts to maintain the Ca^{2+} signal for a period of 2 h that is necessary to activate lymphocyte proliferation. This prolonged Ca^{2+} signal activates the transcription factor NFAT that enters the nucleus where it induces the genes responsible for triggering T-cell proliferation.

Alterations in this $InsP_3/Ca^{2+}$ signaling pathway result in acute lymphoblastic leukemia (282), whereas SCID is caused by mutations of the Orai1 channel (110).

C. Cancer

There is increasing evidence for a link between Ca^{2+} signaling and cancer (260, 303, 313). Alterations in the $InsP_3/Ca^{2+}$ signaling system is responsible for some of the aberrant Ca^{2+} signaling changes in cancer cells. For example, chromosome instability results in changes in phosphoinositide signaling pathways, some of which lead to elevated levels of $InsP_3$, have been described in glioblastoma multiform that is one of the commonest brain tumors (396). The proliferation and migration of human gastric adenocarcinoma cells is driven by the $InsP_3/Ca^{2+}$ and DAG/PKC signaling pathways operating in parallel with each other (86).

Mutations in the *PLCG1* and *PLCG2* genes that encode PLCγ1 and PLCγ2, respectively, have been linked to a number of cancers (196). The PLCγ1 mutations have been found in secondary angiosarcoma (30) and cutaneous T-cell lymphoma (CTCL) (386). Deletions in the *INPP5A* gene, which encodes the $InsP_3$ 5-phosphatase that metabolizes $InsP_3$ **(FIGURE 2)**, have been found in squamous cell carcinoma (SCC) (337) and brain tumors (205). Likewise, there is a decline in the expression of the 5-phosphatase in human leukemias (245). Chronic lymphocytic leukemia (CLL), which is driven by alterations in B-cell Ca^{2+} signaling (89), has been linked to mutations in PLCγ2 (404). Genetic polymorphisms of the *ITPKC* gene, which encodes the $InsP_3$ 3-kinase C protein that inactivates $InsP_3$ **(FIGURE 2)**, have been linked to an increased risk of developing cervical squamous cell carcinoma (413). Proliferation of cancerous pancreatic duct cells is driven by uridine triphosphate (UTP) that acts through the $InsP_3/Ca^{2+}$ signaling pathway (76). The high expression of $InsP_3$R2 has been considered to be a novel biomarker of acute myeloid leukemia (341). In many of these cases, there are indications that the mutations in the $InsP_3$ pathway result in the elevated Ca^{2+} signals that contribute to the control proliferation.

The $InsP_3$R, which releases Ca^{2+} from the ER, has been linked to processes that contribute to cancer (3, 150, 321, 364). The proliferation of breast cancer cells depends on $InsP_3$R3 channels (263). Dissemination of gastric cancer cells may depend on $InsP_3$R3-induced elevation of Ca^{2+} (321). Caffeine inhibition of $InsP_3$R3s was found to reduce the survival, migration, and invasion of glioblastoma cells (180). In colon cancers, higher expression levels of $InsP_3$R3s are associated with enhanced aggressiveness and poorer prognosis (343). Locomotion of human melanoma cells is enhanced by autocrine motility factor (AMF) that acts through the $InsP_3/Ca^{2+}$ signaling pathway (195). Many of the regulatory proteins that control the activity of these $InsP_3$Rs are protooncogenes and tumor suppressors such as Bcl-2, Beclin 1, BRCA1, MCL-1, PTEN, and PML **(FIGURE 4)** (3, 57, 140). In B cells, PKB/Akt2 can inhibit Ca^{2+} release by promoting the activity of Bcl-2, which is known to inhibit the $InsP_3$Rs (235).

In general, the protooncogenes reduce $InsP_3$R activity, whereas tumor suppressors tend to enhance $InsP_3$R function resulting in apoptotic cell death. For example, breast cancer 1 (BRCA1) binds to the $InsP_3$R to enhance Ca^{2+} release that then induces apoptosis (57, 149). Altering the activity of the $InsP_3$Rs may enable prostate cancer cells to resist the androgen deprivation treatment that normally acts to kill these cancer cells (64). Conversely, Bcl-2 acts to inhibit the $InsP_3$R to reduce Ca^{2+} release (73, 318) with important implications for human diseases such as cancer, BPD, AD, and HD (98, 140). For example, Bcl-2 interacts with the $InsP_3$Rs to reduce the release of Ca^{2+}, which prevents apoptosis and is responsible for the survival of cancer cells (140). In a similar way, oncogenic K-Ras can promote cancer cell survival by suppressing the $InsP_3$-mediated release of Ca^{2+} that drives apoptosis (297).

V. NEURONAL SIGNALING

The $InsP_3/Ca^{2+}$ signaling pathway contributes to both brain development and many of its functions such as axonal

growth (137), memory formation (166, 320), excitability, brain rhythms (42, 151, 358), and gene transcription (209). The neural circuits in the brain consist of excitatory and inhibitory neurons that interact with each other as part of the mechanisms responsible for generating brain rhythms. Changes in the role of $InsP_3/Ca^{2+}$ signaling in regulating these neuronal functions are responsible for many neurodegenerative diseases (40, 41, 52, 53, 118).

A. Brain Development

Development of the brain proceeds through a number of distinct phases such as proliferation, migration, and differentiation. First, the embryonic cells, which are set aside to form the brain, begin to proliferate rapidly to form a large population of neuronal precursors. In the next step, these neuronal progenitors begin to differentiate into the specific neuronal cell types that constitute fully functional neuronal circuits. PLCγ1, which generates the $InsP_3/Ca^{2+}$ signaling pathway, plays an important role in brain development (181). This pathway induces the Ca^{2+} oscillations that regulate both proliferation and differentiation (380, 398). As neurons develop, axons grow out to interact with other neurons and the $InsP_3$ signaling systems contributes to the mechanism that steers the growth cones towards their targets (378). During differentiation, neurons begin to express different neurotransmitters, which mark the emergence of either excitatory or inhibitory neurons. This specification seems to be determined by the generation of spontaneous Ca^{2+} transients. All the cells become active, and those with the highest oscillation frequency act as pacemakers that then recruit neighboring cells giving rise to a Ca^{2+} wave that creates oscillating hubs of cells.

Expression of excitatory transmitters such as acetylcholine (ACh) and glutamate occur in neurons that have low-frequency oscillations, whereas inhibitory transmitters such as glycine and γ-aminobutyric acid (GABA) are expressed in those neurons that display more frequent Ca^{2+} transients. Fully functional neuronal circuits depend on this emergence of the excitatory and inhibitory neurons that interact with each other to generate the rhythms that are essential for brain function (42). The normal function of the brain is critically dependent on the activity of these neurons being balanced. Such excitation-inhibition balance (E-I balance) is critical to maintain normal brain rhythms, and alterations in this balance have been implicated in a number of neural diseases as described below.

B. Brain Rhythms

Having contributed to the development of the brain, the $InsP_3/Ca^{2+}$ signaling pathway continues to control adult brain functions such as the regulation of brain rhythms and synaptic plasticity.

During the sleep/wake cycle, the brain has different neural rhythms **(FIGURE 5)**. During the awake state there are a number of brain rhythms such as the fast gamma (20-80 Hz), alpha (8–12 Hz), and theta (6–10 Hz) oscillations. During sleep, the rhythm frequency declines resulting in the delta (1–4 Hz) and slow oscillations (<1 Hz). The ascending arousal system is responsible for regulating the activity of these different oscillatory modes. This arousal system consists of a variety of neurons that project their axons throughout the brain where they release transmitters such as orexin, ACh, norepinephrine (NE), 5-hydroxytryptamine (5-HT), histamine, and dopamine (DA). These transmitters are released globally and are thus able to act simultaneously on both the excitatory and inhibitory neurons that form the functional neural circuits (42, 87, 283). These transmitters act through a number of pathways to induce the depolarization that constitutes the tonic excitatory drive that controls the different brain rhythms. Different signaling mechanisms are responsible for generating this tonic excitatory drive **(FIGURE 5)**. $PtdIns4,5P_2$ hydrolysis causes depolarization by closing the $K_V7.2/K_V7.3$ K^+ channels that depolarizes the membrane by switching off the M current. The $InsP_3$ that is released by the hydrolysis of $PtdIns4,5P_2$ also contributes to depolarization by releasing Ca^{2+} that activates the Ca^{2+}-activated nonselective cation (CAN) channel. The Cav1.2 L-type Ca^{2+} channel also contributes to the membrane depolarization in that it generates a Ca^{2+} signal that also activates the CAN channel. Neuronal excitability is also regulated by DA and NE that operate through the cAMP signaling pathway. Inactivation of the D2 receptors in the dorsolateral prefrontal cortex (DLPFC) is prevented by neuronal calcium sensor 1 (NCS-1). It is of interest, therefore, to find that the levels of NCS-1, which activates the $InsP_3R$, are markedly elevated in BPD (332).

Most of the neural circuits in the brain depend on interactions between excitatory and inhibitory neurons that are responsible for the oscillatory activity that characterizes these brain rhythms. In order for the system to operate normally, the response of each neuronal cell type to the tonic excitatory drive must be finely balanced. To achieve this balance, the synaptic inputs operating between the excitatory and inhibitory neurons must be equal. There are indications that alterations in this excitation-inhibition (E-I) balance may occur in various psychiatric diseases such as autism spectrum disorder (ASD), epilepsy, and schizophrenia (102, 234). There may also be a link between alterations in the tonic excitatory drive and BPD in that excessive excitation may be responsible for the manic phase, whereas depression may result from excessive inhibition as described below.

A decline in the activity of these arousal signaling pathways is responsible for sleep. The signaling pathways are not switched off completely as a low level of stimulation is responsible for maintaining the slow wave sleep rhythm

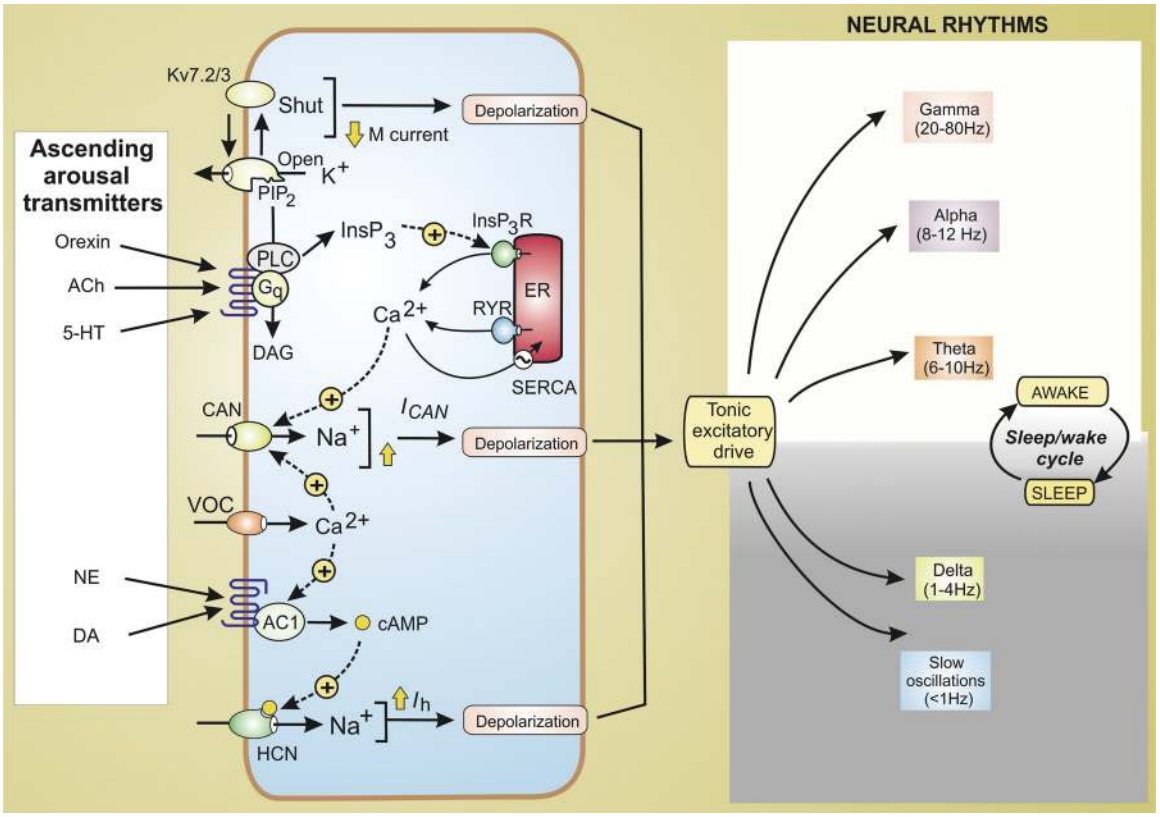

FIGURE 5. The ascending arousal system, which releases transmitters throughout the brain, activates a variety of signaling pathways to generate the tonic excitatory drive responsible for regulating the brain rhythms during the sleep/wake cycle. Orexin, acetylcholine (ACh), and 5-hydroxytryptamine (5-HT) stimulate the hydrolysis of PIP_2 resulting in closure of the K^+ channels that drives the M-current. The $InsP_3$ releases Ca^{2+} that activates the Ca^{2+}-activated nonselective cation (CAN) channels. The norepinephrine (NE) and dopamine (DA) generate cAMP that opens Na^+ channels. These three main pathways depolarize the membrane to produce the alterations in the tonic excitatory drive that regulates the brain rhythms.

(31). The $InsP_3/Ca^{2+}$ signaling pathway may contribute to the operation of the pacemaker mechanism that drives the slow waves that characterize NREM sleep. Such a possibility is consistent with the observation that Li^+, which acts by reducing the activity of the $InsP_3/Ca^{2+}$ signaling pathway (48), is capable of converting rapid eye movement (REM) sleep to NREM sleep (122, 281). Conversely, the accumulation of amyloid-β, which acts to increase the $InsP_3/Ca^{2+}$ signaling pathway, disrupts NREM sleep leading to a decline in memory formation (233).

C. Memory

The first indication that $InsP_3$ may play a role in memory emerged from studies of long-term depression (LTD) in cerebellar Purkinje cells. These Purkinje cells, which play an important role in motor learning and coordination, depend on the process of LTD at the synapses where parallel fibers innervate the Purkinje cells. The parallel fibers release glutamate that acts on metabotropic glutamate receptors (mGluR) that are coupled to PLCβ to generate $InsP_3$ that then acts on $InsP_3$Rs on extensions of the ER that project into the spines to control LTD (166). These $InsP_3$Rs function as coincident detectors in that they only open when both $InsP_3$ and Ca^{2+} signals are present. The parallel fibers produce the $InsP_3$, whereas the climbing fibers induce the membrane depolarization that opens the L-type Ca^{2+} channels to generate the Ca^{2+}. For the channel to open, both messengers need to be present, and this $InsP_3$R-mediated coincident detection then generates the Ca^{2+} signal necessary for the synaptic plasticity that underlies motor learning. In addition to its role in activating LTD in Purkinje neurons, $InsP_3$ also plays a central role in activating LTD in other neurons (22, 65, 411).

In keeping with the role of the $InsP_3/Ca^{2+}$ signaling pathway in many neural functions, there is increasing evidence that alterations in this pathway are responsible for many neural diseases such as AD, ALS, ASD, BPD, epilepsy, HD, and spinocerebellar ataxias (SCAs).

D. Alzheimer's Disease (AD)

AD is driven by an increase in the amyloidogenic pathway, which results in the release of soluble β-amyloid (Aβ) by the neurons. These Aβ monomers form Aβ oligomers that feed

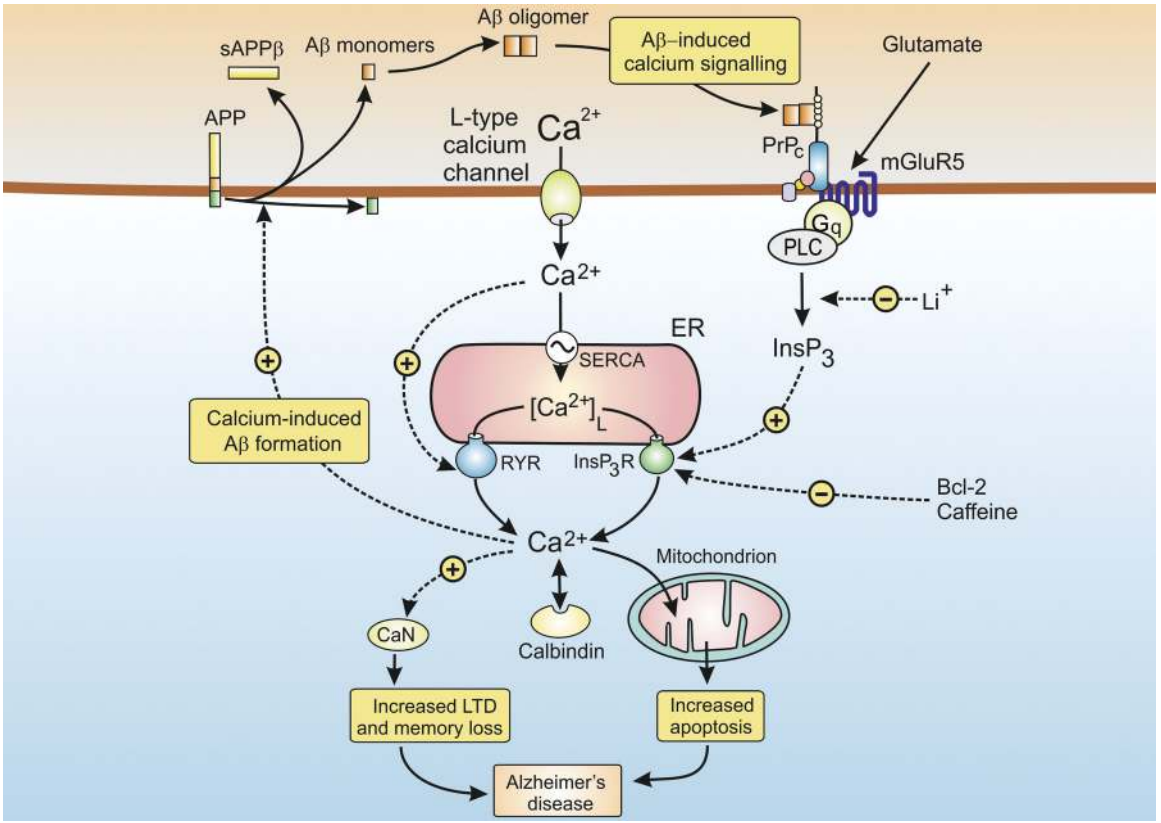

FIGURE 6. The role of the $InsP_3/Ca^{2+}$ signaling pathway in Alzheimer's disease (AD). Hydrolysis of the amyloid precursor protein (APP) releases β-amyloid (Aβ) that forms Aβ oligomers. The latter bind to the prion protein (PrP_c), which then activates the mGluR5 receptors to induce the formation of $InsP_3$, which then releases Ca^{2+} from the internal store. The resulting persistent elevation in Ca^{2+} then activates long-term depression (LTD) resulting in the memory loss in AD. The activation of $InsP_3$ is inhibited by Li^+, and its Ca^{2+}-mobilizing actions is reduced by Bcl-2 and caffeine. These three agents have been found to reduce the effects and onset of AD.

back to activate the neurons to bring about an increase in cytosolic Ca^{2+}, which is the basis of the calcium hypothesis of AD. This elevation in neuronal Ca^{2+} signaling induces a decline in memory and later neuronal cell death (41, 42, 139, 360). A significant feature of this alteration in neuronal Ca^{2+} signaling in AD is the reciprocal relationship between the amyloidogenic and Ca^{2+} signaling pathways. The increase in Ca^{2+} induced by the Aβ oligomers can feed back to stimulate the formation of Aβ by stimulating the hydrolysis of APP (139, 169, 298, 308) **(FIGURE 6)**. This ability of Ca^{2+} to stimulate the formation of Aβ may explain why hypoxia can result in AD pathogenesis. Hypoxia results in an increase in the activation of the Ca^{2+} sensing receptor (CaSR), which is known to increase $InsP_3$ formation that may then lead on to the elevation of Ca^{2+} (21). One of the actions of the Aβ oligomers that are responsible for AD is to stimulate the formation of $InsP_3$ that then acts on the $InsP_3$Rs to release Ca^{2+} from the ER (94, 108, 171, 360, 381). There are indications that the Aβ oligomers can induce this release of internal Ca^{2+} either by acting on cell surface receptors such as the metabotropic glutamate receptor 5 (mGluR5) that acts to increase $InsP_3$ (381) or by influencing the formation of $InsP_3$ through an intracellular action (94). In addition, the activation of the $InsP_3$Rs may depend on the increase in oxidative stress that occurs in AD (176). The effect of Aβ disruption of the internal stores of Ca^{2+} can be rather subtle and are context dependent (203). The contribution of excessive activation of the $InsP_3$R in the etiology of AD has been emphasized in studies on transgenic mouse models where reducing the number of $InsP_3$-sensitive channels greatly improved memory performance (344).

The presenilins, which are part of the γ-secretase intramembrane protease complex that cleaves the amyloid precursor protein (APP) to form the soluble Aβ, have also been found to influence Ca^{2+} homeostasis. Mutations in the presenilins (PS1 and PS2) result in the dysregulation of Ca^{2+} signaling that is responsible for familial AD (FAD) (70). Perhaps the most important action of the PS mutant protein is to increase the gating of the $InsP_3$R Ca^{2+} release channel (118, 208, 230, 359). The resulting enhanced release of Ca^{2+} may contribute to the elevated level of resting Ca^{2+} that rises from 100 to 300 nM (199, 219, 240). It is postulated that this elevation in the resting level of Ca^{2+} will activate LTD to erase memories soon after they are formed, thus accounting for the memory loss that characterizes AD (41, 42). As

the disease progresses, the $InsP_3$-induced dysregulation of Ca^{2+} will begin to drive neuronal cell death resulting in dementia. A very similar sequence of events occurs in the astrocytes, which surround the neurons, in that the Aβ oligomers activate the $InsP_3/Ca^{2+}$ signaling pathway resulting in apoptosis (280).

The symptoms of AD in transgenic mice can be reduced by Bcl-2 (317), and this can be explained by its ability to inhibit $InsP_3$ receptors to reduce the release of Ca^{2+} **(FIGURE 6)** (318). Caffeine is another drug that may act to reduce the risk of dementia (18, 68, 104, 287, 361). This proposed role of caffeine in reducing the risk of AD may be explained by its ability to inhibit Ca^{2+} release from the $InsP_3$Rs (54, 164, 322). There is increasing evidence that Li^+ might be another potential drug to control AD (97, 185, 186, 273, 274, 391). As described below, Li^+ acts to control BPD by reducing the activity of the $InsP_3/Ca^{2+}$ signaling pathway, and such an action could explain how it might act to protect against AD **(FIGURE 6)** (97, 261, 391). Patients with BPD that have been treated with Li^+ for a long period have a much lower incidence of AD (185, 186, 273). Treatment with Li^+ is able to stabilize memory impairment in AD patients (273). There also are indications that Li^+ may be able to prevent the onset of AD. It has been shown that Li^+ was able to prevent individuals displaying mild cognitive impairment from progressing to AD (114, 115). Such a possibility is consistent with the observation that Li^+, which acts by reducing the activity of the $InsP_3/Ca^{2+}$ signaling pathway (48), is capable of reducing REM sleep to increase NREM sleep (122, 281).

There is increasing evidence to show that the NREM sleep responsible for memory consolidation is disrupted by the accumulation of Aβ (175, 223, 224, 233, 316). This decline in NREM sleep is consistent with the evidence discussed earlier that Aβ can act to increase the $InsP_3/Ca^{2+}$ signaling pathway that would enhance the tonic excitatory drive thus preventing the onset of the slow waves that characterize NREM sleep **(FIGURE 5)**. This Aβ-dependent disruption of NREM sleep may also increase the progression of AD, because the rate of Aβ formation is lowest during this phase of sleep. The levels of Aβ are highest during wakefulness and decline during sleep (175, 179, 223). Inhibition of orexin, which is one of the transmitters that drives the sleep-wake cycle **(FIGURE 5)**, results in a decline in Aβ formation (179). Such an action can be explained by the fact that orexin acts to stimulate the $InsP_3/Ca^{2+}$ signaling pathway and its inhibition would reduce the tonic excitatory drive thus restoring NREM sleep during which there is a marked reduction in Aβ formation. All this information is consistent with the notion that Aβ accumulation acts to increase the activity of the $InsP_3/Ca^{2+}$ signaling pathway that not only accounts for memory loss but it also disrupts NREM sleep to enhance Aβ formation thus contributing to the progression of AD.

E. Amyotrophic Lateral Sclerosis

The neurodegenerative disease ALS, which is also known as Lou Gehrig's disease, is caused by degeneration of the motor neurons in the brain stem, spinal cord, and motor cortex. Approximately 10% of ALS cases are caused by familial mutations, whereas the majority are sporadic. Most information is available for the mutations in the oxidant scavenger superoxide dismutase 1 (SOD1). ALS is also caused by mutations in the TAR-DNA binding protein 43 (TDP-43) *TARDBP* gene and in the *FUS* gene, which encodes the fused in sarcoma (FUS) RNA-binding protein, which in some cases can progress to frontotemporal dementia (FTD).

In the case of sporadic ALS, there have been a number of suggestions about what drives the degeneration of motor neurons. These include glutamate excitotoxicity, hyperexcitability, oxidative damage, mitochondrial dysfunction, and Ca^{2+} dysregulation. All of these events are linked together with regard to their role in altering Ca^{2+} homeostasis (167, 204, 366). For example, the increase in oxidation arising from mutations in SOD1 will enhance Ca^{2+} signaling by increasing the sensitivity of both the $InsP_3$Rs and the RYRs (167, 366). Such dysregulation of Ca^{2+} is enhanced by the fact that motor neurons have low levels of Ca^{2+} buffering proteins (167,366), which will place considerably more stress on the mitochondria and thus account for mitochondrial dysfunction. Excessive elevation in mitochondrial Ca^{2+} levels activates the mitochondrial permeability transition pore (mPTP) that results in apoptosis and the death of motor neurons.

One reason for this Ca^{2+} dysregulation may be the glutamate excitotoxicity and hyperexcitability of the motor neurons, which is a characteristic feature of ALS (190). This enhanced excitability may arise through an increase in extracellular glutamate that can alter intracellular Ca^{2+} by enhancing both ionotropic (NMDAR and AMPAR) and metabotropic glutamate receptors (mGluR1 and mGluR5) (136). In a mouse model of ALS, reducing the expression of mGluR1 was found to improve both disease progression and survival (250). Since the mGluR1 receptors act by stimulating phosphoinositide hydrolysis, this observation suggests that the $InsP_3/Ca^{2+}$ signaling pathway may contribute to the dysregulation of Ca^{2+} that is responsible for ALS (366). Such a role for the $InsP_3/Ca^{2+}$ signaling pathway can explain why Li^+ can delay the progression of ALS (116). As described earlier, Li^+ inhibits the IMPase resulting in a reduction in the activity of this $InsP_3/Ca^{2+}$ signaling system (48).

Such a role for $InsP_3/Ca^{2+}$ signaling in ALS is supported by a number of other observations. Antibodies isolated from patients with ALS were found to stimulate the activity of the $InsP_3/Ca^{2+}$ signaling pathway in motor neurons (285). The life span of transgenic mice containing the mutant SOD1

gene was reduced when the expression of the $InsP_3R$ was increased (353). Expression of PLCδ1, which is responsible for generating $InsP_3$, was found to be increased in the neurons of the transgenic ALS mouse. Furthermore, the survival of these ALS mice was prolonged following genetic ablation of PLCδ1 (354). An increase in activity of the $InsP_3/Ca^{2+}$ signaling pathway may contribute to ALS through its ability to alter the activity of 43 kDa TAR DNA-binding domain protein (TDP-43). Mutations in TDP-43 result in the aggregation of TDP-43 in the cytoplasm, and this contributes to the deterioration of the motor neurons in ALS. This pathological activity of TDP-43 is regulated by Ca^{2+} release from the $InsP_3R1$ channels (189). Increasing the activity of $InsP_3/Ca^{2+}$ signaling thus promotes the nucleocytoplasmic shuttling of TDP-43 resulting in its accumulation in the cytoplasm where it exerts its deleterious effects on motor neuron survival.

F. Autism Spectrum Disorders

A number of diseases such as autism, Asperger's syndrome, perverse developmental disorder not otherwise specified (PDD-NOS), and Rett syndrome fall under the umbrella of ASD. ASD is a neurodevelopmental disorder that results in a lack of social communication especially with regard to appreciating how other people feel. ASD appears during childhood and continues into adulthood. Trying to understand this syndrome is difficult because there is considerable heterogeneity at both the genetic and phenotypic levels (135, 299).

The neurodevelopmental aspect of ASD is based on the fact that it appears to be linked to alterations in the mechanism responsible for development of the nervous system. As described earlier, spontaneous Ca^{2+} signals begin to appear in certain neuronal generator cells that become pacemaker cells that spread excitation to neighboring cells to form large signaling hubs. This Ca^{2+} signaling contributes to the neuronal differentiation responsible for synapse formation that creates the neuronal circuits in the developing brain.

Recent evidence suggests that ASD results from defects in the Ca^{2+} signaling processes responsible for setting up the structure and function of neural assemblies and particularly the synapses (101, 135, 198). The Ca^{2+} signaling system is one of the important pathways responsible for orchestrating the complex process of brain development. A key element in this regulation is the expression of the Ca^{2+} buffer parvalbumin (PV). When the level of PV declines, there is an alteration in the function of inhibitory neurons that will alter the excitation-inhibition (E-I) balance, and this leads to the onset of ASD (113, 269). Such a mechanism may explain why vitamin D deficiency, which normally functions to maintain the expression of PV and many other components of the Ca^{2+} signaling toolkit (44, 45), has been linked to ASD (107, 172). The $InsP_3/Ca^{2+}$ signaling pathway plays a key role in regulating both proliferation and differentiation during early development (380, 398). It is not surprising, therefore, to find that alterations in the activity of this $InsP_3/Ca^{2+}$ signaling system may contribute to the onset of autism (135, 333). Studies on the fibroblast taken from autistic patients reveal that there is a marked decline in the $InsP_3$-induced release of Ca^{2+} (333). Such an observation is consistent with a study of the genetic variants of the oxytocin receptor that have been identified in patients with autism, which also displayed a decline in the $InsP_3/Ca^{2+}$ signaling pathway (225).

G. Bipolar Disorder

A characteristic feature of BPD is the extreme swings between mania and depression. It is still not clear what is responsible for these alternating manic-depressive episodes. These changes in behavior seem to depend on alterations of neuronal signaling, which are a feature of the two hypotheses that attempt to explain BPD. In the neurogenesis hypothesis, it is suggested that there is an alteration in the hippocampal circuitry that arises from a change in neurogenesis induced by stress. The inositol depletion hypothesis is based on the observation that Li^+ acts by inhibiting the inositol monophosphatase (IMPase) that hydrolyzes inositol monophosphates (Ins4P, Ins1P, and Ins3P) to form free inositol (46, 48). As a result of this inhibitory action, Li^+ reduces the supply of free inositol necessary to resynthesize the inositol lipids that are required to maintain the $InsP_3/Ca^{2+}$ signaling system, thus resulting in a decline in the activity of this signaling pathway **(FIGURE 2)**. Li^+ acts through an uncompetitive mechanism that enables this drug to have minimal effects when the $InsP_3/Ca^{2+}$ signaling pathway is functioning normally, but its efficacy increases as the signaling pathway becomes increasingly abnormal. In effect, Li^+ can be considered to be a homeostatic drug, because it has no effect when the system is operating normally, but its therapeutic action becomes increasingly effective to match the degree of hyperactivity of the $InsP_3/Ca^{2+}$ signaling pathway. In effect, the therapeutic action of Li^+ is tailored to the severity of the disease state. These actions of Li^+ to reduce the $InsP_3/Ca^{2+}$ signaling pathway led to the idea that BPD may arise as a result of an overactive phosphoinositide signaling pathway (46, 48). Such a conclusion is supported by the observation that the levels of $G\alpha_{q/11}$ and PLCβ1, which are key components of the phosphoinositide signaling pathway, are elevated in the occipital cortex from patients with BPD (236). In addition, it has been shown that stimulating $InsP_3Rs$ and RYRs creates a depression-like response in mice, whereas inhibition of these channels has an antidepressant-like effect (125).

Ebselen, which is a Li^+ mimetic that also acts by inhibiting the IMPase, may be a safer drug for controlling BPD (347, 348). Li^{2+} may also act by inhibiting the stimulatory action of the neuronal calcium sensor 1 (NCS-1) on the $InsP_3R1$

(332). The mood-stabilizing drug valproate may also act by reducing the activity of the $InsP_3/Ca^{2+}$ signaling pathway (103). All this evidence suggests that enhanced neural $InsP_3/Ca^{2+}$ signaling contributes to both BPD pathology and the nature of the switching process. Enhanced release of ER Ca^{2+} is of major importance in the pathophysiology of BPD (395).

A characteristic feature of BPD is the process of switching from depression to the opposite state of mania, and vice versa (323, 373, 417). Alterations in the activity of various neurotransmitters may play a role in this switching process and is the basis of the catecholaminergic-cholinergic balance hypothesis (385). For example, the switch from depression to mania may be regulated by elevations in the levels of norepinephrine and dopamine (417). Conversely, the switch from mania to depression may depend on elevations in acetylcholine. Understanding the nature of this switching process would greatly enhance our understanding of BPD, but as yet the mechanism is still unclear.

It is possible that the symptoms of BPD, and particularly the switching between depression and mania, may arise from defects in the E-I balance that controls the neuronal activity responsible for driving brain rhythms as described earlier **(FIGURE 5)** (43, 369). Similarly, it has been proposed that major depressive disorder (MDD) may be caused by an alteration in excitatory transmission (374). Such a mechanism is particularly interesting in that Li^+, which acts to restore the neuronal imbalance, acts to enhance synapse formation by altering the level of phosphoinositides (187). It is also significant that the transmitters that have been implicated in the switching process also regulate the tonic excitatory drive. An alteration in the activity of these transmitters is thus consistent with the idea that an E-I imbalance may be the cause of BPD, because many of these transmitters activate the tonic excitatory drive using a variety of signaling mechanisms **(FIGURE 5)** (42). For example, some of these transmitters (ACh, NE, and orexin) act to induce depolarization by stimulating the hydrolysis of $PtdIns4,5P_2$ to decrease the M current while the $InsP_3/Ca^{2+}$ pathway promotes the Ca^{2+}-activated nonselective cation current (I_{CAN}) **(FIGURE 5)**. The possibility that hyperactivity of the $InsP_3/Ca^{2+}$ pathway contributes to BPD is supported by studies showing that this disease is associated with Bcl-2 gene single nucleotide polymorphisms (SNPs), which reduce Bcl-2 expression that could result in an increase in Ca^{2+} levels that are normally suppressed by Bcl-2 (98, 226).

Another reason for considering a possible role for changes in the tonic excitatory drive in BPD is the finding that two of the genes that have consistently been linked to BPD play a role in regulating neuronal activity. A number of genes such as *CACNA1C* that encodes the α-1C subunit of the Cav1.2 L-type Ca^{2+} have been identified in a genome-wide association studies (12, 152, 346, 349, 373). This observation may be particularly significant because the Cav1.2 L-type Ca^{2+} generates a Ca^{2+} signal that contributes to the tonic excitatory drive by activating the CAN channel **(FIGURE 5)**. The other gene is *ANK3* that encodes ankyrin-G, which plays a role in positioning the $K_V7.2/K_V7.3$ channels to the correct location in the neuronal membrane. $K_v7.2$ and $K_v7.3$ are delayed rectifier channels that contribute to the regulation of neuronal excitability by controlling the M current.

In summary, a characteristic feature of BPD is the switching between depression and mania that may result from changes in the E-I balance that will cause mania if the excitatory neurons are hyperactive or depression if the inhibitory neurons are hyperactive (43). Such hyperactivity, which is reduced by Li^+, has been confirmed in neurons taken from bipolar patients (246). One of the causes of this imbalance is likely to be an increase in the activity of the $InsP_3/Ca^{2+}$ signaling pathway. In the case of a mouse model of depression, inhibition of the $InsP_3/Ca^{2+}$ signaling pathway was found to exert an antidepressant effect (125). Correcting this signaling abnormality may explain the therapeutic action of Li^+, which acts by reducing the activity of the $InsP_3/Ca^{2+}$ signaling pathway.

H. Epilepsy

Spontaneous recurrent epileptiform discharges (SREDs) are a characteristic feature of epilepsy. Such seizure activity, which is usually induced by brain injuries such as trauma, stroke, or infections, seem to arise through an alteration in the E-I balance described earlier (355). The activity of the inhibitory neurons appears to decline to account for the increased activity of the excitatory neurons. A number of intracellular signaling pathways such as an increases in Ca^{2+} (92, 93, 242, 286) and nitric oxide (NO) (197) or a decrease in the $PtdIns3,4,5P_3$ levels (71) have been implicated in this alteration in the E-I balance. The Ca^{2+} hypothesis (92) that proposes there is an alteration in Ca^{2+} homeostasis appears to be particularly important because it can account for a number of features of epilepsy such as the decline in cognition (161, 402) and its relationship to AD (63, 75).

The alteration in Ca^{2+} homeostasis that occurs in epilepsy is caused by various brain injuries that result in a large release of glutamate that then stimulates the NMDARs to bring about a large Ca^{2+} influx that alters the Ca^{2+} signaling system. In particular, there is a decline in the expression of the SERCA pump on the ER and an increase in the $InsP_3/Ca^{2+}$ signaling pathway (93, 286). A role for $InsP_3/Ca^{2+}$ signaling has also been implicated in the onset of seizures induced by the organophosphorus (OP) compound soman, which is a chemical warfare agent. Soman was found to induce an increase in $InsP_3$ formation (58) that appears to be driven by an increase in the activity of the metabotropic glutamate receptors (264).

The mechanism driving the increase in the $InsP_3/Ca^{2+}$ signaling system is unclear, but it may be caused by an increase in the brain-derived neurotrophic factor (BDNF) that operates through the TrkB receptor to induce epilepsy (217). TrkB activates PLCγ to increase $InsP_3$ that acts to maintain the elevation of Ca^{2+}. Epilepsy can be prevented by using a specific peptide to uncouple the interaction between TrkB and the PLCγ (141). A genome-wide transcriptomic analysis has revealed that the $InsP_3$ signaling pathway is genetically associated with epilepsy (252). The significance of enhanced $InsP_3$ action in epilepsy is highlighted by the observation that the anti-epileptic drug levetiracetum acts to inhibit the release of Ca^{2+} by the $InsP_3Rs$ (265). Depletion of Ca^{2+} within the ER resulting from the decline in SERCA and the increased levels of $InsP_3$ results in an increase of store-operated Ca^{2+} due to the activation of the STIM1/Orai1 entry pathway (356). The decline in SERCA resembles that found in the heart during congestive heart failure (CHF). The net result of the enhanced release of Ca^{2+} from the ER and entry across the plasmalemma is to bring about a persistent increase in the resting level of Ca^{2+} and the enhanced network activity that gives rise to epilepsy (356).

The elevation in Ca^{2+} that is triggered during a seizure persists after the seizure and can account for many of the features of epilepsy. This Ca^{2+} elevation will increase the tonic excitatory drive, which is responsible for controlling brain rhythms **(FIGURE 5)**, and will thus enhance neuronal excitability and could set the stage for subsequent seizures. The decline in cognition could also be explained by the elevated Ca^{2+} that would stimulate LTD to erase memories. It has been proposed that a similar persistent elevation in Ca^{2+} may also explain memory erasure in AD as described above (41, 42), and it could also account for the fact that seizures are a common feature of AD (63, 75). It seems that in both AD and epilepsy, the persistent elevation in the resting levels of Ca^{2+} can account for both memory loss and epileptogenesis.

I. Huntington's Disease

In HD, there is a progressive decline in intellect that culminates in death after 10–15 yr. This neurological disease has been linked to a polyglutamine expansion in the NH_2 terminus of the Huntington protein (Htt^{exp}) that results in an alteration in Ca^{2+} signaling that is responsible for the death of the GABAergic medium spiny neurons located in the striatum (85). The modified Htt^{exp} binds strongly to the COOH-terminal region of the $InsP_3R1$ resulting in an increase in its sensitivity to $InsP_3$, thus giving rise to larger Ca^{2+} signals that disrupt neuronal function and induce neuronal cell death (51, 53, 106, 118, 368). In a mouse model of HD, activation of the $InsP_3R1$ causes depletion of ER Ca^{2+} that results in store-operated Ca^{2+} entry that contributes to the striatal synaptic loss (407). Mutant Htt accumulation and aggregation was reduced when the levels of the $InsP_3R1$ was reduced using shRNA (29), thus confirming that the $InsP_3/Ca^{2+}$ signaling pathway plays a role in HD. The significance of this pathway is also consistent with recent observations suggesting that Li^+, which acts to reduce the activity of $InsP_3/Ca^{2+}$ signaling, may be a significant drug for treating HD (327, 331).

J. Schizophrenia

Schizophrenia occurs in ~1% of the human population and is a severe psychiatric condition that is characterized by hallucinations, paranoia, poor attention, decline in social interactions, and lack of motivation. There also is a decline in cognition. An alteration in brain rhythms may be responsible for the changes in these higher-order brain functions that are a feature of schizophrenia (43). Many of the genetic susceptibility elements code for components of Ca^{2+} signaling, thus supporting the experimental evidence indicating that changes in Ca^{2+} signaling is a feature of schizophrenia. There is increasing support for the NMDA receptor (NMDAR) hypofunction hypothesis (350, 375). A decline in the Ca^{2+} signaling pathway resulting from a decrease in the activity of NMDARs alters the phenotype stability of the GABAergic inhibitory neurons. A decline in the release of the neurotransmitter GABA distorts the brain rhythms leading to an alteration in the information processing that occurs during sensory stimulation, attention selection, and working memory.

The GABAergic inhibitory neurons also express GPCRs such as the mGluR1, mGluR5, and M1 receptors that activate the $InsP_3/Ca^{2+}$ signaling pathway that acts to augment the Ca^{2+} signal that maintains phenotypic stability. There also is evidence of a decline in the activity of serotonergic neurons located in the prefrontal cortex of patients with schizophrenia (178, 239). Many of these neurons express the 5-HT_{2A} that act to increase $InsP_3/Ca^{2+}$ signaling (88). Alteration in this phosphoinositide signaling pathway plays a role in schizophrenia pathogenesis. Considerable interest is now focused on the metabotropic glutamate receptor 5 (mGluR5), which is closely associated with the NMDAR through scaffolding proteins such as Homer, SHANK, guanylate-kinase-associated protein, and PSD95. Alterations in mGluR5 may contribute to schizophrenia (237), and mutations in SHANK have been linked to various neuropsychiatric diseases including schizophrenia (131, 142). Furthermore, a deficit in ACh signaling mediated through muscarinic receptors has also been implicated in schizophrenia (328). A decrease in the expression of the regulators of G protein signaling 4 (RGS4), which modulates the activity of the PLCβ1 that mediates the activity of these GPCRs, is a consistent feature of schizophrenia (251). In schizophrenia patients, there are deletions of PLCβ1 in the orbital-frontal cortex (220). Abnormal expression patterns of PLCβ1 have been observed in patients with schizophrenia (194). Schizophrenic symptoms have also been observed in PLCβ1 knockout mice (243).

In addition to these alterations in the transducing mechanisms responsible for generating the $InsP_3/Ca^{2+}$ signaling pathway, there also is evidence for changes in the function of the $InsP_3R1$s. For example, one of the actions of the susceptibility gene *Disrupted-in-schizophrenia-1* (DISC1) is to alter the activity of the $InsP_3R1$s (290). DISC1 interferes with the transport of the mRNA of the *ITPR1* gene that encodes the $InsP_3R1$s. It attaches the *ITPR1* mRNA to the kinesin-1 molecular motor that then propels it down the microtubules to distribute it throughout the dendritic tree. Once in position, the *ITPR1* mRNA begins to express the $InsP_3R1$ channels (379), which are key components of neuronal Ca^{2+} signaling mechanisms.

K. Spinocerebellar Ataxias

SCA is characterized by poor coordination of movement that can affect the legs, hands, and speech. There are many different types of SCA, and some of the causes have been linked to a dysregulation of the cerebellar $InsP_3/Ca^{2+}$ signaling network that alters its role in the coordination of movement (53, 66, 106, 118, 335). Many of the ataxias have been linked to mutations in the *ITPR1* gene, which encodes the $InsP_3R1$ that releases Ca^{2+} from the ER located within the spines of the Purkinje cells (365). For example, *ITPR1* is one of the genes known to be associated with SCA15 (384). Missense mutations in the *ITPR1* have also been identified in spinocerebellar ataxia type 29 (SCA29) (163). Mutations in the *ITPR1* have also been identified in children with sporadic ataxic cerebral palsy (334). Degeneration of Purkinje cells and the onset of ataxia have been described in mice following deletion of *Inpp5a*, which encodes the $InsP_3$ 5-phosphatase that is one of the major pathways for inactivating $InsP_3$ **(FIGURE 2)** (414). The spinocerebellar ataxia type 6 (SCA6) form of this disease is caused by a mutation in the α_{1A} subunit of the $Ca_V2.1$ P/Q channel that provides the Ca^{2+} signal that acts together with $InsP_3$ to open the $InsP_3Rs$ (67). The SCA2 form is caused by mutations in ataxin-2 (Atx2), which associates with the COOH-terminal region of the Purkinje cell $InsP_3R1$ resulting in an increase in its sensitivity (215). In Russian and Japanese families with SCA, the *ITPR1* gene that encodes the $InsP_3R1$ was found to have a central role in SCA pathogenesis (146, 338).

Autosomal dominant cerebellar ataxia (ADCA), which is a type of SCA, has been linked to mutations in RNF170 that is an ER membrane ubiquitin ligase. RNF170 functions to ubiquitinate activated $InsP_3Rs$. The mutation of RNF170 interferes with this ubiquitination process and results in a decline in Ca^{2+} signaling via the $InsP_3Rs$ and is likely to be the cause of ADCA (405). The dysregulation of the $InsP_3/Ca^{2+}$ signaling pathway results in abnormal elevation of Ca^{2+} that alters motor coordination and progresses to a gradual degeneration of the Purkinje neurons, which is a characteristic feature of SCA. This central role of the $InsP_3R$ in SCA is supported by the fact that the symptoms of SCA in mice can be alleviated by suppression of this signaling pathway in Purkinje cells (183).

VI. MUSCLE CELLS

The $InsP_3/Ca^{2+}$ signaling pathway plays a role in regulating skeletal, cardiac, and smooth muscle cell functions. In skeletal and cardiac cells, $InsP_3$ has a modulatory role. Alterations in this modulatory role in skeletal muscle leads to Duchenne muscular dystrophy (DMD), whereas in cardiac cells it causes congestive heart failure and atrial arrhythmias **(FIGURE 1)**. In the case of certain smooth muscle cells, it provides the primary Ca^{2+} signal and alterations in this signal contribute to asthma and hypertension.

A. Skeletal Muscle

The $InsP_3/Ca^{2+}$ signaling pathway contributes to the regulation of skeletal muscle throughout its life history. During myoblast development, it generates the Ca^{2+} oscillations that are essential to induce the expression of the muscle-specific transcription factors such as myogenin and myocyte enhancer factor 2 (MEF2) (16). As the myoblast develops into skeletal muscle cells, they express the RYR1 that drives muscle contraction. Although the $InsP_3/Ca^{2+}$ pathway does not play a direct role in excitation-contraction (E-C), it has an important modulatory role in various muscle functions.

During the process of E-C coupling, the sarcolemma action potential is converted into an increase in Ca^{2+} that stimulates contraction. The muscle action potential, which invades the entire sarcolemma including the t-tubules where it functions to activate the $Ca_V1.1$ voltage-operated Ca^{2+} channel that interacts directly with the RYR1 to release Ca^{2+} from the SR. Once it is released, the Ca^{2+} diffuses to the sarcomeres where it binds to the troponin C (TnC) that induces contraction by facilitating an interaction between actin and myosin.

In addition to this primary Ca^{2+} signaling pathway, skeletal muscle retains the $InsP_3/Ca^{2+}$ signaling pathway that drove development to regulate processes both in the nucleus and in the cytoplasm (83). There appear to be two mechanisms responsible for activating the PLC that generates $InsP_3$: it is activated by insulin (82) and by membrane depolarization (213, 382). The insulin-dependent activation of the $InsP_3/Ca^{2+}$ pathway regulates metabolism by activating the insertion of the glucose transporter 4 (GLUT4) into the sarcolemma. The glucose that enters the cell through GLUT4 is phosphorylated by hexokinase to form glucose 6-phosphate (G6P) that is synthesized into glycogen by the glycogen synthase (82). The depolarization-induced activation of $InsP_3/Ca^{2+}$ also operates to control gene transcription (382).

B. Duchenne Muscular Dystrophy (DMD)

The $InsP_3/Ca^{2+}$ signaling pathway has been implicated in DMD, which is a progressive muscle-wasting disease. This disease results from mutations in the gene that encodes dystrophin, which has been shown to result in an increase in Ca^{2+} signaling that drives Ca^{2+}-sensitive proteases responsible for muscle degeneration. One of the consequences of the mutations in dystrophin, which is located on the inner surface of the sarcolemma, is to enhance the activity of the $InsP_3/Ca^{2+}$ signaling pathway (23, 212). In fetal muscle, the delayed myogenesis during dystrophy is caused by the $InsP_3$-dependent release of Ca^{2+} (105). The dystrophic phenotype could be reversed by various treatments that reduced the activity of the $InsP_3/Ca^{2+}$ signaling pathway such as the expression of normal dystrophin (23, 81), knockdown of the type 1 $InsP_3R$, or its inhibition by 2-aminoethoxydiphenyl borate (259). Inhibition of the $InsP_3R$ by over expressing Bcl-2 was also able to prevent apoptosis in dystrophic myotubes (28). An increase in the activity of $InsP_3/Ca^{2+}$ signaling also contributes to the muscular dystrophy that occurs in dilated cardiomyopathy (247).

C. Cardiac Cells

The heart, which pumps blood around the body, is driven by the sinoatrial (SA) node pacemaker system. The pacemaker cells in the SA node generate the repetitive action potentials that travel through gap junctions to excite both the ventricular and atrial cells. The functions of these three cardiac cells that drive each heartbeat are modulated by the $InsP_3/Ca^{2+}$ signaling pathway (387).

D. SA Node Pacemaker Cells

The cardiac pacemaker cells in the SA node are responsible for driving the rhythmical contraction of the heart. The specialized pacemaker cells in the SA have a sophisticated oscillatory mechanism based on both a membrane and a cytosolic Ca^{2+} oscillator that generates the repetitive action potentials. The main component of the membrane oscillator is the HCN4 Na^+ channel that is activated by hyperpolarization and then slowly decays to drive the slow pacemaker depolarization. The cytosolic Ca^{2+} oscillator consists of both RYRs and $InsP_3Rs$ that interact with each other to release the pulse of Ca^{2+} that then contributes to this pacemaker depolarization by enhancing the activity of Na^+/Ca^{2+} exchanger (NCX) resulting in a $I_{Na/Ca}$ current. This periodic release of Ca^{2+} from the SR depends on the activity of the SERCA pumps that refills the store, and this slow accumulation of Ca^{2+} within the SR lumen acts to sensitize the RYRs to initiate periodic Ca^{2+} sparks (389). These sparks begin to develop toward the end of the pacemaker depolarization when they trigger a sudden release of Ca^{2+} immediately preceding and contributing to the onset of the action potential. These bursts of Ca^{2+} occur close to the cell surface where there is close apposition between the sarcoplasmic reticulum (SR) and the sarcolemma. The appearance of these sparks is facilitated by the $InsP_3/Ca^{2+}$ signaling pathway that contributes to the activation of the RYRs responsible for the pacemaker depolarization. Activation of $InsP_3$ by either endothelin or α1-adrenergic receptors enhances both the frequency and amplitude of the Ca^{2+} sparks that are driving the cardiac pacemaker potential (174). The primary function of $InsP_3$ is to stimulate the $InsP_3R2$ to release Ca^{2+} that then acts to sensitize the RYRs to increase the frequency and amplitude of the Ca^{2+} sparks (173, 182).

E. Atrial Cardiac Cells

Contraction of the atrial chambers of the heart is driven by the striated atrial cells. Unlike the ventricular cells, the atria do not have t-tubules and the SR is closely applied to the sarcolemma through junctional zones that contain the RYR2 channels. The atrial cell Ca^{2+} signal initiates at these junctional zones. The remainder of the SR sheet, which also contains RYRs, extends into the cell perpendicularly. The initial signal generated at the junctional zone is amplified and spreads into the cell by these nonjunctional RYRs. The atrial $InsP_3R2$ receptors have two locations: the junctional zones and the nucleus (192, 214). Those $InsP_3R2s$ that are located together with the RYRs in the junctional zone have a significant modulatory role in that they respond to endothelin-1 to induce a positive inotropic response.

In response to the atrial action potential, the L-type Ca^{2+} channels in the sarcolemma facing the junctional zone generate a small pulse of Ca^{2+} that activates the RYRs to create a Ca^{2+} spark immediately below the sarcolemma. However, this small spark usually fails to ignite the RYRs on the rest of the SR and thus accounts for why atrial contractions are often rather weak. Much stronger contractions occur when atrial cells are stimulated by either a β-adrenergic agonist or by endothelin. There are two ways whereby these agonists induce a large positive inotropic response. First, they enhance the amplitude of the initial spark at the junctional zone so that it can breach the mitochondrial firewall to gain access to the nonjunctional RYR2s thereby generating a larger global Ca^{2+} signal that drives stronger contractions. Second, these hormones can increase the sensitivity of the RYR2s that also enables the initial spark to create a Ca^{2+} wave that penetrates the cell. The location of the $InsP_3$ receptors at the atrial cell junctional zone in immediate juxtaposition to the RYR2 thus enables them to play an important modulatory role in atrial cell excitation-contraction (E-C) coupling. The endothelin-1 acts on $InsP_3$ receptors in the junctional zone to augment the Ca^{2+} spark sufficiently so that it spreads throughout the cell by recruiting the RYR2s on the nonjunctional SR to increase the force of contraction (192, 228).

F. Atrial Arrhythmias

The most common cardiac arrhythmias are the atrial arrhythmias, which are caused by an increase in the $InsP_3$/Ca^{2+} signaling pathway. Endothelin acts to increase the formation of $InsP_3$ that results in the excessive Ca^{2+} signaling responsible for the development of these atrial arrhythmias (159, 210, 227, 426) that can result in sudden heart death. In patients with chronic atrial fibrillation, there is an upregulation in the expression of the $InsP_3$Rs (412). These arrhythmias also arise following deletion of the GTPase-activating protein RGS4 that inhibits the $G_{q/11}$ responsible for activating the PLCβ that generates $InsP_3$ (278, 377). A role for $InsP_3$ is supported by the observation that application of 2-aminoethoxydiphenyl, which had no effect on Ca^{2+} signaling under control conditions, specifically suppressed atrial arrhythmias (227, 409). Arrhythmias are also abolished in mice lacking $InsP_3$R2 receptors (210). Endothelin can also induce arrhythmias in ventricular cardiac myocytes that also are driven by $InsP_3$ (306).

G. Ventricular Cardiac Cells

In ventricular cells, E-C coupling depends on the entry of Ca^{2+} across the sarcolemma where it then activates the release of Ca^{2+} by RYRs located on the sarcoplasmic reticulum (SR). This Ca^{2+}-induced Ca^{2+} release process is facilitated by a unique structural relationship between the sarcolemma and SR. The sarcolemma has regular tubular invaginations (t-tubules) that extend deep into the cell. At regular intervals along the length of the t-tubule there are junctional zones, which are specialized regions where the SR contacts the t-tubule. Each ventricular cell has ~10,000 junctional zones each of which has about 10 $Ca_V1.2$ L-type channels that face ~100 RYRs in the associated SR region. The L-type channels in the t-tubule region generate the trigger Ca^{2+} that then stimulates the juxtaposed RYRs in the SR that face the t-tubule. Each of these events is induced by the action potential that sweeps along the sarcolemma to initiate ventricular cell E-C coupling.

This ventricular Ca^{2+} signaling system can readily adapt to changes in cardiac function. Both positive and negative inotropy can be induced by various hormones acting in a reversible manner over short periods of time. In response to persistent modulatory signals, the ventricular cells can undergo phenotypic remodeling that induces an enlargement (hypertrophy) of the heart. This onset of hypertrophy can have pathological consequences if it progresses to CHF. Hypertrophy can thus be either physiological or pathological. In the former case, the hypertrophy is a normal compensatory response to an increase in work load and is reversible in that the heart reverts back to its previous shape once the work load is reduced. The irreversible CHF that results in sudden heart death develops when the pressure overload persists and there is a phenotypic change in the remodelling process that switches it from being a compensatory mechanism to a more pathological process.

H. Congestive Heart Failure

The dysfunctional cardiac remodeling that results in CHF is a major cause of human morbidity and mortality. A persistent increase in cardiac work load is one of the main causes that initiates the onset of CHF. One of the major causes of CHF is hypertension, which is associated with an increase in hormones such as endothelin-1, angiotensin II, and catecholamines. These hormones have a profound effect on the Ca^{2+} dynamics of ventricular cells through their activation of phosphoinositide hydrolysis to increase the $InsP_3$/Ca^{2+} signaling pathway (192, 388). In ventricular cells, the $InsP_3$R2s are located on the nuclear membrane. The opening of these release channels depends on the presence of both $InsP_3$ and Ca^{2+} **(FIGURE 7)**. Even though endothelin-1 can enhance the level of $InsP_3$ in cardiac cells, it is not able to release Ca^{2+} when acting by itself. However, during each cardiac Ca^{2+} transient that drives contraction, there is a cytosolic pulse of Ca^{2+} that can provide the costimulatory Ca^{2+} signal necessary to activate the $InsP_3$R2s that then creates a local Ca^{2+} signal in the nucleus during the course of each contraction. This $InsP_3$-dependent nuclear Ca^{2+} signal is modulated by NCS-1, which is one of the regulators of the $InsP_3$Rs **(FIGURE 4)** (266). The $InsP_3$R2s function as coincident detectors in that they integrate the $InsP_3$ signal generated by the endothelin-1 receptors and the contractile Ca^{2+} signal to generate the nuclear Ca^{2+} signal that activates the transcriptional events responsible for the onset of hypertrophy (148, 154, 214, 218, 267, 406, 427). One of the genes that is activated is *ITPR2* that codes for the $InsP_3$R2 that is responsible for the nuclear Ca^{2+} signal that drives hypertrophy (324).

The persistent nuclear Ca^{2+} pulses driven by the $InsP_3$/Ca^{2+} signaling pathway induces a process of dedifferentiation characterized by the activation of a program of fetal cardiac gene transcription. Cardiac function is markedly altered as a result of this remodeling, because there is a reduction in the amplitude of the Ca^{2+} signal and the weaker cardiac contractions result in the failing heart. A particularly important change is the downregulation of the SERCA2a pump resulting from a decrease in its expression. In addition, this inhibition of SERCA2a is exacerbated by the inactivation of the adrenergic modulatory mechanism resulting in an increase in the activity of the Na^+/Ca^{2+} exchanger that reduces the uptake of external Ca^{2+} that further reduces the ability of the SERCA pump to load the SR with Ca^{2+}. This decline in the ability of the SERCA pump to load the store with Ca^{2+} results in larger diastolic Ca^{2+} concentrations and a significant decline in the systolic Ca^{2+} transient. This severe downregulation of Ca^{2+} signaling brought about by the $InsP_3$ nuclear Ca^{2+} signals is a characteristic feature of CHF.

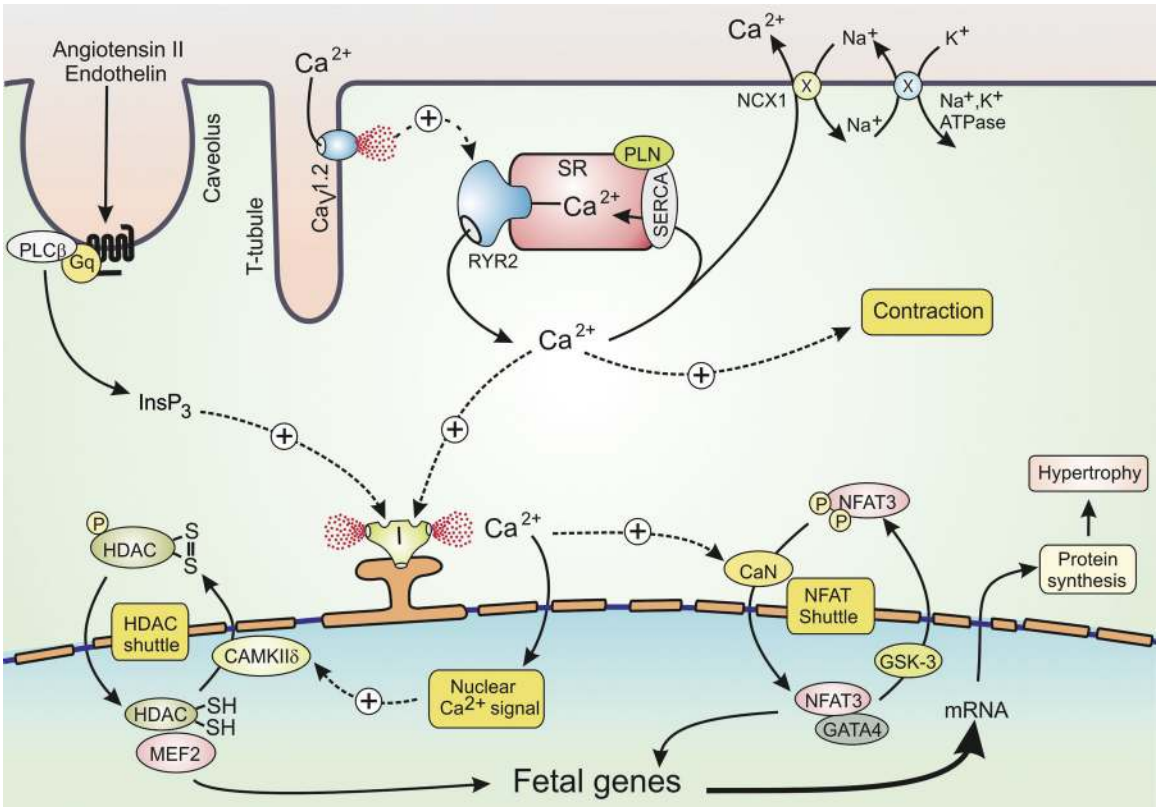

FIGURE 7. The role of $InsP_3/Ca^{2+}$ signaling pathway in cardiac hypertrophy. Angiotensin II and endothelin stimulate the formation of $InsP_3$ that acts together with the Ca^{2+} released from the ryanodine receptor 2 (RYR2) to activate the $InsP_3R2s$ (I) to trigger a nuclear Ca^{2+} signal that activates the HDAC and NFAT shuttles to stimulate the transcription factors responsible for switching on the fetal genes that induce hypertrophy.

I. Kawasaki Disease

Kawasaki disease is caused by vasculitis, and this inflammation of the blood vessels has an effect on many organs such as the heart, lymph nodes, skin, and mucous membranes inside the mouth, nose, and throat. It is characterized by high temperature that can last for 5 days. A significant aspect of the disease is acquired heart disease in children where it damages the coronary arteries resulting in inflammation of the heart, dysrhythmias, and aneurysms. The cause of this disease is still not clear, but there are indications that $InsP_3/Ca^{2+}$ signaling may function to activate the T cells that contribute to the inflammatory response. Kawasaki disease has been linked to a mutation in the *ITPKC* gene that encodes the $InsP_3$ 3-kinase that phosphorylates and inactivates the Ca^{2+}-mobilizing activity of $InsP_3$ **(FIGURE 2)** (200, 277, 416).

J. Smooth Muscle

1. Smooth muscle contraction and hypertension

Contraction of the smooth muscle cells (SMCs), which surround the vascular blood vessels, is driven by oscillatory Ca^{2+} signals that are driven by the $InsP_3/Ca^{2+}$ signaling pathway that is activated by transmitters such as ACh, 5-hydroxytryptamine (5-HT), and norepinephrine (NE) and hormones such as endothelin-1 (ET-1) (38). The release of stored Ca^{2+}, which drives these oscillations to maintain the vascular tone, is driven by both $InsP_3R$ and RYR channels. Variations in transmitter concentration are translated into changes in the frequency of the Ca^{2+} oscillations and is another example of the frequency-modulated mechanism for regulating cellular function as described earlier (36, 47).

An increase in the activity of the $InsP_3/Ca^{2+}$ signaling pathway may contribute to the increased myogenic tone that results in the hypertension that induces cardiac disease (4). For example, in human pulmonary arterial SMCs, the enhanced expression of the Ca^{2+}-sensing receptor (CaSR) acts to increase the activity of the $InsP_3/Ca^{2+}$ signaling pathway (410). In hypertensive rats, expression of the $InsP_3Rs$ is markedly elevated (1). Increased entry of Ca^{2+} through L-type channels acts through the calcineurin/NFAT transcriptional pathway to increase the expression of the $InsP_3Rs$ that contributes to hypertension through increased vascular smooth muscle (VSM) contractility. Such an action is consistent with the observation that there is increase in the expression of $InsP_3Rs$ in spontaneously hypertensive rats (SHRs) (32).

Blood vessels are lined with endothelial cells that play an important role in regulating smooth muscle tone. Various stimuli act on these endothelial cells to stimulate $InsP_3/Ca^{2+}$ signaling that then generates various vasoactive agents such as nitric oxide (NO), prostacyclin, and endothelium-derived hyperpolarizing factor, which act to control smooth muscle contractility. The increased blood pressure that occurs during hypertension results in a marked decline in the activity of $InsP_3/Ca^{2+}$ signaling, and this interferes with the ability of the endothelial cells to reduce smooth muscle contraction (400).

2. Smooth muscle cell proliferation and asthma

Proliferation of smooth muscle cells is an example of how a differentiated cell can switch back into the cell cycle to return to cell division. This return to proliferation by SMCs is particularly significant for wound healing. However, such switching back into a proliferative state has a number of pathophysiological consequences in that it causes asthma, hypertension, and pulmonary vasoconstriction. In the case of pulmonary artery smooth muscle cells, proliferation is activated by a mechanism remarkably similar to that found in T cells (see above). An increase in $InsP_3$ releases Ca^{2+} from the ER, and this then induces prolonged Ca^{2+} signaling through the activation of the STIM1/Orai1 entry pathway (351, 428).

Asthma and chronic obstructive pulmonary disease (COPD) are the two main respiratory diseases. The increase in SMC proliferation described above contributes to asthma because it results in a thickening of the bronchial wall. In addition, asthma is also caused by other alterations in the airways such as inflammation, bronchial hyperresponsiveness, and obstruction of the airways by excessive contraction of the SMCs. The excessive contraction of the airway SMCs, which is driven by the $InsP_3/Ca^{2+}$ pathway, is one of the main causes of asthma (145). In COPD, there is an overexpression of muscarinic M3 receptors that is responsible for the enhanced $InsP_3/Ca^{2+}$ signaling pathway that drives the excessive contraction (294). One of the most successful bronchodilators used to control COPD is tiotropium that acts by inhibiting the M3 receptors to reduce the elevated $InsP_3/Ca^{2+}$ signaling to reduce SMC contraction and sputum production in airway mucous glands (294). The extensive lung tissue damage that occurs during COPD is caused by the infiltration of neutrophils. This damage can be prevented by the secretory leukoprotease inhibitor (SLPI) that acts by reducing the activity of the $InsP_3/Ca^{2+}$ signaling pathway that is responsible for neutrophil functions such as chemotaxis and the release of proteolytic enzymes (312).

VII. CHONDROCYTES

The maintenance of articular cartilage is carried out by the chondrocytes that regulate both the formation and the degradation of the matrix, which is composed of aggregan and collagen type II. The latter provides the tensile support, whereas the negatively charged proteoglycan aggrecan is responsible for the compressive resistance of cartilage in that it attracts water molecules to create its shock absorbing property (231). The chondrocytes, which are embedded within cartilage, are responsible for synthesizing and assembling these extracellular matrix (ECM) components. Alterations in this synthetic role of the chondrocytes lead to changes in the properties of cartilage that are responsible for osteoarthritis.

A. Osteoarthritis

Osteoarthritis (OA) is a debilitating disease that is caused by degenerative changes in the cartilage that results in intense pain in the load-bearing joints such as the knees and hips. Chronic inflammation, which is a major contributory factor for OA, generates the cytokines and proteases that induce the chondrocytes to alter the synthesis of the type II collagen and proteoglycans. In addition, there is an increased release of matrix proteinases (MMPs) (e.g., MMP-1 and MMP-13) resulting in a dramatic alteration in cartilage composition (231). The normal collagen II is replaced with collagen I, and there is a marked decline in the expression of aggrecan.

These pathological changes that give rise to OA depend on an alteration in the secretory activity of the chondrocytes that is driven by proinflammatory cytokines (TNF-α and IL-1β). One of the causes for this alteration on chondrocyte activity is an increase in Ca^{2+} signaling that occurs during OA (271, 304, 419). For example, IL-1β acts on chondrocytes to increase the activity of the $InsP_3/Ca^{2+}$ signaling pathway (304). During OA, calcium phosphate crystals appear in the cartilage and contribute to cartilage destruction by activating Ca^{2+} signals in the chondrocytes (271).

The TNF-α may also act to enhance Ca^{2+} signaling because it is known to increase the expression of the $InsP_3R1$ (289). The importance of the $InsP_3/Ca^{2+}$ signaling pathway in OA is highlighted by the observation that there is an increase in the expression of PLCγ2 and in some of the genes that regulate this enzyme (56). There also is an increase in the expression of PLCγ1 in chondrocytes from patients with OA (410). Reducing the activity of PLCγ1 by U73122 or by siRNA was able to restore the expression of collagen II and reduce the release of MMP-13 (419), thus emphasizing how an abnormal $InsP_3/Ca^{2+}$ signaling pathway contributes to the pathological progression of osteoarthritis.

B. Kashin-Beck Disease

Kashin-Beck disease (KBD) is an osteochondral disease, which is particularly prevalent in Siberia, China, and North

Korea. The KBD symptoms, which arise from cartilage damage, are joint pain, enlarged interphalangeal joints, and reduced movement in many joints of the body (330). The causes of the disease are still not clear, but there does seem to be a link to various dietary components such as mycotoxins, fulvic acid, and deficiencies in selenium and iodine. Recently, a genome-wide association study has revealed that the *ITPR2* gene that encodes the $InsP_3R2$ channel is a susceptibility gene for KBD (423). Chondrocyte necrosis and cell death is driven by mitochondrial-induced apoptosis (216, 393). It is likely that this increase in apoptosis may be driven by an increase in the activity of the $InsP_3R2$, which is known to release Ca^{2+} from the ER to trigger apoptosis through the mitochondria (59, 363).

VIII. EXOCRINE GLANDS

A. Pancreatic Acinar Cells

Both fluid and proteins are secreted by pancreatic acinar cells. The proteins are the digestive enzymes that are stored in the zymogen granules located in the apical part of the cell. Secretagogues such as cholecystokinin (CCK) and ACh induce the Ca^{2+} signals that have spatial and temporal characteristics designed to maximize protein and fluid secretion (296). ACh acts on muscarinic receptors to induce the $InsP_3/Ca^{2+}$ signaling pathway. In addition to being located on the ER, the $InsP_3Rs$ are also found on the zymogen granules (295). Neighboring RYRs act to amplify the Ca^{2+} signal that generates a Ca^{2+} wave that can extend into the basal region. The CCK uses a different signaling pathway in that it generates cyclic ADP ribose (cADPR) and nicotinic acid-adenine dinucleotide phosphate (NAADP) that release Ca^{2+} from the acidic organelles and the ER.

As occurs in many other exocrine cells, the Ca^{2+} signal is normally localized in the apical region where it appears as an oscillation that controls both fluid secretion and the release of zymogen granules. With regard to fluid secretion, the Ca^{2+} stimulates apical Ca^{2+}-sensitive Cl^- channels (CaCCs), and the resulting entry of Cl^- into the lumen provides the driving forces for the entry of both Na^+ and water (288).

The Ca^{2+} signals located in the apical region are usually prevented from spreading into the rest of the cell by a mitochondrial firewall (376). However, when stimuli are increased, there is a much larger apical Ca^{2+} signal that breaches the mitochondrial firewall and spreads out towards the basal region in the form of a propagating Ca^{2+} wave.

B. Pancreatitis

Pancreatitis has two forms. Acute pancreatitis appears suddenly and lasts for a few days. On the other hand, the chronic form can continue for many years. Chronic alcohol abuse is a major causes of pancreatitis. An increase in alcohol reduces the role of alcohol dehydrogenase (ADH) that functions normally to bring about the oxidative metabolism of ethanol. As a consequence, the nonoxidative metabolism of ethanol to fatty acid ethyl esters (FAEEs) is increased, which appears to be responsible for various alcoholic diseases such as pancreatitis (133). In pancreatitis, one of the actions of FAEEs is to stimulate the type 2 and type 3 $InsP_3Rs$ that are found on the ER and zymogen granules. This leads to the pathogenic activation of the trypsin located in the apical zymogen granules (134). Such activation of the digestive enzymes within the cell triggers a process of autodigestion leading to necrosis that is a feature of pancreatitis. In a mouse model, pancreatitis was prevented by deleting the $InsP_3R2$ channels (279). Caffeine can reduce the symptoms of acute pancreatitis by inhibiting the $InsP_3/Ca^{2+}$ signaling pathway (164). All this evidence supports the notion that an alteration in $InsP_3/Ca^{2+}$ signaling plays a key role in the development of pancreatitis.

C. Salivary Gland

The function of salivary glands is to secrete saliva that facilitates the ingestion of food, and it also acts to moisten the oral cavity between meals. It is the small labial, buccal, and palatal glands that continuously secrete saliva to moisten the mouth. During feeding, much more saliva is required, and this is produced by the large submandibular, parotid, and sublingual salivary glands. Secretion by these glands is triggered by mechanical, thermal, or chemical stimuli. The main stimulus released from the parasympathetic neurons is ACh that binds to muscarinic (M3) receptors to activate the $InsP_3/Ca^{2+}$ signaling system (9, 10, 244). In the $InsP_3R2$ and $InsP_3R3$ double knockout mice, there is marked decline in salivary gland secretion (124). The resulting Ca^{2+} signal depends both on Ca^{2+} release from internal stores that is maintained by Ca^{2+} entry through store-operated channels (SOCs). The increase in Ca^{2+} stimulates the CaCCs that enables Cl^- to enter the lumen where it provides the driving force for the entry of both Na^+ and water. The elevated Ca^{2+} also acts to open the BK channel that hyperpolarizes the basolateral membrane to create the electrochemical gradient that drives the movement of Cl^- into the lumen.

D. Sjögren's Syndrome

Sjögren's syndrome (SS) is an autoimmune exocrinopathy that is characterized by a decline in fluid secretion by the salivary glands. A recent study has revealed that this secretory defect in the salivary glands of SS patients results from a decline in the expression of the $InsP_3Rs$ that function to release the Ca^{2+} that activates fluid secretion (372). This observation is consistent with the observation that patients with SS express anti-$InsP_3R$ antibodies (254).

E. Sweat Glands

The tubular epithelial sweat glands located on the surface of the body consist of a distal secretory coil followed by a reabsorptive region. The secretory coil cells secrete an isotonic NaCl solution that then passes through the straighter reabsorptive region where most of the Na^+ and Cl^- is reabsorbed, and this results in the hypotonic sweat that is then transferred through pores onto the skin surface. Both parasympathetic and sympathetic neurons function to regulate the secretion of sweat. The norepinephrine (NE) released from the sympathetic neurons stimulates the cAMP signaling pathway to activate the cystic fibrosis transmembrane conductance regulator (CFTR) channel that transfers Cl^- into the lumen of the sweat gland. In addition, the $InsP_3/Ca^{2+}$ signaling pathway, which is activated by ACh released from the parasympathetic neurons, functions by activating CaCCs to create a flux of Cl^- into the lumen. This Cl^- transfer drives a parallel flux of Na^+ which thus creates the accumulation of NaCl to provide the osmotic gradient for the flow of water.

F. Anhidrosis

In anhidrosis, which is also known as hypohidrosis, there is a marked decline in the formation of sweat that results in hyperthermia or heat stroke and can lead to death. The importance of the $InsP_3/Ca^{2+}$ signaling pathway in sweat secretion, as described above, has emerged from the study of a missense *ITPR2* gene mutation that encodes $InsP_3R2$, which has been linked to anhidrosis in five members of a consanguineous family (191).

G. Lung Submucosal Glands

The serous fluid-secreting cells in the submucosal glands of the lung function to secrete the fluid that contributes to the formation of the mucous that protects the lung airway epithelium against viruses, pathogens, and foreign particles. Various stimuli such as ACh, ATP, histamine, and substance P, which act through the $InsP_3/Ca^{2+}$ signaling pathway, regulate the rate of fluid secretion (206). The $InsP_3$ formed by these stimuli activates the type 1 $InsP_3R1$ embedded in the ER positioned close to the apical membrane, to release Ca^{2+} that then acts to open the CaCC.

IX. ENDOCRINE GLANDS

A. Pancreatic β-Cell Insulin Secretion

Elevation of glucose in the plasma stimulates insulin release from pancreatic β-cells by regulating both the biosynthesis and release of insulin. The way insulin is secreted is of interest clinically, because the development of diabetes results from the onset of insulin resistance caused by a decline in the secretion of insulin.

In addition to glucose, the activity of β-cells is also sensitive to other factors such as ACh, which is released by the α-cells, that acts in a paracrine manner to sensitize the β-cells to respond to glucose (315). When considering the control of insulin secretion, therefore, it is necessary to understand both the primary action of glucose and how ACh acts through the $InsP_3/Ca^{2+}$ pathway to modulate the activity of glucose **(FIGURE 1)**. Elevated levels of plasma glucose induce a slow Ca^{2+} oscillation (4–6 min periodicity) that drives the secretion of insulin. Faster Ca^{2+} spikes (10- to 20-s periodicity) occur during the crest of the slow Ca^{2+} spikes.

The glucose transporter 2 (GLUT2) enables glucose to enter the β-cell where it is immediately phosphorylated by hexokinase IV to form glucose-6-phosphate (G-6-P). The G-6-P is then metabolized to fructose 6-phosphate (F-6-P), which is transformed into fructose-2,6-P_2 (F-2,6-P_2) by phosphofructose kinase-2 (PFK2). The next step is for the F-2,6-P_2 to activate PFK1 that transforms F-6-P to fructose-1,6-P_2 (F-1,6-P_2). The latter enters the glycolytic and tricarboxylic acid (TCA) cycles resulting in an elevation in ATP. The latter acts by inhibiting the ATP-sensitive K^+ (K_{ATP}) channel resulting in the membrane depolarization that then activates the L-type voltage-operated channels (VOCs) to generate localized Ca^{2+} pulses to induce the release insulin.

This primary role of glucose in stimulating insulin secretions can be modulated by the activity of other stimuli as illustrated by the action of ACh and free fatty acids (FFAs). The ACh acts through the M3 muscarinic receptor that operates through the $InsP_3/Ca^{2+}$ pathway (25) and is another example of the modulatory role of this signaling system **(FIGURE 1)**. Similarly, the FFAs activate the GPR40 receptor that increases the $InsP_3/Ca^{2+}$ pathway, which acts to potentiate glucose-induced insulin secretion (232). There is a complex relationship between the glucose-induced Ca^{2+} signal and the contribution from the $InsP_3/Ca^{2+}$ pathway, which appear to act synergistically to control the release of insulin (130, 352).

B. Diabetes and Gallstone Formation

Alterations in the activity of the modulatory role of the $InsP_3/Ca^{2+}$ pathway in regulating insulin secretion may contribute to the onset of diabetes (25). For example, genetic variations in the M3 receptor, which normally activates the $InsP_3/Ca^{2+}$ pathway, have been linked to early-onset type 2 diabetes in Pima Indians (143). Second-generation antipsychotics, such as olanzapine and clozapine, can result in insulin resistance through their ability to inhibit M3 receptors (399). In a transgenic mouse line, a mutation in the *Itpr1* gene that encodes the $InsP_3R1$ channel has been

linked to glucose intolerance and susceptibility to diet-induced diabetes (415). It is also significant that there are alterations in the $InsP_3/Ca^{2+}$ pathway during aging, and these changes may contribute to the onset of diabetes (26). Vascular smooth muscle cell growth and dysfunction is induced by transforming growth factor-β (TGF-β) (424). One of the actions of TGF-β is to reduce the activity of $InsP_3R1$, which may contribute to the diabetic pathophysiology of aortic and preglomerular smooth muscle cells (284, 340).

In diabetic patients, there was a decreased expression of $InsP_3R$ and the cholycystokinin receptor (CCK-R), which generates $InsP_3$ (422). The resulting decline in the $InsP_3/Ca^{2+}$ signaling pathway accounts for the decline in gallbladder emptying and gallstone formation, which is a comorbidity often associated with diabetes.

X. LIVER

The liver has important functions, many of which are regulated through the $InsP_3/Ca^{2+}$ signaling pathway (7, 27, 127, 128). It regulates glucose and energy metabolism, synthesizes urea and a large number of plasma proteins, and is also responsible for bile secretion. $InsP_3/Ca^{2+}$ signaling plays a central role in controlling the process of gluconeogenesis (238, 394). Oxidative substrates are constantly being transferred between the plasma and liver cells. For example, when the supply of glucose is plentiful, insulin controls the uptake of glucose that is converted by glycogen synthase to glycogen that is stored in the liver. When glucose levels decline, the hormone glucagon stimulates glycogenolysis that results in the hydrolysis of glycogen to release glucose that can reenter the plasma. This glycogen hydrolysis is mediated by the enzyme phosphorylase, which is activated by phosphorylase kinase, which is a Ca^{2+}-sensitive enzyme. Hormones such as vasopressin and norepinephrine act through the $InsP_3/Ca^{2+}$ signaling system to stimulate the phosphorylase kinase to increase glycogenolysis.

The $InsP_3/Ca^{2+}$ signaling pathway also acts to regulate bile secretion (8, 307). The bile that is formed by the liver is transferred and stored in the gallbladder where it has two main functions. It contributes to fat digestion and absorption by the intestine, and it also functions to remove waste products from the blood. Bile secretion begins in the distal hepatocytes that transfer bile salts and other organic solutes into the canalicular lumen. This initial fluid is then passed down the canaliculus where it is modified by the cholangiocytes that are particularly active in secreting bicarbonate (HCO_3^-).

This secretion of HCO_3^- is regulated by two main signaling pathways. Agonists such as acetylcholine generate $InsP_3$ that acts on the type 3 $InsP_3$ receptor ($InsP_3R3$) located in the apical region of the cell to release Ca^{2+} that then stimulates a CaCC (TMEM16A) to enable Cl^- to flow into the canalicular lumen. The accumulation of luminal Cl^- then provides the driving force for the transfer of bicarbonate (HCO_3^-), which creates the osmotic gradient for the transfer of water. In addition to regulating Cl^- transport into the lumen, Ca^{2+} also controls the SK Ca^{2+}-activated K^+ channels on the basolateral membrane that act to maintain a hyperpolarized membrane potential that is necessary to drive the flux of Cl^- into the lumen. The apical membrane is also sensitive to ATP that is either released upstream by the hepatocytes and thus acts in a paracrine manner or is released by the cholangiocytes to act in an autocrine manner. The ATP stimulates P2Y receptors that generate $InsP_3$ that increases the release of Ca^{2+} that drives secretion as described above.

A. Liver Cholestasis

Since the $InsP_3/Ca^{2+}$ signaling pathway contributes to the control of many liver cell functions, it is not surprising to find that alteration in $InsP_3$ function plays a pivotal role in a number of liver diseases (8, 27, 342). One of the serious liver diseases is cholestasis, which is caused by an alteration in the function of bile secretion. A decline in the expression of the type 3 $InsP_3R$ ($InsP_3R3$) contributes to a number of cholestatic disorders such as obstruction of the bile duct, biliary atresia, biliary cholangitis/cirrhosis, and sclerosing cholangitis (7, 8). The decline in the $InsP_3R$ may depend on various factors such as the nuclear factor, erythroid 2-like 2 (NRF2) transcription factor that acts to inhibit the expression of the *ITP3R* gene (397) and an increase in microRNA 506 (miR-506) that acts by reducing the expression of the $InsP_3R3$ in the cholangiocytes (13). Alterations in the activity of the $InsP_3R3$ have also been implicated in various metabolic diseases. In particular, an increase in the $InsP_3/Ca^{2+}$ signaling pathway contributes to the dysregulation of metabolism that occurs during insulin resistance and obesity (27).

XI. OSTEOCLAST

The balance between the activity of the osteoclasts (bone resorption) and osteoblasts (bone formation) is central to the process of bone remodeling. Osteoclasts, which are derived from haematopoietic stem cells, are large multinucleated motile bone resorptive cells (153). Their primary function is to degrade bone, and they are responsible for normal skeletal function and for calcium homeostasis. The ratio of osteoblasts to osteoclasts determines the process of bone remodeling. The rate of bone resorption depends on the formation and activity of the osteoclasts. As the osteoclasts are formed, they attach and spread out over the bone surface to initiate the process of bone resorption. The formation of osteoclasts, which is known as osteoclastogenesis, is controlled by factors such as colony-stimulating factor-1

(CSF-1), tumor necrosis-related factor called receptor activator of nuclear factor κB (NF-κB) ligand (RANKL), and inflammatory cytokines such as interleukins and TNF. Of the various signaling pathways that are activated by these factors, the Ca^{2+} signaling pathway is beginning to attract considerable attention (123, 165, 268, 367, 420).

Activation of the RANK pathway, which is particularly important for generating Ca^{2+} signals, stimulates costimulatory transducing system such as FcRγ and DAP12 that then activate PLCγ to induce the formation of $InsP_3$ (193, 345). The RANK pathway can also increase $InsP_3$ by acting on Rac1 to generate ROS that then activate PLCγ1 (188). The $InsP_3$ formed by these two pathways then acts on the $InsP_3R2$s to release Ca^{2+} that sets up a prolonged Ca^{2+} oscillation that then stimulates entry of NFATc1 into the nucleus where it induces transcription of those genes that drive osteoclast development (268, 367). The ability of osteoprotegerin to inhibit osteoclast differentiation depends on its ability to reduce this Ca^{2+} signaling pathway (123). As described below, the onset of rheumatoid arthritis is driven by excessive activation of this Ca^{2+} signaling pathway.

A. Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory disease that results in synovial inflammation and joint destruction that can lead to severe morbidity and premature mortality (5, 357). The pathogenesis of RA is driven by autoreactive B cells (302). One of the major cytokines driving osteoclast inflammation in RA is TNF-α (241, 270). Periodonitis is a related disease that is also caused by inflammation driven by TNF-α (153). One of the actions of TNF-α is to enhance $InsP_3R1$ expression, which induces osteoclastogenesis by increasing the Ca^{2+} oscillations that are driven by the RANK signaling pathway (408).

XII. NEPHROLITHIASIS

Nephrolithiasis arises due to an increase in kidney calcification that results in the formation of kidney stones (17). These stones, which consist mainly of calcium phosphate and calcium oxalate, can develop both in the lumen of the kidney tubules and in the surrounding tissue. In addition to obstructing the tubule lumen, these Ca^{2+} crystals may also damage the kidney through inflammatory reactions driven by cytokines such as TNF-α (184). There are multiple causes of nephrolithiasis, which is a complex disease. Stone formation has been linked to mutations of a number of genes that function in Ca^{2+} signaling. A number of these genes such as *CaSR* (77, 339), *ITPKC* (177), and *Orai1* (78) function in the $InsP_3/Ca^{2+}$ signaling pathway. The Ca^{2+}-sensing receptor (CaSR) is strongly expressed on the basolateral membrane of the thick ascending loop of Henle (TALH) cells where it reacts to increases in extracellular Ca^{2+} by initiating the formation of $InsP_3$ that then releases Ca^{2+} from the ER to activate Ca^{2+} entry through the Orai1 channel. The *ITPKC* gene encodes the $InsP_3$ 3-kinase that phosphorylates and inactivates the Ca^{2+}-mobilizing activity of $InsP_3$ **(FIGURE 2)**. Mutations in the *ITPKC* gene will result in an increase in the $InsP_3/Ca^{2+}$ signaling pathway that will enhance the transepithelial flux of Ca^{2+} that contributes to the formation of kidney stones.

XIII. CONCLUSION

The $InsP_3/Ca^{2+}$ signaling pathway functions to regulate many different cellular processes. The versatility and universality of this signaling pathway is based on two main operational modes. In many cells, it provides the primary Ca^{2+} signal that plays a direct role in regulating processes as diverse as fertilization, cell proliferation, secretion, metabolism, and smooth muscle contraction. Its other mode of action is to modulate the activity of various excitable cells such as neurons, insulin-secreting beta cells, as well as cardiac and skeletal muscle. In these cells the primary Ca^{2+} signal is generated by the entry of Ca^{2+} through voltage-operated channels and the release of Ca^{2+} from internal stores by RYRs. The generation and function of this voltage-dependent primary Ca^{2+} signaling system is altered in subtle ways by the modulatory activity of the $InsP_3/Ca^{2+}$ signaling pathway.

What is remarkable about the primary and modulatory actions of the $InsP_3/Ca^{2+}$ pathway is how it has been implicated in a large number diseases including some of the major human diseases such as cardiac and Alzheimer's diseases. The formation of $InsP_3$ is inhibited by Li^+ and the release of Ca^{2+} by the $InsP_3Rs$ is inhibited by caffeine. These two drugs have now been shown to alleviate or reduce the symptoms of a number of diseases such as Alzheimer's disease, bipolar disorder, Huntington's disease, and acute pancreatitis.

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DISCLOSURES

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