



S100 calcium binding proteins and ion channels

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S100 Ca²⁺-binding proteins have been associated with a multitude of intracellular Ca²⁺-dependent functions including regulation of the cell cycle, cell differentiation, cell motility and apoptosis, modulation of membrane–cytoskeletal interactions, transduction of intracellular Ca²⁺ signals, and in mediating learning and memory. S100 proteins are fine tuned to read the intracellular free Ca²⁺ concentration and affect protein phosphorylation, which makes them candidates to modulate certain ion channels and neuronal electrical behavior. Certain S100s are secreted from cells and are found in extracellular fluids where they exert unique extracellular functions. In addition to their neurotrophic activity, some S100 proteins modulate neuronal electrical discharge activity and appear to act directly on ion channels. The first reports regarding these effects suggested S100-mediated alterations in Ca²⁺ fluxes, K⁺ currents, and neuronal discharge activity. Recent reports revealed direct and indirect interactions with Ca²⁺, K⁺, Cl⁻, and ligand activated channels. This review focuses on studies of the physical and functional interactions of S100 proteins and ion channels.

Keywords: S100, calcium binding protein, ion channel, EF-hand

ION CHANNELS

Ion channel proteins form hydrophilic pores integrated into lipid bilayer membranes allowing the passage of ions into and out of cells. Channels are incorporated not only in the plasma membrane, but also in membranes of intracellular organelles, including the endoplasmic reticulum, nuclear membrane, and mitochondria. Ion channels are found early in the evolution of life and are essential for the function of cells in every organism from bacteria, protozoa, and plants, to animals. Their functions range from the

modulation of bioelectric processes, such as sensory transduction, action potential generation and propagation, and synaptic transmission, to muscle contraction and osmoregulation, control of hormone release, and cell cycle coordination (e.g., in Hille, 2001; Weiger et al., 2002). Many ion channels are highly selective for a certain type of ion, such as K⁺, Na⁺, Ca²⁺, or Cl⁻; others, like NMDA or AMPA receptors, are less selective and allow different cations to pass. An element known as the selectivity filter within the channel pore is the critical determinant of what type of ions can be transmitted by a channel.

Conformational changes between closed, open, and inactive states are termed channel gating. Since there are many channels within a membrane, the equilibrium between these conformational states determines the amount of current that flows across the membrane as a function of time. Importantly, channel gating is initiated by: (i) changes of the voltage across the membrane, (ii) binding of ligands such as neurotransmitters, hormones, intracellular messengers (e.g., Ca²⁺, cyclic nucleotides), (iii) mechanical stress to the protein or via the cytoskeleton linked to channels, or (iv) covalent modifications such as protein phosphorylation, carboxylation, or sulfuration (Levitani, 1999; Hermann et al., 2012). Ion channels can be blocked by chemical agents or by peptide toxins, which can be used for separation of ion currents or for identification of certain types of channels. Modifications to channel gating function can occur across a large range of timescales from milliseconds to hours or even days. Long-term changes of the electrical excitability of neurons may be considered as a kind of cellular memory.

Mutations at ion channels are involved in causing a number of diseases, including diabetes, epilepsy, heart failure, myotonia, and deafness (Shieh et al., 2000; Ashcroft, 2006; Bernard and Shevell,

Abbreviations: 5-HT, serotonin receptor; AMPA, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; ASIC, acid-sensing ion channels; BK, big or large conductance calcium activated K⁺ channels; Ca²⁺, calcium ion; CaBP, calcium binding protein; cAMP/PKA/CnA, cyclic adenosine monophosphate/protein kinase A/calmodulin dependent protein phosphatase; CFTR, cystic fibrosis transmembrane conductance; cGMP, cyclic guanosine monophosphate; C-terminal, carboxy terminus of proteins; Cl⁻, chloride ion; D3–D4, linker between domains 3 and 4 (channel); EF-hand, helix-loop-helix structural motif of calcium binding proteins; EK, potassium equilibrium potential; hEAG, human ether a-go-go K⁺ channel; IK, calcium activated intermediate conductance K⁺ channels; IQ motif, proteins that contain IQ motifs typically bind calmodulin in the absence of Ca²⁺; K⁺, potassium ion; K_{2p}, two-pore domain K⁺ channel; K_{ir}, inward rectifier K⁺ channel; K_v, voltage gated K⁺ channel; KRR, lysine–arginine–arginine; L-type Ca²⁺ channel, voltage gated Ca²⁺ channel with large conductance and long-lasting activation; MAPK, mitogen-activated protein kinase; Mn²⁺, manganese ion; Na⁺, sodium ion; Na_v, voltage gated Na⁺ channel; NMDA, N-methyl-D-aspartate; N-terminal, amino-terminus of proteins; p11, S100A10 protein; PKA, protein kinase A; pS, piko Siemens; RAGE, receptor for advanced glycation end products; ROS-GC, rod outer segment guanylate cyclase; RyR, ryanodine receptor; S100, protein soluble in 100% ammonium sulfate; S100B-s-s, disulfide linked form of S100B; S1–S6 TMS, transmembrane segments 1–6 (channel); SCG, superior cervical ganglion; SK, small conductance calcium activated K⁺ channels; SR, sarcoplasmic reticulum; SSV, serine–serine–valine; TASK, TWIK-related Acid Sensitive K⁺ channel; TMS, transmembrane segments; T-tubulus, transverse tubulus (muscle); TRP, transient receptor potential; TTX, tetrodotoxin; Zn²⁺, zinc ion.

2008; Kullmann, 2010). Patch clamp techniques have proven as powerful means to study ion channels in action. Together with molecular biology techniques, in particular site-directed mutagenesis, it has become possible to investigate intimate details of channel structure and function, and the molecular basis for channel-associated diseases.

A number of ion channels are activated or modulated by intracellular Ca^{2+} signals giving rise to the notion that Ca^{2+} binding proteins (CaBP) may play a role in regulating channel gating function. For example, CaBPs have been found to modulate neuronal electrical discharge activity (Celio, 1986; Kawaguchi et al., 1987; Barger and van Eldik, 1992; Hermann and Kerschbaum, 1994; Kubista et al., 1999; Burgoyne and Weiss, 2001; Schwaller, 2010). These effects are based on either alterations of intracellular Ca^{2+} , which secondarily affects ion channels, transmitter release, and activation of second messengers, or on direct action of a CaBP on ion channels (i.e., in Neher and Sakaba, 2008; Nejatbakhsh and Feng, 2011). Some K^+ , Na^+ , and Cl^- channels are regulated directly by intracellular Ca^{2+} . Among these, Ca^{2+} -activated K^+ channels are prominent in this respect, as they are found in a wide variety of excitable and non-excitable cells and in many species. The most prominent of these CaBPs is the ubiquitous intracellular Ca^{2+} sensor calmodulin. Ca^{2+} -dependent regulation of ion channels was reviewed 6 years ago (Shah et al., 2006a). Here, we focus on the relatively recent and growing evidence for roles played by the S100 proteins.

S100 CALCIUM BINDING PROTEINS

S100 proteins are a group of >20 EF-hand Ca^{2+} -binding proteins that are distinguished by several unique characteristics including expression in a cell-specific manner and functions in both intracellular and extracellular contexts (Donato, 2001; Heizmann, 2002; Chazin, 2011). The proteins appear to be exclusively expressed in vertebrates on the basis of genomic analyses, which points to specialized roles evolved late in evolution. These roles are believed to involve the refinement or fine tuning of cell-specific activities and/or responses. Of the 24 human S100 genes, 19, plus a number of S100A pseudogenes are located within chromosome 1q21. Other gene locations include S100A11P, which maps to chromosome 7q22-q3, S100B, which maps to chromosome 21q22, S100G, which maps to chromosome Xp22, S100P, which maps to chromosome 4p16, and S100Z, which maps to chromosome 5q13 (Marenholz et al., 2004). S100 proteins are distinguished from other EF-hand proteins by the unique manner in which they bind Ca^{2+} ions in their N-terminal binding sites, a distinctive dimeric architecture, and the ability to bind transition metals such as zinc, copper, and manganese at histidine-rich binding sites at the dimer interface. The large number of atomic resolution structures determined for S100 proteins reveal a very common structure. Thus, they can be best classified on the basis of their functional roles (for overview of structure and function of S100 proteins see Donato, 2001, 2003; Heizmann, 2002; Chazin, 2011).

S100 proteins regulate a diverse array of cellular activities, including the cell cycle (Arcuri et al., 2005; Brozzi et al., 2009), cell differentiation and survival (Arcuri et al., 2005; Tsoporis et al., 2005; Rosenberger et al., 2007; Cheng et al., 2008; Tubaro et al., 2010; Beccafico et al., 2011; Liu et al., 2011; Riuzzi et al., 2011),

apoptosis (van Dieck et al., 2009; Lin et al., 2010; Tubaro et al., 2011), cell motility (Brozzi et al., 2009; Chen et al., 2009), membrane-cytoskeleton interactions and cytoskeleton dynamics (Donato, 2001; Brozzi et al., 2009), intracellular Ca^{2+} homeostasis (Donato et al., 2009; Rohde et al., 2010), transduction of intracellular Ca^{2+} signals (Donato, 2001; Heizmann, 2002; Gilquin et al., 2010), learning and memory (Nishiyama et al., 2002), phototransduction (Pozdnyakov et al., 1997; Rambotti et al., 1999; Duda et al., 2002), adaptive responses to antidepressants (Svenningsson and Greengard, 2007; Rescher and Gerke, 2008; Baudry et al., 2010), and innate and adaptive immunity (Donato, 2001; Heizmann, 2002; Bode et al., 2008). They are also associated with a wide array of pathological conditions such as inflammation (Donato, 2001, 2007; Heizmann, 2002; Vogl et al., 2007; Cheng et al., 2008; Donato et al., 2009; Ehrchen et al., 2009; Hsu et al., 2009; Hofmann Bowman et al., 2010; Lim et al., 2010, 2011; Wolf et al., 2011a), cancer (Donato, 2001, 2007; Heizmann, 2002; Emberley et al., 2005; Stein et al., 2006; Ismail et al., 2008; Chen et al., 2009; Donato et al., 2009; Slomnicki et al., 2009; van Dieck et al., 2009; Lin et al., 2010; Malashkevich et al., 2010; Wolf et al., 2011b), diabetes and its complications (Eggers et al., 2011), atherosclerosis (Averill et al., 2011), mood and personality disorders (Steiner et al., 2010, 2011), and neurodegeneration (Donato, 2001, 2007; Heizmann, 2002; Donato et al., 2009; Sorci et al., 2010).

Most S100 proteins exert intracellular regulatory activities by interacting with specific target sites in a Ca^{2+} -dependent manner (Donato, 2003; Bhattacharya et al., 2004; Donato et al., 2009; Zimmer and Weber, 2010). At low internal Ca^{2+} concentration, as in the resting state of cells, S100 proteins occupy a closed relatively hydrophilic conformation. During cell activation the intracellular Ca^{2+} concentration increases due to Ca^{2+} influx via plasma membrane Ca^{2+} channels or liberation from intracellular Ca^{2+} stores such as the endoplasmic or sarcoplasmic reticulum (SR). S100 proteins have affinities for Ca^{2+} in a range that allows them to respond to these higher Ca^{2+} concentrations (with one exception of S100A10, which is Ca^{2+} insensitive). Binding of Ca^{2+} to S100s exposes hydrophobic sites, which enable them to interact with specific target proteins or membranes (Bhattacharya et al., 2004). A great variety of targets have been identified over the years, including enzymes, cytoskeletal constituents, transcription factors, scaffolding proteins, unsaturated fatty acids, channels, receptors, signaling molecules, and toll-like receptor ligands (Donato, 2003; Sorci et al., 2011). Thus, S100 proteins are extremely versatile and are able to perform functions in an array of cellular pathways.

Some S100 proteins can be secreted and have the potential to act on the external surface of plasma membranes. In contrast to intracellular function, extracellular S100 proteins will have all Ca^{2+} binding sites occupied so the molecular basis for their function is dependent on other properties, including their ability to oligomerize or to bind transition metals such as Zn^{2+} and Mn^{2+} . Due to their hydrophobic nature in the Ca^{2+} loaded state, it is possible that S100 proteins may directly interact with the lipid phase of the membrane (Curatola et al., 1985; Zolese et al., 1988) and perturbation of membrane lipids may affect membrane channel activity. Direct interactions of S100G with phospholipids have been characterized (Malmendal et al., 2005). S100 proteins could also act at the extracellular face on membrane localized proteins such as

receptors or ion channels. One such receptor is RAGE (receptor for advanced glycation end products), which is found in inflamed tissue and in several human cancers. RAGE binds and signals through a number of S100 proteins, including S100A1, S100A2, S100A5, S100A6, S100A7, S100A8/A9, S100A11, S100A12, S100A13, S100B, and S100P in a high number of cell types (Donato, 2007; Heizmann et al., 2007; Ghavami et al., 2008; Leclerc et al., 2009; Beccafico et al., 2011; Eggers et al., 2011). In addition, G-protein-coupled receptors, scavenger receptors, and toll-like receptor 4 transduce effects of certain S100 proteins (Vogl et al., 2007; Yan et al., 2008; Pietzsch and Hoppmann, 2009; Hoppmann et al., 2010). Lastly, S100A4 and S100B interact with epidermal growth factor ligands and basic fibroblast growth factor, respectively (Klingelhöfer et al., 2009; Riuzzi et al., 2011, 2012) thereby enhancing cognate receptor activity. External binding of S100 proteins to ion channels has, however, not been reported so far.

S100 PROTEINS AND MODULATION OF ION CHANNELS

The first reports relating to an S100 protein (likely S100B) modulating channel activity involved effects on discharge activity in mollusk neurons (Shtark et al., 1981; Nikitin et al., 1988). In particular, anti-S100 antiserum was found to inhibit electrical activity of these neurons and caused a reduction of both inward and outward currents (Pozdnyakova, 1988; Andrianov et al., 2003; Gainutdinov et al., 2006; Timoshenko et al., 2009). From these studies it was concluded that the S100-antigen is accessible to S100 antibodies and therefore is localized at the plasma membrane. S100 immunoreactivity was also found in protozoa, earthworms, crustacean, and insects (Michetti and Cocchia, 1982; Endo and Endo, 1988). In the snail (*Helix pomatia*) central nervous system, an S100 immunoreactive protein of 12–14 kDa, as revealed by Western blot analysis, was localized in a subpopulation of neurons (Kubista et al., 1996). These neurons are specified by their spontaneous discharge activity and a prominent Ca^{2+} -activated K^+ outward current (Hermann et al., 1995). S100 immunoreactivity was present in neurons, but not in glial cells, endocrine cells, or in muscle, and its presence was correlated with spontaneous discharge activity of these cells. Extracellular S100B-s-s, a disulfide linked form of S100B, which is secreted and/or released from several mammalian cells (Donato et al., 2009) in nanogram quantities caused hyperpolarization of the membrane resting potential and inhibition of the spontaneous discharge activity of action potentials (Kubista et al., 1999). Furthermore, the stimulus–response property of neurons was found to be altered from tonic to phasic discharge, the duration of action potentials was decreased, their after hyperpolarization increased, and the membrane input resistance reduced. Voltage clamp experiments revealed that the total outward current was increased by S100B-s-s-. Detailed analysis of outward currents showed that three types of K^+ currents were altered: the inward rectifying current was increased by S100B-s-s- as was the Ca^{2+} -activated K^+ outward current, whereas the delayed, voltage-dependent K^+ current was decreased. The transient K^+ outward current and the Ca^{2+} inward current also present in these neurons were not affected by S100B-s-s-. Immunocytochemistry revealed that after extracellular application of S100B-s-s-, intracellular labeling of the cytoplasm revealed internalization. Injection of S100A1 mimicked the effects of S100B-s-s- on discharge activity and action

potentials. From these experiments it was concluded that S100 may play a role as neuromodulator in nervous functions (Kubista et al., 1999). Although evidence is still missing that S100 proteins are present in invertebrates there are clear effects on electrical activity, which indicates that channel proteins interact with S100 and alter their conductive properties.

S100s AND Ca^{2+} CHANNELS

Recently, ion channels have been recognized as potential targets for S100 proteins. S100A1, for example, increases the L-type Ca^{2+} channel current in embryonic mouse and neonatal rat ventricular cardiomyocytes. Because protein kinase A (PKA) block abolished the S100A1 effect on Ca^{2+} channels it was concluded that a S100A1 mediated increase of PKA enhances Ca^{2+} influx (Reppel et al., 2005). Chronic deficiency of S100A1 in knock-out mice results in an elevated Ca^{2+} inward current but a blunted β -adrenergic response due to an impaired fractional Ca^{2+} release mechanism from intracellular stores (Gusev et al., 2009).

S100A10, also known as p11 or calpactinI light chain, is “ Ca^{2+} insensitive” because of mutations within the Ca^{2+} binding loops of its EF-hands. The S100A10 molecular structure is equivalent to the Ca^{2+} bound forms of other S100 proteins with exposed hydrophobic sites which render the protein in a permanently active state. The protein associates with annexin 2 into a heterotetrameric complex and hence is able to specifically target membranes (Gerke and Moss, 2002; Rescher and Gerke, 2008). Ca^{2+} binding to annexin 2 (a phospholipid and Ca^{2+} binding protein) allows for interaction with membranes. Thus, S100A10-annexin 2 can link proteins to membranes or attach to and modulate other proteins. Interestingly, the protein predominantly binds to the plasma membrane where it interacts for example with phosphatidylinositol-bisphosphate ($\text{PI}(4,5)\text{P}_2$) or cholesterol-rich domains (Rescher et al., 2004). S100A10-annexin 2 has been identified as auxiliary protein in epithelial Ca^{2+} permeant TRPV5 and TRPV6 channels (van de Graaf et al., 2003). TRP (transient receptor potential) channels constitute a superfamily of sensory channels whose functions range from phototransduction (where they were first described), olfaction, heat, cold sensation, etc., to Ca^{2+} sensors/transporters. The TRP Ca^{2+} channels are important for absorption of Ca^{2+} into kidney, placenta, or intestine to maintain systemic Ca^{2+} homeostasis. The S100A10-annexin 2 complex specifically associates with the C-terminal of TRP channels and is suggested to play a role in guiding and localizing channels to the plasma membrane and/or in the modulation of channel activity. The later has been shown by using annexin 2 interfering RNA, which inhibited currents through TRP channels (van de Graaf et al., 2003). S100A10-annexin 2 is also involved in nociceptive function. It appears to act as scaffolding protein that conjugates appropriate proteins at the plasma membrane. Deletion of the proteins exclusively from nociceptive sensory neurons in mice was attended by a loss of TTX-resistant Na^+ ($\text{Na}_v1.8$) channels and compromised neuropathic pain behavior (Foulkes et al., 2006).

S100A10-annexin 2 also interacts with acid-sensing ion channels (ASIC1a; Donier et al., 2005). Coexpression of S100A10-annexin 2 and the ASIC1a channels led to an increased expression of ion channels at the plasma membrane and a concomitant increase of the peak current. Since no other parameters

were affected it was suggested that the primary role of S100A10-annexin 2 is to enhance the expression of the acid-sensing channels in the plasma membrane, which supports the notion of S100A10-annexin 2 functioning as trafficking device.

S100B and likely S100A1 interact with and stimulate rod outer segment and photoreceptor bipolar cell synapse membrane guanylate cyclase (ROS-GC1), which is a bimodal Ca^{2+} signal transduction switch that increases its rate of cyclic GMP synthesis when intracellular Ca^{2+} rises to high levels and when Ca^{2+} falls to very low levels (Pozdnyakov et al., 1997; Rambotti et al., 1999; Duda et al., 2002). S100B and likely S100A1 stimulate photoreceptor ROS-GC1 activity as Ca^{2+} approaches micromolar levels, i.e., when photoreceptors are dark adapted, implying that S100B and likely S100A1 are important in dark adaptation. Thus, S100B and S100A1 indirectly regulate a photoreceptor Ca^{2+} channel via stimulation of ROS-GC1. However, S100B and S100A1 also activate a membrane bound guanylate cyclase in retinal Müller cells (Rambotti et al., 1999), and S100B stimulates a membrane bound guanylate cyclase in the photoreceptor bipolar synapse (Duda et al., 2002), which suggests that at those sites also at least S100B might indirectly regulate Ca^{2+} flux via activation of a membrane bound guanylate cyclase.

S100A1 and S100B each promote Ca^{2+} flux across artificial membranes (Garbuglia et al., 2000) as do annexins 5 and 6 (Gerke and Moss, 2002). S100A1 and S100B interact with annexins 5 and 6 which results in reduced ability of these two annexins and of S100A1 and S100B to stimulate Ca^{2+} flux across artificial membranes likely via reciprocal sequestration within the cytoplasm (Garbuglia et al., 2000). These four proteins are located close to or on skeletal muscle membrane structures such as the sarcolemma, the sarcoplasmic reticulum, and T-tubules (Arcuri et al., 2002) that are critically involved in the regulation of Ca^{2+} fluxes. This suggests that S100A1 and S100B might modulate the proposed Ca^{2+} channel activity of annexins 5 and 6 and/or annexin 6-dependent regulation of Ca^{2+} release from the sarcoplasmic reticulum (Díaz-Muñoz et al., 1990).

Signaling via ion channels appears to be also involved in regulation of S100B secretion. Hippocampal brain slices in the absence of extracellular Ca^{2+} or low K^{+} caused an increase of S100B secretion (probably by internal Ca^{2+} liberation which is a common mechanism in glial cells), whereas high extracellular K^{+} or Ca^{2+} channel blockers had the opposite effect (Nardin et al., 2009). This may be relevant during/after neuronal activity, particularly after excessive excitation such as in epileptic seizure, where within a small interstitial volume around cells ion concentrations may change significantly.

S100A1 binds to ryanodine receptors at nanomolar Ca^{2+} concentrations and enhances Ca^{2+} release in skeletal and in cardiac muscle (Treves et al., 1997; Prosser et al., 2008; Wright et al., 2008). Ryanodine receptors are L-type Ca^{2+} channels located in the SR, which after opening allow Ca^{2+} ions to flow down their electrochemical gradient from the higher concentration with the SR to the lower concentrated cytoplasm. S100A1 increased the open probability of the ryanodine Ca^{2+} channels reconstituted into planar lipid bilayers (Treves et al., 1997). S100A1, after binding of Ca^{2+} exposes hydrophobic pockets and competes with calmodulin for the same binding site, which is conserved in striated

muscle (Schäfer and Heizmann, 1996). S100A1 knock-out mice exhibit decreased action potential evoked Ca^{2+} release via SR ryanodine receptors (Prosser et al., 2010). From these experiments it appears that intracellular S100A1 regulates Ca^{2+} channels that subsequently promote muscle contractility. The authors further examined the effect of S100A1 on the voltage sensor of excitation–contraction coupling (Prosser et al., 2009a,b). Depolarization of the transverse (T) tubulus system by action potentials that spread over the muscle sarcolemma acts at the voltage sensor of the ruthenium/calcium receptor/channel. The conformational changes of the protein mechanically transmit to dihydropyridine receptors, which are also L-type Ca^{2+} channels, located in the SR membrane. Charge movement within these channels is responsible for opening and release of Ca^{2+} from the SR. Part of the charge movement, the so called “delayed charge movement” (termed Q_{gamma}), is selectively suppressed in S100A1 knock-out muscle fibers. Both, skeletal and cardiac ryanodine receptors are regulated this way by S100A1. The Q_{gamma} component activated by S100A1, however, appears not to be linked to gating of dihydropyridine Ca^{2+} channels, but is more likely involved in the excitation–contraction coupling machinery (Prosser et al., 2009a). S100A1 also improves Ca^{2+} cycling and contractility in cardiac muscle (Most et al., 2007) and increased Ca^{2+} release and force of contraction in skinned muscle fibers (Most et al., 2003).

Cardiomyocytes secrete S100A1 during ischemia which is taken up by superior cervical ganglion (SCG) neurons (which do not contain the protein) and distribute the protein intracellularly via axonal transport (Hernández-Ochoa et al., 2009). Extra- or intracellularly applied S100A1 enhanced voltage activated Ca^{2+} channels dependent on PKA activity, prolonged action potentials, and augmented transient cytosolic Ca^{2+} increase. S100A1 was shown to directly interact with PKA and this complex appears to affect Ca^{2+} channels. S100A1 therefore appears to act as a signaling molecule that increases sympathetic output.

S100s AND K^{+} CHANNELS

K^{+} channels are the most abundant and versatile kind of channel ubiquitously present in cells. K^{+} channels once activated allow K^{+} ions to move down their electrochemical gradient, which is usually from inside (high concentration and negative membrane potential) to the external side of the plasma membrane. Since the equilibrium potential (E_{K}) for K^{+} is negative ($E_{\text{K}} \sim -60$ to -90 mV in nerve and glial cells), opening of K^{+} channels drives the membrane potential toward the equilibrium for K^{+} and causes hyperpolarization of cells. K^{+} channels are therefore involved in establishing and maintenance of the membrane resting potential, in repolarization of action potentials, or in membrane potential oscillations. In essence K^{+} channels provide a negative feedback to adjust the excitability of cells.

The many types of K^{+} channels are classified into three major families depending on their number of transmembrane segments/helices (TMS). Formation of a functional channel involves the assembly of two to four units, depending on the number of TMSs in each family. The simplest K^{+} channel is the four times two helix set, each containing a pore loop (P) and together forming the channel – the so called “inward rectifier,” K_{ir} (2TMS/1P) channel. Doubling of this basic structure yields four helices each

containing two pore loops. Dimerization in the membrane provides four pore loops which form a channel – the so called “two-pore domain K⁺ channels” (K_{2P} or 4TMS/2P). These channels are highly sensitive and modulated by external pH, by neurotransmitters and hormones and are a target of volatile anesthetics (review Lotshaw, 2007; Mathie et al., 2010). These types of channels contribute to the membrane resting potential and are involved in modulating electrical activity of cells. The “voltage-dependent K⁺ channels” consist of 6 TMS containing 1 pore loop (6TMS/1P) each and on tetramerisation in the membrane assemble to one K⁺ channel (Armstrong, 2003). A variation of this channel type has 7 transmembrane segments (7-TMS) and a long C-terminus that provides binding of Ca²⁺ ions – these channels therefore have been termed “Ca²⁺ activated K⁺ channels” (for recent reviews see Berkefeld et al., 2010; Lee and Cui, 2010; Wu et al., 2010).

Ca²⁺ activated K⁺ channels are divided into three subfamilies mainly defined by their biophysical and pharmacological properties. (a) Three types of “small K or SK channels” identified have a single channel conductance (γ) of ~ 10 pS, are voltage independent, associated with the EF-hand Ca²⁺-binding protein calmodulin, activated by Ca²⁺ binding to calmodulin, and some are specifically blocked by the bee toxin apamin. (b) “Intermediate K or IK channels,” which have a γ of 20–80 pS, are constitutively associated with calmodulin, which is bound to the C-terminal of the protein and confers Ca²⁺ sensitivity to the channels. These channels have no or only weak voltage dependence and are blocked by charybdotoxin (from scorpion) but are resistant to blockade by apamin or iberiotoxin (scorpion toxin). (c) “Big (large or maxi) conductance K⁺ channels (big K, BK)” with a γ of 100–300 pS are activated by Ca²⁺/Mg²⁺ ions and membrane voltage synergistically. These channels are specifically blocked by iberiotoxin and modulated by a great variety of compounds such as ethanol, polyamines, or gasotransmitters (Weiger and Hermann, 1994, 2009; Jakab et al., 1997; Hermann et al., 2012). The various types of SK, IK, or BK channels can be expressed alone or in combination in many cells and tissues, as in the nervous or the vascular system. These types of K⁺ channels are involved in action potential repolarization, modulation of action potential frequency, or oscillatory electrical discharge activity.

In some Ca²⁺ activated K⁺ channels calmodulin exerts important functions as Ca²⁺ sensor at the internal side as outlined above. Since certain S100 proteins are able to compete with calmodulin (Schäfer and Heizmann, 1996), this allows them to interact with ion channels via this pathway. Ca²⁺ activated BK channels typically contain Ca²⁺ binding sites (of non EF-hand type) at their C-terminal end. There is some indication that Ca²⁺ activated K⁺ conductance of invertebrate neurons is increased by S100 proteins (Kubista et al., 1999). It should be noted that various S100 proteins (A1, A6, A8, A9, A10, A13, and B) are enriched in cochlea, which also expresses BK channels (Pyott et al., 2007). S100 proteins have, however, not been yet reported being involved in activation or modulation of these channels.

In Alzheimer’s disease a correlation between a loss of inward rectifier K⁺ channels (K_{ir}4.1), BK channels, water channels (aquaporin 4), and a gain of S100B-positive astrocytes was found (Wilcock et al., 2009). This has been attributed to a loss of a

common anchoring protein. Efflux of K⁺ ions via BK channels at the astrocyte end feet results in vasodilation, which suggests an important function of these channels in maintenance of vascular tone (Filosa et al., 2006). The correlation to S100B, however, remains elusive.

S100A10-annexin 2 interacts specifically with one of the two-pore domain K⁺ channels (K_{2P}) – termed “TASK-1 channels” (Girard et al., 2002). TASK channels (TWIK-related Acid Sensitive K⁺ channels) are characterized by the absence of activation and inactivation kinetics, hence are voltage independent and therefore are referred to as leak or background conductances involved in setting the membrane resting potential. The channels sense external H⁺ around the physiological pH and are inhibited by hormones and neurotransmitters (Lotshaw, 2007). The association with S100A10-annexin 2 is essential for TASK-1 channel trafficking to the plasma membrane and hence for functionality. The authors found that association requires the presence of a serine-serine-valine (SSV) amino acid sequence in the C-terminus of the channel. Another sequence – lysine-arginine-arginine (KRR) just upstream of the SSV sequence – appeared as retention signal which makes TASK channels to reside within the endoplasmic reticulum. It has been suggested that only after camouflaging the KRR sequence by binding of S100A10-annexin 2 the channels can move to the plasma membrane (Girard et al., 2002).

S100A10-annexin 2 also regulates trafficking of the TTX-resistant Na⁺ channels to the plasma membrane. However, these channels do neither contain a SSV terminal sequence nor a KRR motif but appear to exhibit similar motifs. Using different techniques other authors found that S100A10-annexin 2 is localized to a more distant site to the C-terminal end of TASK-1 and binding of S100A10-annexin 2 to TASK-1 may represent the retention factor that causes channels to remain in the ER hence retarding plasma membrane expression of the channels (Renigunta et al., 2006).

S100B inhibits voltage-dependent and Ca²⁺ sensitive human ether a-go-go (hEAG1) K⁺ channels – a S1–S6 TMS containing 1 pore loop (6TMS/1P) type channel (Sahoo et al., 2010). These K⁺ channels are ubiquitously expressed in neuronal tissue and appear to play a role in tumor proliferation and progression. When applied to the internal face of inside-out patches, S100B caused a Ca²⁺-dependent block of the channels. S100B was further shown to share the same binding sites with calmodulin and hence was suggested to function as an alternative Ca²⁺ sensor for these channels (Sahoo et al., 2010).

S100s AND Cl⁻ CHANNELS

Cl⁻ channels are found in various non-excitabile cells, being involved in volume and pH regulation, cell proliferation, or Ca²⁺ signaling (Suzuki et al., 2006). Cl⁻ channels contain 10 or 12 transmembrane helices but bear no resemblance to cation channels. Functionally, these channels are involved in setting the resting membrane potential of skeletal muscle, in solute transport, in pH and volume regulation, in cell migration, cell proliferation, and differentiation. The S100A10-annexin 2 complex was reported to directly or indirectly activate mechano-/volume-sensitive Cl⁻ channels in endothelial cells (Nilius et al., 1996). S100A10-annexin 2 also relates to the functioning of the cystic fibrosis transmembrane conductance (CFTR) under normal and pathologic

Table 1 | Interactions of S100 proteins with ion channels¹.

S100 protein	Ion channel				Other channels receptors	Reference
	Na ⁺	K ⁺	Ca ²⁺	Cl ⁻		
S100A1			heart, T-type in rods Art. memb. SR RyR/L-type in neurons (SCG)			Reppel et al. (2005) Pozdnyakov et al. (1997), Rambotti et al. (1999), Duda et al. (2002) Garbuglia et al. (2000), Arcuri et al. (2002) Díaz-Muñoz et al. (1990), Treves et al. (1997) Prosser et al. (2008, 2010), Wright et al. (2008), Most et al. (2003) Hernández-Ochoa et al. (2009)
S100B		K _v /hEAG1	in rods		Dopamine D2	Pozdnyakov et al. (1997), Rambotti et al. (1999), Duda et al. (2002), Sahoo et al. (2010), Neve et al. (2004)
S100A10-annexin 2	Na _v 1.8	K _{2p} /TASK		in CFTR	TRP 5, 6, ASC1a, 5-HT _{1B}	van de Graaf et al. (2003), Okuse et al. (2002), Foulkes et al. (2006), Donier et al. (2005), Lotshaw (2007), Girard et al. (2002), Renigunta et al. (2006), Svenningsson et al. (2006)

¹Abbreviations: Art. memb., Artificial membrane; ASC, acid-sensing ion channel; CFTR, cystic fibrosis transmembrane conductance; hEAG, human ether a go-go K⁺ channel; 5-HT_{1B}, serotonin receptor; K_{2p}, two-pore domain K⁺ channel; K_v, voltage gated K⁺ channel; Na_v, voltage gated Na⁺ channel; RyR, ryanodine receptor; SCG, superior cervical ganglion; SR, sarcoplasmic reticulum; TASK, TWIK-related Acid Sensitive K⁺ channel; TRP transient receptor potential.

conditions (Muimo, 2009). Mutations at this protein lead to an impairment of salt and water transport across respiratory, digestive, and reproductive epithelia causing excessive mucous accumulation and/or tissue fibrosis. The S100A10-annexin 2 complex is regulated in these tissues by a cyclic adenosine monophosphate (cAMP)/PKA/calceinurin A (CnA) – protein phosphatase and interacts with CFTR. Inhibition of CnA disrupts complex formation and attenuates CFTR function. Thus only the multi-protein complex associated with S100A10-annexin 2 in its assembled form is able to open CFTR Cl⁻ channels within the cell surface membrane (Borthwick et al., 2007, 2008). In summary, the S100A10-annexin 2 complex is well suited for regulation of membrane receptors and ion channels with annexin providing the attachment to the membrane bilayer and S100A10 providing the link to receptor, ion channel, or cytoskeletal proteins. In some cases the binding motifs for S100A10-annexin 2 are not resolved, as in TTX-resistant Na⁺ or in CFTR channels.

S100s AND LIGAND ACTIVATED CHANNELS

S100B also interacts with and modulates ligand activated channels such as dopamine D2 metabotropic receptors (Liu et al., 2008). Mutations at the dopaminergic system are linked to Parkinson's disease, schizophrenia, or drug addiction (Beaulieu and Gainetdinov, 2011). The dopamine D2 receptor is a 7-TMS receptor that acts via G-proteins G α_i and G α_o inhibiting adenylyl cyclase (AC), K⁺ channels, or the mitogen-activated protein kinase (MAPK; Neve et al., 2004). S100B appears to bind to the D2 receptor's third cytoplasmic loop at the amino acid terminus and this way enhances receptor signaling. The third cytoplasmic loop is also prominent as a contact site for G-protein coupling as well as for binding of calmodulin (Liu et al., 2007). Also the metabotropic serotonin 1B receptor (5-HT_{1B}) has been found

to interact with S100A10-annexin 2 causing an increased localization of the receptors to the plasma membrane (Svenningsson et al., 2006). S100A10-annexin 2 was decreased during depression attacks or depression-like states in knock-out animals but was increased after antidepressant therapy or overexpression. Interactions of S100 proteins with ion channels are summarized in **Table 1**.

RELATIONSHIP TO CALMODULIN – ION CHANNEL INTERACTIONS

It is likely that certain S100 proteins modulate the activity of ion channels by competing with calmodulin for target binding sites (Schäfer and Heizmann, 1996). Hence, some ion channels that are regulated by calmodulin may in fact be modulated by S100 proteins, either under resting conditions or under special circumstances. Whether the effect of S100 proteins is direct or indirect, knowledge of the molecular basis for calmodulin interactions with ion channels may be helpful in discerning how S100 proteins modulate ion channels, in particular since there may well be a similarity in their mode of action. Progress has been made in understanding the molecular basis for calmodulin modulation of voltage activated Ca²⁺ and Na²⁺ channels (Shah et al., 2006a). The mechanism for Ca²⁺-dependent regulation of voltage gated Na⁺ channels (Na_v) is particularly complex, with involvement of calmodulin, a Ca²⁺ binding EF-hand domain in the C-terminal cytoplasmic domain (Wingo et al., 2004) and a calmodulin binding IQ motif just downstream the EF-hand domain (Shah et al., 2006b). These two Ca²⁺ sensors mutually influence each other and modulate the fast inactivation gate in the D3–D4 linker domain (Potet et al., 2009; Sarhan et al., 2009). The physiological relevance of Ca²⁺ regulation of Na_v channels is underscored by mutations in the Ca²⁺ regulatory apparatus being associated with a variety

of heart arrhythmia syndromes. In tetrodotoxin-insensitive Na⁺ channels (Na_v1.8) S100A10-annexin 2 binds to the N-terminus and promotes their translocation to the plasma membrane producing functional channels (Okuse et al., 2002). Increased Na_v1.8 activity has been proposed to cause hyperexcitability of sensory neurons, a mechanism that renders nociceptors more sensitive. Whether S100s also play a role in this context in genuine Na⁺ channels remains to be investigated.

S100 PROTEINS IN NON-VERTEBRATE ORGANISMS?

Sequence comparisons of the genomes of yeast, *Caenorhabditis elegans*, and *Drosophila* revealed no typical S100 genes in these species (Heizmann et al., 2002). The EF-hand CaBP family is well conserved as the motif is even found in bacteria. The inability to recognize S100 proteins in non-vertebrate species may arise because the features of the invertebrate protein sequence deviate from the basic form and therefore cannot be recognized by traditional sequence search algorithms. Also, key to identifying S100 proteins is the unique 14-amino acid, S100-specific Ca²⁺ binding loop in their N-terminal binding site. These key sites may be difficult to identify due to the conservation of only the Glu residue in position 14. Although the S100-specific loop is unique, it is in fact not the most distinguishing characteristic of S100 proteins. Rather, it is their integrated dimeric structural unit that makes S100 proteins different from all other EF-hand CaBPs. Since there is no current method to recognize dimeric proteins based on protein sequence, one cannot completely rule out that S100 proteins are not present in non-vertebrate organisms.

This line of reasoning also suggests that the use of vertebrate S100 antibodies to identify S100 in invertebrates is questionable. The antibodies to invertebrate S100 proteins may need to recognize a different epitope that has no sequence resemblance to vertebrate

S100 proteins. Further studies are necessary to obtain and analyze more sequence and structural information from a range of species to investigate the evolution of this protein family in more detail (Heizmann et al., 2002), and to possibly identify the presence or absence of a S100-like protein in invertebrates. Even if S100-like CaBPs can not be recognized in invertebrates, S100 proteins can clearly affect their electrical discharge activity and alter membrane conductances. Thus, S100 proteins from a vertebrate host have the potential to interact with binding sites on channels or to modulate intracellular signaling to an extent that channel gating is affected in an invading non-vertebrate organism.

CONCLUDING REMARKS

S100 EF-hand proteins exhibit a remarkably diverse range of cellular functions. Accumulating evidence indicates that they can modulate the activities of ion channels. We hypothesize that various ion channels, in particular K⁺ channels, exhibit intracellular binding sites for several S100 proteins, which serve as Ca²⁺ sensor to modulate their electrical behavior. These binding sites may correspond to known sites for the ubiquitous EF-hand Ca²⁺ sensor calmodulin, but might also be distinct. The potential for overlap complicates efforts to assign specific biological functions to S100 proteins. Given the differences in the structural basis for target activation by monomeric calmodulin versus oligomeric S100 proteins, it is conceivable that the effects of S100 proteins will be distinct from those of calmodulin. Further biochemical, structural, and functional studies are required to elucidate the physiological role(s) of S100 protein in modulating the function of ion channels.

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