Ca\textsuperscript{2+} acts as a ubiquitous second messenger to control a wide variety of physiological processes by relaying information within mammalian cells (6). For example, Ca\textsuperscript{2+} signals trigger fertilization, control development and differentiation, coordinate cellular functions, and even play roles in cell death. The large variety of functional effects are dictated by the spatial and temporal nature of the Ca\textsuperscript{2+} signals and by the cellular context in which they occur, that is, the tissue and cell-specific complement of Ca\textsuperscript{2+} influx/efflux pathways and downstream targets determine the final outcome. Cytosolic Ca\textsuperscript{2+} influx typically occurs when Ca\textsuperscript{2+} channels localized to the plasma or endoplasmic reticular membranes open in response to various stimuli such as membrane depolarization or ligand binding (5). Ca\textsuperscript{2+} can be subsequently removed from the cytosol by various mechanisms: sarco/endoplasmic reticulum Ca\textsuperscript{2+} ATPases (SERCA) and plasma membrane Ca\textsuperscript{2+} ATPases (PMCA) utilize the energy from ATP hydrolysis to pump Ca\textsuperscript{2+} into the endoplasmic reticulum or outside the cell, respectively, and Na\textsuperscript{+}/Ca\textsuperscript{2+} exchangers extrude cytosolic Ca\textsuperscript{2+} in exchange for extracellular Na\textsuperscript{+} ions, whereas NCKX proteins extrude cytosolic Ca\textsuperscript{2+} and K\textsuperscript{+} in exchange for Na\textsuperscript{+} ions, which in both cases is referred to as forward mode exchange. In conditions of altered ion gradients and membrane potential, these exchangers can also mediate Ca\textsuperscript{2+} entry or so-called reverse mode operation. Three NCX and five NCKX isoforms have been identified by molecular cloning. NCX1 is predominantly expressed in the heart, brain, and kidney, although it is also present in a broad variety of cell types, whereas NCX2 and 3 expression is limited to brain and skeletal muscle (38, 42, 43). NCKX1 is exclusively expressed in retinal rod outer segments, whereas NCKX2 is expressed in brain and cone photoreceptors (47, 48, 59). NCKX3 and 4 display a broader pattern of tissue expression, although they are also prominently expressed in the brain (31, 36, 39). These observations indicate that NCKX2, 3, and 4 are likely to play important roles in neuronal Ca\textsuperscript{2+} signaling. A fifth member of the NCKX family, NCKX5, is predominantly found in intracellular compartments in skin and the pigmented epithelium of the eye, where it appears to play a critical role in pigmentation (32).

**Localization**

The first K\textsuperscript{-}-dependent Na\textsuperscript{+}/Ca\textsuperscript{2+} exchanger to be identified by molecular cloning was NCKX1 from bovine rod photoreceptors (48). Northern blotting and in situ hybridization have demonstrated that the mRNA encoding for this exchanger is found almost exclusively in rod photoreceptors (39). In contrast, when NCKX2 was cloned, the mRNA for this isoform was found in rat brain and in cone photoreceptors of chicken retina, although it was absent from most other tissues (47, 59). The localization of rat brain NCKX2 was investigated by in situ hybridization where its expression was found to be limited to neuronal cell bodies with particularly notable staining evident in all six layers of the parietal cortex, the molecular layer of the cerebellum, and throughout the neurons of the hippocampus, with CA3 neurons containing the highest levels. NCKX2 expres-
FIGURE 1. Physiological contexts for NCKX function in Ca\(^{2+}\) signaling

A: Ca\(^{2+}\) signaling in presynaptic and postsynaptic nerve terminals. Presynaptically, Ca\(^{2+}\) entry occurs via voltage-operated Ca\(^{2+}\) channels (VOCC) and is subsequently extruded across the plasma membrane in exchange for extracellular Na\(^{+}\) either alone (NCX) or together with K\(^{+}\) ions (NCKX). Na\(^{+}\) entry via voltage-gated Na\(^{+}\) channels (Nav) inactivates both the NCX and NCKX exchangers (dashed red lines). The plasma membrane Ca\(^{2+}\) ATPase (PMCA) maintains a low resting level of cytosolic Ca\(^{2+}\). Ca\(^{2+}\) entry triggers exocytosis of neurotransmitter (glutamate)-containing vesicles, resulting in glutamate release and binding to postsynaptic NMDA or AMPA receptors. Agonist binding by NMDA and AMPA receptors induces Ca\(^{2+}\) entry, resulting in membrane depolarization, and the elevated Ca\(^{2+}\) is subsequently removed by NCX and NCKX proteins. Glutamate binding to G-protein coupled metabotropic glutamate receptors (mGluR) results in activation of phospholipase C (PLC) and the production of inositol triphosphate (IP3) and diacylglycerol (DAG). IP3 can bind to IP3 receptors on the endoplasmic reticulum (ER), resulting in the release of Ca\(^{2+}\) that is taken back up by the sarco/endoplasmic reticulum Ca\(^{2+}\) ATPase (SERCA). DAG activates PKC, which enhances the activity of NCKX2 (dashed green arrow).

B: Ca\(^{2+}\) signaling in rod photoreceptor outer segments. In the dark, cGMP channels are constitutively open, allowing Na\(^{+}\) and Ca\(^{2+}\) entry and resulting in membrane depolarization. Illumination of Rhodopsin results in activation of the G-protein transducin that activates cyclic nucleotide phosphodiesterase (PDE), which subsequently hydrolyzes cGMP. The reduction in cGMP levels results in closure of cGMP-gated channels and reduced Ca\(^{2+}\) entry, hyperpolarizing the membrane and allowing NCKX1 to rapidly extrude Ca\(^{2+}\), hyperpolarizing the membrane and initiating the photoreceptor electrical response by reducing the release of inhibitory neurotransmitters at the photoreceptor synapse. Rapid NCKX1-mediated Ca\(^{2+}\) extrusion results in reduced Ca\(^{2+}\) levels, activating Guanylyl cyclase, which resynthesizes cGMP to re-open the cGMP-gated channels. C: putative Ca\(^{2+}\) entry mechanism across the melanosomal membrane. Vesicles derived from the ER and trans-golgi network (TGN) undergo a four-stage process to become fully mature melanosomes, a process that apparently requires Ca\(^{2+}\) ions. The acidic interior of the maturing melanocyte is generated by the action of the V-ATPase proton pump, which drives Na\(^{+}\)/H\(^{+}\) exchange (NHE), generating a Na\(^{+}\) gradient utilized by NCKX5 for melanosomal Ca\(^{2+}\) uptake.
...signaling and have demonstrated that in situ hybridization and were also found to be restricted to neuronal cell bodies (31, 36). NCKX3 displayed particularly strong staining throughout the thalamus, CA1 hippocampal neurons, and cortical layer IV, whereas NCKX4 expression was restricted to the anterodorsal nucleus of the thalamus, throughout the hippocampal neurons, and in cortical layers II to VI. The physiological significance of the apparently distinct localization patterns of the various NCX and NCKX isoforms in brain is not fully understood, although it could be anticipated that different neuronal subtypes will have distinct Ca\(^{2+}\)-handling requirements for which the functional, thermodynamic, and regulatory properties of the various exchanger isoforms will be uniquely suited. For example, in cells where plasma membrane Ca\(^{2+}\) flux is very high and membrane potential dramatically reduced, only the NCX exchangers would have sufficient thermodynamic driving force to extrude Ca\(^{2+}\) by virtue of their K\(^+-\)dependence. Furthermore, the various NCX and NCKX isoforms, if present in the same cell, may be restricted to particular subcellular locations where they may play important roles in localized Ca\(^{2+}\) signaling events such as those that occur in dendritic spines (2, 49).

Interestingly, multiple tissue northern blotting and reverse-transcriptase PCR have revealed that, unlike NCKX1 and 2, NCKX3–5 display significant expression in tissues other than eye and brain (32, 39). NCKX3 displayed an almost ubiquitous pattern of expression, whereas NCKX4 expression was somewhat more limited but notable in aorta, small and large intestine, lung, and adrenal gland. These results suggest that NCKX3 and 4 may also play roles in Ca\(^{2+}\) signaling in smooth muscle cells as well as nonexcitable cell types. Recently, K\(^+-\)-dependent Na\(^{+}/Ca\(^{2+}\) exchange activity was demonstrated in arterial smooth muscle in which NCKX3 and 4 mRNA and protein expression were also detected (10). NCKX5 also displays a broad tissue distribution, although it is most abundant in the skin and pigmented epithelium of the eye (32). Nonetheless, its presence in multiple tissues suggests that this protein may contribute to other Ca\(^{2+}\) signaling events in addition to those involved in skin pigmentation. These were the first studies to identify NCKX proteins outside the brain, but the physiological significance of these exchangers in nonneuronal tissues remains a largely unexplored area of investigation.

**Neuronal Physiology**

In neurons, Ca\(^{2+}\) signals are critical at both presynaptic and postsynaptic sites (**FIGURE 1A**). Presynaptically, Ca\(^{2+}\) influx occurs upon membrane depolarization via voltage-gated channels, which initiates the fusion of vesicular compartments containing neurotransmitters with the plasma membrane. Postsynaptically, Ca\(^{2+}\) entry and subsequent membrane depolarization occurs via ligand-gated channels such as the NMDA and AMPA receptors. The elevated cytosolic Ca\(^{2+}\) is subsequently removed by various plasma membrane transporters, including PMCA, NCX, and NCKX proteins (2). Several studies have investigated the relative contributions of the various Ca\(^{2+}\)-clearance mechanisms in neuronal Ca\(^{2+}\) signaling and have demonstrated a prominent role for K\(^+-\)dependent Na\(^{+}/Ca\(^{2+}\) exchangers. In acute preparations of axon terminals from rat neurohypophysis (posterior pituitary), >60% of the Ca\(^{2+}\) clearance was mediated via Na\(^{+}/Ca\(^{2+}\) exchangers, -90% of which was dependent on K\(^+\) (34). Furthermore, a follow-up study demonstrated that NCKX2 was likely to be responsible for the observed K\(^+-\)-dependent Ca\(^{2+}\) clearance from these neurons and that the NCKX contribution was localized to the axon terminals, whereas in the somata other Ca\(^{2+}\)-clearance mechanisms predominated (27). A prominent contribution by K\(^+-\)-dependent Na\(^{+}/Ca\(^{2+}\) exchangers was also recently demonstrated at the mammalian giant presynaptic terminal, the calyx of Held (26). Lastly, consistent with the in situ hybridization studies, NCKX activity has been shown to predominate in hippocampal CA1 neurons, whereas NCX activity predominated in forebrain neurons (24, 25). The results of these studies have demonstrated that NCKX proteins play important functional roles in neuronal Ca\(^{2+}\) signaling, although the precise impact of these exchangers on neuronal function is only beginning to be elucidated. Recently, knockout mice lacking NCKX2 were shown to display deficits in motor learning and memory that could be attributed to compromised hippocampal synaptic plasticity (35). Future studies on acute brain preparations and cultured neurons from mice lacking specific NCKX isoforms will more clearly define their functional roles in Ca\(^{2+}\) signaling and the subsequent impact on neuronal function.

**Vision**

The role of NCKX1 in photoreceptor physiology has been clearly defined (**FIGURE 1B**). NCKX1 is associated in a hetero-oligomeric complex with cGMP-gated channels, which are constitutively open in the dark...
(19). The combined activities of the NCKX1-mediated Ca\(^{2+}\) extrusion and Ca\(^{2+}\) influx through the cGMP-gated channels results in a resting Ca\(^{2+}\) level of ~500 nM. NCKX1 is ideally suited for Ca\(^{2+}\) extrusion under these conditions because its K\(^+\) dependence provides an additional thermodynamic driving force to extrude Ca\(^{2+}\) in the face of depolarized membrane potentials resulting from Ca\(^{2+}\) and Na\(^+\) influx through the cGMP-gated channels. Illumination causes rhodopsin binding to and activation of the G-protein transducin, which in turn activates the membrane-bound cyclic nucleotide phosphodiesterase (PDE) (15). PDE catalyzes cGMP hydrolysis, resulting in the closure of the cGMP-gated channels. The resulting membrane hyperpolarization initiates an electrical response from the photoreceptor by reducing the release of inhibitory neurotransmitters at the photoreceptor synapse. Continued activity of NCKX1 under these conditions leads to a rapid drop in cytosolic Ca\(^{2+}\). Specialized photoreceptor guanylyl cyclases become activated by the reduced Ca\(^{2+}\) concentration and resynthesize cGMP, which subsequently binds to and re-opens the cGMP-gated channels (23). The cGMP concentration, which is controlled by the Ca\(^{2+}\) concentration, determines the open probability of the cGMP-gated channels to regulate the duration of the photoreceptor electrical response, a balance that is the basis of light adaptation (15).

Cone outer segments are less sensitive, display faster kinetics, and respond to a broader range of light intensities than rods. These differential characteristics can be attributed, in part, to differences in Ca\(^{2+}\) handling processes and suggest that rods and cones possess different NCKX isoforms (30). The cloning of NCKX2 from chicken retina, which is abundant in cone photoreceptors, suggested a role for this exchanger in cone physiology that was analogous to that of NCKX1 in rod photoreceptors (47). An NCKX2 paralog was also recently cloned from the retina of stripped bass, and isolated cone outer segments were shown to contain K\(^+\)-dependent Na\(^+\)/Ca\(^{2+}\) exchange activity (45). However, NCKX2 knockout mice did not display any obvious deficits in either cone number or function, suggesting that either other Ca\(^{2+}\) efflux pathways compensated for the absence of NCKX2 or that NCKX function plays a more subtle role in Ca\(^{2+}\) homeostasis in cone photoreceptors that would require more detailed analyses to elucidate (35).

### Skin Pigmentation

Recently the fifth member of the NCKX family, NCKX5, was identified as being mutated in zebrafish, which display the “golden” phenotype due to impaired skin pigmentation. Introduction of wild-type zebrafish or human NCKX5 constructs into these mutant fish was able to restore normal skin pigmentation (32). It was subsequently found that, in the human orthologs of NCKX5, a single nucleotide polymorphism resulting in the conversion of the highly conserved Ala 111 to Thr was strongly associated with individuals of European descent, whereas individuals of African and Asian descent contained the conserved ancestral allele. Recombinant NCKX5 is strongly expressed in skin and eye tissue and localizes to intracellular membranes, possibly melanosomes or premelanosomal compartments, which is in sharp contrast to the plasma membrane localization of the previously identified NCX and NCKX isoforms. It has been shown that Ca\(^{2+}\) uptake into maturing melanosomes is ATP-independent, insensitive to P-type ATPase inhibitors, but strongly dependent on a H\(^+\) gradient generated by the putative V-type H\(^+\)-ATPase and that several subunits of this enzyme have been localized to the melanosomal membrane, as have intracellular Na\(^+\)/H\(^+\) exchangers (4, 52, 56). Based on this evidence, it has been postulated that the acidic interior of maturing melanosomes drives Na\(^+\) uptake via Na\(^+\)/H\(^+\) exchangers, which provide the driving force for Ca\(^{2+}\) uptake mediated by NCKX5 (FIGURE 1C). Although some early studies have suggested that the Ca\(^{2+}\) content of melanosomes is positively correlated with the extent of pigmentation and that Ca\(^{2+}\) is also required for melanosome motility (12, 17, 46, 51), the specific role of Ca\(^{2+}\) transport in melanosome maturation and melanin biosynthesis remains unclear. Furthermore, the functional properties of NCKX5 and the impact of the A111T mutation on these properties have not been demonstrated. Therefore, the currently proposed model and its impact on melanin biosynthesis requires additional experimental investigation.

### Structure and Function

Early studies on isolated bovine rod outer segments were the first to functionally identify Na\(^+\)/Ca\(^{2+}\) exchange activity that was dependent on K\(^+\) ions that were co-transported with Ca\(^{2+}\) with an apparent stoichiometry of 4 Na\(^+\): 1 Ca\(^{2+}\): 1 K\(^+\) (9, 54). These functional properties were subsequently confirmed for recombinant NCKX1 and 2 using either 45Ca\(^{2+}\) uptake into insect cells or electrophysiological recordings in HEK293 cells (11, 55, 57). Furthermore, NCKX1 and 2 display similar apparent affinities for Ca\(^{2+}\) and Na\(^+\) as NCKX2 but much higher affinities for K\(^+\) (~1–2 mM) (61). Recombinant NCKX3 and 4 have been demonstrated to be electrogenic (31, 36) and were recently shown to display similar apparent affinities for Ca\(^{2+}\) and Na\(^+\) as NCKX2 but much higher affinities for K\(^+\) (~1 mM) (61). The various NCKX isoforms share the same overall predicted membrane topology, with 11 transmembrane segments (TMs 0–10), the first of which (TM 0) is thought to be cleaved by a signal peptidase after protein translation (20) (FIGURE 2). Glycosylation-scan-
ning mutagenesis and cysteine-accessibility experiments involving NCKX2 have confirmed that, in the mature protein, both the NH₂ and COOH termini are extracellular, the NH₂-terminal extracellular loop is glycosylated, and TMs 1–5 are connected to TMs 6–10 via a large cytoplasmic loop (8, 29). There is also some evidence that NCKX2 may form a homo- or hetero-oligomer, but the functional significance of this finding is unknown (19, 65).

The molecular cloning of NCKX isoforms has revealed that sequence identity with the NCX family is limited to two internally homologous regions known as α-repeats 1 and 2 (FIGURE 2). Furthermore, detailed phylogenetic analyses based on sequence similarity within the α-repeats have revealed that the NCX and NCKX families belong to a much larger superfamily of cation exchangers [CaCA family (50)] from various organisms, including bacteria, fungi, plants, and animals (7). Among the five mammalian NCKX isoforms, NCKX1 shares the highest amino acid sequence identity with NCKX2 (~60%), whereas NCKX3 shares the highest identity with NCKX4 (~65%), and NCKX1/2 are ~41% identical to NCKX3/4. NCKX5 is most closely related to NCKX2 (~40% identity), although it also shares notable sequence identity with NCKX1/2 (~30%).

In the folded NCKX proteins, the α-repeats are thought to be oppositely oriented and contain amino acid residues critical for cation liganding and translocation. The mechanism of NCKX-mediated exchange activity has not been determined in detail but is likely to follow a sequential transport mechanism. The exchanger protein likely contains a single cation binding pocket that can accommodate either, 4 Na⁺ ions or 1 Ca²⁺ + 1 K⁺ to form a “transport competent” complex that is capable of conformational change from inward-facing to outward facing or vice-versa. Moreover, NCKX proteins are “obligate exchangers”, meaning that the empty carrier cannot undergo such conformational changes and requires bound substrate cations to do so.

Evidence that the same amino acid residues are involved in liganding of both K⁺ and Ca²⁺ in NCKX proteins is based on the observations that mutations of key residues in the α-repeats often result in parallel decreases in affinity for both cations (21). A survey of the currently available literature from mutagenesis studies on NCX and NCKX family proteins suggests that there are four critical residues, one in the middle of each of the TMs in the α-repeats that contribute to forming the cation binding pocket (FIGURE 2). In NCKX2, E188 and D548 in TMs 2 and 7, respectively, have been shown to be virtually irreplaceable and D575 in TM 8, when converted to the corresponding residue in NCX (Asn), renders NCKX2 capable of K⁻ independent Na⁺/Ca²⁺ exchange (21, 22, 62). Mutational analyses of N143 of NCX1 revealed that this residue can only tolerate substitution by Asp (44). Therefore, the corresponding NCKX2 residue (N215) may be a fourth critical residue involved in cation liganding, although its impact on NCKX function has not been reported. In NCKX2, sulphydryl cross-linking studies have revealed that E188, D548, and D575, although far apart in the primary sequence, are close together in the folded protein where they could form the K⁺ and Ca²⁺ binding pocket (28). Thr 551 of NCKX2, which is close to D548 in the primary sequence, was recently shown to be responsible for the apparent low K⁺ affinity of NCKX2 compared with that of NCKX3 and 4 (61) (FIGURE 2).

Each of the four critical residues is preceded by a stretch of small side chain amino acid residues (i.e., Ala, Ser, Gly) that may form flexible loop regions within the otherwise helical transmembrane segments to confer enhanced freedom of movement to the critical cation binding residues. Similar structural motifs have been observed in the substrate binding pockets of the crystal structures of several transporters including the glutamate transporter, Na⁺/H⁺ exchanger, the Na⁺/Leucine co-transporter, and SERCA (18, 58, 63, 64).

Although progress in the area of structure/function of NCKX proteins has been made, there are still many
questions that need to be addressed, such as the arrangement of the transmembrane helices, the identification of Na+-liganding residues, and the detailed functional properties of forward-mode NCKX activity. Moreover, although many studies have provided fairly compelling evidence that certain amino acid residues of NCKX proteins are critical for exchanger function, detailed structural studies clearly demonstrating direct interactions with K+ and/or Ca2+ have not been reported. Knowledge of the structural and functional properties of the various NCKX isoforms will be critical to fully understand their physiological roles.

Regulation

Although very little is known about regulation of the genes encoding NCKX proteins, genetic regulation of NCX1 has been thoroughly studied and is fairly well understood. The NCX1 gene is under the control of tissue-specific promoters that contain regulatory elements that respond to tissue-specific transcriptional regulation (3, 40, 41, 53). In contrast, the promoter regions of the genes encoding NCKX proteins have not been analyzed in any detail for transcription factor binding sites or tissue-specific elements (31, 60). The regions encoding the large cytosolic loop of NCX1 are alternatively spliced to yield protein products that are subject to differential functional regulation by cations (13, 14). NCKX2 and 4 were found to be alternatively spliced, with the longer forms possessing an additional 17 or 19 amino acid residues, respectively, in the large cytosolic loops, although there are no obvious functional consequences and no detailed analyses of possible differential regulation have been performed (36, 47, 59). However, NCKX2 was recently shown to become inactivated in a time- and Na+-dependent manner, a phenomenon that has already been well described for NCX1 (16), suggesting that NCKX2 is also subject to ionic regulation (1). Physiologically, high internal Na+ levels that result from persistent neuronal membrane depolarization may inactivate NCKX2, leading to persistent Ca2+ elevation. It is currently not known whether Na+-dependent inactivation is also an intrinsic property of other NCKX family members.

NCKX2, 3, and 4 all possess several consensus sites for protein kinase C (PKC) phosphorylation in their putative cytoplasmic loops, although these sites are not conserved between the isoforms. When HEK293 cells expressing NCKX2, 3, or 4 were stimulated with phorbol esters, only NCKX2 displayed increased functional activity, whereas NCKX3 and 4 were unaffected (33). It was subsequently determined that the Ca2+-independent PKCe isoform, which predominates in neurons, was responsible for the phorbol ester-induced enhancement of activity and that mutation of the PKC consensus sites (T166, T176, and S504) to Ala abrogated this effect (FIGURE 2). It was also shown that PKCe stimulation resulted in increased phosphorylation of NCKX2, which suggested that this protein may be a direct substrate for this enzyme. In neurons, activation of metabotropic glutamate receptors (mGluRs) would result in diacylglycerol and inositol triphosphate (IP3) production and hence activation of PKCe and Ca2+ release from internal stores via IP3 receptors. PKCe activation would presumably enhance the NCKX2 activity and hence Ca2+ clearance in this context, although the prevalence and importance of this potential mechanism requires further study (FIGURE 1A).

Another mode by which these exchangers might be regulated is through the formation of intermolecular complexes that may dictate their localization and/or functional activity and thus impact their influence on Ca2+ homeostasis. When NCKX2 is subjected to polyacrylamide gel electrophoresis under non-reducing conditions, the protein migrates as a high molecular weight species, whereas under reducing conditions it migrates at a molecular weight that is roughly consistent with that predicted from its primary sequence (19, 65). Subjecting the protein to reducing conditions was shown to stimulate its functional activity (8). One intriguing possibility is that the Cys residue responsible (C395) forms a disulfide bond with another molecule of unknown identity that may regulate its activity. Furthermore, it is possible that other NCKX isoforms may have diverse interacting partners that regulate their trafficking and localization. Clearly, these interesting questions warrant further investigation.

Perspectives

Since the molecular cloning of NCKX1 in 1992, there has been a molecular explosion of information regarding these interesting exchangers, resulting in the identification of five gene products with distinct tissue, cellular, and subcellular localizations. Important progress has also been made in the knowledge of their detailed functional properties and their structure/function relationships. The unique physiological roles of the exchanger isoforms are only beginning to be elucidated, but what has been discovered so far suggests that the overall impact of NCKX function has not been fully appreciated. Although preliminary, the physiological contributions of NCKX activity to Ca2+ signaling have been demonstrated in neurons, rod, and cone photoreceptors and implied in skin pigmentation. Many additional studies will be required to gain a more detailed understanding of the respective mechanisms involved. Therefore, the key questions for the future concern the details of the unique functional and regulatory properties of the NCKX isoforms and how these properties within their endogenous physiological contexts determine NCKX contributions to the control of various Ca2+-dependent cellular processes.
55. Sheng JZ, Prinsen CF, Clark RB, Giles WR, Schnetkamp PP. Na⁺-Ca²⁺-K⁺ currents measured in insect cells transfected with the retinal cone or rod Na⁺-Ca²⁺-K⁺ exchanger cDNA. Biophys J 79: 1945–1953, 2000.