Pflugers Arch - Eur J Physiol (2004) 447:683–688
DOI 10.1007/s00424-003-1069-0

The ABC of Solute Carriers

Guest Editor: Matthias A. Hediger

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The *SLC24* Na^+/Ca^{2+}-K^+ exchanger family: vision and beyond

Received: 16 January 2003 / Accepted: 21 March 2003 / Published online: 6 May 2003

Abstract Na^+/Ca^{2+}-K^+ exchange (NCKX) was first discovered in the outer segments of vertebrate rod photoreceptors (ROS), where it is the only mechanism for extruding the Ca^{2+} that enters ROS via the light-sensitive and cGMP-gated channels. ROS NCKX1 is the only *NCKX* gene family member studied extensively in situ. ROS NCKX1 cDNAs have been cloned subsequently from a number of species including man and shown to be the first member of a new gene family (*SLCA24*). Three further members of the human *NCKX* gene family have been cloned subsequently (*NCKX2–4*) by homology with *NCKX1*, while a partial sequence of a fifth human *NCKX* gene has appeared in the data base. *NCKX*-related genes have also been identified in lower animals including fruit flies, worms and sea urchins. NCKX2 is expressed in the brain, in retinal cone photoreceptors and in retinal ganglion cells, while NCKX3 and NCKX4 show a broader expression pattern. In situ NCKX1 and heterologously expressed NCKX2 operate at a $4Na^+$:$1Ca^{2+}$+1 K^+ stoichiometry; both NCKX1 and NCKX2 are bidirectional transporters normally extruding Ca^{2+} from the cell (forward exchange), but also able to carry Ca^{2+} into the cell (reverse exchange) when the transmembrane Na^+ gradient is reversed. Sequence changes have been observed for both NCKX1 and NCKX2 in patients with retinal diseases, but a definitive association with retinal disease has not been shown.

Keywords Calcium homeostasis · Sodium-calcium exchange · Sodium-calcium-potassium exchange · Vision · Rod photoreceptors · Cone photoreceptors

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Introduction

By the early 1980s it had become clear that Na^+/Ca^{2+} exchange plays a critical role in retinal rod photoreceptor function, and isolated rod outer segments (ROS) had become a preparation of choice for studying its functional characteristics. Na^+/Ca^{2+} exchange in ROS was shown to be electrogenic with one positive charge moved into the cell for each Ca^{2+} extruded [39], and other functional characteristics appeared very similar to Na^+/Ca^{2+} exchange (NCX) studied extensively in the heart, except for the effects of K^+ [21]. In 1989, two studies showed that Na^+/Ca^{2+} exchange in ROS required and transported K^+ with a transport stoichiometry of $4Na^+$:$1Ca^{2+}$+1 K^+ [2, 25]. Since then, Na^+/Ca^{2+}-K^+ exchange (NCKX) has been studied extensively in isolated bovine and tiger salamander ROS (reviewed in [13, 22, 23]). Bovine NCKX1 was purified in 1988 [3], and NCKX1 cDNA was cloned from bovine retina in 1992 [19], followed by NCKX1 from man [37] and several other species [4, 17, 18]. Three further members of the *NCKX* gene family have been cloned by homology with NCKX1. NCKX2 was cloned independently from rat brain [36] and from human and chicken retina [18]. Recently, NCKX3 [12] and NCKX4 [14] have been cloned and characterized, while a partial sequence of a fifth human *NCKX* gene has appeared in the database but still needs to be characterized further. Analysis of evolutionary relationships shows that although all *NCKX* genes are related, *NCKX1* is more closely related to *NCKX2*, and *NCKX3* is more closely related to *NCKX4*. Expressed in cell lines, the first four members of the *NCKX* gene family have been shown to be K^+-dependent Na^+/Ca^{2+} exchangers as demonstrated by the dependence of reverse Na^+/Ca^{2+} exchange on extracellular K^+.

Table 1 *SLC24*: the sodium calcium potassium exchanger family

Human gene name	Protein name	Aliases	Predominant substrates	Transport type/Coupling ions*	Tissue distribution and cellular/subcellular expression	Link to disease	Human gene locus	Sequence accession ID	Splice variants and their specific features
SLC24A1	NCKX1		Na^+,Ca^{2+}, K^+	E/4Na^+/Ca^{2+}-K^+	Rod photoreceptors, platelets		15q22	AF026132	Several splice variants, function unknown
SLC24A2	NCKX2		Na^+,Ca^{2+}, K^+	E/4Na^+/Ca^{2+}-K^+	Brain, retinal cone photoreceptors, retinal ganglion cells		9p22	AF097366	Two splice variants, function unknown
SLC24A3	NCKX3		Na^+,Ca^{2+}, K^+	E/Na^+/Ca^{2+}-K^+	Brain, aorta, uterus, intestine		20p11	AF288087	Three splice variants, function unknown
SLC24A4	NCKX4		Na^+,Ca^{2+}, K^+	E/Na^+/Ca^{2+}-K^+	Brain, aorta, lung, thymus		14q32	AF520705/6/7	
SLC24A5	NCKX5		–		–		–	XP_208771	

* *E* Exchanger

NCKX family members, tissue distribution, splice variants

Table 1 summarizes some of the features of the *NCKX* gene family. NCKX1 is a considerably larger protein of 1098 residues compared with NCKX2 (661 residues), NCKX3 (644 residues), or NCKX4 (605 residues); this appears to be a unique feature of the subclass of mammalian NCKX1 [18]. NCKX1 appears to have the most restricted tissue distribution and is only found in retinal ROS and in platelets [10]; NCKX2 is found in brain, in retinal ganglion cells and in cone photoreceptors, while NCKX3 and NCKX4 are more widely expressed. Splice variants have been found, mostly within the large cytosolic loop that separates two sets of transmembrane spanning segments (Fig. 1), but the functional significance of these splice variants and their tissue distribution are still unclear.

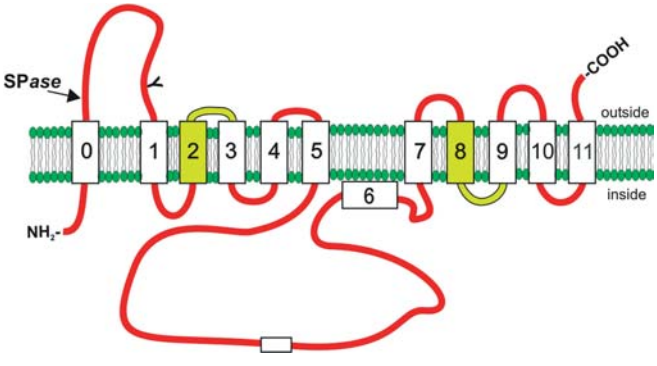

Fig. 1 Topology of NCKX2. *SPase* indicates the position of cleavage by a putative signal peptidase. The N-terminal extracellular domain contains a single glycosylation site. The *white bar* in the *large cytosolic loop* indicates the site of alternate splicing in NCKX2 which removes17 residues. The *yellow transmembrane spanning segments* indicate the location of the alpha-1 and alpha-2 repeats, respectively

NCKX physiology in retinal rod and cone photoreceptors

A clear physiological role for NCKX has only been established in retinal rod and cone photoreceptors (reviewed in [6, 9]) and is summarized briefly here. Fig. 2 illustrates retinal rod photoreceptors and some of the proteins important for visual transduction; a related, but distinct, set of gene products mediates vision in retinal cone photoreceptors. In darkness, the light-sensitive and cGMP-gated channels in the plasma membrane of rod and cone outer segments pass a depolarizing current carried in part (10–20%) by Ca^{2+}. Ca^{2+} influx via cGMP-gated channels is balanced by Ca^{2+} extrusion via NCKX, the only Ca^{2+} extrusion protein present in the outer segment plasma membrane, leading to a high equilibrium free [Ca^{2+}] of about 500 nM in the outer segments of photoreceptors in darkness. Illumination closes cGMP-gated channels and eliminates Ca^{2+} influx, while continued Ca^{2+} extrusion via NCKX leads to a rapid (tens of milliseconds) lowering of intracellular free Ca^{2+}. This initiates a negative feedback loop in which lowering of intracellular free Ca^{2+} stimulates reopening of cGMP-gated channels by increasing the activity of guanylyl cyclase via the so-called guanylyl cyclase-activating proteins (GCAP proteins) and by a calmodulin-mediated change in the affinity of the channel for cGMP. This negative feedback loop is thought to be the main

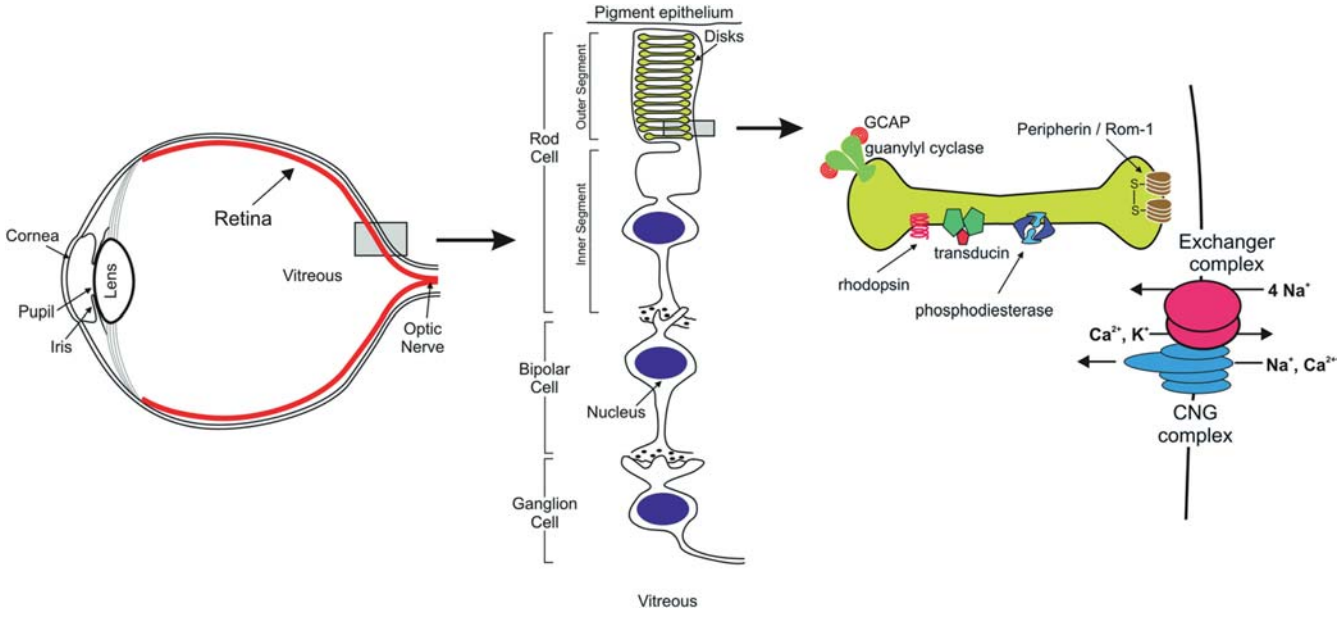

Fig. 2 Role of NCKX in retinal rod photoreceptors. The position of the retina and some (not all) of the major cell types present in the retina are indicated in the *left part* of the diagram. The rod photoreceptor (not drawn to scale) and some of the proteins important for visual transduction are indicated at the *right*. *Rhodopsin* is the visual pigment, *transducin* is the heterotrimeric G-protein activated by photolyzed rhodopsin, and *GCAP* is the guanylyl cyclase activating protein. The CNG-NCKX complex is directly associated with the peripherin/rom-1 complex [16]

contributor to the process of light adaptation in both rod and cone photoreceptors.

Functional characteristics

In situ characterization has only been carried out extensively for NCKX1 (reviewed in [13, 22, 23]), while recent studies have addressed properties of heterologously expressed NCKX1 and NCKX2 [5, 18, 32, 34, 35]. Little is yet known about NCKX3 and NCKX4. The basic transport characteristics of NCKX1 and NCKX2 from several species appear very similar:

1. Transport stoichiometry is $4Na^+$:$1Ca^{2+}$+1 K^+.
2. NCKX is a bidirectional transporter and can mediate both forward and reverse Na^+/Ca^{2+}-K^+ exchange.
3. NCKX1 is an efficient mediator of Ca^{2+}-K^+/Ca^{2+}-K^+ self-exchange, consistent with a consecutive mechanism of transport.
4. The selectivity for Na^+ is absolute, Na^+ cannot be replaced by any other cation. Ca^{2+} can be replaced by Sr^{2+}, while Mg^{2+}, Mn^{2+} or Ba^{2+} are not transported but compete with Ca^{2+} for binding and inhibit transport. K^+ can be replaced by Rb^+ and NH_4^+, but not by Cs^+, Na^+ or Li^+.
5. The cation dissociation constants are 1–3 μM for both external and intracellular Ca^{2+}, 2–10 mM for both external and intracellular K^+, and 25–45 mM for external Na^+. A sigmoidal relationship between transport rate and cation concentration is observed invariably for Na^+, but not for Ca^{2+} or K^+, consistent with the transport stoichiometry that requires binding of multiple Na^+, but only a single Ca^{2+} or K^+.

Little is known about regulation of NCKX function. In the absence of any Ca^{2+} influx, Na^+/Ca^{2+}-K^+ exchange is expected to lower cytosolic Ca^{2+} to less than 2 nM, yet this is not observed in ROS [20, 26]. After a short burst of operation at full rate, NCKX1 appears to become nearly completely inactivated [24], and this mechanism appears to prevent intracellular free Ca^{2+} from dropping below 2 nM when rod photoreceptors are saturated for prolonged periods of time during bright daylight illumination [20].

Pharmacology

L-*cis* Diltiazem, tetracaine and 3′,4′-dichlorobenzamil inhibit NCKX1 in situ, albeit at high concentrations (>10 μM) [15, 22]; curiously, the same compounds are effective inhibitors of the rod cGMP-gated channels, but at much lower concentrations. This may be related to the fact that the rod cGMP-gated channel and NCKX1 form a complex in bovine ROS membranes (see below).

Interaction of NCKX with other proteins

In bovine ROS membranes, NCKX1 forms a dimer and associates with the cGMP-gated channel (cyclic nucleotide-gated, CNG) [29, 30], the latter a heteromultimer consisting of three CNGA subunits and one CNGB subunit [40]. Interestingly, the NCKX1-CNG complex in

the plasma membrane also associates with two small integral membrane proteins found in the rims of the intracellular disk membranes, thus forming a complex that spans two membranes [16] (see also Fig. 2). The functional consequences of this arrangement remain to be explored. Very recently, it has been shown that both NCKX1 and NCKX2 form oligomers when expressed in cell lines, and that in heterologous systems both NCKX1 and NCKX2 can form complexes with their respective CNGA subunits [8].

Structure-function and topology

All four full-length members of the human *NCKX* gene family as well as related proteins found in lower organisms are predicted to contain two large hydrophilic loops and two sets of multiple transmembrane spanning segments (TMs) (Fig. 1). The extracellular loop at the N-terminus may contain a cleavable signal peptide. The two hydrophilic loops show very limited sequence similarity among different *NCKX* family members, and also vary significantly among NCKX1 proteins from different species. For example, the hydrophilic loops of human NCKX1 contain 531 residues more than those in chicken NCKX1, despite the fact that vertebrate rod vision is highly invariant. In contrast, the two sets of TMs are well conserved among different NCKX family members, in particular between NCKX1 and NCKX2, and between NCKX3 and NCKX4, respectively. The TMs also contain the two alpha repeats (Fig. 1), two sequence elements that are thought to have arisen from an ancient gene duplication event and that contain the only sequence elements that are shared between members of the *NCKX* gene family and members of the *NCX* gene family (*SLC8*) [28]. Different aspects of the NCKX2 topology have been reported in two recent studies [1, 11], both consistent with the topology illustrated in Fig. 1.

The two large hydrophilic loops can be deleted from bovine NCKX1, eliminating close to 60% of the protein, but without affecting transport function [34]. At this point, the role of the hydrophilic loops in NCKX function remains to be explored. Scanning mutagenesis of the alpha repeats of human NCKX2 (see Fig. 1) showed that mutagenesis of about 25% of these residues led to functionally compromised NCKX2 proteins; six acidic and hydroxyl-containing residues were identified that contribute to the major cation binding site of NCKX2 [38].

Role of NCKX in hereditary retinal disease?

To examine the possible role of NCKX mutations in retinal disease, DNA from 815 patients has been screened for rod NCKX1 mutations, and DNA from 166 patients for cone NCKX2 mutations [31]. Some 27 novel sequence changes were found in the human rod NCKX1 gene, 6 of which were considered to be likely pathogenic changes; 14 novel sequence changes were found in the human cone NCKX2 gene, 3 of which lead to mis-sense changes but are unlikely to be pathogenic.

Phylogenetic distribution of NCKX

NCKX cDNAs have been cloned from various other mammalian species including rat, mouse, cow and dolphin; NCKX1 and NCKX2 have also been cloned from chicken retina [18]. Data base searches reveal many NCKX-related sequences in lower animals and in certain prokaryotes. Three of these NCKX-related cDNAs have been cloned from *Drosophila* [7], *Caenorhabditis elegans* [34], and sea urchin [33], respectively, and shown to code for K^+-dependent Na^+/Ca^{2+} exchangers when expressed in cell lines.

Comparison with the SLC8 Na^+/Ca^{2+} exchangers

The Na^+/Ca^{2+}-K^+ exchangers are functionally related to the K^+-independent Na^+/Ca^{2+} exchangers (NCX) of the *SLC8* gene family. Both NCKX and NCX show an absolute selectivity for Na^+ over any other alkali cation, are bidirectional, and show a very similar and sigmoidal dependence on external [Na^+] [22]. Remarkably, sequence similarity between NCX and NCKX is limited to the two very short sequence elements containing the alpha repeats as mentioned above. Key acidic and hydroxyl-containing residues shown to be critical for cation transport are located in these alpha repeats and are conserved between NCX and NCKX [38]. Although both NCX and NCKX isoforms are widely expressed in the brain, it is unclear whether they are co-expressed in the same locale. At a 3 Na^+:1Ca^{2+} transport stoichiometry, NCX can reverse direction and bring Ca^{2+} into the cell after strong membrane depolarization and/or elevations of internal Na^+; in contrast, at a stoichiometry of 4Na^+:1Ca^{2+}+1 K^+, NCKX is unlikely to reverse under any physiological or pathophysiological conditions [27].

Perspective

Although five members of the NCKX gene family have been identified, a clear understanding of NCKX physiology is limited to the role of NCKX1 and NCKX2 in retinal rod and cone photoreceptors. It is tempting to speculate that in most settings NCKX is co-expressed with cGMP-gated channels or other ligand-gated channels that can produce a prolonged influx of Ca^{2+} combined with membrane depolarization as is the case for photoreceptors in darkness. An important goal of future work should be elucidation of the role of NCKX in the various tissues in which it is expressed. To assist in this, development of compounds that selectively inhibit NCKX is highly desirable.

Acknowledgements This work was supported by an operating grant from the Canadian Institutes for Health Research. PPMS is a Scientist of the Alberta Heritage Foundation for Medical Research. The invaluable help of Robert Szerenscei in preparing the figures and in many other ways is much appreciated.

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