Lithium-Calcium Exchange Is Mediated by a Distinct Potassium-independent Sodium-Calcium Exchanger*

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Sodium-calcium exchangers have long been considered inert with respect to monovalent cations such as lithium, choline, and N-methyl-D-glucamine. A key question that has remained unsolved is how despite this, Li⁺ catalyzes calcium exchange in mammalian tissues. We report that a Na⁺/Ca²⁺ exchanger, NCLX, cloned from human cells (known as FLJ22233), is distinct from both known forms of the exchanger, NCX and NCKX in structure and kinetics. Surprisingly, NCLX catalyzes active Li⁺/Ca²⁺ exchange, thereby explaining the exchange of these ions in mammalian tissues. The NCLX protein, detected as both 70- and 55-kDa polypeptides, is highly expressed in rat pancreas, skeletal muscle, and stomach. We demonstrate, moreover, that NCLX is a K⁺-independent exchanger that catalyzes Ca²⁺ flux at a rate comparable with NCX but without promoting Na⁺/Ba²⁺ exchange. The activity of NCLX is strongly inhibited by zinc, although it does not transport this ion. NCLX activity is only partially inhibited by the NCX inhibitor, KB-R7943. Our results provide a cogent explanation for a fundamental question. How can Li⁺ promote Ca²⁺ exchange whereas the known exchangers are inert to Li⁺ ions? Identification of this novel member of the Na⁺/Ca²⁺ superfamily, with distinct characteristics, including the ability to transport Li⁺, may provide an explanation for this phenomenon.

Plasma membrane Na⁺/Ca²⁺ exchange is an important element in cellular Ca²⁺ homeostasis. It has been extensively investigated in mammals, especially in cardiac and neuronal tissues (1), where this mechanism is essential for regulation of Ca²⁺ homeostasis. Na⁺/Ca²⁺ exchange also plays a key role in many other organs and tissues by modulating the intracellular Ca²⁺ response (2). The Na⁺/Ca²⁺ exchangers described to date are members of four major families (1). Of these, only NCX1–3 and NCKX1–4 are found in mammalian cells, whereas the other two are expressed in plants, yeast, and bacteria. The stoichiometry of NCX exchangers is based on 3–4Na⁺/1Ca²⁺, and the protein is structurally organized as nine transmembrane helices divided by a large cytoplasmic loop (3). NCKX family proteins have a stoichiometry of 4Na⁺/1Ca⁺/1K⁺, and their topology is thought to consist of two sets of five membrane helices divided by a cytoplasmic loop and NH₂-terminal extracellular domain (4). The two families share several important functional and structural motifs: a structural hallmark of the Na⁺/Ca²⁺ exchanger superfamily is the presence of two regions of sequence similarity, called α1 and α2, which are considered necessary and sufficient for generating exchange activity (1, 5). Functionally, these exchangers are considered catalytically inert to inorganic and organic monovalent cations such as Li⁺, NMG, 1 and choline, which are often used in “sodium-free” solutions to reverse Na⁺/Ca²⁺ exchange activity (2).

Although Li⁺ ions are not transported by either NCX or NCKX, numerous physiological studies have reported a significant effect of this ion on Ca²⁺ exchange (6–8). Earlier studies, conducted on squid axons and barnacle muscle, observed an inhibitory effect on intracellular Li⁺, whereas extracellular Li⁺ accelerated ⁴⁰Ca efflux (9, 10). These studies, therefore, suggested that Li⁺ may interact with a regulatory site on Na⁺/Ca²⁺ exchangers (2). More recent studies, conducted on striated muscle, have suggested that Li⁺ may catalytically participate in Li⁺/Ca²⁺ exchange mediated by an unidentified exchanger that is distinct from NCX and NCKX (11).

During our search for candidates for the Na⁺/Zn²⁺ exchanger gene (12), we cloned the full open reading frame of the FLJ22233 gene from Hek293 cells and analyzed its activity with respect to ion transport. While this work was in progress, it was reported (13) that the full-length FLJ22233 protein, heterologously expressed in HEK293 cells, is retained in the endoplasmic reticulum, and therefore, is non-functional. A mouse spliced isoform with a disrupted α2 repeat was shown to mediate active K⁺-dependent Na⁺/Ca²⁺ exchange. Our findings, however, indicate that the full-length protein encoded by the human FLJ22233 gene, is in fact, functional, mediating Na⁺/Ca²⁺ exchange independent of K⁺. We further demonstrate that FLJ22233 is distinct from both NCX and NCKX in its ability to catalyze Li⁺/Ca²⁺ exchange. The protein is highly selective for Ca²⁺ and does not catalyze either Ba²⁺ or Zn²⁺ transport. We therefore propose that FLJ22233, named here NCLX, is a novel member of the Na⁺/Ca²⁺ exchanger family with distinct ion selectivity.

EXPERIMENTAL PROCEDURES

Cloning of the Human NCLX—The conserved sequences of α1 and α2 repeats from AtMHX1 and from six different members of the human Na⁺/Ca²⁺ exchanger superfamily (NCX1–3, NCKX1–3) were used to
screen the human genome sequence protein data base using BLAST search (14). This search revealed a hypothetical protein, FLJ22233 (GenBank access number NP_079235).

Based on the NCBI assembly sequence annotation (using ReSeq, at www.ncbi.nlm.nih.gov/IEB/Research/Assembly), one of the primers was designed to enhance the longest deduced open reading frame of this gene using reverse transcriptase-PCR. Total RNA was extracted from HEK293 cells using RNasey Midi kit (Qiagen), and mRNA was further purified using Poly Tract mRNA isolation system III (Promega). Reverse transcriptase-PCR was performed with a one-step reverse transcriptase-PCR Kit (Qiagen) using 200 ng of mRNA and the following primers: (forward primer) 5'-CCAGCGTGGTTGAACTGAGC-3' and (reverse primer) 5'-TCATAGCTTTCAGGAATCTCCACA-3'. The amplified and ligated inserts were cloned into a pGEM-T cloning vector. Both strands of the two clones were sequenced (Sequencing Unit, Biological Core Facility at the Institute for Applied Sciences at Ben-Gurion University). The long and short transcriptions were excised from pGEM-T vector (Promega), ligated into a pCNAAS.1 + vector using EcoRI endonuclease, and termed NCLX and s-NCLX for the full-length and the shorter isoform, respectively. Two opposite orientations for each transcript were selected using the reverse-oriented transcript as control. Plasmids were purified using the Hi-Speed plasmid purification kit (Qiagen).

**Cell Cultures and Plasmid Transfection**—HEK293-T cells (human embryonic kidney cell line) were cultured in Dulbecco’s modified Eagle’s medium as described previously (15). Briefly, cells grown on glass coverslips were transfected with 8 μg of NCLX, control, or rat NCX1 (kindly provided by Dr. Hanna Rahamimoff, The Hebrew University, Jerusalem, Israel) using standard calcium phosphate (CaPO4) precipitation as described previously (12). The EYPF (0.35 μg) plasmid (Clontech) was added as a fluorescence reporter for the identification of transfected cells. Transport experiments or cell harvesting were carried out 25–35 h following transfection.

**Fluorescent Imaging of Ion Transport**—Two imaging systems were used. The first consisted of a Zeiss Axiovert 100 microscope (Zeiss) and the second consisted of an Olympus IX (Olympus) inverted microscope, Polychrome II monochromator (T.I.L.L. Photonics) equipped with a cooled charge-coupled camera (PCO Imaging) as described previously (15). Fluorescent imaging measurements were acquired using Axon Imaging Workbench 2 software (Axon Instruments, Foster City, CA). HEK293-T cells grown on coverslips were incubated for 30 min with 5 μM Fura-2 AM (TEF Labs, Austin, TX) in 0.1% bovine serum albumin in sodium Ringer’s solution (140 mM NaCl, 10 mM HEPES, 20 mM glucose, 0.8 mM MgCl2, 0.5 mM CaCl2, at pH 7.4). Following dye loading, the cells were washed in sodium Ringer’s solution, and the coverslips were mounted in a chamber that allowed the perfusion of cells. Fura-2 was excited at 340- and 380-nm wavelength light and imaged with a 510-nm-long pass filter. Influx assays were performed by perfusing the cells with Na+-free Ringer’s solution such that Na+ was isosmotically replaced by NMG+ with or without 5 mM KCl. Active calcium efflux was monitored by first loading the cells with Ca2+ by perfusion with the NMG+- or choline+-reversal medium and then switching to a Na+- or Na+-free (NMG+-, Li+-, or choline+-containing) Ringer’s solution. Zinc and barium transport mediated by the Na+-Ca2+-exchanger was monitored using the influx assay using NMG+-reversal medium in which Ca2+ was replaced with 400 μM Zn2+ or 1 mM Ba2+. The effect of inhibitors on calcium influx rate mediated by the Na+-Ca2+-exchanger was assayed in the same manner while adding different inhibitors to Ca2+-containing NMG+-Ringer’s solution. The results shown are the means of 5–6 independent experiments, with averaged responses from 20–40 cells in each experiment.

**Generation of NCLX Antibody**—The peptide CPVTPEILOSDDEDR, located at the start of the putative cytoplasmic loop of NCLX, was synthesized in the Peptide Core Facility at the Weizmann Institute of Science. The peptide (4 mg) was conjugated to maleimide KLH (Pierce) according to the manufacturer’s instructions and used to immunize New Zealand White rabbits according to standard procedures (16). The peptide (4 mg) was conjugated to maleimide KLH (Pierce) according to the manufacturer’s instructions and used to immunize New Zealand White rabbits according to standard procedures (16).

**Sample Preparation and Immunoblot Analysis**—Rats were deeply anesthetized and killed according to the protocol approved by the Committee for the Ethical Care and Use of Animal in Experiments at the Faculty of Health Sciences at Ben-Gurion University. Appropriate tissues were placed in ice-cold phosphate-buffered saline solution, scraped from the plate using a rubber policeman, and placed into radioimmune precipitation buffer. Protein was quantified by the Bradford dye binding procedure (Bio-Rad). Equal amounts of protein were resolved by SDS-PAGE and transferred onto nitrocellulose membranes. Immunoblot analysis was carried as described previously (17), using the NCLX-antiserum (or the pre-immune serum) at a 1:2500 dilution.

**RESULTS**

**Na+-Ca2+ Exchange Mediated by NCLX**—We have cloned the FLJ22233 gene during our search for cation transporters expressed in HEK293 cells (12). The complete open reading frame was obtained and inserted into a pCNAAS-3 mammalian expression vector. The activity of this putative transporter was determined by monitoring intracellular Ca2+ changes in HEK293-T cells heterologously expressing the FLJ22233 gene product, loaded with Fura-2 AM. Cells were superfused with Ringer’s solution, which was replaced with NMG+-Ringer’s solution (NMG+-iso-osmotically substituting for Na+), as shown in Fig. 1. The removal of Na+ was followed by robust Ca2+ influx. The subsequent addition of Na+ into the Ringer’s solution induced a rapid efflux of Ca2+. This Na+/Ca2+ exchange activity was not monitored in control HEK293-T cells (transfected with vector containing a reverse-oriented insert). The exchange activity was compared with the activity mediated by NCX1. For both exchangers, a significant Ca2+ influx was monitored at the absence of Na+, which was replaced by NMG+, and active Ca2+ efflux was subsequently monitored when Na+ was reintroduced. Our results indicate that the full-length NCLX codes for a functional Na+/Ca2+ exchanger.

**K+ Dependence of NCLX**—To determine the K+ dependence of NCLX, we applied the paradigm described in Fig. 1 while using either choline+ or NMG+ (Fig. 2) in the reversal solution to verify that the exchange activity is not affected non-specifically by either NMG+ or choline+. If the exchanger is K+-dependent, a robust reduction in the Ca2+ influx rate in the absence of K+ would be expected using the reversal mode. As shown in Fig. 2, rates of Ca2+ influx were similar in the presence or absence of K+, using either choline+ or NMG+. Our results, therefore, indicate that the Na+/Ca2+ exchange mediated by NCLX is not K+-dependent.

**Li+/Ca2+ Exchange Mediated by NCLX**—Lithium has often been used as an inert ion to study the reversal of Na+/Ca2+ exchangers. We have, therefore, employed Li+ as an additional control for the activity of the NCLX as compared with NCX1, again employing the same paradigm as shown in Fig. 1. In NCX1-expressing cells, an enhanced Ca2+ influx was observed, consistent with the reversal of the exchanger activity. Unex-
Expectedly, NCLX-expressing cells showed a much slower rate of Ca\(^{2+}\) influx in the presence of Li\(^+\) (Fig. 3). This striking difference between the two exchangers suggests that although NCX1 is inert to Li\(^+\) transport, this ion is either inhibitory to Na\(^+\)/Ca\(^{2+}\) exchange or transported by NCLX.

To distinguish between the two mechanisms, Ca\(^{2+}\) was loaded into cells expressing NCLX using NMG\(^-\)/Ringer’s, and the rate of active Ca\(^{2+}\) efflux was compared in the presence of Na\(^+\), NMG\(^-\), or Li\(^+\). As shown in Fig. 4, whereas rates of Ca\(^{2+}\) efflux were somewhat slower in the presence of Li\(^+\) as compared with Na\(^+\) (1.6 ± 0.5-fold), Li\(^+\) ions were strikingly more effective (8 ± 1-fold) as compared with NMG\(^-\) in promoting active Ca\(^{2+}\) efflux. The small, residual efflux activity observed in the presence of NMG\(^-\) may be related to the activity of the sarco(endo)plasmic reticulum Ca\(^{2+}\)-ATPase (SERCA). Taken together, the failure of Li\(^+\) to promote Ca\(^{2+}\) influx in the reverse mode on the one hand and the acceleration of efflux in cells loaded with Ca\(^{2+}\) on the other indicate that Li\(^+\) is transported by NCLX. Thus, Li\(^+\)-containing Ringer’s inhibits the reversal of the exchanger.
extracellular Ca\(^{2+}\) concentration and yielded an apparent Hill coefficient of 1.5 ± 0.4 and an apparent affinity of 0.8 ± 0.2 mM for Ca\(^{2+}\). To determine the Na\(^+\) dependence of Ca\(^{2+}\) efflux mediated by NCLX-expressing cells, the cells were first loaded with Ca\(^{2+}\), using the reversal of NCLX, and then extracellular Na\(^+\) was gradually iso-osmotically replaced with NMG\(^+\), and the rates of Ca\(^{2+}\) efflux were monitored. As shown in Fig. 5b, Ca\(^{2+}\) efflux rates increased with external Na\(^+\) concentrations, fitting a Michaelis-Menten equation with an apparent half-maximal rate at 60 ± 5 mM Na\(^+\) and a 3.5 ± 1 Hill coefficient. Only minor changes in Ca\(^{2+}\) efflux rate are monitored when Na\(^+\) is replaced with Li\(^+\), indicating that Li\(^+\) and Na\(^+\) act additively in catalyzing Ca\(^{2+}\) efflux.

Since Li\(^+\) was transported by NCLX in the absence of Na\(^+\), we further studied whether Li\(^+\) will functionally replace Na\(^+\) at physiological concentrations. The same experimental paradigm described for Na\(^+\)/NMG\(^+\) replacement was applied for Na\(^+\)/Li\(^+\). Remarkably, only a slight change in Ca\(^{2+}\) efflux rate is observed over the whole range, beginning with 140 mM Na\(^+\) and gradually changing to 140 mM Li\(^+\). Our results clearly indicate that Li\(^+\) and Na\(^+\) act additively in catalyzing Ca\(^{2+}\) efflux mediated by NCLX.

As the Na\(^+\)-dependent exchange activity of other cations such as Ba\(^{2+}\), Mg\(^{2+}\), and Zn\(^{2+}\) has been previously functionally described (12, 18), we sought to determine the cation selectivity of the NCLX in its reversal mode. Rates of Ba\(^{2+}\) or Zn\(^{2+}\) transport by NCLX are negligible (not shown), indicating that at least with respect to these cations, NCLX activity is specific to Ca\(^{2+}\).

**Inhibitors for NCLX Activity**—The use of inhibitors is an important tool for the functional identification and character-
**Fig. 7. Activity and structure of the s-NCLX isoform.** a, the alignment of the full-length NCLX primary amino acid sequence to that of s-NCLX showing the region of deletion. Putative transmembrane domains 3 and 4 are underlined. b, the reversal of Ca$^{2+}$ exchange in control, NCLX (the same as the graph for NCLX in Figs. 1 and 2), or s-NCLX-expressing cells was monitored by substituting Na$^+$ with choline$^+$ without (b) or with (c) 5 mM K$. Substituting Na$^+$ with choline$^+$ was followed by Ca$^{2+}$ influx into cells expressing s-NCLX (short isoform). Superfusion with Na$^+$-containing Ringer’s solution was followed by Ca$^{2+}$ efflux. The short isoform of NCLX exhibits similar transport characteristics, in the presence or absence of K$. These results indicate that, as is true of the full-length NCLX, the s-NCLX is a K$^+$-independent Na$^+/Ca^{2+}$ exchanger. d, cells expressing s-NCLX were loaded with Ca$^{2+}$-using NMG$^+$-reversal Ringer’s and then were superfused with NMG$^+$-, Li$^+$-, or Na$^+$-containing Ringer’s while monitoring calcium efflux. The s-NCLX Li$^+$ dependence is similar to that of the full-length NCLX.

**DISCUSSION**

Our findings indicate that NCLX is kinetically distinct from both the NCX and NCKX. Although both NCX and NCKX are
We found, in contrast, that heterologous expression of NCLX in HEK293-T cells resulted in a fully functional protein. It is possible that the tagging by the FLAG epitope interfered with the proper sorting of the mouse gene described by Cai et al. (13). Immunoblot analysis indicated that NCLX migrated as a major band of 70 KDa in addition to a much weaker 55-KDa protein. In native tissue, however, both the study of Cai et al. (13) and our study have identified both forms. It may be possible, therefore, that post-translational modifications have yielded the differences in molecular weight and functionality between our respective studies (13). Another major difference between our findings is the K⁺ dependence of Ca²⁺ exchange. Thus, we found that NCLX is K⁺-independent; the spliced short mouse isoform studied by Cai et al. (13) was K⁺-dependent and was inert to Li⁺. This discrepancy may be linked to structural differences between the full-length human gene and the short mouse isoform, which has a putatively disrupted second α-repeat and a long intracellular tail. We did not find a similar isoform to the mouse in human. It remains to be seen whether these changes in the primary sequence of the mouse gene are converting this isoform to a K⁺-dependent and Li⁺-inert Na⁺/Ca²⁺ exchanger.

We were able to clone a human isoform lacking exon 7, which results in the deletion of the transmembrane domains 3 and 4. These domains are highly conserved in NCX and NCKX families. Although in NCKX2, mutations of several amino acids located in this region have resulted in the loss of activity (24), we find that the truncation of this region from NCLX, manifested in s-NCLX, had no effect on activity.

It was previously shown that although NCX1 does not transport Li⁺, a single point mutation of Thr-103/Val-103 did activate Li⁺/Ca²⁺ exchange that was mediated by canine NCX1 (25). This threonine residue is conserved among all members of NCX, NCKX, and NCLX. Interestingly however, and only in NCLX, the amino acid preceding threonine is valine. Whether this specific residue or its domain is responsible for Li⁺/Ca²⁺ exchange, or whether other regions participate in Li⁺/Ca²⁺ exchange mediated by NCLX, is an intriguing and open question.

Although mRNAs for FLJ22233 are found in many tissues (13), the expression level of the protein varies markedly in these tissues. In rat, the protein is highly expressed in the pancreas, skeletal muscle, and stomach, and to lesser extent, in cardiac tissue, brain, spleen, and skin. In human, the protein is highly expressed in the brain and skeletal muscle, and low expression levels are observed in the pancreas (data not shown). The lower expression of NCLX in human tissues, especially in the pancreas, should be taken with a degree of caution, considering the high content of proteolytic enzymes that exist there and that may be activated in a cadaver. In the rat pancreas, we have found that NCLX is primarily found in the exocrine part (data not shown). In this regard, Na⁺/Ca²⁺ exchange in pancreatic ducts was reported previously to be more intense than in acini where the plasma membrane Ca²⁺ pump is the primary transporter for Ca²⁺ efflux (26). In mouse brain, NCX2 was recently shown to play a role in synaptic transmission, and specifically, in the context of learning and memory (27). The importance of Na⁺/Ca²⁺ exchange in skeletal muscle was recently demonstrated by the effect of NCX3 knockout on muscle activity (28).

The potential physiological importance of NCLX is highlighted by numerous reports on observed effects of Li⁺ on Ca²⁺ exchange. Both voltage sensitivity and magnitude of Na⁺/Ca²⁺ exchange have been described as depending on the presence of Li⁺ as opposed to NMG⁺ (replacing Na⁺) (6, 7). A growing body of evidence, particularly in skeletal muscle, suggests that Li⁺...
ions may directly participate in Ca\(^{2+}\) exchange (11). Since neither NCX nor NCXK family members transport Li\(^+\), it has been conjectured that an as yet unidentified exchanger may be involved in this mode of transport. The Li\(^+\) transport mediated by NCLX, taken together with its high abundance in skeletal muscle, is consistent with the conclusion that NCLX is that by NCLX, taken together with its high abundance in skeletal muscle, is consistent with the conclusion that NCLX is that involved in this mode of transport. The Li\(^+\)/Ca\(^{2+}\) exchange mediated by NCLX, it may well be that the exchange activity of NCLX regulating intracellular Ca\(^{2+}\) homeostasis is underestimated. Expression of NCLX in cardiac muscle may also explain the significant residual activity of Na\(^+\)/Ca\(^{2+}\) exchange found in cardiomyocytes cultured from NCX1-null embryos (29). Future studies combining the silencing of specific members of the Na\(^+\)/Ca\(^{2+}\) exchangers superfamily, together with functional studies comparing the role of Li\(^+\) or Na\(^+\) in Ca\(^{2+}\) exchange, can now be undertaken to determine whether the activity of NCLX is related to this intriguing effect.

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