The PDZ Domain Protein PICK1 and the Sodium Channel BNaC1 Interact and Localize at Mechanosensory Terminals of Dorsal Root Ganglion Neurons and Dendrites of Central Neurons*

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Members of the BNaC/ASIC family of ion channels have been implicated in mechanotransduction and nociception mediated by dorsal root ganglion (DRG) neurons. These ion channels are also expressed in the CNS. We identified the PDZ domain protein PICK1 as an interactor of BNaC1(ASIC2) in a yeast two-hybrid screen. We show by two-hybrid assays, glutathione S-transferase pull-down assays, and coimmunoprecipitations that the BNaC1-PICK1 interaction is specific, and that coexpression of both proteins leads to their clustering in intracellular compartments. The interaction between BNaC1 and PICK1 requires the PDZ domain of PICK1 and the last four amino acids of BNaC1. BNaC1 is similar to two other BNaC/ASIC family members, BNaC2 (ASIC1) and ASIC4, at its extreme C terminus, and we show that PICK1 also interacts with BNaC2. We found that PICK1, like BNaC1 and BNaC2, is expressed by DRG neurons and, like the BNaC1 isoform, is present at their peripheral mechanosensory endings. Both PICK1 and BNaC1 are also coexpressed by some pyramidal neurons of the cortex, by pyramidal neurons of the CA3 region of hippocampus, and by cerebellar Purkinje neurons, localizing to their dendrites and cell bodies. Therefore, PICK1 interacts with BNaC/ASIC channels and may regulate their subcellular distribution or function in both peripheral and central neurons.

BNaC1 and BNaC2 are members of the DEG/ENaC superfAMILY of ion channel subunits (1–4). Members of this family have two transmembrane domains separated by a large extracellular loop, with cytoplasmic amino and C termini (5–8). They form homomeric and heteromeric channels that are permeable to sodium but are not gated by voltage. DEG/ENaC channels have been implicated in several forms of mechanosensation. For example, certain members of the degenerin branch are necessary for the sensation of touch in Caenorhabditis elegans (9). Members of the ENaC branch in mammals control Na+ fluid absorption in the kidney, colon, and lung (10–12), but they have also been found at baroreceptor (13) and somatic touch receptor endings (14, 15). The Pickpocket channel of Drosophila melanogaster also localizes to putative mechanosensory nerve endings (16).

The mammalian BNaC/ASIC branch of the superfamily contains four genes, encoding at least six isoforms: BNaC1α (also known as BNC1, MDEG, and ASIC2) (2–4) and its differentially spliced isoform, BNaC1β (MDEG2) (17); BNaC2α (ASICα or ASIC1) (4, 18) and its differentially spliced isoform, BNaC2β (ASICβ) (19); DRASIC (ASIC3 or TNaC) (20–23); and ASIC4 (SPASIC) (24, 25). These genes are expressed in both central and peripheral neurons and form channels that can be activated by extracellular protons (26). Because tissue acidosis is a source of pain (27), it has been proposed that these ion channels may play a role in acid-induced nociception (26, 28).

In addition, recent work has demonstrated that BNaC1 is required for normal mechanosensation. Mice with a targeted deletion of the BNaC1 gene show reduced sensitivity of rapidly and slowly adapting mechanoreceptors, which correspond to a subset of large diameter DRG neurons (29). With an isoform-specific antiserum, we found that BNaC1α is expressed by most large diameter, mechanosensory DRG neurons, is transported to the periphery, and is present at a variety of specialized cutaneous mechanosensory terminals (30). Together these findings suggest that BNaC1 isoforms may form subunits of a mechanosensory ion channel complex in peripheral neurons. BNaC1 is thus the only mammalian ion channel known to play a role in touch. In addition, heteromultimerization of BNaC/ASIC family members has been demonstrated in heterologous expression systems (17, 31, 32, 33). Channels composed of different combinations of the BNaC/ASIC subunits may participate in both mechanotransduction and nociception.

Both the targeting of BNaC1α to specialized touch terminals and its function in touch transduction are likely to require interacting proteins. We have used a yeast two-hybrid screen to identify proteins that interact with the C terminus of BNaC1. Here we report that the PDZ domain protein PICK1 interacts with the C termini of both BNaC1 and BNaC2 and that PICK1 and the BNaC1α isoform are coexpressed by peripheral (sensory) and central (Purkinje and pyramidal) neurons.

EXPERIMENTAL PROCEDURES

Plasmid Construction—DNA encoding residues 481–512 or 481–508 of mouse BNaC1 were amplified and cloned into pBHA, a LexA DNA binding domain fusion vector, to create ctBNaC1BHA and ctBNaC1A4BHA, respectively. DNA encoding residues 477–526 of rat...
BNaC2 was amplified and cloned into pBH to create ctBNaC2BHA. PCR was used to add a tyrosine to residues 481–512 to create ctBNaC1–1YBHA. DNA encoding mouse BNaC1 residues 481–512, 481–508, and 481–512, followed by a tyrosine, were then subcloned into pGEX6p1 (Amersham Biosciences, Inc., Buckinghamshire, UK) to create the GST-human BNaC1 fusion protein GST-ctBNaC1, GST-ctBNaC2, and GST-ctBNaC1–1Y. The GW4 plasmid contains the complete coding sequence of human BNaC1a under the CMV promoter (30). The full-length coding sequence of mouse PICK1 was amplified from mouse brain cDNA and subcloned into pCMV (CLONTECH, Palo Alto, CA) to generate PICK1CMVMyc and PICK1CMVtag. The QuickChange site-directed mutagenesis kit (Stratagene) was used to change residues 27 and 28 of PICK1 from KD to AA.

**Yeast Two-hybrid Methods**—Yeast two-hybrid screens and reporter gene assays were performed in the L40 yeast strain that contains the HIS3 and βGal reporter genes (34). ctBNaC1BHA was used to screen a mouse inner ear cDNA library constructed in the Gal4 activation domain vector pGAL4-2.1 with the Hybrizap-2.1 two-hybrid Gigapack cloning kit and cDNA synthesis kit (Stratagene).

**Transfections**—Plasmids were introduced into COS-7 cells with LipofectAMINE (Invitrogen, Gaithersburg, MD) or FuGENE 6 transfection reagent (Roche Diagnostics, Indianapolis, IN) on protamine-coated coverslips for immunocytochemistry and in 35 mm or 100 mm tissue culture dishes for pull-down assays and immunoprecipitations. HEK293T cells were transfected using calcium phosphate.

**Immunocytochemistry**—Transfected COS-7 cells were stained 2 days after transfection. Cells were fixed in 4% paraformaldehyde in PBS for 10 min, rinsed three times with PBS, permeabilized with 0.1% Triton X-100 for 15 min, rinsed four times with PBS, and then blocked with 3% normal donkey serum and 3% BSA in PBS for 90 min. Cells were incubated with primary antibodies in blocking buffer overnight at 4 °C. After four washes with PBS, cells were incubated with the secondary antibodies in PBS with 0.05% Tween 20 for 1 h at room temperature. Cells were washed five times with PBS with 0.05% Tween 20 and mounted with Vectashield mounting medium (Vector Laboratories, Burlingame, CA). DRG and skin sections were prepared and stained as described previously (30). Anti-BNaC1a antibody R6798 (30), anti-Myc antibody 9E10 (Roche Molecular Biochemicals, GmbH, Germany), an anti-PICK1 rabbit affinity-purified polyclonal antibody generated to residues 2–31 of mPICK1 (kindly provided by J. Xia and R. Huganir (35, 36)), a rabbit antisera to residues 1–300 of PICK1 (H-300; Santa Cruz Biotechnology, Santa Cruz, CA) and a goat anti-PICK1 antibody (N18; Santa Cruz Biotechnology) were used for immunocytochemistry. Cy3 donkey anti-rabbit, FITC donkey anti-goat and FITC donkey anti-mouse were used (Jackson ImmunoResearch, West Grove, PA) secondary antibodies were used.

For brain immunohistochemistry, rats were perfused with 4% paraformaldehyde, their brains were postfixed in 4% paraformaldehyde overnight at 4 °C. After four washes with PBS, tissues were incubated in the secondary antibodies in PBS with 0.05% Tween 20 and mounted with Vectashield mounting medium (Vector Laboratories, Burlingame, CA). DRG and skin sections were prepared and stained as described previously (30). Anti-BNaC1a antibody R6798 (30), anti-Myc antibody 9E10 (Roche Molecular Biochemicals, GmbH, Germany), an anti-PICK1 rabbit affinity-purified polyclonal antibody generated to residues 2–31 of mPICK1 (kindly provided by J. Xia and R. Huganir (35, 36)), a rabbit antisera to residues 1–300 of PICK1 (H-300; Santa Cruz Biotechnology, Santa Cruz, CA) and a goat anti-PICK1 antibody (N18; Santa Cruz Biotechnology) were used for immunocytochemistry. Cy3 donkey anti-rabbit, FITC donkey anti-goat and FITC donkey anti-mouse were used (Jackson ImmunoResearch, West Grove, PA) secondary antibodies were used.

For brain immunohistochemistry, rats were perfused with 4% paraformaldehyde, their brains were postfixed in 4% paraformaldehyde for 2 h at 4 °C, and 50-μm sections were cut with a vibratome. Floating sections were permeabilized in 50% ethanol for 30 min and then blocked and labeled with antibodies as indicated above for cultured cells. Mouse anti-BNaC1b antibody (Chemicon, Temecula, CA) and a rabbit anti-PICK1 antibody were used (30). The last 32 amino acids of the BNaC1 C terminus were fused to the GST-FLAG domain vector pGAL4.2.1 with the Hybrizap-2.1 two-hybrid Gigapack cloning kit and cDNA synthesis kit (Stratagene).

**Isolation of PICK1 in a Yeast Two-hybrid Screen**—Examination of the sequences of the BNaC1 and BNaC2 channels reveals that, although their intracellular C termini are largely divergent, the extreme C-terminal eight residues are conserved (Fig. 1A) (4). ASIC4 is also similar to BNaC1 and BNaC2 in this region. The residues DRASIC, the remaining residues in the BNaC/ASIC branch, is not. Because many ion channels and receptors interact with other proteins through their C termini, it seemed likely that BNaC channels might also. Therefore, we performed a yeast two-hybrid screen with the last 32 amino acids of the BNaC1 C terminus (ctBNaC1 as bait. From a screen of 660,000 transformants, we obtained four positive clones. Par-
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The C Terminus of BNaC1 Is Necessary for the Interaction with PICK1—PICK1 was first identified as a protein that interacts with protein kinase C (38) and has subsequently been shown to interact with other proteins. The 416-amino acid PICK1 protein contains a PDZ domain at its N terminus (39) followed by a predicted coiled-coil domain (35). PDZ domains are protein-protein interaction domains that bind to short peptide sequences, which usually occur at C termini (40–43). To test whether PICK1 interacts with the C-terminal residues of BNaC1, we deleted the last four amino acids of the BNaC1 C terminus bait to create the construct cBNaC1Δ4. This deletion eliminated the interaction with PICK1 (Fig. 1B). In addition, we added a tyrosine to the BNaC1 C terminus bait to create the construct cBNaC1Δ-Y. This alteration also eliminated the interaction with PICK1. Therefore, the last residues of BNaC1 are required for interaction with PICK1, and they must be located at the C terminus. Because of the similarity between the C-terminal residues of BNaC1 and BNaC2, we asked whether the C terminus of BNaC2 also interacts with PICK1 and found that it does (Fig. 1B).

Based on their target binding specificity, PDZ domains have been classified into at least three types, each of which recognizes a site with a hydrophobic amino acid at the most C-terminal, or 0 position. The three types are distinguished by their binding preference at the −2 position with type I PDZ domains binding T or S, type II PDZ domains binding bulky hydrophobic residues, and type III PDZ domains binding E or D at this position (44–46). BNaC1 and BNaC2 contain I or F at the −2 position and, thus, are similar to type II targets, although they differ in having a cysteine at their C terminus. Although a cysteine at the 0 position is not common in PDZ target peptides, it has been found in the binding partners of the PDZ proteins SITAC (47) and Mint1 (48). Examination of other PICK1 target peptide sequences reveals that PICK1 has atypical specificity. PICK1 can bind to type 1 (39) and type 2 (35, 49–55) PDZ ligands and, as reported here, to BNaC isoforms that have a cysteine at the 0 position.

The PICK1 PDZ Domain Is Required for Interaction with the BNaC1 C Terminus—PDZ domains possess a 7- to 8-amino acid segment known as the carboxylate-binding loop, which includes a conserved lysine or arginine that interacts with the free carboxylate of the C-terminal residue of target peptides (44, 56). As in previous studies (35, 39), we mutated this conserved lysine and an adjacent aspartate to alanines (PICK1(K27A,D28A)). This double-mutant form of PICK1 did not interact with cBNaC1 in yeast (Fig. 1B). Therefore, the PDZ domain of PICK1 is necessary for the interaction of PICK1 with the C terminus of BNaC1.

In Vitro Binding of BNaC1α and PICK1—To confirm in vitro the ability of the C terminus of BNaC1 to bind PICK1, we expressed myc-tagged-PICK1 in COS cells and performed pulldown experiments with a bacterially expressed GST fusion to the C terminus of BNaC1 (GST-ctBNaC1) (Fig. 2A). GST-ctBNaC1 retained mycPICK1, whereas GST alone or the mutated GST-ctBNaC1Δ4 and GST-ctBNaC1+Y did not. However, GST-ctBNaC1 did not retain the double-mutant form of PICK1 (mycPICK1(K27A,D28A)) (Fig. 2B).

Coimmunoprecipitation of BNaC1α and PICK1 from Heterologous Cells and Cerebellar Membranes—To demonstrate that BNaC1α and PICK1 can also interact in mammalian cells, we coexpressed full-length human BNaC1α and mycPICK1 in HEK293 cells. MycPICK1 was coimmunoprecipitated with a BNaC1α-specific antibody but not with control IgG (Fig. 3A). Inclusion of antigenic peptide prevented coimmunoprecipitation. Therefore, PICK1 and BNaC1α can interact specifically in mammalian cells as well as in yeast.

We also demonstrated an association between endogenous PICK1 and BNaC1α in tissue by coimmunoprecipitating BNaC1α from rat cerebellar membrane extracts using a PICK1 antibody, but not control IgG (Fig. 3B). However, only a small amount of the total BNaC1α was coimmunoprecipitated. This may be because PICK1 has other binding partners in the cerebellum (36) but may also be accounted for if only a fraction of cerebellar BNaC1α is bound to PICK1 at any one moment. We were unable to demonstrate coimmunoprecipitation of PICK1 from cerebellar membrane extracts using a BNaC1α antibody; coimmunoprecipitation may be obscured in this case, because the precipitating antibody migrates with a mobility similar to that of PICK1 and is recognized at a low level by the secondary antibody used for immunoblotting.

Coexpression and Clustering of BNaC1α and PICK1 in Heterologous Cells—We expressed BNaC1α and mycPICK1 in COS cells and found that they colocalized within cells (Fig. 4, A–C). As previously reported (38, 50), PICK1 immunoreactivity in COS cells was observed throughout the cytoplasm and around the nucleus, concentrated to one side of the nucleus. BNaC1α immunoreactivity in COS cells is present in intracellular compartments throughout the cytoplasm and in the plasma membrane (Fig. 4E and data not shown). However, in cells that express both BNaC1 and mycPICK1, these two proteins appar-
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BNaC1α and PICK1 Are Coexpressed by Central Neurons and Localize at Their Sensory Terminals—Several BNaC/ASIC genes are expressed in subsets of sensory neurons of the dorsal root ganglia (DRG): ASIC4 is expressed weakly in a subset of sensory neurons of the dorsal root ganglia (DRG): ASIC4 is expressed weakly in a subset of sensory neurons of the dorsal root ganglia (DRG): ASIC4 is expressed weakly in a subset of sensory neurons of the dorsal root ganglia (DRG): ASIC4 is expressed weakly in a subset of sensory neurons of the dorsal root ganglia (DRG): ASIC4 is expressed weakly in a subset of sensory neurons of the dorsal root ganglia (DRG). In addition, we performed immunocytochemistry with a PICK1 antibody and observed PICK1 immunoreactivity in small and large diameter DRG neurons (18, 19, 57), and BNaC1α is expressed in large diameter DRG neurons (30).

It has been shown by Western blotting that PICK1 is expressed in the brain, heart, lung, muscle, liver, spleen, kidney, and testis (35). Similarly, we performed Western blots on rat DRG lysates with an anti-PICK1 antibody and observed a band of the expected molecular mass, ~50 kDa (Fig. 5A). In addition, we performed immunocytochemistry with a PICK1 antibody and observed PICK1 immunoreactivity in small and large diameter neurons (Fig. 5B). This staining was eliminated by absorption control with the PICK1 peptide that had been used to generate the antibody. Thus, PICK1 is present with BNaC proteins in the soma of DRG neurons.

The BNaC1α protein product is transported unidirectionally to the periphery and localizes at the specialized mechanosensory endings of large DRG neurons (30). We find that PICK1 is also present at touch terminals innervating Meissner corpuscles, hair follicles (palisades), and Merkel cells (Fig. 5, D–G).

BNaC1α and PICK1 Are Coexpressed by Central Neurons and Localize at Their Dendrites—It has been reported that BNaC1α is expressed in Purkinje cells of the cerebellum (36). In tissue sections, PICK1 immunoreactivity is strong in the Purkinje cell bodies and dendrites, but it is not detected in their axons (Fig. 6A). We found that BNaC1α is also expressed in...
FIG. 6. PICK1 and BNaC1α in dendrites and soma of brain neurons. A–E, Purkinje neurons of cerebellum. A, anti-PICK1 immunoreactivity was present in the soma and dendrites. C and D, anti-BNaC1α immunoreactivity was present in the dendrites (C) and in some cases also in the cell bodies (D). Labeling was prevented by preincubation of the antisera with the PICK1 (B) or BNaC1α (E) antigenic peptides. Scale bars are 100 μm (A–F), F–M, pyramidal neurons of parietal cortex. Immunoreactivity to PICK1 (H300 antibody) (I, G) and BNaC1α (J, K) in the dendrites (F, J) and soma (G, K). Colabeling of the same sections with the HM2 monoclonal antibody to the MAP-2 dendritic marker reveals that only a sub- set of the dendrites contains above-background levels of PICK1 (H, I) and BNaC1α (L). Anti-BNaC1α labeling was prevented by preincubation with the antigenic peptide (M). Magnification is the same for panels F–M, N–Q, CA3 region of hippocampus. Anti-PICK1 (N) and anti-BNaC1α (P) immunoreactivities at the region of the proximal dendritic branch of pyramidal neurons. Labeling was prevented by preincubation of the antisera with the PICK1 (O) or the BNaC1α (Q) antigenic peptides. Magnification is the same for panels N–Q.

Purkinje cells and absent (or below detection levels) in other cell types in the cerebellum. BNaC1α immunoreactivity is present in the dendrites of Purkinje cells, sometimes in their soma, but not in their axons. In the dendrites of Purkinje neurons, both PICK1 and BNaC1α antisera labeled in a punctate pattern (Fig. 6D). The staining was substantially reduced by absorption controls with the peptides that were used to generate the antisera (Fig. 6, C and F).

We also found immunoreactivity to PICK1 and BNaC1α in pyramidal neurons of brain cortex. Once again, labeling was in dendrites and soma, but not in axons. Colabeling of the dendritic marker protein MAP-2 revealed that only a subset of dendrites contain detectable levels of BNaC1α or PICK1 (Fig. 6, F–M). Finally, we found PICK1 and BNaC1α in the hippocampus, in a crescent-shaped area that corresponds to the proximal dendritic branch of CA3 pyramidal neurons (Fig. 6, N–Q). The specificities of these antibodies were confirmed by competition with antigenic peptides (Fig. 6, M, O, Q). In summary, PICK1 and BNaC1α are coexpressed in certain central and peripheral neurons, and both localize at their dendrites and soma.

DISCUSSION

By two-hybrid assays, pull-down assays, coimmunoprecipitations, colocalization, and coaggregation we have shown that PICK1 specifically interacts via its PDZ domain with the C termini of the BNaC1 and BNaC2 ion channels. BNaC1 and BNaC2 each have two alternative splice forms, α and β, which have the same C-terminal sequence, and ASIC4 has a very similar C terminus; thus, PICK1 may interact with up to five BNaC/ASIC channel isoforms.

BNaC1 and BNaC2 mRNAs are expressed in the CNS and peripheral nervous system (2–4, 17–19, 57), and PICK1 is expressed in most tissues, including the brain (35). With immunocytochemistry, we found that PICK1 and BNaC1α are coexpressed in Purkinje cells of cerebellum and in some pyramidal neurons of cortex and hippocampus (Fig. 6). In all these central neurons both proteins localize in clusters in dendrites and sometimes also at soma. Future experiments will determine whether and to what extent clusters containing BNaC1α and PICK1 overlap, and if these clusters are at postsynaptic sites or at dendritic spines.

This is the first report of the subcellular distribution of a BNaC/ASIC channel in central neurons. If acid-sensitive BNaC channels respond to the transient acidification in the synaptic cleft due to acidic vesicle exocytosis, they could play roles in synaptic communication. These channels could also participate in brain responses to ischemia or waves of acidification (58). Finally, because of the active mobility of dendritic spines, there are also possible mechanosensitive roles of BNaC1α and related channels in dendrites.

Although their function in the CNS is unknown, BNaC1 and BNaC2 may mediate mechanosensation and acid-evoked nociception in the peripheral nervous system. BNaC1α is specifically transported to the peripheral processes of large diameter DRG neurons where it accumulates in a variety of cutaneous mechanoreceptor terminals (30), and mice with a knockout of the BNaC1 gene have a deficit in touch sensation (29). The subcellular localization of BNaC1α and PICK1 in brain and sensory neurons reveals a similarity, not necessarily coincidental, between dendrites of central neurons and sensory terminals of peripheral neurons. Dendrites and sensory endings are functionally equivalent, both specialized in detecting stimuli, and might have evolved from the same ancestral subcellular structure. Furthermore, DRG sensory processes originate embryonically as dendrites, and only later differentiate into axon-like structures. The sorting mechanisms that target BNaC1α (and perhaps PICK1) to sensory terminals and to dendrites might be the same.

PDZ domain proteins can organize supramolecular signaling complexes and can regulate channel activity, trafficking, and localization (59–63). PICK1 was first identified as an interactor of protein kinase Cα (38, 39) and has since been shown to...
interact with many receptors, channels, and transporters (35, 49, 51–54, 64, 65). Although PICK1 has only one PDZ domain, it can multimerize through its coiled-coil region (35, 39) and can, therefore, cross-link different binding partners. PICK1 might play a role in clustering or anchoring of BNaC channels or it may play a role in the assembly of a channel complex. The presence of PICK1 at touch terminals suggests it may functionally interact with BNaC1α in mediating this sense. A proposed role for BNaC1α and related channels in mechanosensory endings is the formation of channels that are physically tethered to the cytoskeleton, so that force can be applied to them (9, 29, 30). A protein like PICK1 could connect the channels to the cytoskeleton or to other proteins. In small diameter DRG cells, where BNaC1α is not expressed, PICK1 could interact with BNaC1β or BNaC2α/ASICβ.

PICK1 interacts with the C termini of α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors (35, 50) and has been implicated in the internalization or stabilization of internal pools of α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors during cerebellar and hippocampal long term depression (36, 66, 67, 68). Interestingly, most BNaC1α is not distributed throughout the plasma membrane in the DRG soma, but instead accumulates in the cytoplasm near the axon hillock and is transported to sensory terminals. Similarly, in brain neurons BNaC1α is targeted to dendrites. Perhaps PICK1 retains BNaC1α within the cytoplasm and may play a role in the sorting and transport of this channel to peripheral mechanosensory neuron terminals and central neuron dendrites.

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