Differential Phospholipid Binding by Site 3 and Site 4 Toxins

IMPLICATIONS FOR STRUCTURAL VARIABILITY BETWEEN VOLTAGE-SENSITIVE SODIUM CHANNEL DOMAINS*

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Jaime J. Smith, Sujith Alphy, Anna L. Seibert‡, and Kenneth M. Blumenthal§

From the Department of Biochemistry, School of Medicine and Biomedical Sciences, State University of New York, Buffalo, New York 14214

It has been shown recently that polypeptide toxins that modulate the gating properties of voltage-sensitive cation channels are able to bind to phospholipid membranes, leading to the suggestion that these toxins are able to access a channel-binding site that remains membrane-restricted (Lee, S.-Y., and MacKinnon, R. (2004) Nature 430, 232–235). We therefore examined the ability of anthopleurin B (ApB), a sea anemone toxin that selectively modifies inactivation kinetics of NaV\(_{1.1}\) channels, and ProTx-II, a spider toxin that modifies activation kinetics of the same channels, to bind to liposomes. Whereas ProTx-II can be quantitatively depleted from solution upon incubation with phosphatidylcholine/phosphatidylserine liposomes, ApB displays no discernible phospholipid binding activity. We therefore examined the activities of structurally unrelated site 3 and site 4 toxins derived from *Leiurus* and *Centruroides* venoms, respectively, in the same assay. Like ApB, the site 3 toxin LqqV shows no lipid binding activity, whereas the site 4 toxin *Centruroides* toxin II, like ProTx-II, is completely bound. We conclude that toxins that modify inactivation kinetics via binding to NaV\(_{1.1}\) site 3 lack the ability to bind phospholipids, whereas site 4 toxins, which modify activation, have this activity. This inherent difference suggests that the conformation of domain II more closely resembles that of the KvAP channel than does the conformation of domain IV.

Chemically diverse neurotoxins have historically been of great value in defining the overall architecture of voltage-dependent Na\(^+\) (Na\(_{V}\)) and K\(^+\) (K\(_{V}\)) channels. The pores of such channels have been mapped by analysis of their interactions with conotoxins (Na\(_{V}\)) and a variety of polypeptides from scorpion venoms, such as charybotoxin and agitoxins (1–4). More recently, regions of these channels involved in gating have been identified by using gating modifier toxins derived from scorpion (5), sea anemone (6), and spider (7–9) venoms. Most interestingly, gating modifier toxins appear to interact with the same channel region, designated the S3-S4 linker, irrespective of the type of channel being studied (10).

Gating modifier toxins can also be important probes for the accessibility of defined regions of a given channel. Very recently, the MacKinnon laboratory has employed a novel spider toxin, VSTX, to probe the accessibility of defined regions of the voltage sensor of the archaeabacterial KvAP channel (9). The resulting data were interpreted in the context of a channel three-dimensional structure (11) in which the KvAP S3-S4 linker was located either near the cytoplasmic surface or buried within the bilayer, depending on whether the channel was in the resting or activated state (9). The observation that VSTX possessed phospholipid binding activity (12) provided a potential explanation for the ability of this toxin to modify channels via interaction with sequences that were never exposed at the extracellular surface.

To understand the extent to which this model could be generalized, we examined two other gating modifier polypeptides, anthopleurin B (ApB) and Protx-II (PT-II). ApB is a 49-amino acid residue polypeptide toxin that functions to delay channel inactivation upon binding to site 3 of Na\(_{V}\)\(_{8}\) (13), where it competes with a number of scorpion \(\alpha\)-toxins that have functionally identical effects. Site 3 has been mapped by mutant cycle analysis to the S3-S4 linker of Na\(_{V}\) domain IV (5, 6). ProTx-II (PT-II) is a recently discovered 30-amino acid residue polypeptide that conforms to the inhibitory cysteine knot motif and functions as a gating modulator to inhibit Na\(_{V}\) activation (14). Although the binding site of PT-II is not as well characterized as that of ApB, preliminary evidence suggests that it is located in or near the S3-S4 linker of channel domain II (15). This binding site is either similar or identical to the one characterized previously for site 4 or \(\beta\)-scorpion toxins (16, 17) that modulate channel activation kinetics.

We have demonstrated previously that hydrophobic residues that are exposed on the surface of ApB are essential to its activity (18, 19), perhaps suggesting that ApB, like VSTX, has the ability to access its binding site following insertion into the phospholipid bilayer. We show here that two structurally distinct site 3 toxins, ApB and *Leiurus* toxin V (LqqV), are both incapable of phospholipid binding. In contrast, the two structurally distinct site 4 toxins, PT-II and *Centruroides* toxin II (CsiII), are phospholipid binders. Moreover, both ApB and PT-II are capable of fully modifying Na\(_{V}\)\(_{1.5}\) maintained under hyperpolarized conditions. We interpret these results as meaning that domains II and IV of the sodium channel may differ in their overall conformations, with the S3-S4 linker being relatively more accessible in domain IV than in domain II.

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† Fellow of the American Heart Association of Western New York.
‡ To whom correspondence should be addressed: Dept. of Biochemistry, School of Medicine and Biomedical Sciences, State University of New York, 3435 Main St., Buffalo, NY 14214. Tel.: 716-829-2727; Fax: 716-829-2725; E-mail: kblumen@buffalo.edu.
§ To whom correspondence should be addressed: Dept. of Biochemistry, School of Medicine and Biomedical Sciences, State University of New York, 3435 Main St., Buffalo, NY 14214. Tel.: 716-829-2727; Fax: 716-829-2725; E-mail: kblumen@buffalo.edu.

The abbreviations used are: Na\(_{V}\), voltage-dependent Na\(^+\) channel; K\(_{V}\), voltage-dependent K\(^+\) channel; ApB, anthopleurin B; PT-II, Protx-II; RP-HPLC, reverse phase-high pressure liquid chromatography; GUVs, giant unilamellar vesicles; CsiII, C. suffusus suffusus toxin II; rPT-II, recombinant ProTx-II; LqqV, L. quinquestratus quinquestratus toxin V; MALDI-TOF, matrix-assisted laser desorption ionization time-of-flight; VSTX, voltage-sensor toxin.
Production of Recombinant Toxins—Plasmid DNA encoding a synthetic gene for ProTx-II fused to the coding sequence for glutathione S-transferase was obtained from Dr. Charles Cohen. The PT-II coding sequence was subcloned into pET32a vector (Invitrogen) between the BamHI and EagI restriction sites using standard molecular biology protocols. Deletion mutagenesis was employed to remove nucleotides encoding an 11-amino acid N-terminal extension, leaving two extra N-terminal amino acids derived from a StuI restriction site, and the construct was verified by sequencing. A fusion protein containing the N-terminal thioredoxin and C-terminal PT-II was expressed in Esche-
richia coli BL21(DE3) cells by induction in mid-log phase with 0.25 mM isopropyl-$\beta$-D-thiogalactopyranoside for 2 h at 37 °C. Cells were harvested and suspended in a lysis buffer containing 10 mM Tris-HCl, 50 mM KCl, 2 mM EDTA, 10 mM MgCl$_2$, 10 mM dithiothreitol, 1 mM each of leupeptin and pepstatin, 100 $\mu$g/ml each of RNase and DNase, and 0.5 mg/ml lysozyme, pH 7.3. Following lysis in a French press, the pellet obtained was extracted with 6 mM guanidine HCl, and the solubilized protein was purified on Ni$^{2+}$-nitrilotriacetic acid resin equilibrated with 4 mM guanidine HCl. Following elution from the resin with 1 M imidazole and 4 M guanidine HCl, fusion protein was dialyzed against 50 mM ammonium bicarbonate buffer and cleaved overnight at room temperature with enterokinase and pipette solution, 95 mM CsF, 30 mM CsCl, 5 mM NaCl, 10 mM EGTA, a selective KV2.1 channel inhibitor, has identified a hydrophobic face that is important for binding (23). This hydrophobic protrusion, referred to as a “dimple,” is also present in other 

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**RESULTS**

It has been shown recently that VSTX1, a voltage-sensor toxin that inhibits activation kinetics of the archaeabacterial channel $K_{\mathrm{A}}$AP, binds liposomes. Based on this, and its slow rate of channel modification, Lee and MacKinnon (12) have proposed that gating modifier toxins are able to access their target channel after first partitioning into the lipid membrane. Consistent with these results, scanning mutagenesis of SGTx1, a selective $K_{\mathrm{A}}$ channel inhibitor, has identified a hydrophobic face that is important for binding (23). This hydrophobic protrusion, referred to as a “dimple,” is also present in other gating modifier toxins. Therefore, we investigated whether a similar membrane-access mechanism might be common to gating modifier toxins targeting other channels. For this purpose, we initially employed ApB, a well characterized site 3 toxin from sea anemone that inhibits inactivation of $Na_v$ channels (6) (see also Fig. 2A). We have shown previously (18, 19) that mutagenesis of surface-exposed hydrophobic residues of ApB greatly decreases its binding affinity. Incubation of ApB with GUVs for 1 h at 37 °C followed by centrifugation results in complete recovery of the toxin in the supernatant as demonstrated by HPLC analysis, thus indicating that ApB lacks the ability to bind phospholipids (Fig. 1A).

This unexpected result led us to examine the recently characterized polypeptide gating modifier, ProTx-II, purified from venom of the tarantula *Thrixopelma pruriens* (14). ProTx-II has been demonstrated to inhibit activation of $Na_v$ and $Ca_v$ channels by shifting their voltage dependence toward more...
depolarized potentials (14). On the basis of this activity, ProTx-II is assumed to be a site 4 β-toxin, and data have been presented consistent with the conclusion that ProTx-II binds to the S3-S4 region of Naᵥ domain II (15). We have produced recombinant ProTx-II (rPT-II) by using a bacterial expression system. As shown in Fig. 2B, the activity of the recombinant peptide is identical to that of the natural material, inhibiting Naᵥ1.5 activation and inducing a voltage-dependent depolarizing shift of the I-V curve of the channel (14). Incubation of rPT-II with GUVs for 1 h at 37 °C, followed by centrifugation, results in a quantitative depletion of toxin from solution (Fig. 1B). Chromatographic analysis verifies that the toxin is

Fig. 3. A, depletion of *L. quinquestriatus* quinquestriatus venom constituents by phospholipids. Crude *L. quinquestriatus* quinquestriatus venom was fractionated by RP-HPLC on a C4 column without additional treatment (solid line) or after incubation with GUVs and centrifugation (dashed line). B, depletion of *C. suffusus* suffusus venom constituents by phospholipids. The experiment was done as described for *L. quinquestriatus* quinquestriatus venom above. Solid line, venom alone; dashed line, GUV supernatant.
completely recovered in the liposomal pellet. As a positive control in these experiments, we used GsMTx4, a gating modifier of mechanosensor channels isolated from the spider Grammostola spatulata, that has been shown by fluorescence analysis to bind phospholipids (24). We observe that this toxin is also completely removed from the solution phase following incubation with GUVs (data not shown). These results raise the possibility of a fundamental difference between channel access mechanisms for site 3 and site 4 toxins.

In order to further evaluate this possibility, we sought to examine additional, structurally unrelated probes of each site. Venom from the scorpion L. quinquestriatus quinquestriatus is known to contain site 3 toxins that inhibit sodium channel inactivation (25), with the most extensively characterized toxin being designated LqqV. Binding of LqqV has been shown to be competitive with that of anemone toxins like ApB (26). The venom of a different scorpion C. suffusus suffusus is known to contain a family of β-toxins that are homologous to the α-toxins, but bind to a distinct site (site 4) to modify channel activation (16, 27, 28) in an isoform-specific fashion.

L. quinquestriatus quinquestriatus venom was incubated with GUVs using the same protocol described above for ApB and rPT-II. HPLC analysis revealed the presence of multiple components (Fig. 3A), a subset of which were selectively depleted upon incubation with GUVs. Analysis of individual peaks by MALDI-TOF reveals species of molecular weights identical to the α-toxins LqqI, LqqII, and LqqV that are not removed upon incubation with GUVs (Table I). Whole-cell voltage clamp analysis reveals that the putative LqqV polypeptide eluting close to 21 min delays inactivation of Naᵥ1.5 (Fig. 4A). Together with the identified molecular weights, the functional data confirm that this material is authentic LqqV and demonstrates that a second, structurally unrelated, site 3-toxin is unable to bind GUVs. In contrast, the L. quinquestriatus quinquestriatus venom components that elute later in the gradient are partially to completely depleted by GUVs and are recovered in the post-liposomal pellet (Fig. 3A). MALDI-TOF analysis of this material allowed us to identify the site 4 β-toxin, LqqIV, which elutes in this region (Table I).

C. suffusus suffusus venom also contains components that are completely depleted from solution in the presence of phospholipids (Fig. 3B). Upon analysis using mass spectrometry, we were able to identify a well characterized site 4 toxin, CsIII, that elutes close to 16 min and is depleted by phospholipids (Table I). After HPLC purification of this polypeptide, we were able to demonstrate its ability to inhibit activation of Naᵥ1.5 and simultaneously shift the voltage dependence of channel activation by 5–7 mV in the depolarizing direction (Fig. 4B), as demonstrated previously for CsII (16). These results demonstrate that two structurally unrelated α-toxins, ApB and LqqV, both of which bind to

### Table 1

| Toxin name | Toxin class | Molecular weight |
|------------|-------------|-----------------|
| LqqI       | Site 3-α    | 7484.98         |
| LqqII      | Site 3-α    | 7240.2          |
| LqqIV      | Site 3-α    | 6652.54         |
| LqqV       | Site 3-α    | 7293.26         |
| LqqIV-T-1  | Site 4-β    | 7855.01         |
| CsII       | Site 4-β    | 7546.61         |
| CsIII      | Site 4-β    | 7291.8          |
| CsIV       | Site 4-β    | 6840.7          |
| CsP1       | ?           | 7299.77         |

The molecular weights of toxins isolated in the HPLC experiments depicted in Fig. 3, A and B, were determined by MALDI-TOF mass spectrometry and are compared with the calculated molecular weights for known components of L. quinquestriatus quinquestriatus and C. suffusus suffusus, respectively.

The increase in current at 8-ms post-stimulation confirms the presence of a site 3 toxin in this fraction. Data shown are representative of those obtained from three cells. B, modification of Naᵥ1.5 currents by Centruroides toxin. The HPLC peak denoted by the asterisk in Fig. 3B and found to contain a polypeptide of Mᵣ 7546, identical to the calculated Mᵣ of CsIII, was analyzed for its ability to modify Naᵥ1.5 currents as described under “Experimental Procedures.” The inhibition of current, coupled with a rightward shift in the I-V curve (closed symbols), confirms the presence of a site 4 toxin in this peak. Data shown are representative of those obtained from three cells.

The ability of these toxins to bind phospholipids in a site-dependent manner could have important implications for models of channel architecture and voltage-dependent gating, provided that their binding is independent of channel state. To assess state dependence, we analyzed the ability of both rPT-II and ApB to modify channel activation and inactivation kinetics, respectively, using the protocol described under “Experimental
site of this toxin is either available to externally added polypeptides in the resting channel or that the ability of such toxins to bind lipids allows them to access their binding site following binding to or insertion into the phospholipid bilayer (Fig. 5B). This degree of inhibition is consistent with that reported previously for ProTx-II (14).

**DISCUSSION**

In this paper we have analyzed the ability of toxins that interact with sites 3 and 4 of Na\textsubscript{V} channels (Table II) to bind to phospholipid vesicles, and we found that toxins targeting these sites differ sharply in this property; lipid binding activity is associated solely with those toxins that bind to site 4. Our data also demonstrate that modification of the channel by either ApB or PT-II occurs regardless of whether the channel is in an open or closed conformation. The simplest interpretation of our results is that the architecture of domains II and IV of Na\textsubscript{V} channels is sufficiently different to allow for multiple access mechanisms by toxins targeting these regions.

Our interpretation that these results point to inherent differences in the architecture of Na\textsubscript{V} domains II and IV, rather than simply in the structures of the toxins being analyzed, is reinforced by a comparison of the structures of PT-II andCssII on the one hand and LqqV and ApB on the other. LqqV andCssII share a common \(\alpha/\beta\) fold, have the same disulfide pairings, and are 30% homologous overall, despite their distinct physiologic and phospholipid binding properties. The amino acid sequence of PT-II, which shares a common disulfide structure with VSTX and GsMTX4 but is only weakly homologous otherwise, is unrelated to CssII. Nonetheless, CssII and PT-II are functionally similar to one another, and both are able to bind GUVs. ApB, a largely \(\beta\)-structure polypeptide, is not related to either the scorpion or spider toxins at any structural level, although its electrophysiologic signature and inability to bind lipids is identical to LqqV, the other site 3 toxin.

Moreover, in comparing channel domains II and IV, independent biochemical and physiologic evidence exists supporting the possibility of conformational heterogeneity. Binding analyses using radiolabeled site 3 and site 4 toxins demonstrated that site 3 toxins bind channels in a voltage-dependent manner, whereas the affinity of site 4 toxins is unaffected by membrane depolarization (28, 29). Furthermore, voltage clamp analysis of activation kinetics of chimeric cardiac/skeletal muscle Na\textsubscript{V} channels indicates that although the S4 segments of domains I and II initiate the conformational change leading to activation, domains III and IV play the predominant role in inactivation (30). Elegant site-directed fluorescent labeling studies of S4 segments of all domains of Na\textsubscript{V} have likewise shown that determinants of inactivation kinetics are associated with domains III and IV, whereas the S4 regions of domains I and II lead channel activation (31).

The three-dimensional structure of the archaeabacterial K\textsubscript{V}AP channel depicts a molecule dramatically different from the one predicted by scanning mutagenesis and other solution studies (32–34). Most strikingly, the crystal structure places the gating charges carried by S4, as well as the entire S3-S4 linker region, either near the cytoplasmic face of the membrane or in the center of the lipid bilayer, depending on whether the
channel is in a closed or open state (9). Because this region contains the binding site for gating modifier toxins, the KvAP structure raised obvious questions about the mechanism by which these polypeptides gain access to their binding sites.

A common feature of such gating modifier toxins is a hydrophobic protrusion referred to as a dimple that contains residues essential for channel modification (23). The existence of this hydrophobic dimple led Lee and MacKinnon to ask whether VSTX, a KvAP toxin, also has the ability to bind phospholipids in an in vitro assay. Their demonstration that VSTX could be completely depleted from solution upon incubation with phospholipids led to the hypothesis that gating modifier toxins access their receptor sites by partitioning into the lipid membrane (12). Although our data are consistent with this interpretation as it applies to site 4, they clearly preclude its generalization to include site 3.

Kv and NaV channels differ in one fundamental aspect; the functional unit of the Kv channel is a noncovalent tetramer of identical subunits, and in NaV channels these four domains have been fused and mutated during evolution. The likelihood that the conformations of individual NaV domains may differ from one another is thus greater than would be anticipated for Kv channel subunits, and the results we have reported here are consistent with this hypothesis. Moreover, our results could help to resolve the inconsistencies between the KvAP structure and accessibility studies of both NaV and Kv channels using gating modifier toxins. Finally, we recognize the possibility that phospholipid binding might not be correlated with channel modification, and studies with PT-II are currently underway to test this possibility.

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