

***Pandinus imperator* Scorpion Venom Blocks Voltage-Gated Potassium Channels in Nerve Fibers**

Pamela A. Pappone¹ and Michael D. Cahalan²

¹Department of Animal Physiology, University of California, Davis, California 95616, and ²Department of Physiology and Biophysics, University of California, Irvine, California 92717

We have examined the effects of venom from the scorpion *Pandinus imperator* on the membrane currents of voltage-clamped frog myelinated nerve fibers using the Vaseline-gap method. Crude venom, applied externally in concentrations from 50 to 500 $\mu\text{g/ml}$, selectively blocked the voltage-gated potassium currents without affecting nodal sodium currents or resting conductances. Block of potassium channels by *Pandinus* venom was highly dependent on the membrane voltage, being greater at negative potentials than at positive potentials. The blocking effects of *Pandinus* venom were irreversible on the time scale of our experiments; however, even high concentrations of venom failed to block potassium currents completely at positive potentials. These results suggest that *Pandinus* venom contains a component(s) that interacts specifically and strongly with a subpopulation of axonal potassium channels.

Many scorpion venoms contain toxins that modify action potential generation in nerves. Most of these venoms act selectively on the voltage-activated Na channels, inducing a prolonged nerve action potential through alterations in the gating properties of these channels (Cahalan, 1980; Catterall, 1984). A few scorpion venoms have been described that have, in addition to the Na channel toxins, minor components that act selectively on K channels (Koppenhoefer and Schmidt, 1968; Narahashi et al., 1972; Romey et al., 1975; Carbone et al., 1982, 1983; Miller et al., 1985). Like the Na channel scorpion neurotoxins, these K channel toxins are basic polypeptides with molecular weights of several thousand daltons. Unlike the Na channel toxins, which have voltage-dependent actions, the K channel toxins described thus far have actions that are independent of the membrane electrical potential. In addition, the effects of these K channel toxins are readily reversed upon their removal from the bathing medium.

In this paper we describe the effects of venom from the scorpion *Pandinus imperator*. *Pandinus* venom is not known to be deadly to vertebrates, and its effects in man are limited to pain at the site of envenomation (Keegan, 1980). We find that *Pandinus* venom acts specifically on axonal K currents in a voltage-dependent manner, selectively blocking the delayed rectifier K channels of frog myelinated nerve fibers. *Pandinus* venom differs

from other known K channel scorpion toxins in that the effects of the venom are highly voltage-dependent and are not readily reversible. The high affinity and specificity of the toxin could make *Pandinus* venom a useful tool for biochemical studies of voltage-gated K channels. A preliminary report of this work has been presented in abstract form (Cahalan and Culp, 1981).

Materials and Methods

Experiments were performed on single myelinated nerve fibers or skeletal muscle fibers of the bullfrog, *Rana catesbeiana*. Fibers were voltage-clamped using the Vaseline-gap method (Dodge and Frankenhaeuser, 1958; Hille and Campbell, 1976), and records of membrane current were sampled and stored on the disk of a minicomputer as described previously (Cahalan and Pappone, 1981, 1983; Armstrong and Matesson, 1986). The amplitude of nodal membrane currents was calculated assuming a node resistance of 12.9 M Ω (Cahalan and Hall, 1982). In most experiments a P/4 pulse procedure was used to subtract the linear components from the membrane current records (Armstrong and Bezanilla, 1974). Fiber ends were cut in internal solutions of 120 mM KF, 2 mM HEPES, pH 7.4, or 80 mM K₂EGTA, 2 mM HEPES, pH 7.4. External solutions were either normal Na-Ringer's, consisting of 115 mM NaCl, 2.5 mM KCl, 1.8 mM CaCl₂, 5 mM 3-(*N*-morpholino)-propanesulfonic acid (MOPS), pH 7.4, or K-Ringer's plus TTX, which had the same composition, except that the NaCl was replaced with KCl and 100 nM TTX was added to block currents through the Na channels. The mounted fibers were allowed to equilibrate for 30 min before starting the experiment. The holding potential was nominally -100 or -110 mV. Lyophilized *Pandinus imperator* venom was obtained from B. R. Tomberlin II (Duarte, CA) or from Latoxan (Rosans, France).

Results

Pandinus venom blocks K channels in myelinated nerve fibers

Venom from the scorpion *Pandinus imperator* selectively reduces the voltage-dependent K currents of frog axons without affecting the Na currents. Figure 1A illustrates the effects of 200 $\mu\text{g/ml}$ *Pandinus* venom on the Na and K currents measured in a voltage-clamped frog myelinated nerve fiber. In the control records, depolarization of the fiber elicits the familiar transient Na current, followed by a delayed and sustained outward K current. In the presence of *Pandinus* venom, the size of the delayed K current is substantially decreased, with no change in the amplitude or activation and inactivation kinetics of the Na currents. Peak Na and K currents from this experiment are plotted in Figure 1B, illustrating that approximately 50% of the K current was blocked, while neither the magnitude nor the voltage dependence of the Na current activation was affected. The block of K currents by the venom was specific for axonal K currents, since in 2 experiments crude venom in concentrations up to 500 $\mu\text{g/ml}$ had no effect on the K currents of voltage-clamped frog skeletal muscle fibers.

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Correspondence should be addressed to Pamela A. Pappone at the above address.

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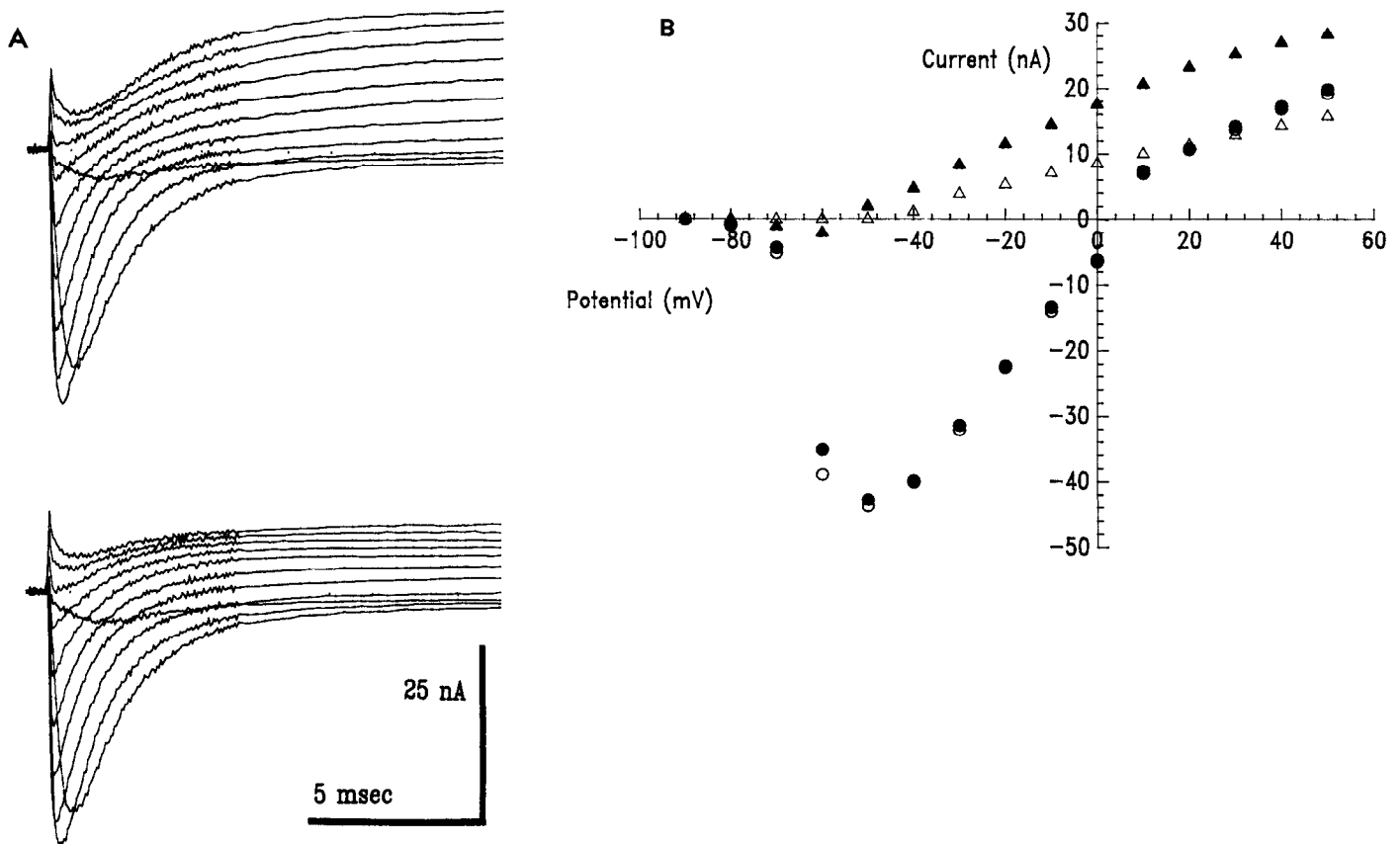


Figure 1. *Pandinus imperator* venom selectively blocks the voltage-dependent K conductance of nerve fibers. *A*, Membrane currents recorded in a voltage-clamped frog myelinated nerve fiber before (*top*) and 3 min after (*bottom*) exposure to 200 µg/ml *Pandinus imperator* venom. The membrane potential was held at -100 mV and stepped for 30 msec to potentials ranging from -90 to +50 mV in increments of 10 mV to produce each set of current records. External solution, Na-Ringer's. Internal solution, KF. Temperature, 10°C. Current records filtered at 15 kHz. Fiber SVND18. *B*, Peak Na (circles) and K (triangles) currents as a function of membrane potential from the records in *A*. Filled symbols are control values and open symbols represent measurements with venom present.

Block of K currents by *Pandinus* venom is voltage-dependent

Pandinus venom blocks K currents more effectively at negative potentials than at positive membrane potentials. The voltage dependence of K channel block can be seen most clearly in the absence of other ionic currents. Figure 2 shows K currents measured in a nerve fiber bathed in a high-K solution. TTX is present to block the Na currents and linear components of the membrane current have been digitally subtracted from the record. Since the reversal potential for K channels is near 0 mV under these ionic conditions, activation of the channels results in both inward and outward K currents in the control records. In the presence of *Pandinus* venom, the inward currents during the depolarizing voltage-clamp steps to negative potentials are abolished, while outward currents at more positive potentials are still present, although their amplitude is reduced. In Figure 2, all of the inward K current was blocked for a depolarization to -50 mV, while the current during a depolarization to +30 mV was only 12% less than that of the control. Data for Figure 2 indicate that the block of K currents is dependent on voltage, but not on the direction of current flow, since inward tail currents are still present at the holding potential of -110 mV at the termination of the pulse in the presence of venom. Thus, the potential dependence of the venom block is evident whether the peak current during a depolarizing pulse or the magnitude of

the tail current on returning to the holding potential is used to measure the amount of K conductance present.

The potential dependence of *Pandinus* venom's effects on K channel activation over the entire voltage range studied is shown in Figure 3, in which the relative K conductance derived from tail-current peak amplitudes measured at the holding potential is plotted as a function of activating pulse potential at 2 venom concentrations. The venom is seen to be more effective in blocking K currents elicited by small depolarizations than in blocking those caused by large depolarizations. K currents were never completely blocked at positive membrane potentials by *Pandinus* venom in our experiments, even at concentrations of 500 µg/ml, 10 times the concentration needed to block half the current at -50 mV. The degree of block measured at negative and positive membrane potentials in various concentrations of *Pandinus* venom is shown in Table 1. These data show that the block of K current was more complete at -50 mV than at +30 mV for all concentrations of venom examined.

The voltage-dependence of *Pandinus* venom effects seem to be due to changes in the number of open K channels, since the conductance properties of the open channel apparently are unaffected by the venom. Figure 4 shows instantaneous current-voltage relations measured in high-K solution with and without venom present. Under both conditions the relation is linear and reverses direction at the same potential, although the magnitude

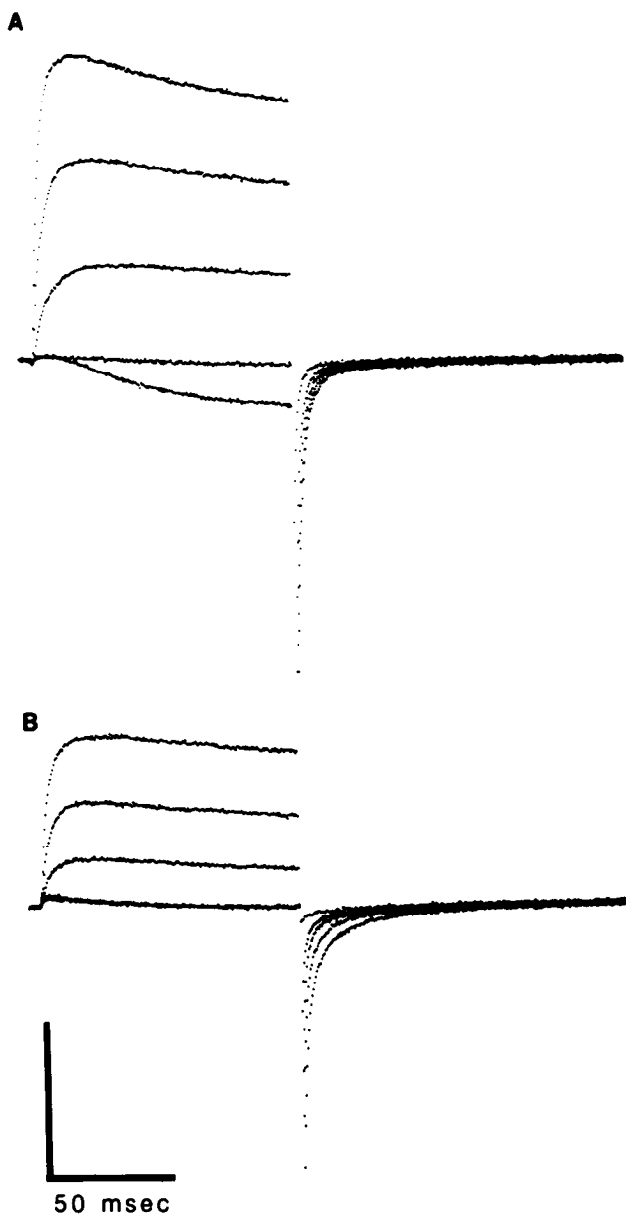


Figure 2. Membrane currents in a voltage-clamped nerve fiber. The fiber was bathed in K-Ringer's with 100 nM TTX added to block the Na currents. The membrane potential was stepped to -50 , -30 , -10 , 10 , and 30 mV from the holding potential of -110 mV. Internal solution, KF. 8°C . Fiber SVND21. *A*, Control. *B*, Venom, $250\ \mu\text{g}/\text{ml}$.

of the currents is reduced by the venom. Thus, if the venom affects the conductance properties of K channels, its effects are constant over the voltage range from -150 to $+30$ mV.

Pandinus venom alters channel-closing without affecting channel-opening rates

While the voltage dependence of the steady-state activation of K channels is altered by *Pandinus* venom, this effect occurs without any changes in the rates of K channel opening. Figure 5 shows K currents activated by a depolarization to $+30$ mV, measured with and without $250\ \mu\text{g}/\text{ml}$ venom present, and scaled to have the same peak amplitude. The rate of K current activation is identical under the 2 conditions. Similar comparisons of the rates of turn-on of K currents over the whole voltage

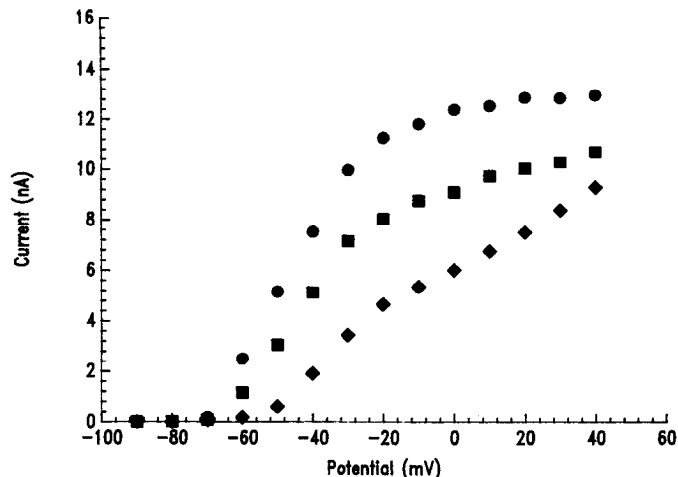


Figure 3. Effects of *Pandinus* venom on the activation of K currents. Peak inward tail current measured at the holding potential of -110 mV following a 100 msec depolarization to the potential shown on the abscissa. Circles are control values, squares are measurements in $50\ \mu\text{g}/\text{ml}$ venom, and diamonds in $250\ \mu\text{g}/\text{ml}$ venom. External solution, K-Ringer's. Same fiber and conditions as in Figure 2.

range in which K currents are activated failed to show any effect of *Pandinus* venom on channel-opening kinetics. In 5 experiments, the ratio of the time required for the K currents to reach their half-maximal value upon depolarization before and during exposure to 50 – $500\ \mu\text{g}/\text{ml}$ venom was 0.98 ± 0.06 , measured at -50 mV.

In contrast to the unaffected channel-opening rates, K channel-closing rates were usually somewhat reduced at the holding potential following venom exposure, as can be seen in Figure 5. Comparison of the times required for half the channels to close upon repolarization to the holding potential of -110 mV showed that, for 50% deactivation of the current, the rates both increased and decreased in different fibers following exposure to the venom. Examination of deactivation rates over the voltage range between -160 and -80 mV showed a decrease in the voltage dependence of channel-closing rates. This resulted in closing kinetics that were faster than control values at more positive potentials, and slower than control values at more negative potentials, with the rates near the holding potential being little affected.

Effects of Pandinus venom are not readily reversed

Figure 6 shows K current magnitude measured before, during, and after exposure to the venom. At time 0 the nerve was exposed to $120\ \mu\text{g}/\text{ml}$ of crude venom. The K current decreased rapidly, and within 100 sec reached a new steady level. When the venom was washed off after a 125 sec exposure, there was no recovery of the current in the remaining 10 min of the experiment. These effects were consistent throughout the course of our experiments. The onset of venom block was rapid, with a steady-state level of block being achieved within a few seconds. Block of K currents was irreversible, and in no experiment did we observe a recovery of current magnitude, even with wash times as long as 30 min.

Effect of Pandinus venom on nodal action potentials

Block of voltage-dependent K currents by *Pandinus* venom might be expected to prolong the duration of the axonal action poten-

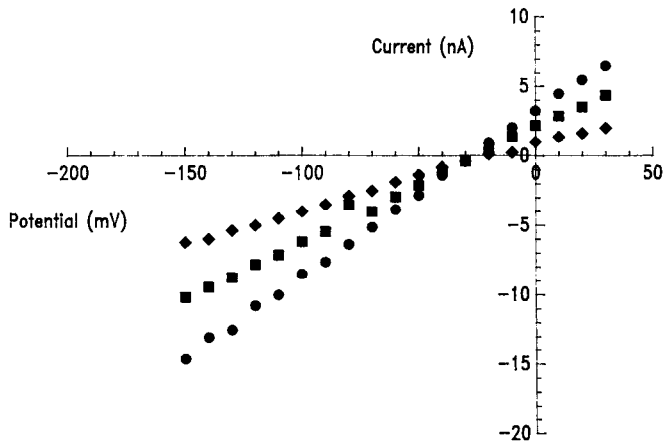


Figure 4. Instantaneous current-voltage relation in a nerve fiber. The fiber was bathed in K-Ringer's plus TTX before exposure to venom (circles) and in the presence of 50 $\mu\text{g}/\text{ml}$ (squares) or 250 $\mu\text{g}/\text{ml}$ (diamonds) venom. Peak tail-current amplitude was measured at the potential shown on the abscissa following a 40 msec depolarization to -30 mV, near the reversal potential for the K currents under our ionic conditions. Same fiber as in Figure 3.

tial by decreasing the rate of repolarization of the action potential. Thus, the net effect on nerve excitability would be similar to that of the scorpion toxins, which act by increasing Na current duration. However, as is shown in Figure 7, action potentials recorded in nerve fibers in the presence of *Pandinus* venom show only minimal differences from controls, these differences being a slight slowing of repolarization and a decrease in membrane conductance following the action potential. This finding agrees with the results obtained when decreasing the magnitude of the K current in calculated model action potentials, simulated using parameters derived for myelinated nerve fibers from voltage-clamp data (Hille, 1971). Evidently voltage-dependent K currents are not very important in determining the shape of the action potential in myelinated nerve, since in the model calculations, eliminating the voltage-gated K currents only increased the action potential duration by 25%.

Comparison of zinc and *Pandinus* venom

Crude *Pandinus* venom contains approximately 2×10^{-7} mol of zinc/mg of venom (W. Craig, personal communication). Since external Zn is known to affect the properties of K channels (Århem, 1980; Gilly and Armstrong, 1982), we explored the possibility that the effects of *Pandinus* venom were due to the Zn it contains. In agreement with previous studies, we found

Table 1. Voltage dependence of venom block of K currents

Venom conc. ($\mu\text{g}/\text{ml}$)	Block (%)		n
	-50 mV	$+30$ mV	
50	49 ± 8	16 ± 9	3
100	77 ± 6	54 ± 7	5
250	98	49	2
500	98	65	2

Percentage block of K currents was measured from the ratios of the peak tail currents, in the presence of the indicated concentration of venom, to the current measure before venom application, at the holding potential of -110 mV. Currents were elicited by a pulse to a membrane potential of -50 or $+30$ mV, respectively. All measurements were made in high-K Ringer's.

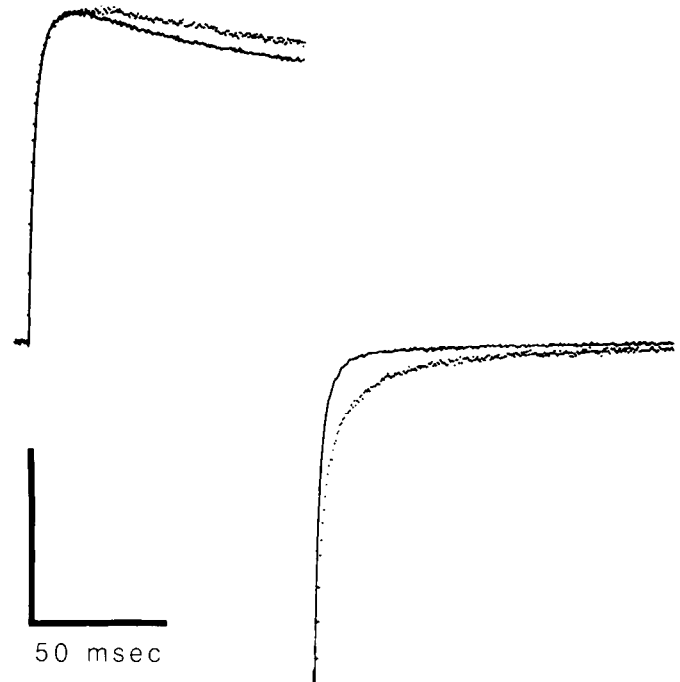


Figure 5. Comparison of K currents with and without venom. Membrane currents were measured during a 100 msec pulse to $+30$ mV from the holding potential of -100 mV. Solid line is the control record; dots represent the current recorded in the presence of 250 $\mu\text{g}/\text{ml}$ venom, scaled by 1.8 to have the same amplitude.

that externally applied Zn (0.1–0.5 mM) slows the opening of K channels and has little effect on the rate of channel closing. The steady-state activation of K current was shifted slightly (0–10 mV) towards more positive potentials by Zn in this concentration range. However, the magnitude of the K current was unaffected by Zn. These effects of Zn were largely reversed within a few minutes of washing out the Zn solution. Thus, the effects of Zn are quite different from those of *Pandinus* venom, in that the kinetics of the currents are affected more than their magnitude by Zn, and the Zn effects are readily reversed. We therefore conclude that free Zn itself is not responsible for the venom effects we have observed, although it remains possible that Zn participates in the action of other venom components.

Discussion

This paper describes the effects of *Pandinus imperator* scorpion venom on the ionic currents of voltage-clamped myelinated nerve fibers. We find that *Pandinus* venom blocks the currents through the voltage-gated potassium channels of nerve fibers specifically and irreversibly.

Previous voltage-clamp studies of scorpion venoms have shown that the venoms from *Leiurus quinquestriatus*, *Buthus tamulus*, *Tityus serrulatus*, *Androctonus australis* Hector, and a number of species of *Centruroides* can all act to decrease the voltage-gated K currents of axons (Koppenhoefer and Schmidt, 1968; Narahashi et al., 1972; Romey et al., 1975; Carbone et al., 1982, 1983). The K channel toxins contained in these venoms share the properties of having effects that are independent of voltage, binding that is of relatively low affinity (in the μM range), and ready reversibility. In contrast, the action of K channel toxin(s) from the venom of *Pandinus imperator* is highly voltage-dependent, occurs apparently with high affinity, and is irreversible on the time scale of voltage-clamp experiments.

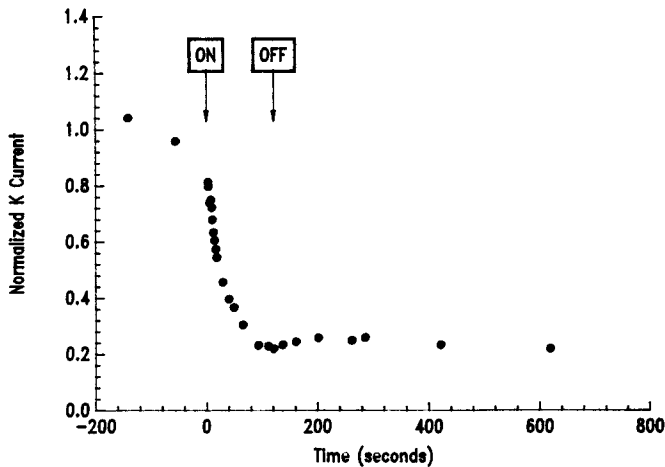


Figure 6. Time course of *Pandinus* venom effects. The ordinate shows the peak amplitude of the K current recorded during a 100 msec pulse to +10 mV, normalized to the average of the control values. At time 0, 120 $\mu\text{g}/\text{ml}$ of venom was washed onto the fiber (ON). The venom was washed off after 125 sec (OFF). External solution, K-Ringer's plus TTX. Internal solution, KF. 22°C. Fiber SVND40.

Block of K current by *Pandinus* venom is much greater at negative membrane potentials than at positive potentials. The lack of venom effects on the shape of the instantaneous current-voltage relation for K channels argues against the voltage dependence's being due to rectification of the open-channel conductance properties induced by the venom. Nor are our results consistent with the idea that the voltage dependence of venom effects is due to potential-dependent binding and dissociation of the toxin to the nerve membrane, since channel-opening kinetics are unaffected by the venom, strong depolarizations fail to remove the block, and repeated depolarization after washout of the venom does not restore the normal K conductance. Two remaining possibilities are that (1) there is a selective block of a subpopulation of K channels by the venom, or (2) there is an alteration of K channel gating properties by venom binding.

The nodal membrane is known to contain at least 3 populations of K channels, which can be distinguished on the basis of their kinetic properties and susceptibility to block by 4-aminopyridine (Dubois, 1981). The bulk of the K conductance is due to 2 of these populations, termed the "fast K conductances," g_{f1} and g_{f2} . The g_{f1} conductance activates in the voltage range from -80 to -40 mV and comprises 30–65% of the fast K conductance, with g_{f2} making up the rest of the fast K conductance and activating in the potential range from -40 to +50 mV. Thus, a selective block of g_{f1} by *Pandinus* venom, or a greater susceptibility of the g_{f1} channels compared to that of the g_{f2} channels would result in the observed voltage dependence of its actions. Such a selective block of g_{f1} channels by a component of black mamba snake venom has recently been reported (Benoit and Dubois, 1986).

Pandinus venom reduces the voltage dependence of channel-closing rates, causing a decrease in the rate of closing at hyperpolarized potentials and an increase in the rate of closing at depolarized potentials, with little change in the closing rates near the holding potential. Thus, the apparent voltage-dependent block of K channels could be due to venom-induced changes in channel kinetics. If venom-modified channels had a less stable or energetically favorable open state, this could result in both an increase in channel-closing rates and a shift in the voltage

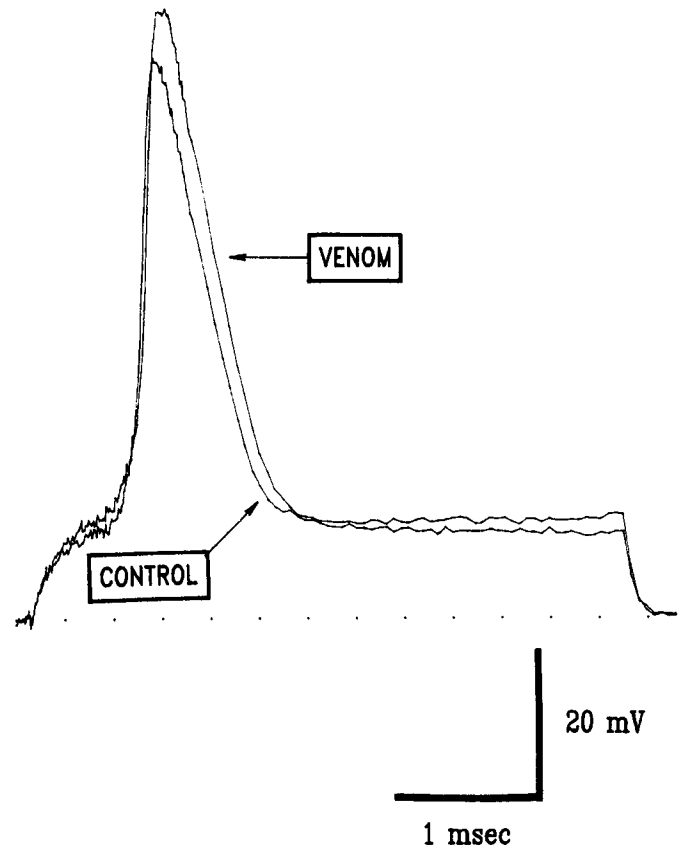


Figure 7. Superimposed action potentials in a myelinated nerve fiber, recorded before and during exposure to 100 $\mu\text{g}/\text{ml}$ *Pandinus* venom, show only minimal differences. In each case an action potential was elicited from the fiber under "current-clamp" conditions by applying a 10 mV stimulus to the cut end of the fiber. The resting membrane potential is assumed to be -80 mV. Stimulus duration was 4 msec. External solution, Na-Ringer's. Internal solution, K-EGTA. 22°C. Fiber SVND16.

dependence of steady-state activation to more depolarized potentials. Because K channel activation is a multistep process, these changes in closing rates and steady-state activation could occur without corresponding alterations in the rates of channel opening. Such an action of *Pandinus* venom on K channel gating would resemble those seen with other scorpion venoms on Na channel gating, in which venom binding results in shifts in the potential dependence of channel activation or inactivation processes (Cahalan, 1980; Catterall, 1980). Alternatively, the changes in channel-closing rates seen in venom could be due to differences in the closing rates of blocked and unblocked subpopulations of K channels. The g_{f1} and g_{f2} K conductances have indistinguishable closing kinetics when measured at -90 mV (Dubois, 1981), but their deactivation kinetics may differ at other membrane potentials.

In contrast to the previously described K channel scorpion toxins, the toxic component(s) of *Pandinus* venom apparently bind to K channels with a very high affinity. We have seen no reversal of *Pandinus* venom effects following washout of the venom for periods as long as 30 min, suggesting that the binding of the toxic component(s) are at best only very slowly reversible. Preliminary experiments examining fractions of the crude venom also suggest a high-affinity binding by the toxin(s). More than 95% of the crude venom consists of inert mucous proteins

(unpublished observations). Since 50 $\mu\text{g/ml}$ of crude venom is sufficient to block 50% of the K current for a depolarization to -50 mV, less than 1 $\mu\text{g/ml}$ of active components must be capable of producing this level of block. If the toxin has a molecular weight of 5 kDa, similar to that of the other scorpion toxins, this would indicate a dissociation constant of less than 200 nM for a toxin that acted by simply blocking the channel. If the toxin acts by altering channel kinetics or by blocking a subset of the channels, as discussed above, the affinity would be even higher.

Animal toxins have proven invaluable in the purification and molecular characterization of other ion channels, such as the Na channel and the ACh receptor channel. Knowledge of the molecular properties of voltage-gated K channels has lagged behind these, at least in part because of the lack of suitable specific high-affinity ligands for these channels. The K channel toxins of *Pandinus* venom seem to have the characteristics necessary to be a valuable tool for isolation and characterization of axonal K channels.

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