The phosphoinositide sensitivity of the $K_V$ channel family

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Recently, we screened several $K_V$ channels for possible dependence on plasma membrane phosphatidylinositol 4,5-bisphosphate (PI(4,5)P$_2$). The channels were expressed in tsA-201 cells and the PI(4,5)P$_2$ was depleted by several manipulations in whole-cell experiments with parallel measurements of channel activity. In contrast to reports on excised-patches using *Xenopus laevis* oocytes, we found only $K_{Ca}$, but none of the other tested $K_V$ channels, to be strongly dependent on PI(4,5)P$_2$. We now have extended our study to $K_{Ca}1.2$ channels, a $K_V$ channel we had not previously tested, because a new published study on excised patches showed regulation of the voltage-dependence of activation by PI(4,5)P$_2$. In full agreement with those published results, we found a reduction of current amplitude by ~20% after depletion of PI(4,5)P$_2$, and a small left shift in the activation curve of $K_{Ca}1.2$ channels. We also found a small reduction of $K_{Ca}11.1$ (hERG) currents that was not accompanied by a gating shift. In conclusion, our whole-cell methods yield a PI(4,5)P$_2$-dependence of $K_{Ca}1.2$ currents in tsA-201 cells that is comparable to findings from excised patches of *Xenopus laevis* oocytes. We discuss possible physiological rationales for PI(4,5)P$_2$ sensitivity of some ion channels and insensitivity of others.

**Introduction**

Here we revisit the regulation of voltage-gated potassium ($K_V$) channels by plasma membrane phosphoinositide phospholipids. Although not in high abundance, the phosphoinositides of eukaryotic biological membranes regulate many membrane proteins through protein-lipid interaction domains. At the plasma membrane, phosphatidylinositol 4,5-bisphosphate (PI(4,5)P$_2$) is the dominant phosphoinositide. It enhances the activity of many ion channels, and, for some channels, is necessary for activity. Thus, it is obligatory for function of all 5 members of the $K_{Ca}$ channel family and of nearly all inward rectifiers and TRP channels. In recent reviews, the number of ion channels said to be regulated by PI(4,5)P$_2$ has grown so large (> 80) that one might anticipate that all plasma membrane channels are sensitive. However, using whole-cell recording and enzymatic methods to deplete endogenous PI(4,5)P$_2$, our laboratory failed to find PI(4,5)P$_2$ sensitivity in several channels. For example, we found that only 4 out of 8 tested voltage-gated calcium ($Ca_{Ca}$) channel subtypes were significantly depressed when PI(4,5)P$_2$ levels were enzymatically lowered, and some of these sensitive $Ca_{Ca}$ channels became nearly insensitive when coexpressed with a different $Ca_{Ca}$ subunit.

Recently, we screened for PI(4,5)P$_2$ sensitivity of 8 voltage-gated potassium ($K_V$) channels from the $K_{Ca}$, 1, 2, 3, and 4 families, again using whole-cell methods and enzyme recruitment. Three of the channels we tested, $K_{Ca}1.1$, 1.4, and 3.4, had been studied before in excised patches from *Xenopus laevis* oocytes. The authors had reported interesting changes of current kinetics and amplitude when exogenous brain PI(4,5)P$_2$ was applied to the cytoplasmic face. Thus, we assumed our screen would identify many lipid-sensitive channels, yet we saw no sensitivity to PI(4,5)P$_2$ depletion for any of them ($K_{Ca}1.1$, 1.3, 1.4, 1.5, 2.1, 3.4, 4.2, and 4.3). For large test depolarizations, neither the current amplitude nor the gating...
Figure 1. For figure legend, see page 532.
kinetics were changed. In the same study, we did confirm that our methods easily resolved the well-known lipid sensitivity of K_1.2, 7.1, 7.2, and 7.3 and K_2.1 channels. Subsequently, using mostly different approaches, Rodriguez-Menchaca et al. reported that K_1.2 channels are sensitive to PI(4,5)P_2 depletion. They found a ~30% decrease in current amplitude from Xenopus oocytes by depleting excised patches of PI(4,5)P_2 and a restoration of the original current amplitude by perfusing PI(4,5)P_2 onto the inside-out patches. They recognized a dual effect of depleting PI(4,5)P_2: First, a decrease of maximum open probability and, second, a left-shift of ~14 mV in the voltage dependence of the activation curve. This result was not in contradiction to ours since we had not tested K_1.2 channels in our screen. Nevertheless, we were stimulated by this new work to check whether our whole-cell assay system, which had given negative results with other channels, would confirm PI(4,5)P_2 sensitivity of K_1.2.

Results

As in our previous paper, the experimental design was to study ion channels transfected in mammalian tsA-201 cells by whole-cell voltage clamp. Plasma membrane phosphoinositides were depleted by 2 enzymatic maneuvers: (1) by stimulating a G protein coupled receptor (GPCR) coupled to phospholipase C (PLC), and (2) by using chemical dimerization to recruit lipid phosphatases to the plasma membrane.

PI(4,5)P_2 dependence of K_1.2 channels

We first tested PI(4,5)P_2 depletion by PLC. K_1.2 channels were co-expressed with PLC-coupled M_γ muscarinic receptors (M_γR) in tsA-201 cells, and depolarizing pulses to 20 mV elicited outward K' currents (Fig. 1A). Application of the muscarinic agonist oxotremorine methiodide (Oxo-M) led to a clear decrease in the current amplitude on average by 27 ± 6% (n = 5, Fig. 1D). Activation of phospholipase C (PLC) is a complex stimulus. It generates several intracellular signals including depletion of PI(4,5)P_2, rise of cytoplasmic inositol trisphosphate (Ins(1,4,5)P_3) and calcium, production of diacylglycerol (DAG) and activation of protein kinase C (PKC).

To check whether the effects were really due to PI(4,5)P_2 depletion, we turned to recruitment of the lipid phosphatase pseudojanin (Pj) to the plasma membrane as another tool to deplete PI(4,5)P_2. Pseudojanin is an engineered fusion protein containing a rapamycin-binding domain (FKBP) and 2 lipid phosphatase domains in tandem (derived from Inp54p and Sac1 enzymes), which dephosphorylate PI(4,5)P_2 at the 5-position (Ins(1,4,5)P_3) and PI(4,5)P_2 at the 4-position (Sac1) to yield phosphatidylinositol (PI). Addition of the membrane-permeable drug rapamycin dimerizes the FKBP domain with the coexpressed membrane anchor Lyn-FRB-CFP, thus recruiting the pseudojanin phosphatases to the plasma membrane. This dimerization strategy depletes PI(4,5)P_2 at the plasma membrane without generating downstream signaling molecules like Ins(1,4,5)P_3 or DAG. As the FKBP-rapamycin-FRB complex is very stable, the recruitment of pseudojanin to the plasma membrane is irreversible and results in a lasting depletion of PI(4,5)P_2. Rapamycin addition to cells coexpressing K_1.2, pseudojanin, and LDR-CFP resulted in a clear 19 ± 2% decrease in current amplitude (n = 5, Fig. 1C and D). These experiments show that K_1.2 channel current is PI(4,5)P_2 sensitive as previously reported.

We next asked whether the voltage-dependence of activation can be shifted by turning on PLC. We coexpressed K_1.2 with MγR and measured the conductance-voltage (G-V) relation before and after activation of MγR (Fig. 1E). There was a small, but significant left shift in the normalized activation curve by 3.5 ± 0.4 mV (n = 5) (Fig. 1F). Thus, we confirm the observations of Rodriguez-Menchaca et al.

PI(4,5)P_2 dependence of hERG channel activation

We and others have reported a change in the voltage-dependence of activation of erg channels if PI(4,5)P_2 levels are altered. Bian et al. reported a left shift of about ~19 mV for the activation curve of hERG channels upon dialysis of 10 μM PI(4,5)P_2 into the cells via the patch pipette, while we found a right shift of about ~5 mV in the activation curve for rat erg1 channels upon depletion of PI(4,5)P_2 by activating MγR. We decided to extend our previously published recordings on rat erg1 channels to hERG channels to test whether we would observe a similar right shift in the voltage-dependence.

We co-expressed hERG and MγR in tsA-201 cells and measured current amplitudes before and after MγR activation. After addition of Oxo-M we observed an inhibition of hERG mediated current of 31 ± 7% (n = 5) (Fig. 2A and B), in good agreement with our work on rat erg1 channels after MγR activation. We next asked whether this decrease in current amplitude is accompanied by a change in the activation curve for hERG channels. Again, we co-expressed hERG channels with MγR and measured G-V curves before and after addition of Oxo-M to deplete PI(4,5)P_2. We detected a right shift of the activation curve of about ~7 mV (n = 5), which correlates very well with the 5 mV right shift Hirdes at al. had observed for rat erg1 channels (Fig. 2C).

Our next step asked whether the observed right shift in the activation curve is caused by the depletion of PI(4,5)P_2 at the plasma membrane or by signaling pathways downstream of PI(4,5)P_2 hydrolysis, such as activation of protein kinases. Unlike K_1.2 channels, it had been shown for hERG channels that...
Figure 2. For figure legend, see page 534.
activation of PKC leads to a right shift of the activation curve.\(^1\) We expressed hERG channels together with pseudojsoanin-YFP and LDR-CFP in tsA-201 cells and applied rapamycin to induce translocation of pseudojsoanin-YFP to the plasma membrane. Recruiting Pj to deplete PI(4,5)P\(_2\) led to a significant decrease (15 ± 1%, n = 5) of hERG mediated current amplitude (Fig. 2D) but, in the same cells, no significant shift in the voltage-dependence of activation (Fig. 2E and F). We conclude from this result that a depletion of PI(4,5)P\(_2\) does not alter the voltage-dependence of activation of hERG channels and that our finding of a right shift in the activation curve after M\(_R\)-activation should be attributed to other signals downstream of PI(4,5)P\(_2\) cleavage by PLC.

**Discussion**

We now review 2 broad questions briefly: (1) Are K\(_\beta\) channels sensitive to plasma membrane PI(4,5)P\(_2\); and (2) is there a physiological benefit from such sensitivity or insensitivity?

For excitable cells, the K\(_\beta\) channels whose PI(4,5)P\(_2\) sensitivity is best studied are the K\(_{\beta7}\) (KCNQ) family.\(^7\,20\) It is widely accepted that the 5 members of this family absolutely require PI(4,5)P\(_2\) to function. They bind PI(4,5)P\(_2\) with low enough affinity that when the lipid is depleted enzymatically by 90–95% either by PLC or by 5-phosphatases, the current falls by 80–95%. In addition, K\(_{1,2}\) channels have clear PI(4,5)P\(_2\) sensitivity. In whole-cell experiments, currents decrease and gating is shifted in response to M\(_R\) or voltage-sensing phosphatase activation, and in excised patches, the same effects are induced by rundown, by anti-PI(4,5)P\(_2\) antibodies, and by blocking lipid kinases, and current is restored by application of PI(4,5)P\(_2\).\(^14\,22\,23\)

With K\(_{1,2}\) however, rather than eliminating current, PI(4,5)P\(_2\) depletion modulates channel properties more gently, reducing the amplitude by 25–30% and shifting gating. Possibly with a more severe elimination of PI(4,5)P\(_2\), the channel could be shown above current traces. (B) Time course of hERG channel mediated current at +40 mV from the experiment shown in (A). (C) Voltages of half-maximal activation (V\(_{1/2}\)) of hERG channels before and after M\(_R\)-activation. (D) Current traces for hERG channels expressed together with pseudojsoanin-YFP (PJ) and LDR-CFP (before solid black) and after (dashed gray) recruitment of Pj to the plasma membrane by rapamycin-application. (E) Representative G-V curve of hERG channels generated from test pulses to membrane potentials of −80 to +60 mV from a holding potential of −80 mV before (solid black) and after (dashed gray) recruitment of PJ to the plasma membrane. (F) Voltages of half-maximal activation (V\(_{1/2}\)) for hERG channels before and after PJ-recruitment.

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membranes, a subject we know less about. We would need further information about the physiology of intracellular compartments. What are the ion gradients across their membranes? What is their membrane potential? Is this electrical potential important for the compartment’s function? Does it change during cellular activities? From such information we might be able to deduce which ion channels would be good to silence and which to promote as they traffic through that compartment. Phosphoinositides would be likely candidates to accomplish such regulation since each compartment has different lipids. We already know of compartments with lumens that are acidic or have high sodium or calcium concentrations, and we know of stimuli that release stored calcium. This knowledge probably only scratches the surface of a much fuller understanding that will eventually emerge about compartmental electrophysiology.

We envision several possible outcomes of these inquiries. Internal membranes may have membrane potentials more positive than the resting potential of the plasma membrane. If so, ion channels with voltage-dependent inactivation might already be inactivated during internal trafficking, and that category of channels would not need a lipid-based mechanism to ensure lack of activity. In addition, when we understand the membrane potential of a compartment, we should recognize some transiting ion channels that would be compatible with that membrane potential and others that are not that must be kept silent there by some mechanism.

In sum, we propose hypotheses for why some channels are sensitive and some channels are not sensitive to the lipid PI(4,5)P2.

Materials and Methods

Cell culture and plasmids

All experiments were performed in tsA-201 cells cultured at 37 °C and 5% CO2 in DMEM (Invitrogen) supplemented with 10% FBS (PAA) and 0.2% penicillin/streptomycin (Invitrogen). Transient transfection of cells was performed as previously described.12

The following plasmids were generously given to us: M, R (M1 muscarinic receptor)–YFP from Neil Nathanson (University of Washington); pseudojanin-YFP from Gerald Hammond and Robin Irvine (University of Cambridge); K1,2 from Diomedes Logothetis (Virginia Commonwealth University); LDR (Lyn–targeted FRB)–CFP from Tamas Balla (National Institute of Health); and hERG from Olaf Pongs (University of Hamburg).

Electrophysiology

Whole-cell recordings were performed as previously described.12

Data analysis and statistics

Data analysis was performed using Igor Pro (Wavemetrics) and Excel (Microsoft). Statistical data are presented as mean ± SEM unless otherwise stated. The Student t-test was used to test for statistical significance. We considered p-values of < 0.05 as significant.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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