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Co-expression of mCysLT$_1$ receptors and IK channels in *Xenopus laevis* oocytes elicits LTD$_4$-stimulated IK current, independent of an increase in $[Ca^{2+}]_i$

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Abstract

Addition of LTD$_4$ (10 nM) to *Xenopus laevis* oocytes expressing the mCysLT$_1$ receptor together with hBK or hIK channels resulted in the activation of both channels secondary to an LTD$_4$-induced increase in $[Ca^{2+}]_i$. In addition, the hIK channel is activated by low concentrations of LTD$_4$ (<0.1 nM), which did not result in any increase in $[Ca^{2+}]_i$. Even though activation of hIK by low concentrations of LTD$_4$ was independent of an increase in $[Ca^{2+}]_i$, a certain "permissive" level of $[Ca^{2+}]_i$ was required for its activation, since buffering of intracellular Ca^{2+} by EGTA completely abolished the response to LTD$_4$. Neither hTBAK1 nor hTASK2 was activated following stimulations with LTD$_4$ (0.1 and 100 nM).

Keywords: Eicosanoide; Leukotriene D$_4$ (LTD$_4$); BK channel; IK channel; TASK channel; Potassium channel

The cysteinyl-leukotriene (CysLT) LTD$_4$ is a lipid mediator derived from arachidonic acid via action of the 5-lipoxygenase (5-LOX). It signals primarily through CysLT$_1$ receptors of which the human [1,2] and the murine [3,4] isoforms have been cloned. LTD$_4$ is known to induce an increase in the intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) in many cell types resulting both from influx across the plasma membrane and from release from intracellular stores following PLC activation and IP$_3$ formation (see, e.g. Ref. [5]). In addition, leukotrienes are involved in the regulatory volume decrease (RVD) response following cell swelling in several cell types (see, e.g. Ref. [6]). In mudpuppy erythrocytes a yet unidentified 5-LOX product is important for activation of the volume-sensitive K^+ conductance [7], and in Ehrlich ascites tumour cells LTD$_4$ activates a charybdotoxin-insensitive K^+ efflux pathway [8] which by patch-clamp studies was found to represent activation of a K^+ conductance with similar electrophysiological and pharmacological properties as the swelling-activated K^+ conductance [9].

Several K^+ channels including the Ca^{2+}-activated, big conductance K^+ channels (BK channels [10–12]), the Ca^{2+}-activated, intermediate conductance K^+ channels (IK channels [13–17]) and certain two-pore domain K^+ channels (TASK channels [18]) are able to mediate volume-sensitive K^+ loss. Since an increase in $[Ca^{2+}]_i$ is observed in some but not all cells undergoing RVD [19,20], activation of some of these volume-sensitive K^+ channels could be secondary to a swelling-induced increase in $[Ca^{2+}]_i$ whereas this cannot be the case for all the volume-sensitive K^+ channels.

The aim of this study was to investigate, by co-expression in *Xenopus laevis* oocytes, which of the abovementioned channels can be activated by stimulation of the mCysLT$_1$ receptor and whether such an activation is secondary to an increase in $[Ca^{2+}]_i$.

Fig. 1a shows that the hIK channel, when expressed together with the mCysLT$_1$ receptor in *Xenopus* oocytes, was activated by addition of LTD$_4$. The effect of LTD$_4$ on hIK activation was measured at a holding potential of +35 mV (i.e. the reversal potential for Cl^-) to avoid possible interference from endogenous Cl^- channels to the mea-

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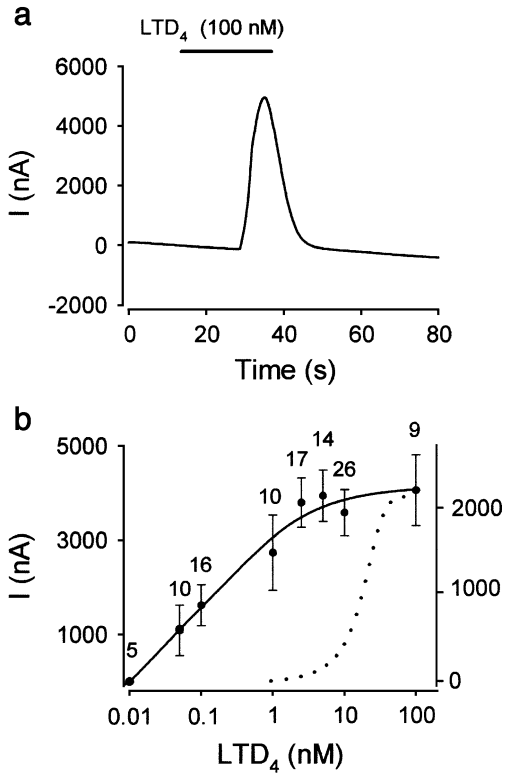

Fig. 1. Co-expression of the mCysLT$_1$ receptor and the hIK channel in *X. laevis* oocytes. Oocytes were isolated as described in Ref. [3] and injected with a mixture of mCysLT$_1$ cRNA (25 ng/36 nl) and hIK cRNA (25 ng/36 nl). After injection, oocytes were maintained individually at 17 °C in ND96ps (in mM): 96 Na^+, 104 Cl^-, 2 K^+, 1 Mg^{2+}, 1.8 Ca^{2+}, 5 HEPES, supplemented with sodium pyruvate (2.5 mM), streptomycin (0.01 mg/ml) and penicillin (0.01 mg/ml). Measurements of current through the expressed K^+ channels were performed 3–5 days after cRNA injection using the two-electrode voltage-clamp technique. Both microelectrodes were filled with 3 M KCl resulting in resistances between 0.5 and 1 MΩ. During experiments the oocytes were clamped at +35 mV using a voltage-clamp amplifier (World precision Instruments, Sarasota, USA). Data were sampled at 10 Hz. Solution changes were effected using a gravity fed pump-suction mechanism throughout the recording session. The solution used during experiments was a modified ND96 medium containing (in mM): 96 Na-gluconate, 5 Cl^-, 1 K^+, 1 Mg^{2+}, 1 Ca^{2+} and 5 HEPES. (a) LTD$_4$-induced activation of the hIK channel in *X. laevis* oocytes. LTD$_4$ (100 nM) was added to the perfusion medium as indicated by the bar ($n=8$). (b) LTD$_4$-induced dose-dependent stimulation of the hIK current (measured as the maximal peak current in (a)). The solid line in (b) (left *Y*-axis) represents the best fit to the Hill equation, while the dotted line (right *Y*-axis) is obtained from Ref. [3] and represents the dose-dependent activation of the endogenous Ca^{2+}-activated Cl^- current (measured at −50 mV) by LTD$_4$ in *X. laevis* oocytes solely expressing the mCysLT$_1$ receptor.

sured current. As seen from Fig. 1b, the hIK channels were activated by LTD$_4$ in a concentration-dependent manner with an estimated EC$_{50}$ of 0.22 nM. The concentration of leukotrienes released to the medium following cell swelling was estimated at 0.5–0.8 nM in Ehrlich ascites tumour cells [21], thus an EC$_{50}$ value of 0.22 nM for the LTD$_4$-induced hIK activation is within a physiologically relevant range.

In hCysLT$_1$-transfected HEK-293 cells, LTD$_4$ induced an increase in $[Ca^{2+}]_i$ with an estimated EC$_{50}$ of 2.5 nM [2]. A series of experiments were performed in order to determine whether the activation of the hIK channel by LTD$_4$ application is mediated through an increase in $[Ca^{2+}]_i$ in the oocytes. For comparison the effect of increasing concentrations of LTD$_4$ on the endogenous Ca^{2+}-activated Cl^- current is shown as a dotted line (EC$_{50}$ = 17 nM). As seen from the activation of the endogenous Ca^{2+}-activated Cl^- current in oocytes, LTD$_4$ concentrations higher than 10 nM induced an increase in $[Ca^{2+}]_i$, but from the experiments it is unclear whether LTD$_4$ concentrations below 1 nM also increased $[Ca^{2+}]_i$ that, in turn, could activate the hIK channel.

Local increases in $[Ca^{2+}]_i$ are difficult to measure in *Xenopus* oocytes, thus we have used the hBK channel co-expressed with the mCysLT$_1$ receptor as a biological sensor of $[Ca^{2+}]_i$ [17,22]. The BK-mediated current was measured at +35 mV, at which potential these channels are sensitive to $[Ca^{2+}]_i$ in the range found in resting oocytes [23,24]. Fig. 2a shows that application of 0.1 nM LTD$_4$ did not result in BK channel activation whereas at higher concentrations (10 nM) LTD$_4$ stimulated a robust BK-derived K^+ current. Fig. 2b summarises the dose-dependent activation of hBK and hIK channels by LTD$_4$ in *Xenopus* oocytes expressing these channels together with the mCysLT$_1$ receptor. Taken together, the experiments presented in Figs. 1 and 2 indicate that at low,

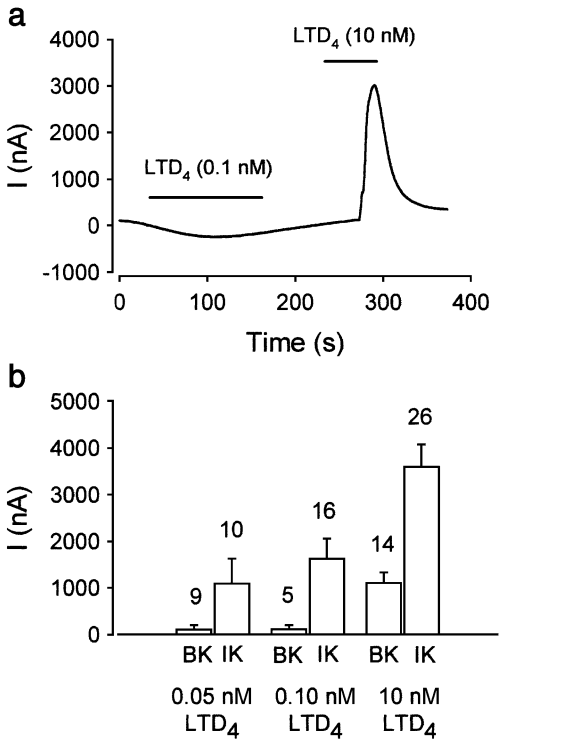

Fig. 2. Co-expression of the mCysLT$_1$ receptor and the hBK channel in *X. laevis* oocytes. The cRNA injected was a mixture of mCysLT$_1$ cRNA (25 ng/36 nl) and hBK cRNA (25 ng/36 nl). (a) LTD$_4$-induced activation of the hBK channel in *X. laevis* oocytes. LTD$_4$ (0.1 or 10 nM) was added to the perfusion medium as indicated by the bars ($n=6$). (b) Comparison of the dose-dependent activation of hBK and hIK channels by LTD$_4$ in *X. laevis* oocytes expressing the mCysLT$_1$ receptor together with either hBK or hIK channels. hIK data are taken from Fig. 1.

physiological relevant concentrations of LTD_4, hIK channels are activated by a pathway independent of an increase in $[Ca^{2+}]_i$, whereas at higher concentrations the hIK channels are further activated, most likely by an LTD_4-induced increase in $[Ca^{2+}]_i$. Using hBK as a sensor of Ca^{2+}, low concentrations of LTD_4 (0.05 and 0.1 nM) were found not to induce an increase in $[Ca^{2+}]_i$ but still to activate the hIK channel. However, it should be noted that it cannot be ruled out that the IK and the BK channels could be differently distributed in the plasma membrane. If this is the case, BK channels may not work as a proper sensor of Ca^{2+} in the vicinity of the expressed IK channels.

Even though the activation of hIK by low concentrations of LTD_4 does not depend on an increase in $[Ca^{2+}]_i$, a certain level of Ca^{2+} is required for hIK activation since buffering of Ca^{2+} by injection of EGTA completely abolished the response to LTD_4 (Fig. 3). This demonstrates that a "permissive" $[Ca^{2+}]_i$ is required either directly for hIK channel activation and/or in the signalling cascade leading to hIK activation upon LTD_4 stimulation. In agreement with the above observations, the hIK channels expressed in oocytes are activated by cell swelling in the absence of an increase in $[Ca^{2+}]_i$ although a "permissive" Ca^{2+} level is also required for hIK channel activation under these conditions

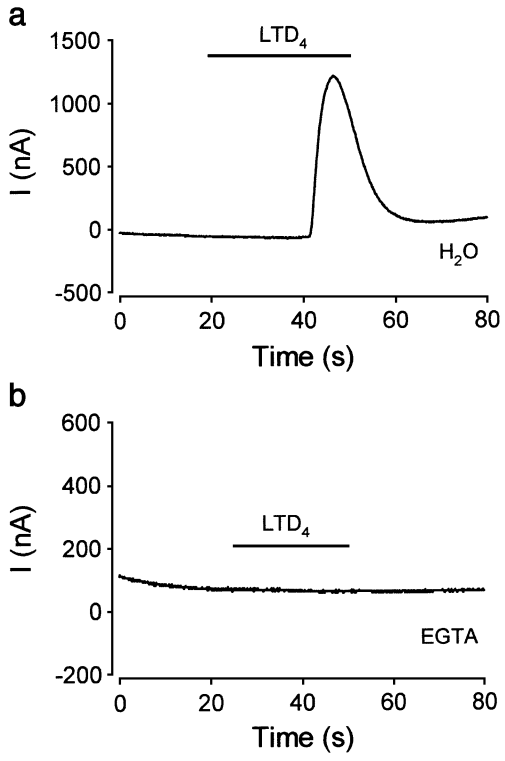

Fig. 3. The role of permissive intracellular Ca^{2+} in the activation of hIK channels. Oocytes were injected with $mCysLT_1$ and hIK cRNA as described in the legend to Fig. 1. (a) LTD_4 (100 nM)-induced activation of the hIK-carried current in oocytes injected with 50 nl H_2O 30 min prior to LTD_4 stimulation. The mean current elicited by LTD_4 was 1470 ± 536 nA ($n=4$). (b) The lack of effect of LTD_4 on the hIK current in oocytes injected with 50 nl 100 mM EGTA 30 min prior to the experiments ($n=7$).

[17]. Furthermore, in cell-attached patch experiments in Ehrlich ascites tumour cells, the IK channel is activated by cell swelling [13], although an increase in $[Ca^{2+}]_i$ is only observed in 6% of the cells undergoing RVD [25]. It should, however, be noted that although the IK channel is activated by cell swelling, it only plays a minor role in the RVD response in Ehrlich cells [25,26]. The Ca^{2+}-independent signalling pathway from $mCysLT_1$ receptor stimulation to IK channel activation remains to be elucidated. It has previously been shown that LTD_4 can induce contraction in smooth muscle cells from human bronchi independent of an increase in $[Ca^{2+}]_i$ [27]. One possibility is that the Ca^{2+}-independent e isoform of PKC could be involved in IK channel activation since this isoform can be activated by LTD_4 [27,28].

In order to examine whether activation of hIK by low concentrations of LTD_4 involves activation of PLC, oocytes were pre-incubated for 45–60 min in the presence of U73122 (2.5 μM) and subsequently stimulated with 0.1 mM LTD_4 in the continuous presence of U73122. This manoeuvre completely abolished the response to 0.1 nM LTD_4 ($n=6$) indicating that although an increase in $[Ca^{2+}]_i$ is not required for hIK activation by low concentrations of LTD_4, a PLC isoform, regulated by a heterotrimeric G-protein (PLC-β), is still part of the signalling pathway from $CysLT_1$ receptor stimulation to hIK channel activation. This could seem surprising, but it was previously demonstrated that M1 muscarinic receptor-mediated modulation of TASK1, depends on PLC-β but is unrelated to an increase in IP_3 or $[Ca^{2+}]_i$ [29]. Another possibility is that the inhibitory effect of U73122 on the hIK current is an unspecific effect on G-proteins, unrelated to PLC. Unspecific effects of U73122 on G-proteins activated by LTD_4 have previously been suggested [30].

Another family of K^+ channels important for swelling-induced K^+ loss in some cell types is the TASK channels [18]. These channels are characterized as being sensitive to extracellular pH, i.e. activated by alkaline and inhibited by acidic pH [31–33], which is also observed in the present study for the hTBAK1 (Fig. 4a) and hTASK2 (Fig. 4c) expressed in oocytes together with the $mCysLT_1$ receptor. As seen from Fig. 4b and d, stimulations with low concentrations of LTD_4 did not result in TASK channel activation. In parallel experiments, 100 nM LTD_4 was likewise unable to activate these channels ($n=4$–6). Although it has been demonstrated that a heterologous expressed receptor can modulate TASK1 activity in oocytes [29], our results indicate that this is not the case for the $mCysLT_1$ receptor when expressed in oocytes together with hTBAK1 and hTASK2. This indicates that LTD_4 is not involved in TASK channel activation. It can, however, not be ruled out that the lack of effect of LTD_4 on TASK channel modulation is cell type-specific, since we have previously shown that in Ehrlich ascites tumour cells, LTD_4 can activate a K^+ conductance with similar electrophysiological and pharmacological characteristics as TASK channels [9].

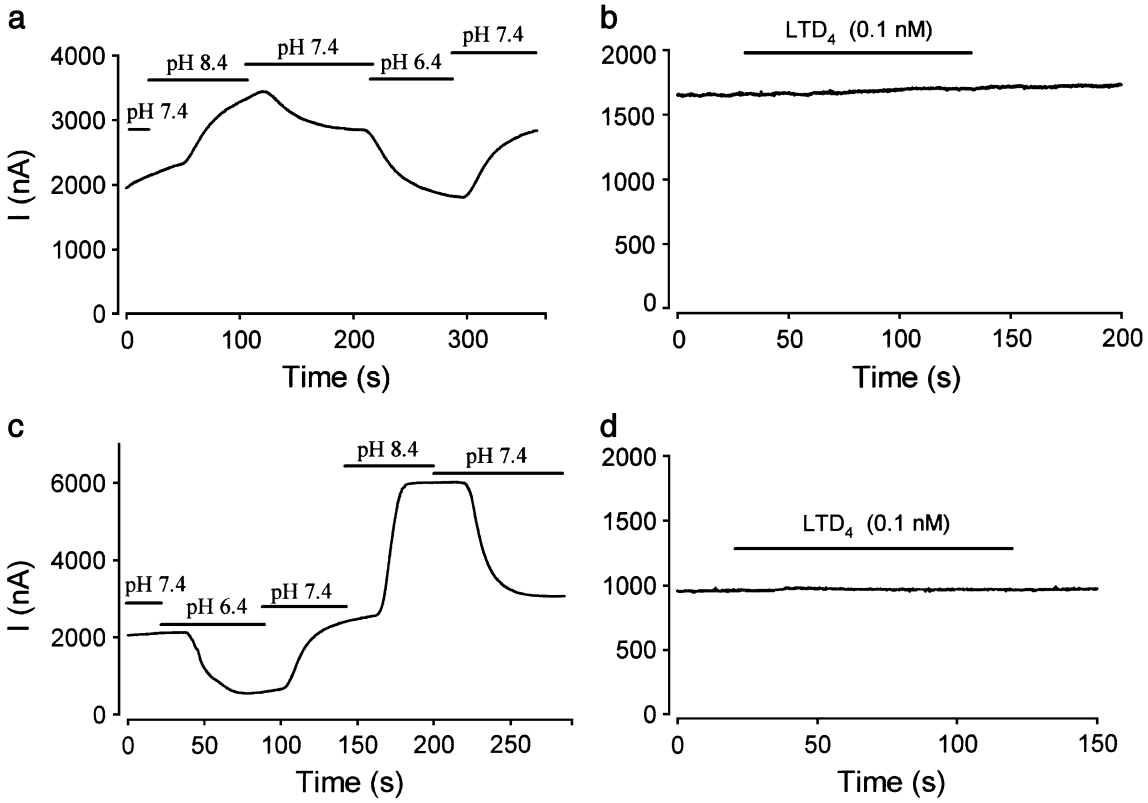

Fig. 4. Co-expression of the mCysLT$_1$ receptor with hTBAK1 and hTASK2 channels in *X. laevis* oocytes. Oocytes were injected with mCysLT$_1$ cRNA (25 ng/36 nl) together with hTBAK1 or hTASK2 cRNA (25 ng/36 nl). (a) hTBAK1-derived current in response to changes in external pH. The pH of the perfusion medium was altered as indicated by the bars ($n=4$). The delay in current change observed after the change in external pH is most likely caused by a delay in the perfusion system. (b) Effect of LTD$_4$ on the hTBAK1 current in *X. laevis* oocytes expressing mCysLT$_1$ receptors and hTBAK1 channels. LTD$_4$ (0.1 nM) was added as indicated by the bar ($n=4$). (c) hTASK2-derived current in response to changes in extracellular pH ($n=3$). (d) Effect of LTD$_4$ on the hTASK 2 current in *X. laevis* oocytes expressing mCysLT$_1$ receptors together with hTASK2 channels. LTD$_4$ (0.1 nM) was added as indicated by the bar ($n=4$).

LTD$_4$ is known to induce proliferation in several cell types [34–37] (for review see also Ref. [5]), and it has been suggested that LTD$_4$ is involved in the coupling between inflammatory bowel conditions and the induction of cancer [38]. If LTD$_4$, as shown in the present study, can activate various K^+ channels, it is possible that the stimulation of proliferation by LTD$_4$ could result from such K^+ channel activation. Several studies have shown that the activation of K^+ channels is required for cell proliferation [39]. Thus, inhibition of ATP-sensitive Ca^{2+}-dependent K^+ channels significantly inhibited proliferation in human breast carcinoma cells [40,41]. Since we here report that LTD$_4$ induces activation of BK and IK channels, it is an interesting possibility that the sequence of events is: release of LTD$_4$, stimulation of the CysLT$_1$ receptor, activation of IK and/or BK channel and stimulation of cell proliferation.

In conclusion, we find that stimulation of the mCysLT$_1$ receptor results in activation of BK and IK channels secondary to an increase in $[Ca^{2+}]_i$. In addition, low concentrations of LTD$_4$ (≤ 0.1 nM) activate hIK in a PLC-β dependent fashion but independent of an increase in $[Ca^{2+}]_i$. hTBAK1 and hTASK2 channels seem not to be modulated by mCysLT$_1$ receptor activation.

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