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Down-regulation of K^+ channels by human parvovirus B19 capsid protein VP1

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ABSTRACT

Parvovirus B19 (B19V) can cause inflammatory cardiomyopathy and endothelial dysfunction. Pathophysiological mechanisms involved include lysophosphatidylcholine producing phospholipase A2 (PLA2) activity of the B19V capsid protein VP1. Most recently, VP1 and lysophosphatidylcholine have been shown to inhibit Na^+/K^+ ATPase. The present study explored whether VP1 modifies the activity of Kv1.3 and Kv1.5 K^+ channels.

cRNA encoding Kv1.3 or Kv1.5 was injected into *Xenopus* oocytes without or with cRNA encoding VP1 isolated from a patient suffering from fatal B19V-induced myocarditis. K^+ channel activity was determined by dual electrode voltage clamp.

Injection of cRNA encoding Kv1.3 or Kv1.5 into *Xenopus* oocytes was followed by appearance of Kv K^+ channel activity, which was significantly decreased by additional injection of cRNA encoding VP1, but not by additional injection of cRNA encoding PLA2-negative VP1 mutant (H153A). The effect of VP1 on Kv current was not significantly modified by transcription inhibitor actinomycin (10 μM for 36 h) but was mimicked by lysophosphatidylcholine (1 μg/ml).

The B19V capsid protein VP1 inhibits host cell Kv channels, an effect at least partially due to phospholipase A2 (PLA) dependent formation of lysophosphatidylcholine.

1. Introduction

The *erythrovirus* parvovirus B19 (B19V) [1] causes common infections [2] leading to diverse clinical entities, such as *erythema infectiosum* (fifth disease), *hydrops fetalis* and transient aplastic anaemia [3,4]. B19V infection may result in further clinical disorders [5,6] including arthritis [7,8], hepatitis [9,10], vasculitic syndromes [11,12], neurological disorders, and myocarditis [13,14]. Endothelial B19V-infection may lead to isolated left ventricular diastolic dysfunction [15] and B19V-associated myocarditis thus causing an endothelial-cell-mediated disease [16]. In pregnancy B19V-infection may be followed by maternal and fetal myocarditis, congenital malformations, stillbirth and abortion [17,18]. B19V preferably invades into proliferating cells thus causing particularly severe disorders during antenatal infection [19].

B19V entry into cells is mediated by blood group P-antigen [20], α5β1 integrin and Ku80 autoantigen [21]. As a result, B19V preferably invades erythroid progenitor cells with strong P antigen, α5β1 integrin and Ku80 autoantigen expression. B19V may, however, further invade fetal myocytes, follicular dendritic cells and endothelial cells [20,21]. Endothelial rather than myocardial B19V was detected in fatal inflammatory cardiomyopathy [22,23]. Endothelial B19V expression was followed by E-selectin expression, margination, adherence, penetration, and perivascular infiltration of T-lymphocytes and macrophages in cardiac tissue [22,23].

The B19V genome encodes the structural capsid proteins VP1 and VP2 [24], which are important for the viral life cycle [4,25]. VP1 contains a sequence homologous to the catalytic site and Ca^{2+}-binding loop of secreted phospholipase A2 (sPLA2) [26,27]. Presumably, BV19 PLA2 generates eicosanoids [27,28], which are required for infectivity of the virus [27]. The vPLA2 enzyme activity

Abbreviation: PLA2, phospholipase A2.

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is disrupted by replacement of a histidine at position 153 with alanine (^{H153A}VP1) [27,28]. Expression of wild type VP1 but not of ^{H153A}VP1 in endothelial cells up-regulates Ca^{2+} entry [29], an effect mimicked by PLA2 product lysophosphatidylcholine (1 μg/ml) [29]. VP1 has further been shown to inhibit Na^+/K^+ ATPase activity [30], an effect again abrogated by loss of function mutation of the PLA2 sequence and mimicked by lysophosphatidylcholine [30,31].

The present study explored, whether expression of VP1 influences K^+ channel activity. Specifically the present paper explored, whether VP1 affects the K^+ channels Kv1.3 and Kv1.5, which are critically important for proliferation of several cell types [32,33].

2. Materials and methods

2.1. Plasmids

B19V DNA was isolated from a patient with fatal B19V-associated inflammatory cardiomyopathy as described previously [29]. Constructs encoding mouse Kv1.5 [34], mouse Kv1.3 [35], wild-type VP1 [29] and PLA2-negative ^{H153A}VP1 mutant [29] were used for generation of cRNA as described previously [36,37].

2.2. Voltage clamp in Xenopus oocytes

Xenopus oocytes were prepared as previously described [38], cRNA encoding VP1 (10 ng) was injected on the same day of preparation of the *Xenopus* oocytes. All experiments were performed at room temperature (about 22 °C) 3 days after the injection [39,40]. Two-electrode voltage-clamp recordings were performed at a holding potential of −100 mV. The currents were recorded following 2 s depolarizing pulses ranging from −80 to +50 mV in 10-mV and 15-s or 20-s increments from a holding potential of −100 mV. The data were filtered at 1 kHz and recorded with a Digidata 1322A A/D-D/A converter and ClampexV .9.2 software for data acquisition (Axon Instruments). The analysis of the data was performed with Clampfit 9.2 (Axon Instruments) software [41,42]. The oocytes were maintained at 17 °C in ND96 solution containing: 88.5 mM NaCl, 2 mM KCl, 1 mM $MgC1_2$, 1.8 mM $CaC1_2$, 5 mM HEPES, Tetracycline (50 mg/l), Ciprofloxacin (1.6 mg/l), Refobacin (100 mg/l) and Theophylin (90 mg/l) as well as Sodium Pyruvate (5 mM) were added to the ND96, pH was adjusted to 7.5 by addition of NaOH. The control superfusate (ND96) contained 96 mM NaCl, 2 mM KCl, 1.8 mM $CaCl_2$, 1 mM $MgCl_2$ and 5 mM HEPES, pH was adjusted

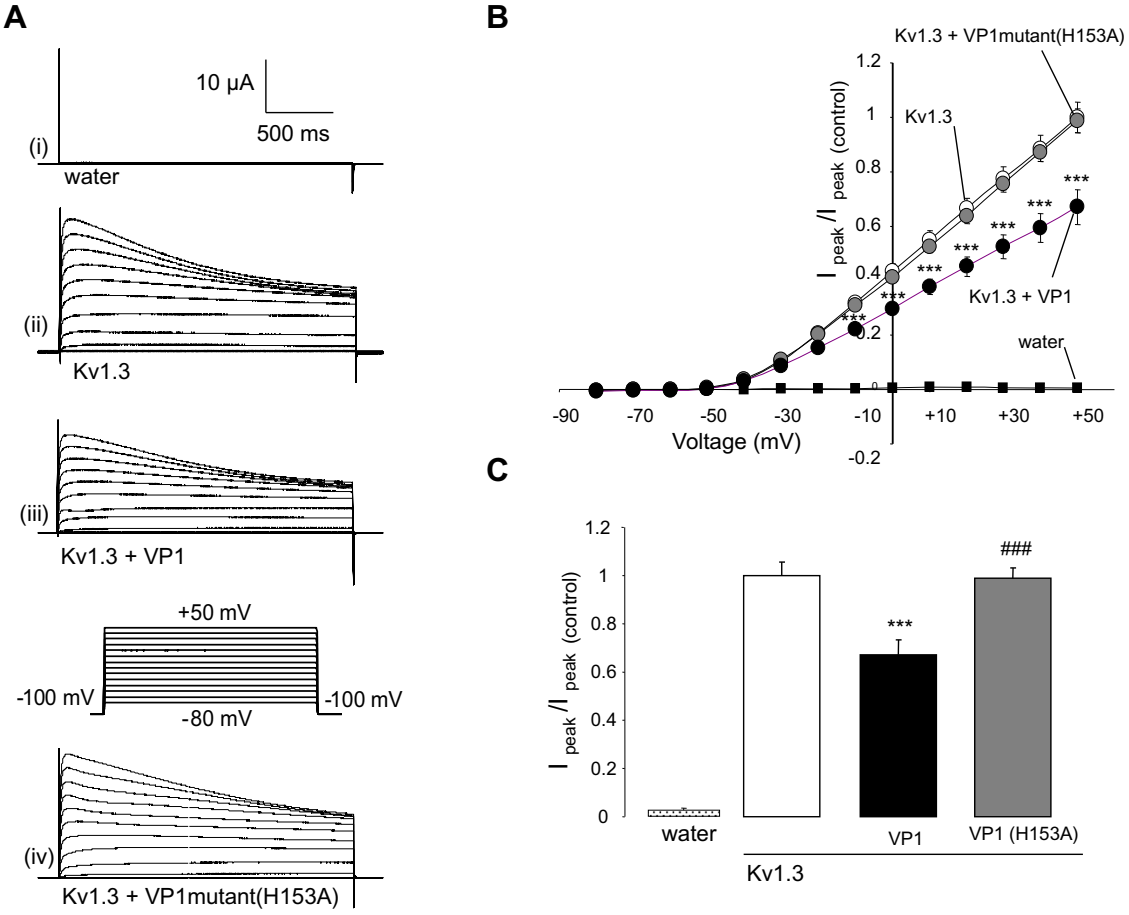

Fig. 1. Inhibition of Kv1.3 currents in Kv1.3 expressing *Xenopus* oocytes by coexpression of VP1 but not of ^{H153A}VP1. (A) Original tracings recorded in *Xenopus* oocytes injected with water (i), with cRNA encoding Kv1.3 alone (ii) with cRNAs encoding both, Kv1.3 and VP1 (iii) and with cRNA encoding both, Kv1.3 and the PLA2-negative ^{H153A}VP1 mutant (iv). The currents were recorded following 2 s depolarizing pulses ranging from −80 to +50 mV in 10 mV and 15 s increments from a holding potential of −100 mV. (B) Arithmetic means ± SEM (n = 9–24) of the normalized depolarization-induced Kv1.3 peak current as a function of voltage in *Xenopus* oocytes injected with water (black squares), or with cRNA encoding $K_{v1.3}$ alone (white circles) or with cRNA encoding both, Kv1.3 and VP1 (black circles) or with cRNA encoding Kv1.3 and PLA2-negative VP1 mutant (grey circles). Peak currents were normalized to the mean peak current at +50 mV in *Xenopus* oocytes injected with cRNA encoding $K_{v1.3}$. *** ($p < 0.001$) indicates statistically significant difference from *Xenopus* oocytes injected with cRNA encoding $K_{v1.3}$ (separated unpaired Student t test). (C) Arithmetic means ± SEM (n = 9–24) of the normalized Kv1.3 peak current at +50 mV in *Xenopus* oocytes injected with water (dotted bar), with cRNA encoding Kv1.3 alone (white bar) with cRNA encoding both, Kv1.3 and VP1 (black bar) or with cRNA encoding Kv1.3 and PLA2-negative VP1 mutant (grey bar). ***, alone, ### (ANOVA-one way).

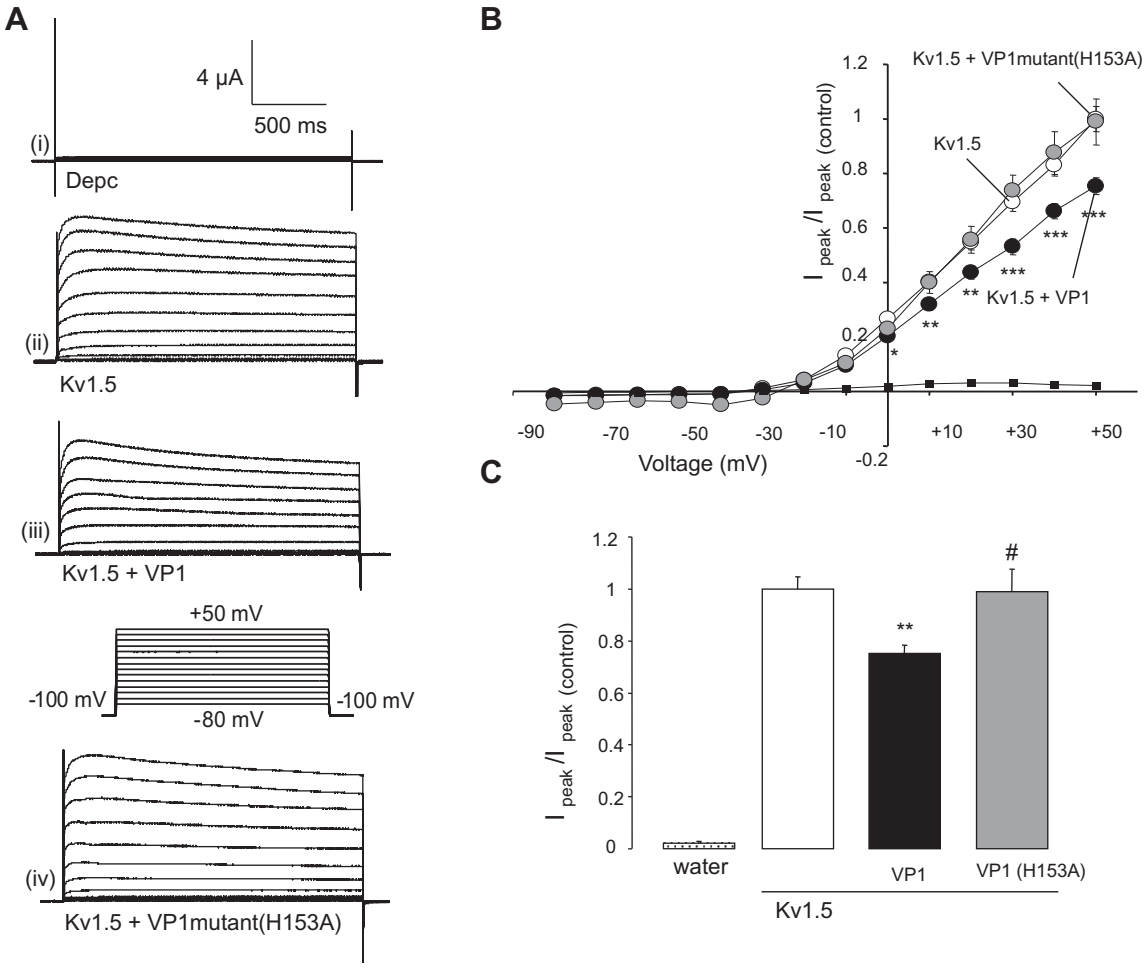

Fig. 2. Inhibition of $K_{v1.5}$ peak current amplitude in Kv1.5 expressing *Xenopus* oocytes by coexpression of VP1 but not of ^{H153A}VP1. (A) Original tracings recorded in oocytes injected with water (i), with cRNA encoding Kv1.5 alone (ii) with cRNAs encoding both, Kv1.5 and VP1 (iii) and with cRNA encoding both, Kv1.5 and the PLA2-negative ^{H153A}VP1 mutant (iv). The currents were recorded following 2 s depolarizing pulses ranging from −80 to +50 mV in 10 mV and 20 s increments from a holding potential of −100 mV. (B) Arithmetic means ± SEM (n = 3–26) of the normalized depolarization-induced $K_{v1.5}$ peak current as a function of voltage in *Xenopus* oocytes injected with water (black squares), or with cRNA encoding $K_{v1.5}$ alone (white circles) or with cRNA encoding both, Kv1.5 and VP1 (black circles) or with cRNA encoding Kv1.5 and PLA2-negative VP1 mutant (grey circles). Peak currents were normalized to the mean peak current at +50 mV in *Xenopus* oocytes injected with cRNA encoding $K_{v1.5}$. *** ($p < 0.001$) indicates statistically significant difference from *Xenopus* oocytes injected with cRNA encoding $K_{v1.5}$ (separated unpaired Student t tests). (C) Arithmetic means ± SEM (n = 3–26) of the normalized Kv1.5-peak current at +50 mV in *Xenopus* oocytes injected with water (dotted bar), with cRNA encoding Kv1.5 alone (white bar) with cRNA encoding both, Kv1.5 and VP1 (black bar) and with cRNA encoding both, Kv1.5 and PLA2-negative VP1 mutant (grey bar). **, # indicates statistically significant ($p < 0.01$, $p < 0.05$) difference from *Xenopus* oocytes injected with cRNA encoding $K_{v1.5}$ (ANOVA-one way).

to 7.4 by addition of NaOH [43]. The flow rate of the superfusion was 20 ml/min, and a complete exchange of the bath solution was reached within about 10 s [44,45].

2.3. Statistical analysis

Data are provided as means ± SEM, n represents the number of oocytes investigated. All experiments were repeated with at least 3 batches of oocytes [46]; in all repetitions qualitatively similar data were obtained. Data were tested for significance using analysis of variance (ANOVA) or t-test, as appropriate. Results with $p < 0.05$ were considered statistically significant.

3. Results

The present study explored the impact of the parvovirus B19 capsid protein VP1 on Kv1.3 and Kv1.5 K^+-channel activity. To this end, Kv1.3 or Kv1.5 was expressed in *Xenopus* oocytes with or without additional expression of VP1 and K^+-peak currents (I_K) taken as a measure of K^+-channel activity.

As illustrated in Fig. 1, Kv current was low in *Xenopus* oocytes injected with water. Expression of Kv1.3 resulted in a strong current, which was significantly decreased by coexpression of VP1 (Fig. 1). In contrast coexpression of the ^{H153A}VP1 mutant lacking PLA2 activity did not significantly modify Kv1.3 currents (Fig. 1). As a result, in Kv1.3 expressing *Xenopus* oocytes the K^+ current was significantly higher following coexpression of ^{H153A}VP1 than following coexpression of VP1 (Fig. 1).

Similar observations were made in Kv1.5 expressing *Xenopus* oocytes. The K^+ current in *Xenopus* oocytes expressing Kv1.5 was significantly decreased by coexpression of VP1 (Fig. 2). Again coexpression of the ^{H153A}VP1 mutant lacking PLA2 activity did not significantly modify Kv1.5 currents (Fig. 2). The K^+ current in Kv1.3 expressing *Xenopus* oocytes was thus significantly higher following coexpression of ^{H153A}VP1 than following coexpression of VP1 (Fig. 2).

In order to test, whether the effect of VP1 required transcription, additional experiments were performed in the presence of

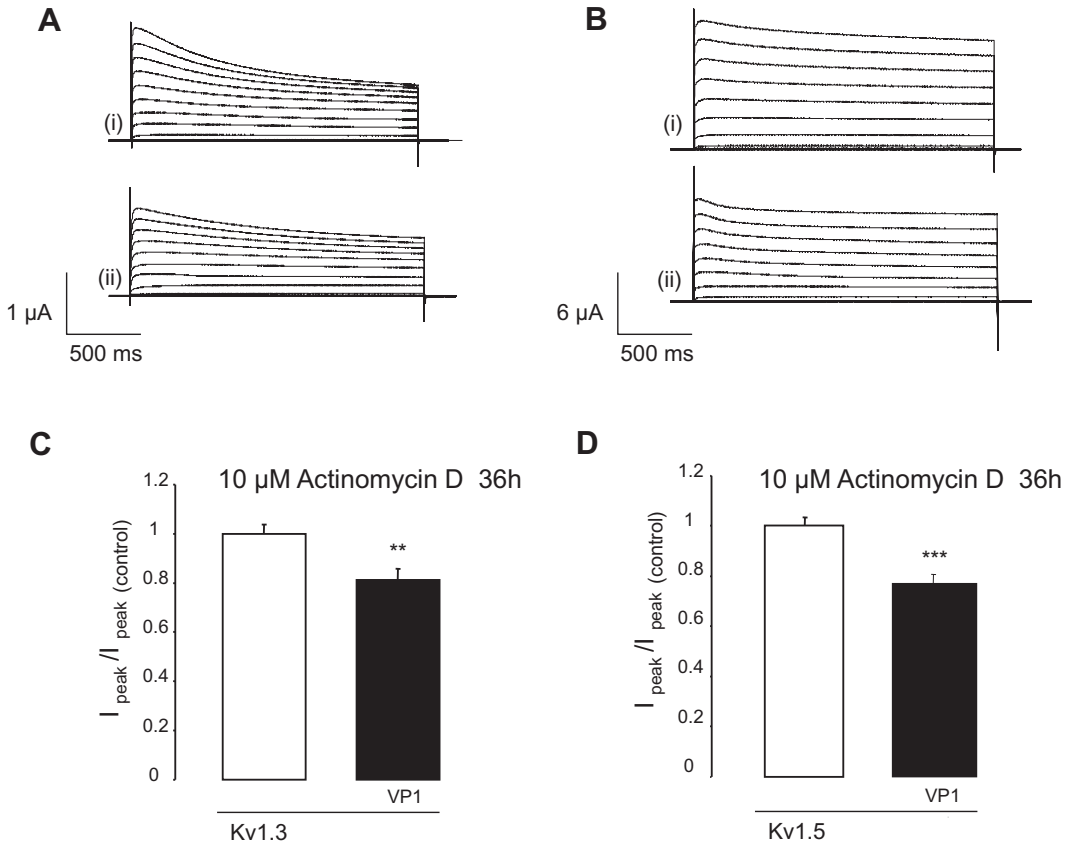

Fig. 3. Inhibition of K^+-current in Kv1.3 or Kv1.5 expressing *Xenopus* oocytes by VP1 expression in presence of D-actinomycin. (A) Original tracings recorded in oocytes injected with cRNA encoding Kv1.3 alone (i) or with cRNA encoding both, VP1 and Kv1.3 (ii), each with prior 36 h treatment with 10 µM D-actinomycin. The currents were recorded following 2 s depolarizing pulses ranging from −80 to +50 mV in 10-mV and 15-s increments from a holding potential of −100 mV. (B) Original tracings recorded in oocytes injected with cRNA encoding Kv1.5 alone (i) or with cRNA encoding both, VP1 and Kv1.5 (ii), each with prior 36 h treatment with 10 µM D-actinomycin. The currents were recorded following 2 s depolarizing pulses ranging from −80 to +50 mV in 10-mV and 20-s increments from a holding potential of −100 mV. (C) Arithmetic means ± SEM (n = 19–20) of the normalized K^+-peak current following a depolarization from −80 to +50 mV in oocytes injected with cRNA encoding Kv1.3 alone with prior 36-h treatment with 10 µM D-actinomycin (white bar) or with cRNA encoding both, VP1and Kv1.3 (black bar), each with prior 36 h treatment with 10 µM D-actinomycin. ** indicates statistically significant ($p < 0.01$) difference from absence of VP1 (unpaired Student t-test). (D) Arithmetic means ± SEM (n = 18) of the normalized K^+-peak current following a depolarization from −80 mV to +50 mV in oocytes injected with cRNA encoding Kv1.5 alone (white bar) or with cRNA encoding both, Kv1.5 and VP1 (black bar), each with prior 36 h treatment with 10 µM D-actinomycin. *** indicates statistically significant ($p < 0.001$) difference from absence of VP1 (unpaired Student t-test).

actinomycin (10 µM, added 36 h prior to the experiment) As illustrated in Fig. 3, even in the presence of actinomycin (10 µM, added 36 h prior to the experiment) the coexpression of VP1 decreased the K^+ current in Kv1.3 expressing oocytes. Similarly, in the presence of actinomycin (10 µM, added 36 h prior to the experiment) the coexpression of VP1 decreased the K^+ current in Kv1.5 expressing oocytes. Thus, the effect of VP1 on Kv1.3 or Kv1.5 did not require transcription.

PLA2 of VP1 is known to generate lysophosphatidylcholine. Thus, additional experiments were performed to explore whether lysophosphatidylcholine influences K^+ currents in Kv1.3 or Kv1.5 expressing *Xenopus* oocytes. As illustrated in Fig. 4, treatment of Kv1.3 expressing *Xenopus* oocytes with lysophosphatidylcholine (1 µg/ml) for 10 min was indeed followed by a decrease of K^+ currents. Similarly, the treatment of Kv1.5 expressing *Xenopus* oocytes with lysophosphatidylcholine (1 µg/ml) for 10 min decreased the K^+ currents (Fig. 4).

4. Discussion

The present observations reveal a novel action of the B19V capsid protein VP1, i.e. the downregulation of the voltage gated K^+ channels Kv1.3 and Kv1.5. The effect requires an intact phospholipase A2-like motif [26,28] in the VP1 protein. Mutation of the motif virtually abrogates the effect of VP1 on Kv1.3 and Kv1.5. The effect of VP1 on Ca^{2+} entry [29] and Na^+/K^+ ATPase activity [30] similarly depended on phospholipase A2 activity and was similarly abolished following site directed mutation of the PLA2 motif, i.e. replacement of the histidine by alanine in the putative catalytic site (^{H153A}VP1). Similar to what has been observed previously on the regulation of Ca^{2+} entry [29] and Na^+/K^+ ATPase activity [30], the effect of VP1 expression on Kv1.3 and Kv1.5 channel activity was mimicked by lysophosphatidylcholine, a product of phospholipase A2.

B19V enters myocardial endothelial cells [22,23] and may thus trigger acute myocarditis resulting in a clinical course similar to myocardial infarction [22,23]. Inhibition of K^+ channels could lead to cell swelling [47,48] and could thus contribute to endothelial dysfunction. The effect is expected to be compounded by inhibition of Na^+/K^+-ATPase [30], which would dissipate the ion gradients across the cell membrane thus further compromizing the ability of the cell to maintain cell volume constancy [30]. K^+ exit through K^+ channels generates a cell-negative potential difference across the cell membrane driving Cl^- exit. Inhibition of K^+ channels is expected to depolarize the cell membrane thus dissipating the electrical driving force for Cl^- exit. As a result, downregulation of K^+ channels is expected to trigger cellular accumulation of KCl with the respective osmotically obliged water and thus to swell the cells [47,48]. Cell swelling is further fostered by cellular NaCl accumulation, if Na^+/K^+-ATPase activity is inhibited [30].

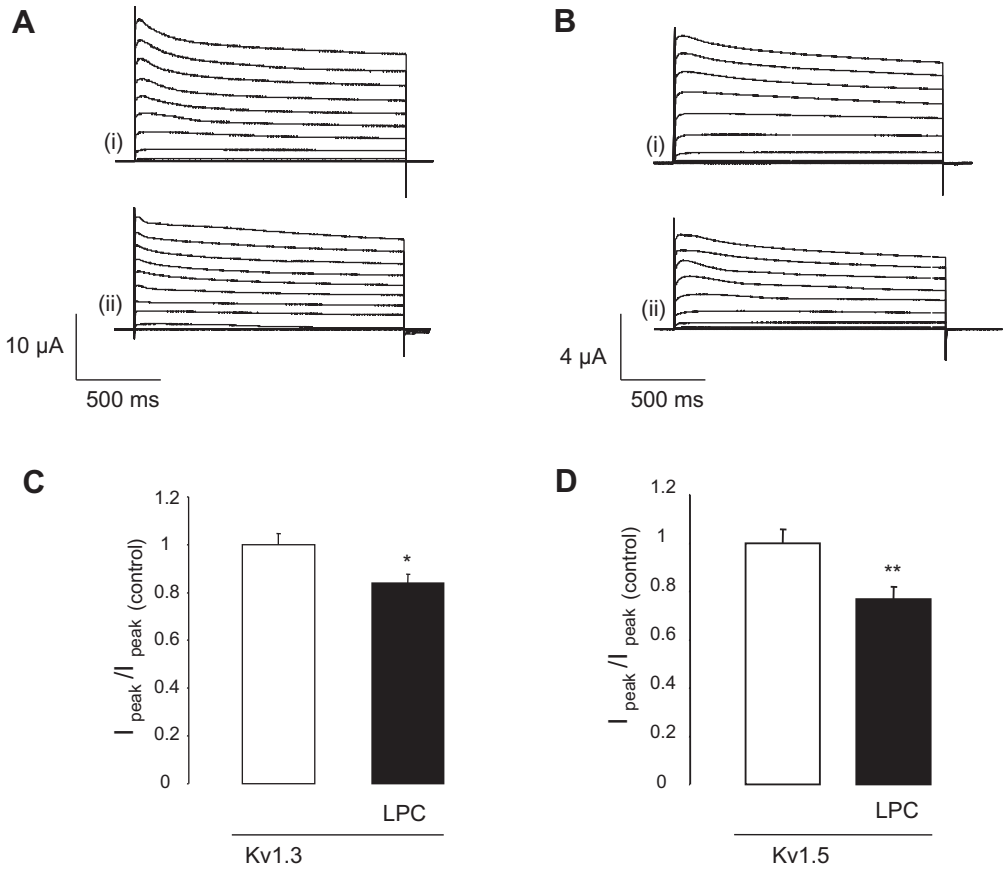

Fig. 4. Inhibition of K^+-channel activity in Kv1.3 or Kv1.5 expressing *Xenopus* oocytes by lysophosphatidylcholine. (A) Original tracings recorded in oocytes injected with cRNA encoding Kv1.3 alone in the absence (i) or presence (ii) of lysophosphatidylcholine (1 μg/ml). The currents were recorded following 2 s depolarizing pulses ranging from −80 to +50 mV in 10-mV and 15-s increments from a holding potential of −100 mV. (B) Original tracings recorded in oocytes injected with cRNA encoding Kv1.5 alone in the absence (i) or presence (ii) of lysophosphatidylcholine (1 μg/ml). The currents were recorded following 2 s depolarizing pulses ranging from −80 to +50 mV in 10-mV and 20-s increments from a holding potential of −100 mV. (C) Arithmetic means ± SEM (n = 16) of the normalized K^+-peak current following a depolarization from −80 mV to +50 mV in oocytes injected with cRNA encoding Kv1.3 alone in the absence (white bar) and presence (black bar) of lysophosphatidylcholine (1 μg/ml). * indicates statistically significant ($p < 0.05$) difference from absence of lysophosphatidylcholine (unpaired Student t test). (D) Arithmetic means ± SEM (n = 14–16) of the normalized K^+-peak current following a depolarization from −80 mV to +50 mV in oocytes injected with cRNA encoding Kv1.5 alone in the absence (white bar) and presence (black bar) of lysophosphatidylcholine (1 μg/ml). ** indicates statistically significant ($p < 0.01$) difference from absence of lysophosphatidylcholine (unpaired Student t test).

Inhibition of Kv1.3 K^+ channels may further affect cell proliferation, which, at least in some cell types, requires Kv1.3 channel activity [32,33]. Whether or not impaired endothelial cell proliferation may contribute to the pathophysiology of B19V infection, remains to be shown.

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