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Downregulation of KCNQ4 by Janus Kinase 2

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Abstract Janus kinase-2 (JAK2) participates in the signaling of several hormones, growth factors and cytokines. Further stimulators of JAK2 include osmotic cell shrinkage, and the kinase activates the cell volume regulatory Na^+/H^+ exchanger. The kinase may thus participate in cell volume regulation. Cell shrinkage is known to inhibit K^+ channels. Volume-regulatory K^+ channels include the voltage-gated K^+ channel KCNQ4. The present study explored the effect of JAK2 on KCNQ4 channel activity. KCNQ4 was expressed in *Xenopus* oocytes with or without wild-type JAK2, constitutively active ^{V617F}JAK2 or inactive ^{K882E}JAK2; and cell membrane conductance was determined by dual-electrode voltage clamp. Expression of KCNQ4 was followed by the appearance of voltage-gated K^+ conductance. Coexpression of JAK2 or of ^{V617F}JAK2, but not of ^{K882E}JAK2, resulted in a significant decrease in conductance. Treatment of KCNQ4 and JAK2 coexpressing oocytes with the JAK2 inhibitor AG490 (40 μM) was followed by an increase in conductance. Treatment of KCNQ4 expressing oocytes with brefeldin A (5 μM) was followed by a decrease in conductance, which was similar in oocytes expressing KCNQ4 together with JAK2 as in oocytes expressing KCNQ4 alone. Thus, JAK2 apparently does not accelerate channel protein retrieval from the cell membrane. In conclusion, JAK2 downregulates KCNQ4 activity and thus counteracts K^+ exit, an effect which may contribute to cell volume regulation.

The first two authors contributed equally and thus share first authorship.

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Introduction

Janus-activated kinase-2 (JAK2), a tyrosine protein kinase, participates in the signaling of leptin (Morris and Rui 2009), growth hormone (Brooks and Waters 2010), erythropoietin (Spivak 2010), thrombopoietin (Spivak 2010), granulocyte colony-stimulating factor (Spivak 2010) and several cytokines (Lopez et al. 2010; Spivak 2010). JAK2 signaling fosters the development of neoplasms, the gain-of-function mutation ^{V617F}JAK2 is observed in the majority of myeloproliferative diseases and JAK2 inhibitors are considered for the treatment of those disorders (Baskin et al. 2010; Ho et al. 2010; Mahfouz et al. 2011; Oh and Gotlib 2010; Pardanani et al. 2011; Santos and Verstovsek 2011; Tefferi et al. 2009; Tefferi 2010). Activators of JAK2 include osmotic cell shrinkage, and the kinase stimulates the cell volume–regulatory Na^+/H^+ exchanger (Garnovskaya et al. 2003; Gatsios et al. 1998).

Cell volume regulation following cell shrinkage involves inhibition of K^+ channels (Macri et al. 1997). Cell volume–regulatory K^+ channels include the voltage-gated K^+ channel KCNQ4 (Hammami et al. 2009; Hougaard et al. 2004).

The present study explored whether JAK2 participates in the regulation of KCNQ4. KCNQ4 was thus expressed with or without wild-type JAK2, constitutively active ^{V617F}JAK2 or inactive ^{K882E}JAK2 in *Xenopus* oocytes; and KCNQ4 current was determined utilizing dual-electrode voltage clamp. As a result, coexpression of JAK2 and active ^{V617F}JAK2, but not of inactive ^{K882E}JAK2, decreased KCNQ4-induced conductance in *Xenopus* oocytes.

Materials and Methods

Constructs

For generation of cRNA the following cDNA constructs were used: wild-type human KCNQ4 (Seebohm et al. 2005; Strutz-Seebohm et al. 2006), wild-type human KCNQ1 (Henrion et al. 2012), wild-type human JAK2 (Imagenes, Berlin, Germany), inactive ^{K882E}JAK2 (Feng et al. 1997) and gain-of-function ^{V617F}JAK2 (Hosseinzadeh et al. 2011b; Mahfouz et al. 2011). The constructs were used for generation of cRNA as described previously (Dermaku-Sopjani et al. 2011).

Voltage Clamp in *Xenopus* Oocytes

Xenopus oocytes were prepared as previously described (Rexhepaj et al. 2010). cRNA encoding wild-type JAK2 or ^{V617F}JAK2 or ^{K882E}JAK2 cRNA (10 ng) and/or KCNQ4 (25 ng) were injected on the first day after preparation of the oocytes (Strutz-Seebohm et al. 2011). Oocytes were maintained at 17 °C in ND96 solution containing (in mM) 96 NaCl, 4 KCl, 1.8 $MgC1_2$, 0.1 $CaC1_2$ and 5 HEPES (pH 7.6). The ND96 solution was supplemented with gentamycin (50 mg/l), tetracycline (50 mg/l), ciprofloxacin (1.6 mg/l), refobacin (100 mg/l) and theophylline (90 mg/l). Experiments were performed at room temperature 3 days after injection (Eckey et al. 2010). Currents were determined in two-electrode voltage clamp utilizing a protocol of 10-s pulses from −100 to +60 mV (KCNQ4) or +80 mV (KCNQ1) in 20-mV increments. The intermediate holding voltage was −80 mV. The current at the end of each voltage step was taken for data analysis. The data were filtered at 10 Hz and recorded with a MacLab digital to analog converter and software for data acquisition and analysis (ADInstruments, Castle Hill, Australia). The control bath solution (ND96) contained (in mM) 96 NaCl, 2 KCl, 1.8 $CaCl_2$, 1 $MgCl_2$ and 5 mM HEPES (pH 7.4). The flow rate of the superfusion was 20 ml/min, and a complete exchange of the bath solution was reached within about 10 s. Where indicated, oocytes were treated with the JAK2 inhibitor AG490 (40 μM final concentration) for the indicated time periods prior to measurements. To test for alterations of KCNQ4 protein stability in the cell membrane, experiments were done with brefeldin A (5 μM final concentration) (Bohmer et al. 2010), which interferes with the function of Golgi-specific coat proteins involved in the regulation of membrane transport in the secretory pathway (Hunziker et al. 1992). As treatment of *Xenopus* oocytes with brefeldin A prevents insertion of new channel protein into the cell membrane, the decay of channel activity could be taken as a measure of channel protein clearance from the cell membrane (Staub et al. 1997).

Statistical Analysis

Data are provided as means ± SEM, and n represents the number of oocytes investigated. All experiments were repeated with at least two to three batches of oocytes; in all repetitions qualitatively similar data were obtained. Data were tested for significance using ANOVA or t test, as appropriate. Results with $p < 0.05$ were considered statistically significant.

Results

To explore the effect of JAK2 on KCNQ4 channels, cRNA encoding KCNQ4 was injected into *Xenopus* oocytes with or without cRNA encoding JAK2 and cell membrane conductance was determined utilizing dual-electrode voltage clamp. Cell membrane conductance was low in water-injected oocytes but markedly increased following expression of KCNQ4 (Fig. 1). The additional expression of JAK2 resulted in a significant decrease in conductance, reflecting downregulation of KCNQ4 activity by JAK2 (Fig. 1). For comparison, experiments were performed in oocytes expressing KCNQ1. The current at +80 mV approached 2.18 ± 0.06 μA ($n = 15$) in *Xenopus* oocytes expressing KCNQ1 alone and 2.01 ± 0.07 μA ($n = 20$) in *Xenopus* oocytes expressing KCNQ1 together with JAK2. The values were not significantly different. Thus, unlike KCNQ4, KCNQ1 appears not to be regulated by JAK2.

The effect of wild-type JAK2 on KCNQ4 was mimicked by constitutively active ^{V617F}JAK2. Coexpression of ^{V617F}JAK2 resulted in a considerable decrease in conductance in KCNQ4 expressing *Xenopus* oocytes (Fig. 2). In contrast, coexpression of the inactive mutant ^{K882E}JAK2 did not significantly alter the conductance in KCNQ4 expressing *Xenopus* oocytes (Fig. 2). Treatment of KCNQ4 and JAK2 expressing *Xenopus* oocytes with the JAK2 inhibitor AG490 (40 μM) was followed by an increase in cell membrane conductance (Fig. 3). Application of the inhibitor AG490 (40 μM) to oocytes expressing KCNQ4 without JAK2 tended to increase the current at +60 mV from 1.64 ± 0.26 μA ($n = 15$) to 2.69 ± 0.40 μA ($n = 23$), an effect that, however, did not reach statistical significance.

At least in theory, JAK2 could have downregulated KCNQ4 activity by decreasing the protein abundance in the cell membrane. JAK2 could modify KCNQ4 protein abundance either by inhibition of channel protein insertion into the cell membrane or by fostering channel protein retrieval from the cell membrane. In order to discriminate between these two possibilities, KCNQ4 and JAK2 expressing *Xenopus* oocytes were exposed to 5 μM brefeldin A. As illustrated in Fig. 4, brefeldin A treatment was

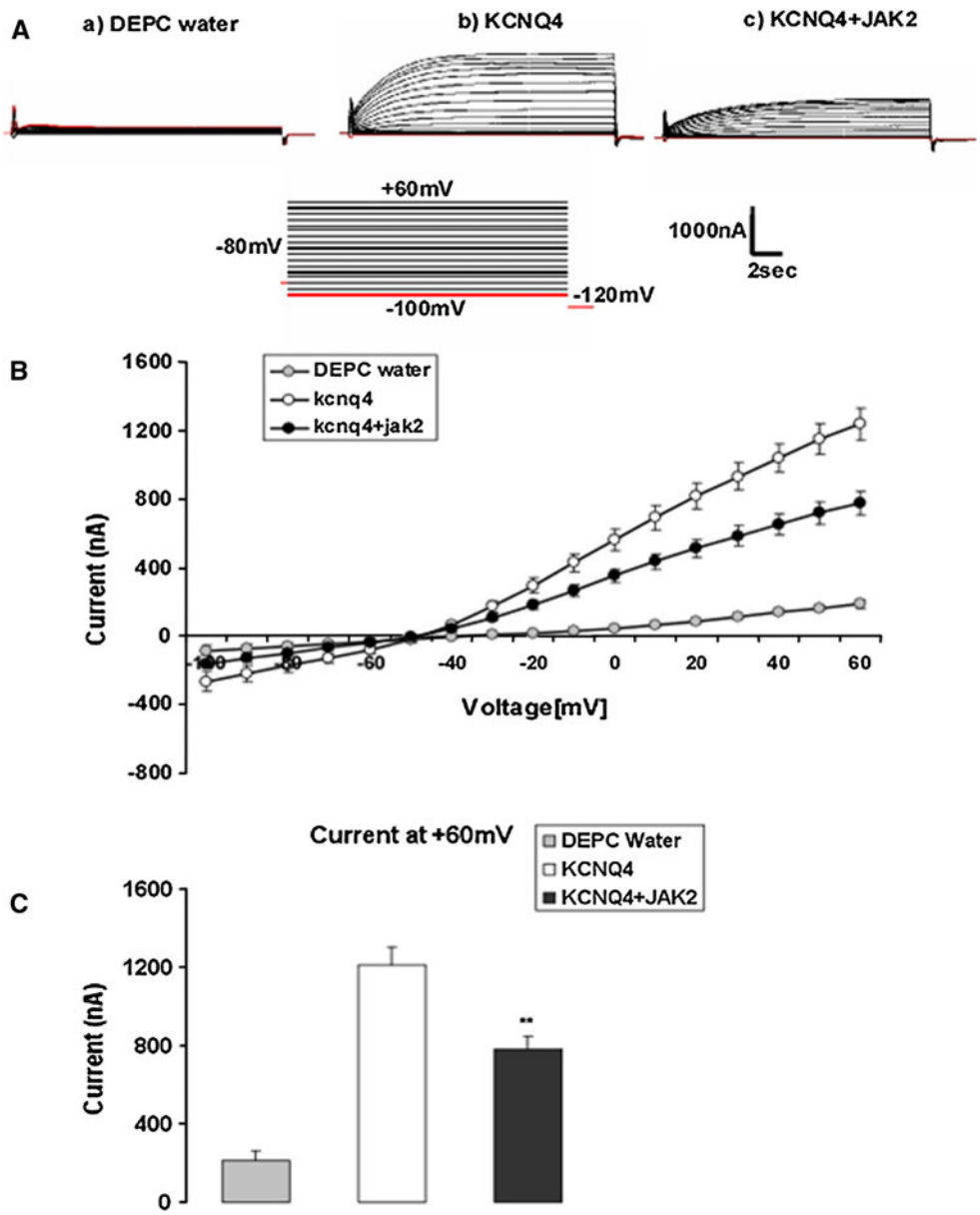

Fig. 1 Coexpression of JAK2 decreases cell membrane conductance in KCNQ4-expressing *Xenopus* oocytes. **a** Representative original tracings showing currents in *Xenopus* oocytes injected with water (*a*) as well as in oocytes expressing KCNQ4 without (*b*) or with (*c*) additional coexpression of wild-type JAK2. **b** Arithmetic means ± SEM ($n = 14$–15) of the current as a function of the potential difference across the cell membrane in *Xenopus* oocytes injected with water (H_2O, *gray circles*) or expressing KCNQ4 without (KCNQ4, *white circles*) or with (KCNQ4 + JAK2, *black circles*) additional coexpression of wild-type JAK2. **c** Arithmetic means ± SEM ($n = 14$–15) of the current at +60 mV in *Xenopus* oocytes injected with water (H_2O, *gray bar*) or expressing KCNQ4 without (KCNQ4, *white bar*) or with (KCNQ4 + JAK2, *black bar*) additional coexpression of wild-type JAK2. **Statistically significant difference from expression of KCNQ4 alone ($p < 0.01$)

followed by a decline in cell membrane conductance, which was similar in oocytes expressing KCNQ4 alone and oocytes expressing KCNQ4 together with JAK2. Accordingly, coexpression of JAK2 apparently did not modify retrieval of channel protein from the cell membrane. Thus, JAK2 decreases KCNQ4 activity, presumably by interfering with channel insertion into the cell membrane.

Discussion

The present observations uncover a novel function of JAK2, i.e., regulation of the K^+ channel KCNQ4. JAK2 decreases KCNQ4 activity and thus counteracts cellular K^+ loss. In view of the effect of brefeldin A, JAK2 does not accelerate channel protein retrieval from the cell membrane. Presumably, the kinase impedes channel protein insertion into the cell membrane or activation of the channel. Wild-type JAK2 is similarly effective as constitutively active JAK2, indicating that wild-type JAK2 is activated in oocytes. JAK2 inhibition by AG490 tended to increase the conductance in oocytes expressing KCNQ4 alone. Possibly, oocytes express an endogenous JAK2, which downregulates heterologously expressed KCNQ4. However, the effect did not reach statistical significance, thus precluding any safe conclusions. Nevertheless, the possibility must be kept in mind that, besides its known effect on JAK2, AG49 may, at least in theory, affect KCNQ4 channel activity by mechanisms other than JAK2 inhibition.

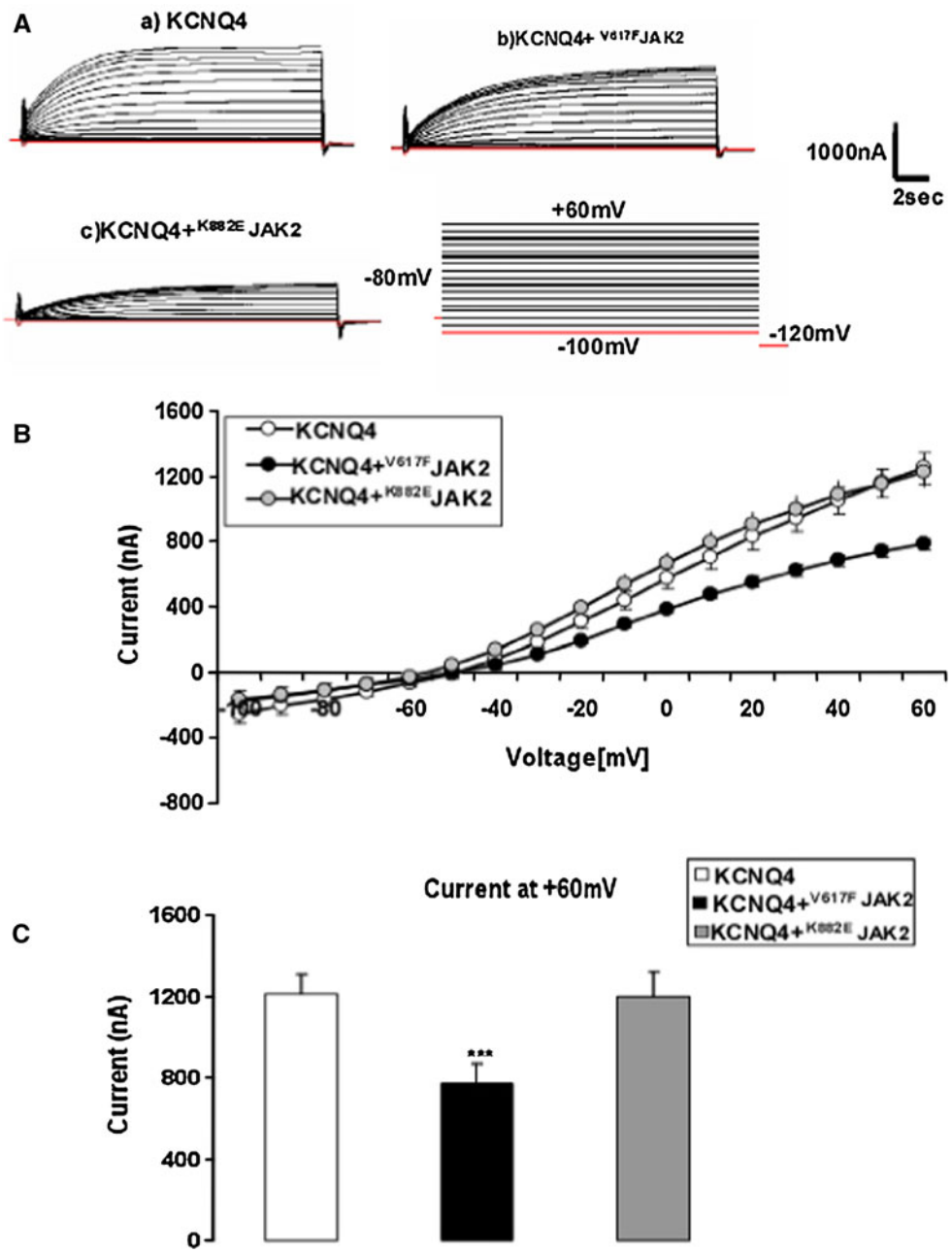

Fig. 2 The effect of wild-type JAK2 is mimicked by ^{V617F}JAK2 but not by inactive ^{K882E}JAK2. **a** Representative original tracings showing currents in *Xenopus* oocytes expressing KCNQ4 without (*a*) or with additional coexpression of constitutively active ^{V617F}JAK2 (*b*) or of inactive ^{K882E}JAK2 (*c*). **b** Arithmetic means ± SEM ($n = 11$–17) of the current as a function of the potential difference across the cell membrane in *Xenopus* oocytes expressing KCNQ4 without (*white circles*) or with additional coexpression of constitutively active ^{V617F}JAK2 (*black circles*) or of inactive ^{K882E}JAK2 (*gray circles*). **c** Arithmetic means ± SEM ($n = 11$–17) of the current at +60 mV in *Xenopus* oocytes expressing KCNQ4 without (KCNQ4, *white bar*) or with additional coexpression of constitutively active ^{V617F}JAK2 (KCNQ4 + ^{V617F}JAK2, *black bar*) or inactive ^{K882E}JAK2 (KCNQ4 + ^{K882E}JAK2, *gray bar*). ***Statistically significant difference from expression of KCNQ4 alone ($p < 0.001$)

The downregulation of KCNQ4 is expected to decrease K^+ exit and to favor depolarization of the cell membrane. Depolarization should foster Cl^- entry, and thus, inhibition of K^+ channels is expected to result in cellular accumulation of KCl, accompanied by osmotically obliged water (Lang et al. 1998). Accordingly, inhibition of K^+ channels may participate in cell volume regulation. JAK2-sensitive regulation of KCNQ4 may impact further functions. KCNQ4 is expressed in the peripheral nerve endings of cutaneous rapidly adapting hair follicle and Meissner corpuscle mechanoreceptors from mice and humans (Heidenreich et al. 2012) as well as in rat primary cultured oligodendrocyte progenitor cells (Wang et al. 2011). Deranged function of KCNQ4 channels may lead to hearing loss (Nie 2008) and mood disorders (Sotty et al. 2009).

Deranged KCNQ4 activity has further been implicated in hypertension (Jepps et al. 2011), preeclampsia (Mistry et al. 2011), pulmonary hypertension (Joshi et al. 2009) and irritable bowel syndrome (Jepps et al. 2009). Moreover, KCNQ4 gene variants have been implicated in aging (Walter et al. 2011). JAK2 may contribute to hypertension induced by angiotensin II (Banes-Berceli et al. 2011). It is

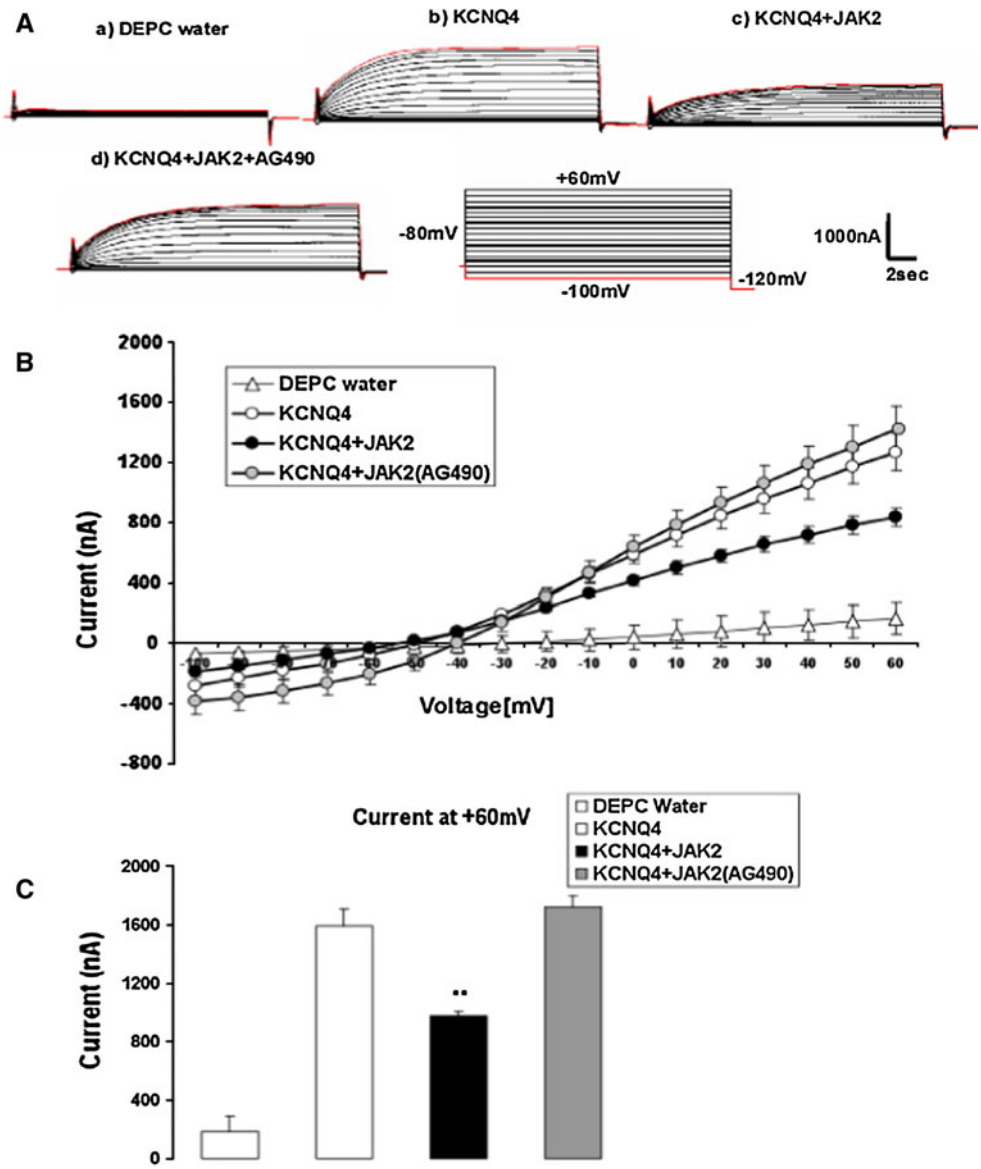

Fig. 3 The effect of JAK2 is reversed by JAK2 inhibitor AG490. **a** Representative original tracings showing currents in *Xenopus* oocytes injected with water (*a*), expressing KCNQ4 alone (*b*) or coexpressing KCNQ4 with JAK2 and pretreated for 24 h without (*c*) and with (*d*) JAK2 inhibitor AG490 (40 μM). **b** Arithmetic means ± SEM ($n = 13$–15) of current as a function of the potential difference across the cell membrane in *Xenopus* oocytes injected with water (H_2O, *white triangles*), with cRNA encoding KCNQ4 alone (*white circles*) or with cRNA encoding both, KCNQ4 + JAK2, in the absence (*black circles*) or presence (*gray circles*) of the JAK2 inhibitor AG490 (40 μM) for 24 h. **c** Arithmetic means ± SEM ($n = 13$–15) of the current at +60 mV in *Xenopus* oocytes injected with water (H_2O, *light gray bar*) or with cRNA encoding KCNQ4 alone (*white bar*) or with cRNA encoding both, KCNQ4 + JAK2, in the absence (*black bar*) or presence (*dark gray bar*) of the JAK2 inhibitor AG490 (40 μM) for 24 h. **Statistically significant difference from expression of KCNQ4 alone ($p < 0.01$)

tempting to speculate that JAK2-dependent regulation of KCNQ4 contributes to the hypertensive effect of angiotensin II. However, further experimental efforts will be needed to elucidate the physiological and pathophysiological roles of JAK2-sensitive regulation of KCNQ4 activity.

JAK2 is considered to participate in the regulation of tumor cell proliferation, and the gain-of-function mutation ^{V617F}JAK2 has been identified in the majority of myeloproliferative diseases (Mahfouz et al. 2011). Along those lines, JAK2 inhibitors exert antineoplastic effects in myeloproliferative disorders (Baskin et al. 2010; Ho et al. 2010; Oh and Gotlib 2010; Pardanani et al. 2011; Santos and Verstovsek 2011; Tefferi et al. 2009; Tefferi 2010). Whether or not KCNQ4 is expressed in tumor cells is to the best of our knowledge not known. Activation of K^+ channels may parallel and support apoptosis (Lang et al. 2006; Wei et al. 2004). Whether downregulation of KCNQ4 influences the survival of KCNQ4 expressing cells remains to be determined.

JAK2 modifies further channels (Hosseinzadeh et al. 2012a) and transporters (Bhavsar et al. 2011; Hosseinzadeh et al. 2011a, b, 2012b; Shojaiefard et al. 2012). The insensitivity of KCNQ1 to JAK2 reveals, however, that the effect of JAK2 is not unspecific.

In conclusion, wild-type JAK2 and the constitutively active ^{V617F}JAK2 decrease the activity of K^+ channel KCNQ4 and may thus contribute to the regulation of cell membrane potential and cell volume in KCNQ4 expressing cells.

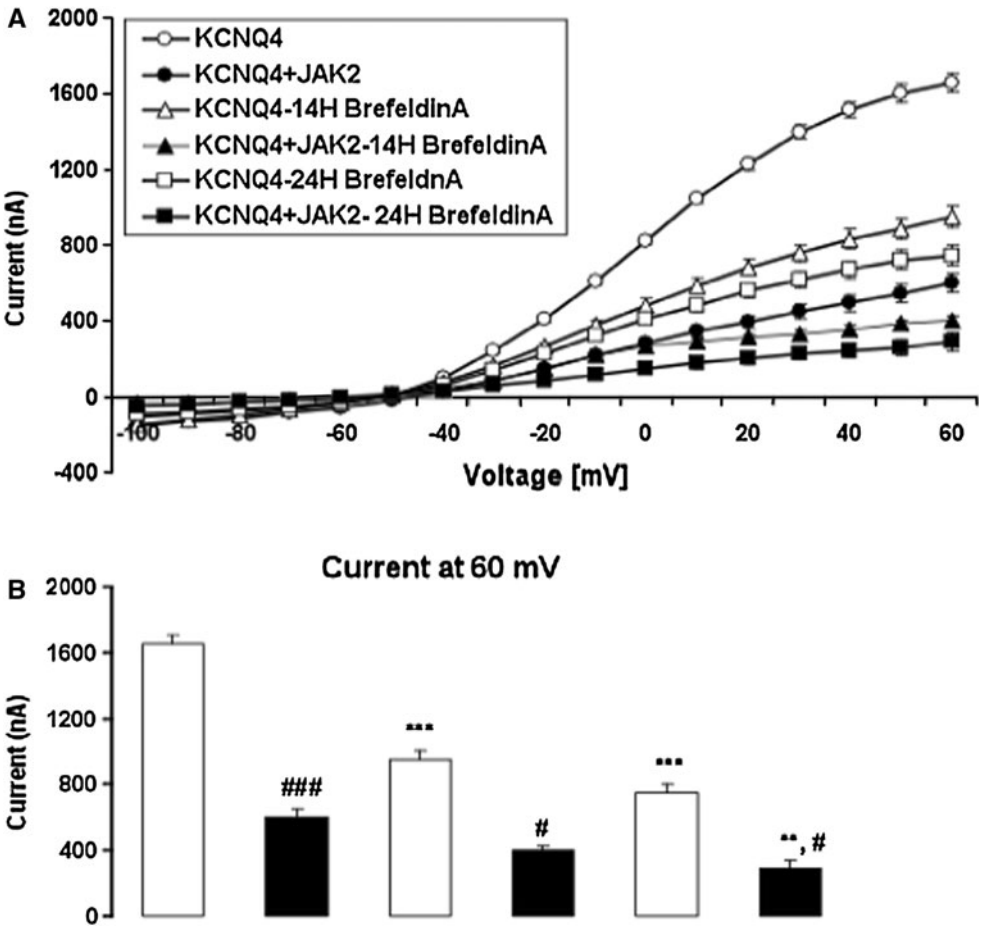

Fig. 4 Effect of brefeldin A on KCNQ4 activity in KCNQ4-expressing *Xenopus* oocytes in the absence and presence of JAK2. **a** Arithmetic means ± SEM ($n = 15$–33) of the current as a function of the potential difference across the cell membrane in *Xenopus* oocytes expressing KCNQ4 without (*open symbols*) or with additional coexpression of JAK2 (*closed symbols*) prior to (*circles*) or 14 h (*triangles*) or 24 h (*squares*) following treatment with brefeldin A (5 μM). **b** Arithmetic means ± SEM ($n = 15$–33) of currents in *Xenopus* oocytes injected with KCNQ4 without (*white bars*) or with (*black bars*) JAK2 in the absence (*left bars*) or presence of 5 μM brefeldin for 14 h (*middle bars*) or 24 h (*right bars*). Statistically significant difference from the absence of brefeldin: $^{**}p < 0.01$, $^{***}p < 0.001$. Significant difference from the absence of JAK2: $\#p < 0.05$, $\#\#\#p < 0.001$

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