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Stimulation of Na^+ coupled phosphate transporter NaPiIIa by janus kinase JAK2

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ABSTRACT

Background: Na^+ coupled phosphate transporter NaPiIIa is the main carrier accomplishing phosphate transport across the apical cell membrane of proximal renal tubules and thus renal tubular phosphate reabsorption. The carrier is regulated by a wide variety of hormones and cellular signaling molecules. Hormones stimulating renal tubular phosphate transport and thus leading to hyperphosphatemia include growth hormone. Signaling of growth hormone involves activation of janus-activated kinase-2 JAK2, which has previously been shown to participate in the regulation of several Na^+ coupled transporters. Experiments exploring the effect of JAK2 on phosphate transport have, however, never been reported. The present study thus addressed the effect of JAK2 on NaPiIIa.

Methods: cRNA encoding NaPiIIa was injected into *Xenopus* oocytes with or without additional injection of cRNA encoding wild type JAK2, the gain of function mutant $JAK2^{V617F}$ or inactive $JAK2^{K882E}$. Phosphate-induced current (I_{NaPi}) reflecting electrogenic phosphate transport was determined by two electrode voltage clamp. Moreover, NaPiIIa protein abundance in the cell membrane was determined by chemiluminescence.

Results: No appreciable I_{NaPi} was observed in water injected oocytes or in oocytes expressing JAK2 alone. In NaPiIIa expressing oocytes I_{NaPi} was significantly increased by additional expression of JAK2 or $JAK2^{V617F}$, but not by coexpression of $JAK2^{K882E}$. In oocytes expressing both, NaPiIIa and JAK2, I_{NaPi} was gradually decreased by JAK2 inhibitor AG490 (40 μM). Coexpression of NaPiIIa and JAK2 or $JAK2^{V617F}$, but not of $JAK2^{K882E}$ increased NaPiIIa protein abundance in the cell membrane. Disruption of carrier protein insertion with Brefeldin A (5 μM) was followed by a decline of I_{NaPi} to a similar extent in *Xenopus* oocytes expressing NaPiIIa with JAK2 and in *Xenopus* oocytes expressing NaPiIIa alone, suggesting that JAK2 did not affect carrier stability in the cell membrane.

Conclusion: JAK2 contributes to the regulation of phosphate transporter NaPiIIa.

1. Introduction

The Na^+-coupled phosphate transporter NaPiIIa (SLC34A1) is the most important carrier accomplishing renal tubular phosphate transport across the apical brush border membrane of proximal renal tubules and thus renal tubular phosphate reabsorption [1–3]. Renal tubular phosphate reabsorption is regulated by dietary phosphate intake, acid-base status, and a variety of hormones including parathyroid hormone, $1,25(OH)_2D_3$, FGF-23, dopamine, growth hormone, insulin and insulin-like growth factor IGF1 [4–12]. Known signaling participating in the regulation of NaPiIIa includes the protein kinases A and C, ERK1/2, Klotho, the PI3K/PKB/GSK3 kinase cascade and NHERF1 [5,13–20].

Signaling involved in the effects of growth hormone include janus-activated kinase-2 JAK2 [21,22], which contributes to effects of several further hormones and cytokines [23–25], such as leptin [25], erythropoietin [25], thrombopoietin [25] and granulocyte colony-stimulating factor [25]. Excessive JAK2 activity may lead to the development of malignancy and JAK2 inhibitors are considered for the treatment of myeloproliferative disorders [26–31]. Along those lines, the gain of function mutation $JAK2^{V617F}$ may contribute to the pathogenesis of myeloproliferative disease [32–34].

Most recent observations revealed the ability of JAK2 to regulate several carriers, such as glucose carriers [35–37], creatine transporter [38], betaine/GABA transporter [39], and amino acid transporters [35,40].

The present study explored whether JAK2 regulates protein abundance and activity of NaPiIIa. To this end, phosphate induced current and NaPiIIa protein abundance were determined in *Xenopus* oocytes expressing NaPiIIa with or without wild type JAK2, the gain of function mutant $JAK2^{V617F}$ or inactive $JAK2^{K882E}$.

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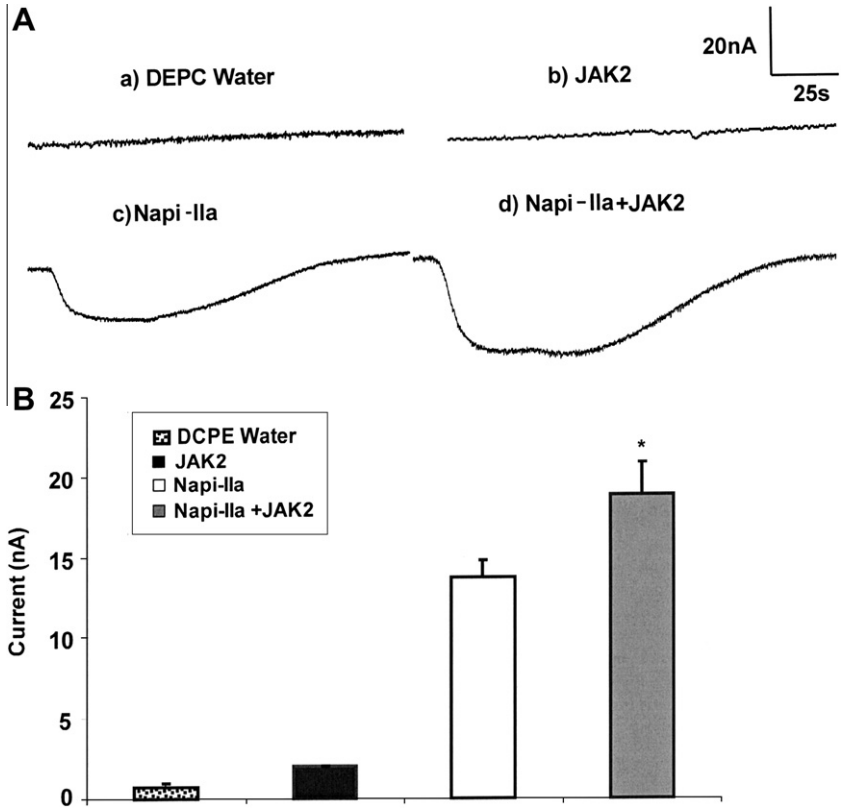

Fig. 1. Coexpression of JAK2 decreases electrogenic phosphate transport in NaPiIIa-expressing *Xenopus* oocytes (A) Representative original tracings showing phosphate (1 mM) -induced current (I_{NaPi}) in *Xenopus* oocytes injected with water (a), or expressing wild type JAK2 alone (b) NaPiIIa alone (c), or NaPiIIa with wild type JAK2 (d). (B) Arithmetic means ± SEM (n = 25–30) of phosphate (1 mM) -induced current (I_{NaPi}) in *Xenopus* oocytes injected with water (H_2O, dotted bar), expressing wild type JAK2 alone (JAK2, dark grey bar), expressing NaPiIIa alone (NaPiIIa, white bar) or expressing wild type JAK2 with NaPiIIa (NaPiIIA + JAK2, dark grey bar).*($p < 0.05$) indicates statistically significant difference to expression of NaPiIIa alone.

2. Materials and methods

2.1. Constructs

Constructs were used encoding wild type NaPiIIa [41], wild-type human JAK2 (Imagenes, Berlin, Germany), inactive $JAK2^{K882E}$ mutant [42] and the gain of function mutant $JAK2^{V617F}$ [43] generated by site-directed mutagenesis (QuikChange II XL Site-Directed Mutagenesis Kit; Stratagene, Heidelberg, Germany) according to the manufacturer's instructions [44]. The constructs were used for generation of cRNA as described previously [45].

2.2. Voltage clamp in Xenopus oocytes

Xenopus oocytes were prepared as described [46]. Where not indicated otherwise, 15 ng NaPiIIa cRNA was injected on the first day and 10 ng of wild type JAK2 cRNA on the second day or at the same day after preparation of the oocytes [47]. The oocytes were maintained at 17 °C in a solution containing (in mM): 96 NaCl, 4 KCl, 1.8 $MgC1_2$, 0.1 $CaC1_2$, 5 HEPES, pH 7.4, gentamycin (50 mg/l), tetracycline (50 mg/l), ciprofloxacin (1.6 mg/l), refobacin (100 mg/l), and theophiline (90 mg/l). Where indicated, the JAK2 inhibitor AG490 (40 μM) or brefeldin A (5 μM) were added to the respective solutions. The voltage clamp experiments were performed at room temperature 4 days at least after injection [16]. Two-electrode voltage-clamp recordings were performed at a holding potential of −60 mV. The data were filtered at 10 Hz and recorded with a Digidata A/D–D/A converter and Clampex 9.2 software for data acquisition and analysis (Axon Instruments) [40]. The control superfusate contained 96 mM NaCl, 2 mM KCl, 1.8 mM $CaCl_2$, 1 mM $MgCl_2$ and 5 mM HEPES, pH 7.4. Phosphate was added to the solutions at a concentration of 1 mM, unless otherwise stated. The flow rate of the superfusion was approx. 20 ml/min, and a complete exchange of the bath solution was reached within about 10 s [48].

2.3. Chemiluminescence

To determine NapiIIa cell surface expression by chemiluminescence [49], the oocytes were incubated with primary SLC34A1 (NapiIIa) rabbit anti-human polyclonal antibody (1:500, Life Span Biosciences, WA, USA) and subsequently with secondary, HRP-conjugated goat anti-rabbit IgG (H&L) antibody (1:1000, Cell Signaling Technology, MA, USA). Individual oocytes were placed in 96 well plates with 20 μl of SuperSignal ELISA Femto Maximum Sensitivity Substrate (Pierce, Rockford, IL, USA) and chemiluminescence of single oocytes was quantified in a luminometer (Walter Wallac 2 plate reader, Perkin Elmer, Juegesheim, Germany) by integrating the signal over a period of 1 s [49]. Results display normalized relative light units. Integrity of the oocytes was assessed by visual control after the measurement to avoid unspecific light signals from the cytosol.

2.4. 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; in all repetitions qualitatively similar data were obtained. Data were tested for significance using One-way ANOVA

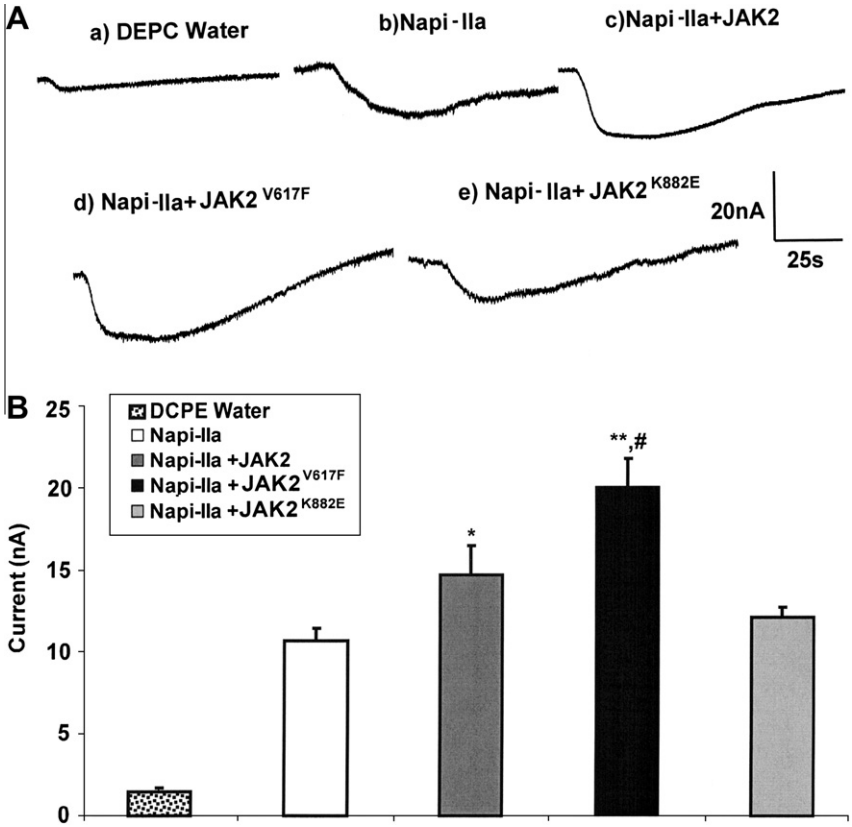

Fig. 2. The effect of wild type JAK2 is mimicked by active ^{V617F}JAK2 but not by inactive mutant ^{K882E}JAK2 (A) Representative original tracings showing phosphate (1 mM) -induced current (I_{NaPi}) in *Xenopus* oocytes injected with water (a), or expressing NaPiIIa alone (b), NaPiIIa with wild type JAK2 (c), NaPiIIa with the gain of function mutant JAK2^{V617F} (d), or NaPiIIa with the inactive mutant JAK2^{K882E} (e). (B) Arithmetic means ± SEM (n = 23–28) of phosphate (1 mM) -induced current (I_{NaPi}) in *Xenopus* oocytes injected with water (H_2O, dotted bar), expressing NaPiIIa alone (NaPiIIa, white bar) or expressing NaPiIIa with wild type JAK2 (NaPiIIa + JAK2, dark grey bar), with the gain of function mutant JAK2^{V617F} (NaPiIIa + JAK2^{V617F}, black bar) or with the inactive mutant JAK2^{K882E} (NaPiIIa + JAK2^{K882E}, light grey bar). $^{*}(p < 0.05)$,$^{**}(p < 0.01)$ indicates statistically significant difference to expression of NaPiIIa alone. $^{\#}(p < 0.05)$ indicates statistically significant difference to I_{NaPi} in oocytes expressing NapiIIa with wild type JAK2.

with Tukey post-hoc test or *t*-test, as appropriate. Results with $p < 0.05$ were considered statistically significant.

3. Results

In order to test, whether the phosphate transporter NaPiIIa is regulated by janus kinase-2 (JAK2), cRNA encoding NaPiIIa was injected into *Xenopus* oocytes with or without additional injection of cRNA encoding JAK2. Electrogenic transport of phosphate was estimated from phosphate (1 mM) induced inward current (I_{NaPi}). No significant I_{NaPi} was observed following phosphate exposure of water-injected *Xenopus* oocytes or of oocytes expressing JAK2 alone (Fig. 1). Thus, neither in the absence nor in the presence of JAK2, *Xenopus* oocytes express appreciable endogenous electrogenic phosphate transport (Fig. 1A and B). A robust I_{NaPi} was, however, observed in Xenopus oocytes injected with cRNA encoding NaPiIIa. The additional injection of cRNA encoding wild type JAK2 was followed by a significant increase of I_{NaPi} in NaPiIIa expressing *Xenopus* oocytes (Fig. 1A and B).

Similar to coexpression of wild type JAK2, coexpression of the gain of function mutant JAK2^{V617F} significantly up-regulated I_{NaPi} (Fig. 2A and B). Accordingly, I_{NaPi} was significantly higher in *Xenopus* oocytes expressing NaPiIIa together with JAK2^{V617F} than in *Xenopus* oocytes expressing NaPiIIa alone. I_{NaPi} was significantly higher in *Xenopus* oocytes expressing NaPiIIa with JAK2^{V617F} than in *Xenopus* oocytes expressing NaPiIIa with wild type JAK2 (Fig. 2A and B). Presumably, expressed wild type JAK2 is not fully activated in Xenopus oocytes. I_{NaPi} was not significantly increased by the inactive mutant JAK2^{K882E} (Fig. 2A and B). Accordingly, I_{NaPi} was similar in *Xenopus* oocytes expressing NaPiIIa together with JAK2^{K882E} and in *Xenopus* oocytes expressing NaPiIIa alone.

Treatment of *Xenopus* oocytes expressing both, NaPiIIa and JAK2, with the JAK2 inhibitor AG490 (40 μM) was followed by a gradual decrease of I_{NaPi} (Fig. 3). Accordingly, in *Xenopus* oocytes expressing both, NaPiIIa and JAK2, I_{NaPi} was significantly lower following a 6 h or a 12 h treatment with AG490 than prior to the treatment.

The up-regulation of I_{NaPi} could, at least in theory, have been the result of increased carrier protein abundance in the plasma membrane. Chemiluminescence was thus employed to quantify NaPiIIa protein abundance in the cell membrane of *Xenopus* oocytes expressing NaPiIIa with or without coexpression of JAK2, JAK2^{V617F} or JAK2^{K882E}. As illustrated in Fig. 4, the NaPiIIa protein abundance was significantly higher in oocytes coexpressing either JAK2 or JAK2^{V617F} than in *Xenopus* oocytes expressing NaPiIIa alone. Again, the effect of JAK2^{V617F} was significantly higher than that of wild type JAK2 (Fig. 4). In contrast to coexpression of JAK2 or JAK2^{V617F}, coexpression of JAK2^{K882E} failed to significantly modify NaPiIIa proetin abundance in the cell membrane (Fig. 4A).

The increase of I_{NaPi} and carrier protein abundance in NaPiIIa expressing *Xenopus* oocytes following coexpression of JAK2 could have been due to accelerated insertion of carrier protein into the cell membrane or delayed clearance of carrier protein from the cell membrane. In order to discriminate between those two possibilities, I_{NaPi} was determined in *Xenopus* oocytes expressing NaPiIIa

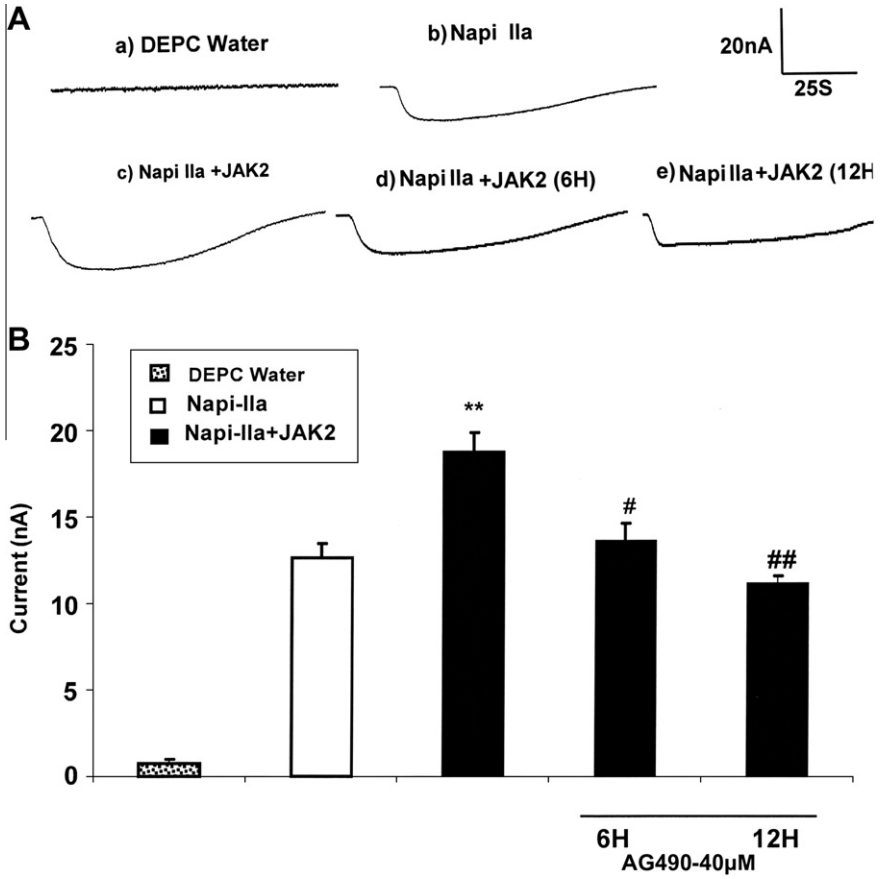

Fig. 3. The effect of JAK2 is reversed by the JAK2 inhibitor AG490 (A) Representative original tracings showing phosphate (1 mM)-induced current (I_{NaPi}) in *Xenopus* oocytes injected with water (a) or with cRNA encoding NaPiIIa (b) or NaPiIIa + JAK2 (c). Currents in the absence of inhibitor (c) or following 6 h (d) or 12 h (e) pretreatment with JAK2 inhibitor AG490 (40 μM). (B) Arithmetic means ± SEM (n = 21–25) of phosphate (1 mM) -induced current (I_{NaPi}) in *Xenopus* oocytes injected with water (H_2O, dotted bar), expressing NaPiIIa alone (NaPiIIa) or expressing NaPiIIa with JAK2 in the absence of inhibitor or following pretreatment with the JAK2 inhibitor AG490 (40 μM, light grey bars) for the indicated time periods. $^{\#}(p < 0.05)$, $^{\#\#}(p < 0.01)$ indicates statistically significant difference from the absence of JAK2 inhibitor AG490. $^{**}(p < 0.01)$ indicates statistically significant difference from NaPiIIa alone (absence of JAK2).

with or without JAK2 prior to or 6 h or 12 h following treatment with 5 μM brefeldin A, a substance blocking the insertion of new carrier protein into the cell membrane. As illustrated in Fig. 4B, brefeldin A resulted in a decline of I_{NaPi}, which was similarly fast in *Xenopus* oocytes coexpressing NaPiIIa with JAK2 as in *Xenopus* oocytes expressing NaPiIIa alone. Thus, JAK2 apparently decreases I_{NaPi} by a mechanism other than delaying carrier clearance from the cell membrane.

4. Discussion

The present study reveals a novel regulator of the Na^+ coupled phosphate transporter NaPiIIa. Coexpression of the janus Kinase 2 (JAK2) significantly increased electrogenic phosphate transport (I_{NaPi}) and NaPiIIa protein abundance in NaPiIIa expressing *Xenopus* oocytes. I_{NaPi} and carrier protein are similarly up-regulated following coexpression of the gain of function mutant $JAK2^{V617F}$, whereas the inactive $JAK2^{K882E}$ did not significantly modify I_{NaPi} and carrier protein abundance. Thus, JAK2 is effective as kinase.

The experiments with brefeldin A reveal that inhibition of carrier insertion into the cell membrane leads to a decline of I_{NaPi}, which is similar in *Xenopus* oocytes expressing NaPiIIa together with JAK2 and in *Xenopus* oocytes expressing NaPiIIa alone. Accordingly, the clearance of carrier protein from the cell membrane is apparently not delayed by JAK2 expression. This observation suggests that the increase of NapiIIa protein abundance in the cell membrane and thus I_{NaPi} following coexpression of JAK2 or $JAK2^{V617F}$ may result from accelerated carrier insertion into the cell membrane rather than inhibition of carrier clearance from the cell membrane.

Treatment of *Xenopus* oocytes coexpressing NaPiIIa and JAK2 with the JAK2 inhibitor AG490 was followed by a gradual decline of I_{NaPi} indicating that the inhibitor counteracts the stimulation of the carrier by coexpressed JAK2.

The stimulation of NaPiIIa by JAK2 may well contribute to the stimulation of renal tubular phosphate transport by growth hormone. Excessive growth hormone plasma levels in acromegaly are paralleled by enhanced tubular phosphate reabsorption and phosphatemia [4]. The increased renal tubular phosphate reabsorption and hyperphosphatemia may, however, be at least partially due to indirect effects of growth hormone on renal tubular phosphate transport, such as lowering of PTH plasma concentrations and increase of plasma $1,25(OH)_2D_3$ concentrations [4]. PTH is known to decrease and $1,25(OH)_2D_3$ rather to stimulate renal tubular phosphate transport [50,51].

JAK2 contributes to the stimulating effect of angiotensin II on renal tubular salt transport [52]. According to the present study, JAK2 may similarly contribute to the stimulating effect of Angiotensin II on Na^+ coupled phosphate transport and insertion of NaPiIIa protein into the proximal renal tubular brush border membrane [53]. Clearly, additional experimental effort is needed to define the functional significance of the observed effect of JAK2 on renal tubular phosphate transport.

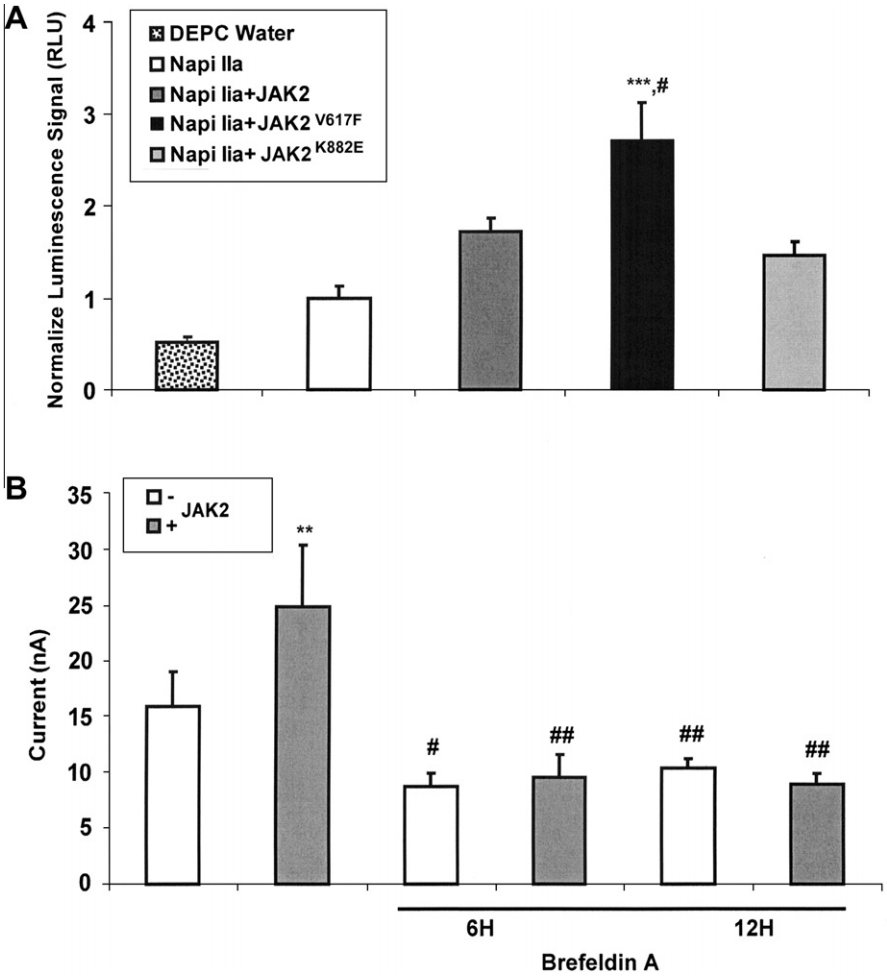

Fig. 4. Coexpression of JAK2 increased NaPiIIa protein abundance without affecting protein stability at the surface of NaPiIIa-expressing *Xenopus* oocytes (A) Arithmetic means ± SEM (n = 40–57) of the chemiluminescence reflecting NaPiIIa protein abundance in *Xenopus* oocytes injected with water (H_2O, dotted bar), expressing NaPiIIa alone (NaPiIIa, white bar) or expressing NaPiIIa with wild type JAK2 (NaPiIIa + JAK2, dark grey bar), with the gain of function mutant $JAK2^{V617F}$ (NaPiIIa + $JAK2^{V617F}$, black bar) or with the inactive mutant $JAK2^{K882E}$ (NaPiIIa + $JAK2^{K882E}$, light grey bar). $^{***}(p < 0.001)$ indicates statistically significant difference from oocytes expressing NaPiIIa alone. $^{\#}(p < 0.05)$ indicates statistically significant difference to protein abundance in oocytes expressing NapiIIa with wild type JAK2. (B) Arithmetic means ± SEM (n = 20–24) of phosphate (1 mM)-induced current (I_{NaPi}) in *Xenopus* oocytes expressingNaPiIIa alone (white bars) or expressing NaPiIIa together with JAK2 and subseqeuntly incubated with or without 5 μM brefeldin A (gray bars). $^{*}(p < 0.05)$ indicates statistically significant difference from the absence of JAK2; $^{\#}(p < 0.05)$,$^{\#\#}(p < 0.01)$ indicate statistically significant difference from the absence of brefeldin A.

In conclusion, the present observations disclose that JAK2 is a powerful stimulator of the Na^+, coupled phosphate transporter NaPiIIa. JAK2 up-regulates NaPiIIa protein abundance in the cell membrane presumably by increasing carrier insertion into the cell membrane.

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