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ORIGINAL ARTICLES

Effect of Janus Kinase 3 on the Peptide Transporters PEPT1 and PEPT2

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Abstract The tyrosine kinase Janus kinase 3 (JAK3) contributes to signaling regulating the proliferation and apoptosis of lymphocytes and tumor cells. Replacement of lysine by alanine in the catalytic subunit yields the inactive ^{K851A}JAK3 mutant that underlies severe combined immune deficiency. The gain-of-function mutation ^{A572V}JAK3 is found in acute megakaryoplastic leukemia and T cell lymphoma. The excessive nutrient demand of tumor cells requires upregulation of transporters in the cell membrane including peptide transporters PEPT1 and PEPT2. The carriers further accomplish intestinal peptide transport. Little is known about signaling regulating peptide transport. The present study explored whether PEPT1 and PEPT2 are upregulated by JAK3. PEPT1 or PEPT2 was expressed in *Xenopus* oocytes with or without additional expression of JAK3, and electrogenic peptide (glycine–glycine) transport was determined by dual-electrode voltage clamp. PEPT2-HA membrane protein abundance was analyzed by chemiluminescence. Intestinal electrogenic peptide transport was estimated from peptide-induced current in Ussing chamber experiments. In PEPT1- and PEPT2-expressing oocytes, but not in water-injected oocytes, the dipeptide gly–gly generated an inward current, which was significantly increased following coexpression of JAK3. The effect of JAK3 on PEPT1 was mimicked by ^{A568V}JAK3 but not by ^{K851A}JAK3. JAK3 increased maximal peptide-induced current in PEPT1-expressing oocytes but rather decreased apparent affinity of the carrier. Coexpression of JAK3 enhanced the PEPT2-HA protein abundance in the cell membrane. In JAK3- and PEPT1-expressing oocytes, peptide-induced current was blunted by the JAK3 inhibitor WHI-P154, 4-[(3′-bromo-4′-hydroxyphenyl) amino]-6,7-dimethoxyquinazoline (22 μM). In intestinal segments gly–gly generated a current which was significantly smaller in JAK3-deficient mice ($jak3^{-/-}$) than in wild-type mice ($jak3^{+/+}$). In conclusion, JAK3 is a powerful regulator of peptide transporters PEPT1 and PEPT2.

Keywords Peptide transport · Janus kinase · Tumor cell

Introduction

Janus kinase 3 (JAK3) is a tyrosine kinase that contributes to signaling of hematopoietic cell cytokine receptors (Ghoreschi et al. 2009). In lymphocytes and tumor cells JAK3 stimulates cell proliferation and inhibits suicidal cell death (Bhavsar et al. 2011; de Totero et al. 2008; Nakayama et al. 2009). Conversely, JAK3 inhibitors stimulate apoptosis of tumor cells (Kim et al. 2010; Uckun et al. 2007). JAK3 further participates in the maintenance of cell survival following hypoxia and ischemia–reperfusion (Ananthakrishnan et al. 2005; Nagel et al. 2012; Wang et al. 2008).

The gain-of-function mutation of ^{A572V}JAK3 (Haan et al. 2011) has been found in acute megakaryoplastic leukemia (Malinge et al. 2008; Walters et al. 2006). Moreover, ^{A572V}JAK3 and ^{A573V}JAK3 have been reported in natural killer (NK)/T-cell lymphoma (Koo et al. 2012). On the other hand, JAK3 deficiency is an autosomal recessive form of severe combined immune deficiency (SCID) (Pesu et al. 2005). It is characterized by the lack of circulating T and NK lymphocytes with normal number of functionally deficient B cells (Notarangelo et al. 2000). The disease is due to mutations in the JAK3 gene that result in

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total absence or severe dysfunction of the intracellular JAK3 tyrosine kinase. Replacement of the ATP coordinating lysine by alanine in the catalytic subunit results in the inactive ^{K855A}JAK3 (Haan et al. 2011). Some other mutations are reported in the JH2 domain, which stimulate the inhibitory effects of this domain and suppress the catalytic activity. These mutations result in abrogation of IL-2 signaling, also leading to SCID (Candotti et al. 1997; Chen et al. 2000).

JAK3 participates in the regulation of glucose metabolism (Ananthakrishnan et al. 2005), and the isoform JAK2 upregulates the Na^+-coupled glucose carrier SGLT1 (Hosseinzadeh et al. 2011a). Carriers accomplishing nutrient uptake across intestinal epithelia and into tumor cells further include the peptide transporters 1 (PEPT1) and 2 (PEPT2), which transport di- and tripeptides (Ingersoll et al. 2012; Inoue et al. 2005; Rubio-Aliaga and Daniel 2008) and peptide-like drugs (Inoue et al. 2005; Rubio-Aliaga and Daniel 2008). Regulators of peptide transport include leptin (Yarandi et al. 2011) and growth hormone (Alteheld et al. 2005). Signaling involved in the regulation of peptide transport includes phosphoinositide (PI) 3-kinase (Rexhepaj et al. 2010), PI-dependent kinase PDK1 (Rexhepaj et al. 2010), serum- and glucocorticoid-inducible kinase SGK1 (Boehmer et al. 2008) and AMP-activated kinase (Pieri et al. 2010).

The present study explored whether JAK3 modifies the function of PEPT1 and/or PEPT2. To this end, cRNA encoding the peptide transporters were injected into *Xenopus* oocytes with or without cRNA encoding wild-type JAK3, constitutively active ^{A568V}JAK3 or inactive ^{K851A}JAK3; and peptide transport was quantified by determination of peptide-induced current. To elucidate the in vivo significance of JAK3-sensitive peptide transport regulation, peptide-induced current was determined in Ussing chamber experiments of intestinal segments isolated from either JAK3-deficient mice (*jak3*$^{-/-}$) or corresponding wild-type (*jak3*$^{+/+}$) mice.

Materials and Methods

Constructs

Constructs encoding PEPT1 and PEPT2 (Boehmer et al. 2008), PEPT2-HA wild-type murine JAK3 (Imagenes, Berlin, Germany), an inactive ^{K851A}JAK3 mutant corresponding to the human ^{K851A}JAK3 mutant (Haan et al. 2011) and the active ^{A568V}JAK3 mutant corresponding to the human ^{A572V}JAK3 mutant (Haan et al. 2011) were used for generation of cRNA as described previously (Dermaku-Sopjani et al. 2011; Strutz-Seebohm et al. 2011).

Voltage Clamp in *Xenopus* Oocytes

Xenopus oocytes were prepared as previously described (Alesutan et al. 2012; Henrion et al. 2012). Where not indicated otherwise, 10 ng PEPT1 or PEPT2 cRNA were injected on the first day and 10 ng of wild-type JAK3 cRNA were injected on the second day or the same day after preparation of the oocytes (Hosseinzadeh et al. 2012; Pathare et al. 2012). Oocytes were maintained at 17 °C in ND96 solution containing (in mM) 93.5 NaCl, 2 KCl, 1 $MgCl_2$, 1.8 $CaCl_2$, 5 HEPES (pH 7.4/NaOH), gentamycin (50 mg/l), tetracycline (50 mg/l), ciprofloxacin (1.6 mg/l), refobacin (100 mg/l) and theophylline (90 mg/l). Where indicated, the JAK3 inhibitor WHI-P154, 4-[(3′-bromo-4′-hydroxyphenyl)amino]-6,7-dimethoxy-quinazoline (22 μM), or brefeldin A (5 μM) was added to the respective solutions. Voltage-clamp experiments were performed at room temperature 3–4 days after injection (Dermaku-Sopjani et al. 2011). Two-electrode voltage-clamp recordings were performed at a holding potential of −70 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 using Clampfit 9.2 (Axon Instruments, Union City, CA) (Hosseinzadeh et al. 2011b). The control superfusate (ND96) contained (in mM) 93.5 NaCl, 2 KCl, 1.8 $CaCl_2$, 1 $MgCl_2$ and 5 HEPES (pH 7.4/NaOH). Glycine-glycine was added to the solutions at a concentration of 2 mM, unless otherwise stated. The flow rate of the superfusion was approximately 20 ml/min, and a complete exchange of the bath solution was reached within about 10 s.

Detection of PEPT2-HA Cell Surface Expression by Chemiluminescence

To determine PEPT2-HA cell surface expression by chemiluminescence, oocytes were incubated with monoclonal anti-HA antibody conjugated to horseradish peroxidase (diluted 1:1,000; Miltenyi Biotec, Bergisch Gladbach, Germany) for 1.5 h. Individual oocytes were placed in 96-well plates with 20 μl of SuperSignal ELISA Femto Maximum Sensitivity Substrate (Pierce, Rockford, IL), and chemiluminescence of the single oocytes was quantified in a luminometer (Walter Wallac two-plate reader; Perkin Elmer, Juegesheim, Germany) by integrating the signal over a period of 1 s. The results display normalized relative light units.

Ussing Chamber Experiments

All animal experiments were conducted according to the German law for the welfare of animals and the guidelines

of the American Physiological Society and approved by local authorities. Experiments were performed using intestinal segments from 6- to 12-weeks-old male and female JAK3-deficient mice ($jak3^{-/-}$) and corresponding wild-type mice ($jak3^{+/+}$) (Charles River Laboratories, Sulzfeld, Germany). The $jak3^{-/-}$ mice have been described previously (Thomis et al. 1997). Mice were fed a control diet (1314; Altromin, Heidenau, Germany) and had free access to tap drinking water.

For analysis of electrogenic intestinal peptide transport, jejunal segments were mounted into a custom-made mini-Ussing chamber with an opening of 0.00769 cm^2. Under control conditions, the serosal and luminal perfusate contained (in mM) 115 NaCl, 2 KCl, 1 $MgCl_2$, 1.25 $CaCl_2$, 0.4 KH_2PO_4, 1.6 K_2HPO_4, 5 Na pyruvate, 25 $NaHCO_3$ and 5 mannitol (pH 7.4, NaOH). Where indicated, the dipeptide glycine–glycine (5 mM) was added to the luminal perfusate at the expense of mannitol (5 mM) (all substances were from Sigma, Schnelldorf, Germany, or from Roth, Karlsruhe, Germany).

In all Ussing chamber experiments the transepithelial potential difference (V_t) was determined continuously and the transepithelial resistance (R_t) was estimated from the voltage deflections (ΔV_t) elicited by imposing test currents (I_t). The resulting R_t was calculated according to Ohm's law.

Statistical Analysis

Data are provided as mean ± SEM, and n represents the number of oocytes or intestinal segments investigated. All voltage-clamp 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

In order to elucidate, whether JAK3 modifies peptide transport, cRNA encoding PEPT1 or PEPT2 were injected into *Xenopus* oocytes with or without additional injection of cRNA encoding JAK3. Peptide transport was estimated from the current observed following addition of the dipeptide glycine–glycine to the bath solution ($I_{gly-gly}$).

No appreciable current was observed in water-injected *Xenopus* oocytes when 2 mM glycine–glycine was added to the bath (Fig. 1A, B). Accordingly, *Xenopus* oocytes did not express appreciable endogenous electrogenic glycine–glycine transport. Moreover, no appreciable $I_{gly-gly}$ was observed in *Xenopus* oocytes expressing wild-type JAK3 alone (Fig. 1A, B). As illustrated in Fig. 1A, B a sizable $I_{gly-gly}$ was observed in PEPT1-expressing *Xenopus* oocytes. Additional expression of wild-type JAK3 resulted in a significant increase of $I_{gly-gly}$ in PEPT1 expressing *Xenopus* oocytes (Fig. 1A, B).

To determine maximal transport rate and affinity of PEPT1, oocytes were exposed to glycine–glycine concentrations ranging 0.01–5 mM. As shown in Fig. 1C, the increase of substrate concentration was followed by an increase of $I_{gly-gly}$ in both PEPT1- and JAK3-expressing *Xenopus* oocytes and *Xenopus* oocytes expressing PEPT1 alone. The increase was, however, larger in PEPT1- and JAK3-expressing *Xenopus* oocytes. Calculation of maximal currents yielded values which were significantly higher ($p < 0.001$) in *Xenopus* oocytes expressing PEPT1 together with JAK3 (22.5 ± 1.4 nA, $n = 10$) than in *Xenopus* oocytes expressing PEPT1 alone (6.0 ± 0.5 nA, $n = 10$). Calculation of glycine–glycine concentrations required for half-maximal current (K_M) yielded values significantly ($p < 0.05$) higher in *Xenopus* oocytes expressing PEPT1 together with JAK3 (537 ± 141 μM, $n = 10$) than in *Xenopus* oocytes expressing PEPT1 alone (128 ± 68 μM, $n = 10$).

As illustrated in Fig. 2, coexpression of JAK3 further upregulated the peptide transporter isoform PEPT2. In *Xenopus* oocytes injected with cRNA encoding PEPT2, $I_{gly-gly}$ was again significantly increased by additional injection of cRNA encoding JAK3.

Similar to the effect of wild-type JAK3, the gain-of-function mutant ^{A568V}JAK3 increased PEPT1 activity (Fig. 3). $I_{gly-gly}$ was significantly higher in *Xenopus* oocytes expressing PEPT1 and ^{A568V}JAK3 than in *Xenopus* oocytes expressing PEPT1 alone. In contrast, the inactive mutant ^{K851A}JAK3 did not significantly modify $I_{gly-gly}$ (Fig. 3). $I_{gly-gly}$ was similar in *Xenopus* oocytes expressing PEPT1 and ^{K851A}JAK3 and in *Xenopus* oocytes expressing PEPT1 alone.

In order to explore whether the effect of JAK3 on PEPT currents resulted from enhanced transporter protein abundance in the cell membrane, the cell surface expression of PEPT2 was quantified by chemiluminescence. As shown in Fig. 4, PEPT2 protein abundance in *Xenopus* oocytes injected with cRNA encoding tagged PEPT2-HA was indeed increased by the coexpression of wild-type JAK3.

The increase of $I_{gly-gly}$ in PEPT1-expressing *Xenopus* oocytes by coexpression of JAK3 could theoretically have resulted from slowed clearance of carrier protein from the cell membrane. Thus, additional experiments were performed to determine the stability of $I_{gly-gly}$. To this end, the PEPT1-expressing *Xenopus* oocytes were treated with 5 μM brefeldin A, a substance preventing insertion of new carrier protein into the cell membrane. As illustrated in Fig. 5, following addition of brefeldin A, $I_{gly-gly}$ declined similarly quickly in *Xenopus* oocytes expressing PEPT1

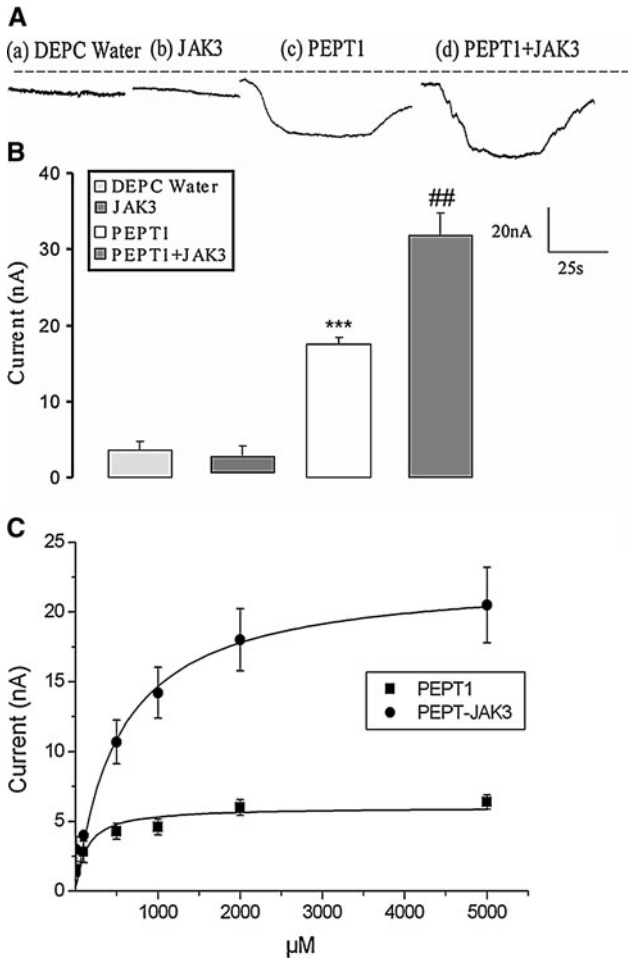

Fig. 1 Coexpression of JAK3 increases electrogenic peptide transport in PEPT1-expressing *Xenopus* oocytes. **A** Representative original tracings showing glycine–glycine (2 mM)—induced current ($I_{gly-gly}$) in *Xenopus* oocytes injected with water (*a*), expressing JAK3 alone (*b*) or expressing PEPT1 without (*c*) or with (*d*) additional coexpression of wild-type JAK3. **B** Arithmetic mean ± SEM ($n = 10$–13) of glycine–glycine (2 mM)—induced current ($I_{gly-gly}$) in *Xenopus* oocytes injected with water (DEPC water, *light gray bar*), expressing JAK3 alone (*dark gray bar*) or expressing PEPT1 without (PEPT1, *white bar*) or with (PEPT1+JAK3, *dark gray bar*) additional coexpression of wild-type JAK3. ***Statistically significant ($p < 0.001$) difference water-injected oocytes, ##statistically significant ($p < 0.01$) difference PEPT1-injected oocytes. **C** Arithmetic mean ± SEM ($n = 9$) of $I_{gly-gly}$ as a function of glycine–glycine concentration in *Xenopus* oocytes expressing PEPT1 without (*closed squares*), or with (*closed circles*) additional coexpression of wild-type JAK3. Data points were fitted with Boltzman function. *DEPC* diethylpyrocarbonate

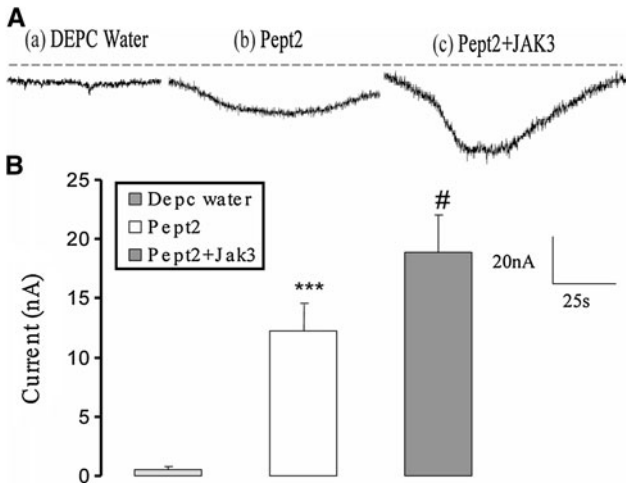

Fig. 2 Coexpression of JAK3 increases electrogenic peptide transport in PEPT2-expressing *Xenopus* oocytes. **A** Representative original tracings showing glycine–glycine (2 mM)—induced current ($I_{gly-gly}$) in *Xenopus* oocytes injected with water (*a*) or expressing PEPT2 without (*b*) or with (*c*) additional coexpression of wild-type JAK3. **B** Arithmetic mean ± SEM ($n = 9$–14) of $I_{gly-gly}$ in *Xenopus* oocytes injected with water (DEPC water, *light gray bar*) or expressing PEPT2 without (PEPT2, *white bar*) or with (PEPT2+JAK3, *dark gray bar*) additional expression of wild-type JAK3. ***Statistically significant ($p < 0.001$) difference from the absence of PEPT2, #statistically significant ($p < 0.05$) difference from the absence of JAK3. *DEPC* diethylpyrocarbonate

together with JAK3 and in *Xenopus* oocytes expressing PEPT1 alone. Thus, JAK3 increased $I_{gly-gly}$ by a mechanism other than slowing carrier clearance from the cell membrane.

Additional experiments were performed to elucidate the effect of the JAK3 inhibitor WHI-P154. In *Xenopus* oocytes expressing both PEPT1 and JAK3, addition of WHI-P154 (22 μM) was followed by a decline of $I_{gly-gly}$ (Fig. 6). The effect of the inhibitor on $I_{gly-gly}$ reached statistical significance within 18 h.

In order to define the in vivo significance of JAK3-sensitive regulation of peptide transporters, peptide-induced current was determined in Ussing chamber experiments of intestinal segments isolated from JAK3-deficient mice ($jak3^{-/-}$) or corresponding wild-type mice ($jak3^{+/+}$). As illustrated in Fig. 7, addition of glycine–glycine (5 mM) to the luminal perfusate generated a transepithelial current ($I_{gly-gly}$), which was significantly smaller in intestinal epithelium from $jak3^{-/-}$ mice than in intestinal epithelium from $jak3^{+/+}$ mice.

Discussion

The present study reveals that, similar to what has been observed for JAK2 (Hosseinzadeh et al. 2013), the peptide transporters PEPT1 and PEPT2 are upregulated by JAK3. Coexpression of JAK3 increased the electrogenic transport of the dipeptide glycine–glycine in *Xenopus* oocytes expressing either PEPT1 or PEPT2. Similar to coexpression of wild-type JAK3 coexpression of the gain-of-function mutant ^{A568V}JAK3 upregulated PEPT1. In contrast, coexpression of the inactive ^{K851A}JAK3 did not significantly modify peptide-induced current in PEPT1-expressing

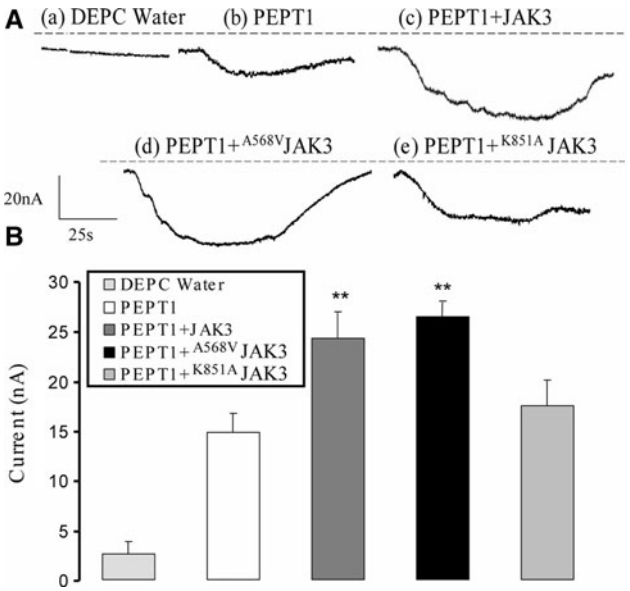

Fig. 3 The effect of JAK3 is mimicked by ^{A568V}JAK3 but not by the inactive mutant ^{K851A}JAK3. **A** Representative original tracings showing glycine–glycine (2 mM)—induced current ($I_{gly-gly}$) in *Xenopus* oocytes injected with water (*a*), expressing PEPT1 alone (*b*) or expressing PEPT1 with JAK3 (*c*), with constitutively active ^{A568V}JAK3 (*d*) or with the inactive mutant ^{K851A}JAK3 (*e*). **B** Arithmetic mean ± SEM ($n = 7$–14) of $I_{gly-gly}$ in *Xenopus* oocytes injected with water (DEPC water, *light gray*) or expressing PEPT1 without (PEPT1, *white bar*) or with wild-type JAK3 (PEPT+JAK3, *dark gray bar*), with constitutively active ^{A568V}JAK3 (PEPT1+^{A568V}JAK3, *black bar*) or with the inactive mutant ^{K851A}JAK3 (PEPT1+^{K851A}JAK3, *light gray bar*). **Statistically significant ($p < 0.001$) difference from expression of PEPT1 alone. *DEPC* diethylpyrocarbonate

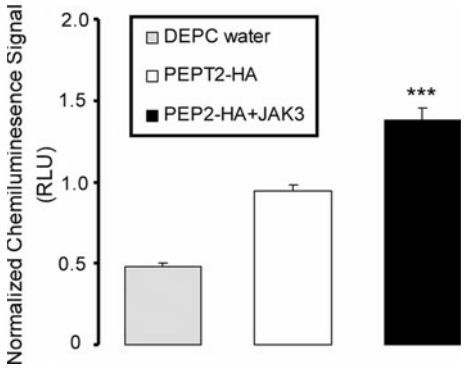

Fig. 4 Coexpression of JAK3 increased the PEPT2-HA protein abundance in the plasma membrane of *Xenopus* oocytes. Arithmetic mean ± SEM ($n = 48$–56) from the normalized data of PEPT2-HA protein abundance as determined by chemiluminescence in the plasma membrane of *Xenopus* oocytes injected with water (DEPC water, *light gray bar*) or expressing PEPT2-HA without (*white bar*) or with (*black bar*) additional expression of wild-type JAK3. ***Statistically significant ($p < 0.001$) difference from oocytes expressing PEPT2-HA alone. *DEPC* diethylpyrocarbonate

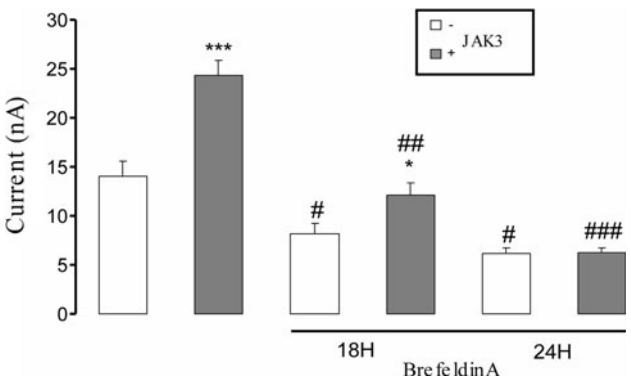

Fig. 5 The decline of electrogenic peptide transport in the presence of brefeldin A is similar in oocytes expressing PEPT1 with JAK3 and oocytes expressing PEPT1 alone. Arithmetic mean ± SEM ($n = 17$–21) of glycine–glycine (2 mM)—induced current ($I_{gly-gly}$) in *Xenopus* oocytes injected with cRNA encoding PEPT1 without (PEPT1, *white bar*) or with (PEPT1+JAK3, *dark gray bar*) wild-type JAK3 and exposed to 5 μM brefeldin A for the indicated time periods. *, ***Statistically significant ($p < 0.05$, $p < 0.001$) difference from the absence of JAK3; $^{\#, \#\#, \#\#}$statistically significant ($p < 0.05$, $p < 0.01$, $p < 0.001$) difference from the absence of brefeldin A

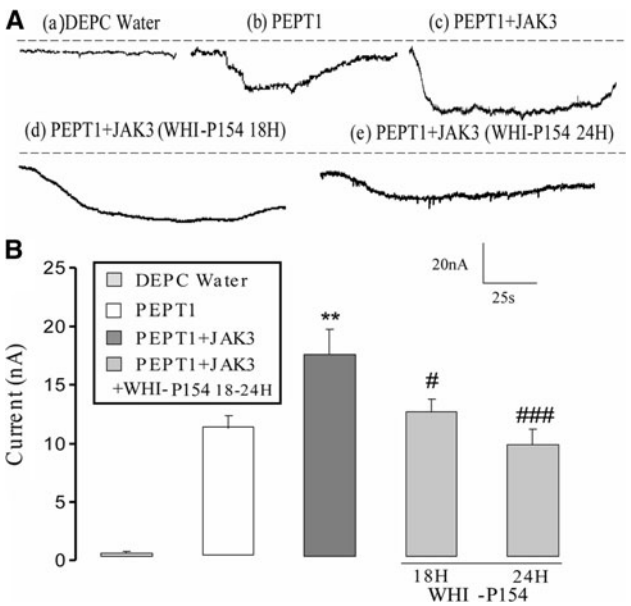

Fig. 6 The effect of JAK3 is reversed by the JAK3 inhibitor WHI-P154. **A** Representative original tracings showing glycine–glycine (2 mM)—induced current ($I_{gly-gly}$) in *Xenopus* oocytes injected with water (*a*), expressing PEPT1 alone (*b*) or expressing PEPT1+JAK3 without (*c*) or with 18-h (*d*) or 24-h (*e*) pretreatment with JAK3 inhibitor WHI-P154 (22 μM). **B** Arithmetic mean ± SEM ($n = 12$–15) of $I_{gly-gly}$ in *Xenopus* oocytes injected with water (DEPC water, *light gray bar*), expressing PEPT1 alone (PEPT1, *white bar*) or expressing PEPT1 with JAK3 without (PEPT1+JAK3, *dark gray bar*) or with pretreatment with the JAK3 inhibitor WHI-P154 (22 μM, *light gray bars*) for the indicated time periods. $^{\#, \#\#\#}$Statistically significant ($p < 0.05$, $p < 0.001$) difference from the absence of JAK3 inhibitor WHI-P154, **statistically significant ($p < 0.01$) difference from PEPT1 alone (absence of JAK3). *DEPC* diethylpyrocarbonate

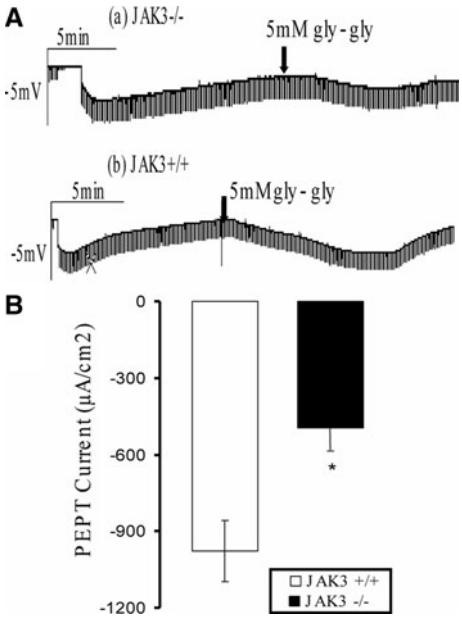

Fig. 7 Glycine–glycine-induced current is decreased in intestinal segments from JAK3-deficient mice. **A** Original representative tracings illustrating the effect of 5 mM glycine–glycine on the transepithelial potential difference across intestinal segments from (*a*) JAK3-deficient mice ($jak3^{-/-}$) and (*b*) corresponding wild-type mice ($jak3^{+/+}$). **B** Arithmetic mean ± SEM ($n = 6$) of glycine–glycine (5 mM)—induced current ($I_{gly-gly}$) in jejunum from $jak3^{-/-}$ (*black*) and $jak3^{+/+}$ (*white*) mice. *Statistically significant ($p < 0.05$) difference from wild-type mice

Xenopus oocytes. Thus, kinase activity is required for the effect. JAK3 enhanced protein abundance of PEPT2-HA in the cell membrane. The experiments with brefeldin A suggest that JAK3 is not effective by delaying carrier retrieval from the cell membrane and are compatible with the assumption that JAK3 stimulates carrier insertion into the cell membrane. The effect of JAK3 was reversed by the JAK3 inhibitor WHI-P154. The peptide-induced current was significantly lower in intestinal segments isolated from JAK3-deficient mice ($jak3^{-/-}$) than in intestinal segments isolated from corresponding wild-type mice ($jak3^{+/+}$), an observation pointing to JAK3-sensitive regulation of peptide transporters in vivo.

Peptide transport contributes to intestinal nutrient uptake (Meredith 2009; Rubio-Aliaga and Daniel 2008) as PEPT1 absorbs the majority of dietary nitrogen (Foley et al. 2010). PEPT1 has further been implicated in inflammatory bowel disease (Ingersoll et al. 2012). In healthy individuals PEPT1 expression is confined to small intestine and colon does not express PEPT1. In contrast, high levels of PEPT1 are expressed in colon following inflammatory bowel disease (Ingersoll et al. 2012). As JAK3 is activated in inflammation (Vijayakrishnan et al. 2011), the kinase could, at least in theory, contribute to the upregulation of PEPT1 activity in inflammatory bowel disease.

Peptide transporters further contribute to transport of various drugs including β-lactam antibiotics, angiotensin-converting enzyme inhibitors, antiviral drugs and anticancer agents (Brandsch 2009; Kamal et al. 2008; Meredith 2009; Nakamura et al. 2008; Newstead 2011; Rubio-Aliaga and Daniel 2008). Peptide transporters are thus relevant not only for nutrient uptake but also for uptake of drugs into tumor cells (Inoue et al. 2005; Mitsuoka et al. 2010; Pieri et al. 2010; Tsume et al. 2008). Expression of the transporters has, for instance, been shown in pancreatic cancer cells (Gonzalez et al. 1998) and prostate cancer cells (Tai et al. 2013). Accordingly, the carriers are considered potential targets for tumor therapy (Tai et al. 2013).

In conclusion, according to the present observations, JAK3 is a powerful regulator of the peptide transporters PEPT1 and PEPT2. The tyrosine kinase upregulates the carriers, an effect which may play a role in the regulation of intestinal peptide transport and peptide uptake into tumor cells.

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