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Altered allosteric regulation of muscle 6-phosphofructokinase causes Tarui disease

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ABSTRACT

Tarui disease is a glycogen storage disease (GSD VII) and characterized by exercise intolerance with muscle weakness and cramping, mild myopathy, myoglobinuria and compensated hemolysis. It is caused by mutations in the muscle 6-phosphofructokinase (Pfk). Pfk is an oligomeric, allosteric enzyme which catalyzes one of the rate-limiting steps of the glycolysis: the phosphorylation of fructose 6-phosphate at position 1. Pfk activity is modulated by a number of regulators including adenine nucleotides. Recent crystal structures from eukaryotic Pfk displayed several allosteric adenine nucleotide binding sites. Functional studies revealed a reciprocal linkage between the activating and inhibitory allosteric binding sites. Herein, we showed that $Asp^{543}Ala$, a naturally occurring disease-causing mutation in the activating binding site, causes an increased efficacy of ATP at the inhibitory allosteric binding site. The reciprocal linkage between the activating and inhibitory binding sites leads to reduced enzyme activity and therefore to the clinical phenotype. Pharmacological blockage of the inhibitory allosteric binding site or highly efficient ligands for the activating allosteric binding site may be of therapeutic relevance for patients with Tarui disease.

1. Introduction

The Tarui disease, glycogen storage disease (GSD VII, OMIM: #232800) is an autosomal recessive metabolic disorder characterized clinically in different variants by exercise-depending skeletal muscle weakness, cramping, myoglobinuria, and hemolysis. It was first described by Tarui, Okuno, Ikura et al. in 1965 [1]. The phosphofructokinase (Pfk) activity was entirely absent in muscle and about half normal in erythrocytes in patients with Tarui disease [2]. First evidence that mutations of the muscle isoform of Pfk is causal for Tarui disease came from Western blot studies showing immunoreactive bands despite loss of enzyme activity in muscle cell culture from patients with GSD VII [3]. In 1990, first report of altered splicing of muscle Pfk mRNA proved the molecular cause of Tarui disease [4].

The ATP-dependent 6-phosphofructokinase (EC 2.7.1.11, phosphofructokinase-1, ATP: D-fructose-6-phosphate-1-phosphotransferase) catalyzes the phosphorylation of fructose 6-phosphate (Fru-6-P) to fructose 1,6-bisphosphate. This irreversible reaction is considered to be one of the rate-limiting steps of glycolysis [5–7]. In eukaryotes the Pfk activity is modulated by a number of allosteric regulators, e.g. ATP, AMP, NH_4^+, fructose 2,6-bisphosphate, citrate and acyl-CoA [8]. Adenine nucleotides implement their allosteric inhibitory (ATP) and activating (AMP) effects by binding to different allosteric sites. Note that ATP serves as a substrate and as an allosteric inhibitor of eukaryotic Pfk. ADP can act as an activator at μM concentrations but inhibits eukaryotic Pfk activity at mM concentrations [9].

To date about 20 different mutations have been indentified in patients with Tarui disease [4,10–18]. Splice site, frame-shifting and premature termination mutations obviously result in non-functional protein fragments. However, the molecular mechanism of disease-causing missense mutations ($Arg^{39}Pro/Leu$, $Gly^{57}Val$, $Arg^{100}Gln$, $Ser^{180}Cys$, $Gly^{209}Asp$, $Asp^{543}Ala$, $Asp^{591}Ala$, $Trp^{686}Cys$, $Arg^{696}His$) causing enzyme inactivation is mainly unknown. In 2011, crystal structures of three eukaryotic Pfk from the yeasts *Pichia pastoris* [19] and *Saccharomyces cerevisiae* [20] and from rabbit muscle [20] were determined now providing hypotheses how missense mutations may interfere with proper enzyme function. Gly^{209} is in the Fru-6-P site in the active center but most lie on the subunit surface [20] giving no clues how they inactivate the enzyme.

Recently, we functionally qualified the adenine nucleotide binding sites in the human muscle Pfk and identified a reciprocal linkage between these allosteric binding sites [21]. Here, mutation of one binding site reciprocally influenced the allosteric regulation through nucleotides interacting with the other binding site. Since

Abbreviations: Pfk, 6-phosphofructokinase; Fru-6-P, fructose 6-phosphate; YP, yeast extract bacto peptone; ME, 2-mercaptoethanol; 2′I-ADP, 2′Iodo-ADP; PRPP, 5-phospho-α-D-ribose 1-diphosphate.

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Asp^{543} is in close proximity to the activating allosteric AMP/ADP binding site we speculate that altered Pfk activity in patients with Tarui disease is caused due to increased ATP inhibition when this position is mutated. Here, we experimentally addressed this hypothesis and demonstrated that loss of Pfk activity in Asp^{543}Ala is caused by an increase in ATP-mediated allosteric enzyme inhibition.

2. Materials and methods

If not otherwise stated, all chemicals and standard substances were purchased from Sigma Aldrich (Taufkirchen, Germany), C. Roth GmbH (Karlsruhe, Germany), Roche Applied Science (Mannheim, Germany), Fermentas GmbH (St. Leon-Rot, Germany) and BD (New Jersey, USA). Restriction enzymes and primers were purchased from New England Biolabs (Frankfurt/Main, Germany) and Invitrogen (Karlsruhe, Germany), respectively. The adenine nucleotide library was from Jena Bioscience (Jena, Germany). For compound details see http://www.jenabioscience.com/images/7c63e6fc71/LIB-101.pdf.

2.1. Strains and growth conditions

The *Escherichia coli* strain DH5α was used for the cloning experiments. Transformants were selected on LB medium containing 100 μg/ml ampicillin. The yeast strain for expressing human wild type and mutant muscle Pfk was *S. cerevisiae* HD114-8D (*MATα Scpfk1::HIS3 Scpfk2::HIS3 his3–11,15 leu2–3,112 ura3–52*) carrying deletion in both yeast Pfk genes [13,22]. Preparation of competent cells was performed as described [22]. Selection for transformation of wild type and mutant Pfk was performed at 30 °C in YP medium (1% yeast extract, 2% bacto peptone) containing 2% glucose as a carbon source.

2.2. Construction and Expression of mutant Pfk and purification of recombinant enzymes

Asn^{341} and Asp^{543} were selected based on the crystal structure of rabbit skeletal muscle Pfk (PDB: 3O8N, 3O8L). These residues

Table 1
Effect of AMP, ADP and ATP on kinetic properties of the wild type human muscle Pfk and Pfk mutated at Asp^{543}.

Parameter	Wild type	D^{543}A	N^{341}A
Without effectors			
K_m^{ATP} (μM)	42.5 ± 3.4	114 ± 30	23.2 ± 3.2
K_i^{ATP} (mM)	2.0 ± 0.1	0.7 ± 0.1	1.4 ± 0.1
Max. specific activity	58 U/mg (51%)	33 U/mg (30%)	38 U/mg (33%)
1 mM AMP			
K_m^{ATP} (μM)	49.8 ± 4.7	67.4 ± 4.2	52.8 ± 6.3
K_i^{ATP} (mM)	8.5 ± 0.1	2.3 ± 0.1	5.2 ± 0.2
Max. specific activity	72 U/mg (64%)	52 U/mg (46%)	63 U/mg (56%)
0.82 mM ADP			
K_m^{ATP} (μM)	169 ± 17	169 ± 26	151 ± 24
K_i^{ATP} (mM)	5.3 ± 0.1	1.1 ± 0.03	2.1 ± 0.1
Max. specific activity	51 U/mg (45%)	29 U/mg (26%)	42 U/mg (37%)
$K_{0.5}^{AMP}$ (μM)	11.9 ± 0.4	1093 ± 21	201 ± 2.9
Max. specific activity	43 U/mg (38%)	15 U/mg (13%)	43 U/mg(38%)
$K_{0.5}^{ADP}$ (μM)	83.6 ± 0.9	n.d.	610 ± 13.1
Max. specific activity	38 U/mg (34%)	0	28 U/mg(25%)

Kinetic properties of wild type and mutant Pfk were determined. Thus, the hyperbolic and the sigmoid parts of the curves (V_{min} to V_{max}) were fit to Michaelis–Menten (K_m) and Hill ($K_{0.5}$, K_i) equations, respectively. For ATP, assays were performed with 2 mM Fru-6-P and either with 1 mM AMP or 0.82 mM ADP, respectively. The kinetic parameters for AMP and ADP were determined at 0.5 mM Fru-6-P and 1 mM ATP. The maximum specific activities were 112 U/mg for each enzyme and were measured at pH 8.5 with 1.2 mM ATP; 1 mM AMP and 3 mM Fru-6-P. The values are means ± SD of three independent experiments. For comparison purposes, data from wild type Pfk and Asn^{341}Ala were taken from [21]. The maximum specific activity is referred to the maximum of specific activity determined under the chosen conditions. n.d. not detectable under chosen conditions.

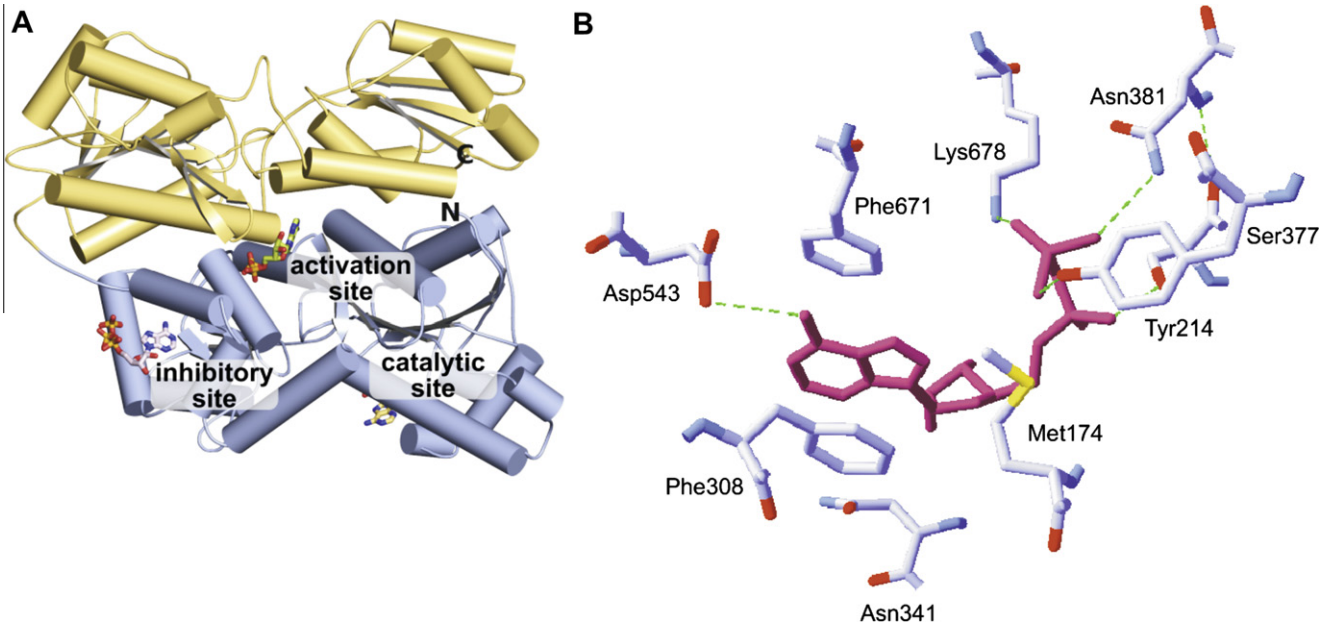

Fig. 1. Adenine nucleotide binding sites in the crystal structure of the rabbit muscle Pfk. (A) Crystal structure of rabbit skeletal muscle Pfk [20]. One monomer of the dimer found in the crystals is shown. The N-terminal half is colored in blue and the C-terminal half in yellow. Three different nucleotide binding sites were identified in the crystal structure: the catalytic center, putative inhibitory and activating allosteric sites (taken from [21]). (B) In the activating allosteric sites, the diphosphate moiety of ADP interacts via hydrogen bonds with Ser^{377} and Lys^{678} whereas the ribose contacts Asn^{341}. Asp^{543}, found mutated in a patient with Tarui disease, is in close proximity to the purine ring of ADP.

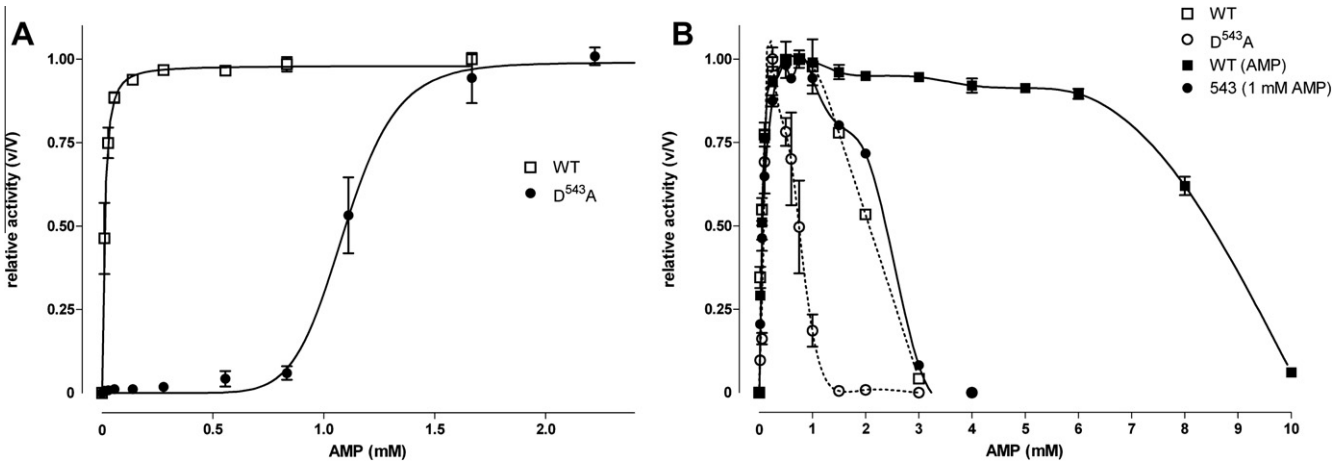

Fig. 2. Effect of AMP and ATP on the activity of wild type and Asp[543]Ala. The effect on the Pfk activity of increasing concentrations of AMP (A) at the wild type and Asp[543]Ala was determined with 0.5 mM Fru-6-P and 1 mM ATP. Activity is expressed relative to maximal activity (*V*) for each enzyme under these conditions (*V* values of wild type were 295 U/ml and 20 U/ml for Asp[543]Ala). (B) For ATP, assays were performed at 2 mM Fru-6-P. Activity is expressed as a relation between the measured (*v*) and maximal possible (*V*) activity for each enzyme under these conditions (*V* values of wild type were 396 U/ml and 434 U/ml without effectors and 1 mM AMP, respectively and 45 U/ml and 70 U/ml for Asp[543]Ala). Dotted line without effectors; continuous line with 1 mM AMP. Data are means ± SD of three independent experiments each performed in duplicate.

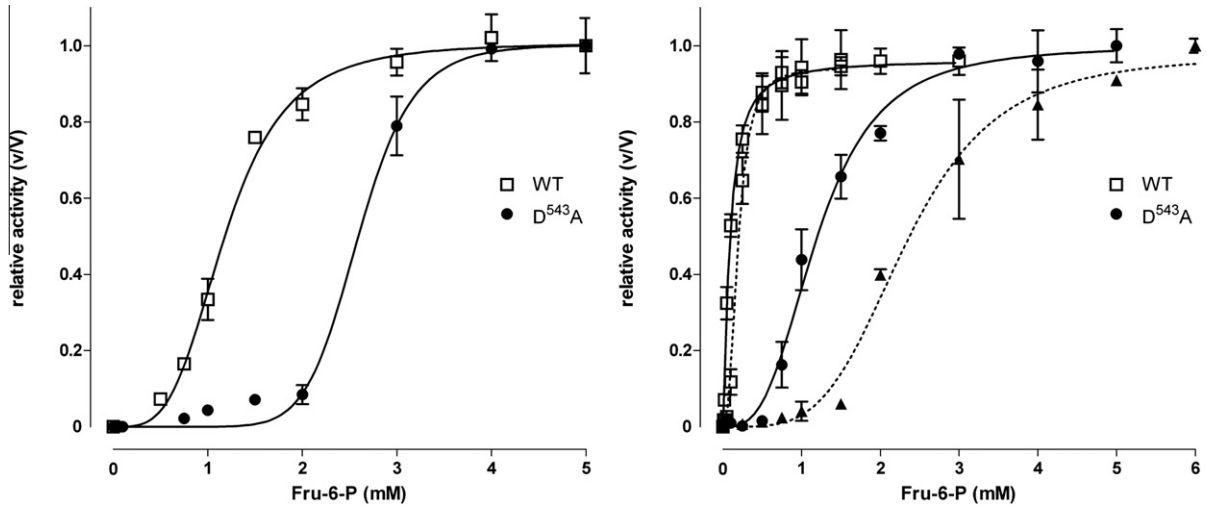

Fig. 3. Fru-6-P dependency of wild type and mutant Asp[543]Ala Pfk. Assays were performed (A) without effectors and (B) with 1 mM AMP (continuous line) and 0.82 mM ADP (dotted line) with fixed concentration of 1 mM ATP and varying concentrations of Fru-6-P as indicated. Activity is expressed relative to maximal activity (for wild type 383, 374 and 359 U/ml without effectors, 1 mM AMP and 0.82 mM ADP, respectively and 53, 68 and 56 U/ml for D[543]A). Data are means ± SD of three independent experiments each performed in duplicate.

participate in the AMP/ADP activator binding sites [19–21] and are conserved between the human and rabbit muscle Pfk. All mutants were constructed using PCR-based site-directed mutagenesis and the fragments were cloned into the plasmid pJJH71PFK (kindly provided by Prof. Dr. Jürgen J. Heinisch, University of Osnabrück [13]). The resulting plasmids were sequenced to ensure sequence correctness. Transformation of yeast strain HD114–8D was performed with LiAc/ssDNA/PEG [23]. Transformants were grown in liquid medium with shaking at 30 °C. After 24 h, besides the mutant D[543]A after 36 h, the cells were harvested by centrifugation at 5700×*g* for 15 min at 4 °C and washed twice with water and once with a 50 mM potassium phosphate buffer, pH 7.2, containing 1 mM EDTA, 5 mM ME and 0.5 mM PMSF (buffer A). Wild type and mutant Asn[341]Ala were purified according to [21]. For mutant D[543]A cell disruption, protamine sulphate precipitation and precipitation with PEG_{6000} was performed according to [21] except that 6% w/v PEG_{6000} were used. Following steps were carried out at 4 °C unless described otherwise. After centrifugation at 75,000×*g* for 30 min, the pellet was dissolved in buffer A, pH 8.0. The enzyme was concentrated by ultrafiltration (Omega 100 kDa-membrane, Pall Life Sciences, Dreieich, Germany). For ion exchange chromatography the concentrated enzyme sample was loaded on a Resource Q-Colum (6 ml, GE Healthcare, Munich, Germany), equilibrated with buffer A, pH 8.0. After washing with buffer A, pH 8.0, the enzyme was eluted with a linear gradient of KCl (0–200 mM) in buffer A, pH 8.0. Fraction of Pfk activity were pooled and supplemented with 1 mM ATP. After concentration by ultrafiltration (Pall Life Sciences, Omega 100 kDa-membrane) and Vivaspin 6 (Sartorius, Göttingen, Germany) 10% glycerol (v/v) was added and the mixture stored at −20 °C. Gel permeation chromatography was done on a BioSep SEC-S4000 (600 × 21.2 mm; Phenomenex, Aschaffenburg, Germany) according to [21] Fractions with Pfk activity were pooled and the enzyme solution was concentrated as before. The purified enzyme can be stored with 10% glycerol (v/v) at −20 °C for two weeks without loss of activity.

2.3. Pfk activity assay

During preparation, Pfk activity was measured spectrophotometrically at 340 nm and 25 °C according to [21]. The reaction was started with the addition of a 2–5 µl enzyme sample.

Kinetic studies were performed in 50 mM HEPES, 100 mM KCl, 5 mM $MgCl_2$, pH 7.0, 0.2 mM NADH, 0.45 U/ml aldolase, 4.5 U/ml triosephophate isomerase and 1.5 U/ml glycerole phosphate dehydrogenase. ATP, Fru-6-P, AMP and ADP were used as indicated. In the case of the ATP-inhibition experiments the $MgCl_2$ concentration was 15 mM. Auxiliary enzymes were dialysed before use (Micro Bio-Spin 6, Bio-Rad Laboratories, Munich, Germany). The reaction was started by the addition of 5 µl enzyme sample appropriately diluted with 50 mM sodium phosphate buffer, pH 7.2, containing 10% glycerol. Curve fittings for kinetic parameters were generated by either Michaelis–Menten or Hill equations using Prism(c) (GraphPad Software, Inc.La Jolla). Thus, the hyperbolic and the sigmoid parts of the curves (V_{min} to V_{max}) were fit to Michaelis–Menten and Hill equations, respectively.

3. Results and discussion

3.1. Enzyme kinetic properties of Asp^{543}Ala

In the crystal structure of rabbit skeletal muscle Pfk (Fig. 1A), Asp^{543} is in close proximity to the exo-amino group of the purine ring of ADP in the allosteric activator binding site (Fig. 1B). Mutation of this residue to Ala drastically increased $K_{0.5}$ for AMP (Table 1, Fig. 2A).

ATP (and ADP) reduces Pfk activity at mM concentrations via binding to the inhibitory nucleotide binding site. Strikingly, the K_i value of ATP was significantly reduced in Asp^{543}Ala (Fig. 2B, Table 1). This effect was found even in the presence of effectors (Fig. 2B, Table 1). With increasing concentrations of ADP no activation of the mutant Asp^{543}Ala could be measured (Table 1). The activating effect of ADP found in wild type enzyme was completely lost.

To test whether mutations in the allosteric activator site influence the substrate dependency of the catalytic activity, the influence of Fru-6-P concentrations was tested in the presence of different effectors. As shown in Fig. 3A and Table 2, activities of wild type and mutant enzymes exhibited cooperativity to Fru-6-P without effectors. In the presence of the effectors AMP and ADP the affinity to this substrate was increased. However, specifically Asp^{543}Ala displayed significantly increased $S_{0.5}$ values in comparison to the wild type under these conditions (Fig. 3B).

Table 2
Saturation kinetics for Fru-6-P on the wild type human muscle Pfk and Pfk mutated at Asp^{543}.

Parameter	Wild type	D^{543}A	N^{341}A
Without effectors			
$S_{0.5}^{Fru-6-P}(mM)$	1.2 ± 0.1	2.6 ± 0.1	1.6 ± 0.1
Max. specific activity	58 U/mg (51%)	33 U/mg (30%)	39 U/mg (35%)
1 mM AMP			
$S_{0.5}^{Fru-6-P}(mM)$	0.09 ± 0.01	1.2 ± 0.05	0.3 ± 0.01
Max. specific activity	70 U/mg (62%)	50 U/mg (45%)	51 U/mg (45%)
0.82 mM ADP			
$S_{0.5}^{Fru-6-P}(mM)$	0.2 ± 0.01	2.4 ± 0.1	0.6 ± 0.02
Max. specific activity	52 U/mg (46%)	37 U/mg (32%)	41 U/mg (37%)

Assays were carried out at in the presence of 1 mM ATP and indicated concentrations of effectors. By fitting with the Hill equation the parameters were determined with $S_{0.5}$ as the substrate concentration at half-maximal activity. For comparison purposes, data from wild type Pfk and Asn^{341}Ala determined under same conditions were taken from [21]. The maximum specific activities were 112 U/mg for each enzyme and were measured at pH 8.5 with 1.2 mM ATP; 1 mM AMP and 3 mM Fru-6-P. The values are means ± SD of three independent experiments. The maximum specific activity is referred to the maximum of specific activity determined under the chosen conditions.

Almost identical enzymatic properties were recently shown with the human Pfk mutant Asn^{341}Ala [21] which is in close proximity to Asp^{543}Ala at the allosteric activator binding site (Fig. 1B). As in case of Asp^{543}Ala, mutation of Asn^{341} resulted in an increased effect of the inhibitor ATP on enzyme activity (Table 1). It was shown that activating and inhibitory allosteric binding sites do not only regulate the catalytic Pfk activity but also modulate the properties of each other in a reciprocal manner.

3.2. Screening for new ligands binding to the allosteric nucleotide sites

Since the loss of Pfk activity of the Asp^{543}Ala mutant is caused by an increased efficacy of ATP at the inhibitory allosteric binding

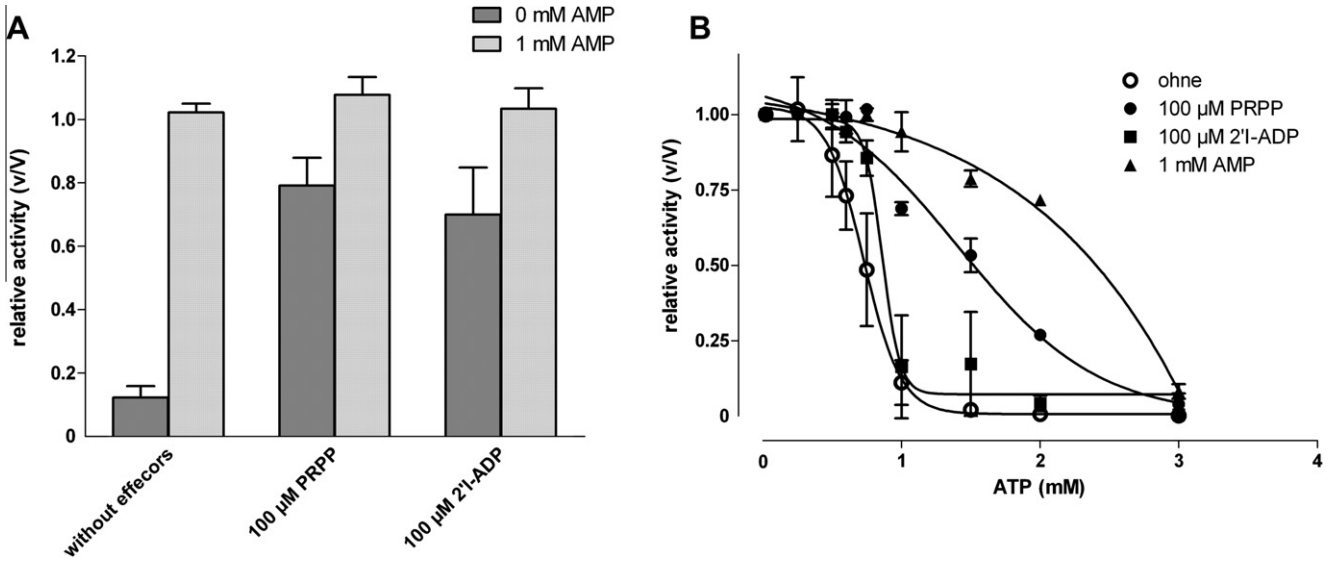

Fig. 4. Effect of AMP, PRPP and 2′I-ADP on kinetic properties of Asp^{543}Ala. (A) PRPP and 2′I-ADP were identified in a screen for compounds increasing the activity of Asp^{543}Ala. Assays were performed at 2 mM Fru-6-P and 0.6 mM ATP. *V* values were 18, 18 and 19 U/ml without effectors, with 100 µM PRPP and 100 µM 2′I-ADP, respectively. Data are means ± SD of three independent experiments. (B) The effect on the Pfk activity of increasing concentrations of ATP was determined with 2 mM Fru-6-P. Activity is expressed relative to maximal activity (*V*) for each enzyme under these conditions (*V* values were 13, 14, 15, and 70 U/ml without effectors, with 100 µM PRPP, with 100 µM 2′I-ADP and 1 mM AMP, respectively).

Table 3
Effect of AMP, PRPP and 2′I-ADP on kinetic properties of Asp[543]Ala.

	Without effectors	1 mM AMP	100 μM PRPP	100 μM 2′I-ADP
$K_m^{ATP}(\mu M)$	64.7 ± 10	67.4 ± 4	76.9 ± 10	89.4 ± 10
$K_i^{ATP}(mM)$	0.7 ± 0.03	2.3 ± 0.1	1.4 ± 0.09	0.9 ± 0.04

Kinetic properties were determined. Thus, the exponential and the sigmoid parts of the curves (V_{min} to V_{max}) were fit to Michaelis–Menten (K_m) and Hill (K_i) equations, respectively. Assays were performed with 2 mM Fru-6-P and either with 1 mM AMP, 100 μM PRPP or 100 μM 2′I-ADP. The values are means ± S.D. of three independent experiments.

site, a blockade of this allosteric binding site should rescue enzyme activity. Ligands with high efficiency at the activator allosteric binding site may also counteract increased allosteric activity of ATP. Therefore, we screened a compound library with approximately 80 adenine nucleotides and their derivates (all 100 μM final concentration) for effects on the Pfk activity of Asp[543]Ala. Out of 80 compounds 4 substances, AMP, cAMP, 2′Iodo-ADP (2′I-ADP) and 5-phospho-α-D-ribose 1-diphosphate (PRPP), significantly increased the Pfk activity of Asp[543]Ala. Since AMP and cAMP are well known allosteric activators of Pfk only the latter two were further tested (see Fig 4A). We analyzed the effect of PRPP and 2′I-ADP on the kinetic properties of Asp[543]Ala by varying ATP concentrations. As shown in Fig. 4B and Table 3 2′I-ADP had an only marginal effect on the K_i value of ATP whereas the ATP inhibition curve of Asp[543]Ala was shifted towards higher ATP concentration in the presence of 100 μM PRPP. At this point we cannot finally clarify whether PRPP acts competitively at the ATP binding site or by interaction with the activator binding site as the allosteric ligand AMP. Because PRPP is an endogenous substance and not a druggable compound we did not follow this issue further.

Our data clearly show that the Tarui disease-causing mutation Asp[543]Ala mediates its disastrous effect by increasing the allosteric inhibitory efficiency of ATP. Since the mutation is located in close proximity to the allosteric activator binding site a previously discovered mechanism, which reciprocally links the opposed actions of the activation and inhibitory allosteric binding sites [21], most probably caused loss-of-enzyme activity in the Asp[543]Ala mutant.

In vivo, ATP and ADP but not AMP appears to be the most important nucleotide regulators of muscle Pfk activity [24]. The Pfk activity of Asp[543]Ala is inhibited at lower ATP concentrations than the activity of the wild type enzyme. Because ADP is not able to activate the mutant enzyme (see above), ATP production by glycolysis during muscle contraction is declined. The inhibitory effect of ATP is pH-dependent [25] and in case of mutant Asp[543]Ala ATP has less inhibitory function on muscle Pfk at pH 8.5 and specific activity at pH 8.5 for mutant D[543]A is comparable to wild type Pfk. Thus, ATP inhibition is more efficient at lower pH values. Therefore, targeting the ATP inhibitor allosteric site by a specific blocker is most straight-forward for therapeutic approaches of such Tarui patients.

Acknowledgment

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