Glutamine phosphoribosylpyrophosphate (PRPP) amidotransferase catalyzes the first reaction of de novo purine nucleotide synthesis in two steps at two sites. Glutamine is hydrolyzed to glutamate plus NH₃ at an N-terminal glutaminase site, and NH₃ is transferred through a 20-Å hydrophobic channel to a distal PRPP site for synthesis of phosphoribosylamine. Binding of PRPP is required to activate the glutaminase site (termed interdomain signaling) to prevent the wasteful hydrolysis of glutamine in the absence of phosphoribosylamine synthesis. Mutations were constructed to analyze the function of the NH₃ channel. In the wild type enzyme, NH₃ derived from glutamine hydrolysis was transferred to the PRPP site, and little or none was released. Replacement of Leu-415 at the PRPP end of the channel with an alanine resulted in a leaky channel and release of NH₃ to the solvent. Mutations in five amino acids that line the channel and two other residues required for the reorganization of phosphoribosyltransferase domain “flexible loop” that leads to formation of the channel perturbed channel function as well as interdomain signaling. The data emphasize the role of the NH₃ channel in coupling interdomain signaling and NH₃ transfer.

Glutamine PRPP¹ amidotransferase catalyzes the first reaction in the pathway for de novo purine nucleotide synthesis and is the key regulatory enzyme in the pathway. The enzyme is a member of an Ntn, N-terminal nucleophile family of glutamine amidotransferases (1). The overall reaction, shown by Equation 1, takes place in two steps at active sites in two domains.

Glutamine + PRPP + H₂O ↔ PRA + Glutamate + PP₃ (Eq. 1)

Glutamine + H₂O → Glutamate + NH₃ (Eq. 2)

PRPP + NH₃ → PRA + PP₃ (Eq. 3)

An N-terminal glutaminase domain is responsible for hydrolysis of glutamine (Equation 2). NH₃ derived from glutamine hydrolysis reacts with PRPP at a site in the C-terminal PRTase domain (Equation 3). Crystal structures have been determined for a ligand-free (2) and an enzyme-substrate analog ternary complex (3). In the ligand-free enzyme, denoted state I, the two active sites are separated by 16 Å, and neither of the sites is properly organized for catalysis. The PRPP site is open to the solvent such that bound substrate would be susceptible to hydrolysis. The glutamine site in the ligand-free enzyme is in a closed conformation, unfavorable for entry of glutamine, and Arg-73, a residue required for glutamine binding, is extensively hydrogen-bonded and unavailable for interaction with the glutamine α-carboxyl group. In the crystal structure of the ternary complex, designated state III, conformational changes have optimized the two sites for catalysis, and a 20-Å hydrophobic tunnel has formed to channel NH₃ derived from glutamine hydrolysis to the PRPP site. There are thus several functional consequences resulting from PRPP binding. First, binding of PRPP activates the glutamine site by lowering the Kₘ for glutamine by 100-fold and increasing k_cat by 3-fold (4). This interdomain signaling prevents the wasteful hydrolysis of glutamine in the absence of PRA synthesis. Formation of the NH₃ channel is a second consequence of PRPP binding. This channel, which connects the physically separated active sites, provides the mechanism to sequester NH₃ from solvent and to deliver it to the PRTase domain for nucleophilic attack at C1 of PRPP. NH₃is not a substrate, and it is therefore important to prevent protonation of NH₃ derived from glutamine hydrolysis.

Molecular interactions important for interdomain signaling were first inferred from the crystal structures of the state I and state III conformers and from an earlier analysis of Tyr-74 mutant enzymes (4). According to the structure-based mechanism (5), PRPP binding results in a reorganization of a PRTase flexible loop (residues 326–350), which closes over the PRPP site and forms the NH₃ channel. Interaction of PRTase loop residue Ile-335 with “glutamine loop” residue Tyr-74 is one consequence of flexible loop ordering. This signaling interaction repositions the glutamine loop and moves Arg-73 for an optimal salt bridge with the carboxyl of glutamine, which is required for high affinity glutamine binding. The interdomain signaling steps that activate the glutamine site in response to PRPP binding have recently been monitored through changes in intrinsic tryptophan fluorescence in enzymes engineered to contain single tryptophan reporters (6, 7). Interestingly, replacements of Ile-335 or Tyr-74 were shown not only to perturb the interdomain signaling that activates the glutamine site but also to perturb channel function. Here we report results of a mutational analysis of conserved, non-polar amino acid residues in the NH₃ channel as well as key amino acids in the PRTase flexible loop. Ordering of the flexible loop is a prerequisite for channel formation. The results indicate that channel function and interdomain signaling are coupled.

EXPERIMENTAL PROCEDURES

Enzyme Production and Purification—Wild type Escherichia coli glutamine PRPP amidotransferase was produced in E. coli strain B834 (DE3) from plasmid pETpurF as described previously (6). Mutations...
were constructed by the procedure of Kunkel et al. (8). Two series of recombinant proteins were constructed. The first series of mutant enzymes was derived from the wild type and contains single amino acid replacements. This series of mutant enzymes was used to assay enzyme activity and $K_i$ for substrates. The second series of enzymes was constructed to assay ligand binding using intrinsic tryptophan fluorescence (6). A parental enzyme with C1S mutation prevents turnover of the enzyme substrate complex. W290F removes the single tryptophan in the wild type enzyme. S345W provides a single tryptophan reporter in the ligand-free enzyme and binding of the interdomain channeling of NH₃.

Enzyme Assays—Standard assays were used for glutamine PRPP amidotransferase. The production of glutamate, referred to as glutaminase, and PRA, referred to as Gln-PRA, was determined as described (6). In the Gln-PRA assay, PRA production is coupled to the synthesis of glycinamide ribonucleotide using an excess of glycinamide ribonucleotide synthetase. In cases where saturation by glutamate was not achieved in the standard assay, maximal velocity was extrapolated from plots of data fit to the Michaelis-Menten equation using Ultrafit software (Biosoft, Cambridge, UK). For all assays, one enzyme unit gives the production of 1.0 μmol of product/min at 37 °C. Specific activity is units/mg of protein. Protein was determined by the method of Lowry et al. (34) using the value 8.2 for a 1% solution (9).

Release of nonchanneled NH₃ derived from glutamine hydrolysis in the Gln-PRA reaction was determined using glutamate dehydrogenase. After the Gln-PRA reaction was stopped by heating for 1 min in a boiling water bath, an aliquot was transferred to a solution containing 50 mM Tris-HCl (pH 7.6), 5 mM α-ketoglutarate, 250 μM NADPH, 0.1 mM EDTA, and 2.8 units of glutamate dehydrogenase. The absorbance at 340 nm was measured after the reaction was completed at room temperature for 5 min.

Calculation of Channeling Efficiency—Channel efficiency was calculated from the ratio of Gln-PRA to glutaminase activities. For the wild type enzyme, NH₃ derived from glutamine hydrolysis was expected to be channeled to the PRPP site and used for synthesis of PRA, thus giving a 1:1 stoichiometry between glutamate and PRA. The experimentally determined Gln-PRA:glutaminase ratio was normalized to 1.0 for the wild type enzyme. Corresponding values for mutant enzymes were determined and compared with the wild type.

Fluorescence Measurements—All fluorescence measurements were carried out in enzymes containing a single tryptophan reporter. Intrinsic fluorescence of Trp-345 was used to monitor conformational changes resulting from binding of PRPP to the ligand-free enzyme and binding of glutamine to the enzyme-PRPP complex (6). $K_i$ values for substrates were determined exactly as described (6).

RESULTS AND DISCUSSION

Biochemical Evidence for Channeling of NH₃—According to the glutamine PRPP amidotransferase structure-based mechanism (5), NH₃ derived from glutamine hydrolysis must be sequestered from solvent and channeled to the PRPTase site for reaction with PRPP. The results of two experiments, shown in Figs. 1 and 2, provide direct evidence for channeling of NH₃ between sites in the glutaminase and PRPTase domains. Data in Fig. 1 show the concentration dependence of glutamine and of NH₄Cl for PRA synthesis at pH 7.0. The initial rate of PRA synthesis using glutamine as the nitrogen donor was 70 times faster than with an equivalent concentration of NH₄Cl. Clearly, NH₃ derived from hydrolysis of glutamine cannot be released from the enzyme and equilibrated with NH₄⁺ in the solvent. The data in Fig. 2A show that for the wild type enzyme the coupling between the two half-reactions, glutamine hydrolysis and synthesis of PRA, was greater than 90%, and detection of released NH₃ was barely perceptible. We have determined whether the small difference between the rates of glutaminase and Gln-PRA reactions seen in Fig. 2A is due to imperfect channeling of NH₃ or to the lability of PRA (10) and less than 100% coupling with glycinamide ribonucleotide synthetase in vitro. In either case, the data in Fig. 2A demonstrate the interdomain channeling of NH₃.

Data in Fig. 2B show the effects of an L415A mutation that results in a leaky NH₃ channel. Leu-415 is at the base of the NH₃ channel in the PRPTase domain (Fig. 3). The rates of the two half-reactions, glutaminase and NH₃-PRA, in the L415A enzyme are 1.8- and 1.3-fold higher than the respective activities in the wild type enzyme (Table I). However, the Gln-PRA activity of the mutant, which is dependent upon interdomain channeling of NH₃, is only 30% that of the wild type activity. The consequences of the L415A channel defect are seen clearly
in Fig. 2B. Approximately 85% of the NH₃ derived from glutamine hydrolysis is released from the enzyme, and only about 15% is channeled to the PRTase domain for synthesis of PRA. The data suggest that the smaller side chain in the L415A replacement results in a leaky NH₃ channel that perturbs the tight coupling between the two half-reactions. The data in Table I show that $K_d$ values for glutamine and NH₃ are similar in the wild type and L415A mutant enzyme.

**Mutational Analysis of NH₃ Channel Function**—The glutamine PRPP amidotransferase NH₃ channel is lined with conserved, mostly nonpolar amino acids. These residues include Tyr-74, Phe-254, Tyr-258, Phe-259, Phe-334, Ile-335, and also Thr-333. The positions of these residues in the enzyme-substrate ternary complex are shown in Fig. 3. To probe their roles, these amino acids were replaced by alanine or by more conservative substitutions. After enzyme purification, several assays were carried out to monitor function of the NH₃ channel and interdomain signaling. Interdomain signaling was assessed by measurement of glutamine $K_m$. In the wild type enzyme, PRPP binding to the PRTase domain catalytic site is required for high affinity binding of glutamine and for glutamine site catalysis. An interaction between Ile-335 in the PRTase domain and Tyr-74 in the glutamine domain has been shown to have a primary role in signaling (7). The roles of Tyr-74 and Ile-335 in signaling and channel function have been reported and, thus, are not considered in detail here. Channel function was assessed by comparison of the glutaminase and Gln-PRA activities. For the wild type enzyme, the stoichiometry between the products glutamate and PRA is expected to be 1:1, as shown by Equation 1, reflecting stoichiometric transfer of the NH₃ derived from glutamine hydrolysis through the NH₃ channel to the PRPP site for synthesis of PRA. However, as seen in Table I and in Fig. 2A, Gln-PRA activity was approximately 90% that of the glutaminase activity for the wild type enzyme. The wild type Gln-PRA:glutaminase ratio has been normalized to 1.0 under “Channeling Efficiency” in Table II. For the purpose of this study, departures from the glutaminase:Gln-PRA stoichiometry seen for the wild type enzyme are considered to reflect defective channel function.

To assess the roles of the conserved, nonpolar amino acids that line the NH₃ channel, we have mutagenized Phe-254, Tyr-258, Phe-259, and Phe-334, and the results are summarized in Table II. Entries for Tyr-74 and Ile-335 from earlier work (7) are also included for comparison. Most of the mutations in the channel residues lead to multiple functional defects. All of the mutant enzymes except for the F259V mutant have perturbations in interdomain signaling as seen in Table II from the increased values of $K_d$ for glutamine binding. Each of the mutant enzymes also had some perturbation of channel function as seen from comparison of Gln-PRA activity with the corresponding value for glutaminase activity.

In addition to the four nonpolar channel residues and Thr-333, listed in Table II, we also mutagenized two conserved amino acids in the PRTase flexible loop. Binding of PRPP initiates the ordering of the flexible loop and results in formation of the NH₃ channel. Of 7 conserved amino acids in the flexible loop (residues 326–350), Arg-332 and Arg-338 are essential and could not be replaced (data not shown), Thr-333 and Phe-334 are included as channel residues, and Ile-335 has a key role in signaling and was examined previously (7), thus leaving Pro-337 and Lys-349. Data for the mutant analyses, given in Table II, are analyzed below.

**Phe-259**—The F259V amino acid replacement is the only mutation of a channel residue listed in Table II that did not perturb signaling. The $K_d$ for glutamine binding to the F259V enzyme and the glutaminase activity were not changed significantly from the wild type. In addition, PRPP binding affinity was similar to that of the wild type enzyme. Channeling efficiency, as calculated from the Gln-PRA:glutaminase activity ratio, was 0.63 compared with the wild type enzyme. Thus, approximately 40% of the NH₃ produced at the glutamine site was not channeled for reaction with PRPP. A decrease in the size of the side chain from valine to alanine at position 259 led to virtually complete loss of glutaminase and Gln-PRA activities in an F259A enzyme (data not shown). Since the F259A enzyme was without activity it is not listed in Table II.

**Phe-254**—Data in Table II indicate that Phe-254 has roles in signaling and channel function. Values of $K_d$ for glutamine binding, shown in Table II, were 4-fold and 36-fold higher, respectively, for F254Y and F254V enzymes relative to the wild type. This suggests that transmission of the PRPP binding signal to the glutamine site was perturbed in the F254Y and

| Enzyme   | Glutaminase Activity | $K_m$ | Gln-PRA Activity | $K_m$ | NH₃-PRA Activity | $K_m$ |
|----------|----------------------|-------|------------------|-------|------------------|-------|
|          | units/mg             | mU    | units/mg         | mU    | units/mg         | mU    |
| Wild type| 59.5 ± 7.2            | 1.57 ± 0.1 | 53.8 ± 3.8       | 1.66 ± 0.2 | 152 ± 6.2       | 10.1 ± 1.7 |
| L415A    | 108 ± 10              | 1.44 ± 0.1 | 17.5 ± 0.7       | 1.63 ± 0.3 | 197 ± 12       | 6.90 ± 1.1 |
were normalized. The wild type enzyme was set to 1.0, and values for the mutant enzymes are calculated from the Gln-PRA:glutaminase activity ratio. The value of 0.90 used for synthesis of PRA. For the wild type enzyme this value was 0.90.

| Enzyme      | Glutaminase | Channeling efficiency<sup>a</sup> | Relative K<sub>d</sub> Gln<sup>b</sup> | Relative K<sub>d</sub> PRPP<sup>b</sup> |
|-------------|-------------|-----------------------------------|---------------------------------|----------------------------------|
| Wild type   | 59.5 ± 7.0  | 1.0                               | 1 (0.25 mM)                     | 1 (2.72 μM)                      |
| Y74F        | 54.1 ± 6.1  | 0.45                              | 29                              | 0.9                              |
| I335V       | 53.9 ± 8.3  | 0.91                              | 61                              | 0.9                              |
| F254V       | 4.9 ± 1.0   | 0.65                              | 36                              | 15                               |
| F254Y       | 35.0 ± 3.8  | 0.37                              | 4                               | 0.6                              |
| Y258F       | 27.3 ± 1.4  | 0.08                              | 6                               | 4                                |
| F259V       | 58.2 ± 4.1  | 0.63                              | 1                               | 2                                |
| T333A       | 30.4 ± 4.9  | 0.61                              | 5                               | 1                                |
| F334A       | 82.1 ± 7.4  | 0.009                             | 40                              | 0.5                              |
| P337A       | 64.8 ± 8.8  | 0.77                              | 2.5                             | 0.5                              |
| K3349A      | 51.4 ± 2.5  | 0.50                              | 5.5                             | 2                                |

<sup>a</sup> Fraction of the NH₃ derived from glutamine hydrolysis that was used for synthesis of PRA. For the wild type enzyme this value was 0.90, as calculated from the Gln-PRA:glutaminase activity ratio. The value of the wild type enzyme was set to 1.0, and values for the mutant enzymes were normalized.

<sup>b</sup> Relative to the value for the wild type enzyme shown in parentheses.

F254V enzymes. There was a significant increase in K<sub>d</sub> for PRPP in the F254V enzyme. The basis for this change in PRPP binding affinity is not apparent. Measurements of fluorescence emission of a Trp-345 reporter group were made to examine the role of channel residue Phe-254 in the interdomain signaling. Intrinsic tryptophan fluorescence in enzymes engineered to contain a single tryptophan reporter group has been used to monitor conformational changes in glutamine PRPP amidotransferase (6). Fluorescence emission is dependent upon the microenvironment of Trp-345 resulting from the conformation of the PRTase flexible loop (residues 326–350). An increase in Trp-345 fluorescence upon binding of PRPP reflects the ordering of the PRTase flexible loop that is required to form the NH₃ channel (Fig. 4A). A comparable Trp-345 fluorescence change in the F254V enzyme indicates that this channel mutation did not significantly perturb the ordering of the flexible loop that occurs when PRPP binds (Fig. 4B). In addition, the PRPP binding signal was communicated to the glutamine site, enabling glutamine to bind, although the K<sub>d</sub> for glutamine binding, determined by fluorescence titration, was increased by 36-fold compared with the wild type enzyme. An F254A mutation, which abolished glutaminase and Gln-PRA activities (data not shown), inhibited the binding of glutamine to the enzyme PRTase binary complex as detected by the Trp-345 reporter (Fig. 4C). This result emphasizes the importance of a channel residue to interdomain signaling.

Data in Table II show reductions of channeling efficiency for the F254Y and F254V enzymes. Channeling efficiency was 0.68 for the F254V enzyme and 0.37 for the F254Y enzyme. Insertion of the hydroxyl group of Tyr-258 into the hydrophobic channel was detrimental to function.

**FIG. 4.** PRTase flexible loop conformational changes monitored by fluorescence of Trp-345. The enzymes contained a C158S mutation to prevent turnover of glutamine and a W290F mutation to remove a nonessential tryptophan. Fluorescence emission of Trp-345 was monitored after the addition of substrates.

**TABLE II**

| Enzyme   | Glutaminase | Channeling efficiency<sup>a</sup> | Relative K<sub>d</sub> Gln<sup>b</sup> | Relative K<sub>d</sub> PRPP<sup>b</sup> |
|----------|-------------|-----------------------------------|---------------------------------|----------------------------------|
| Wild type| 59.5 ± 7.0  | 1.0                               | 1 (0.25 mM)                     | 1 (2.72 μM)                      |
| Y74F     | 54.1 ± 6.1  | 0.45                              | 29                              | 0.9                              |
| I335V    | 53.9 ± 8.3  | 0.91                              | 61                              | 0.9                              |
| F254V    | 4.9 ± 1.0   | 0.65                              | 36                              | 15                               |
| F254Y    | 35.0 ± 3.8  | 0.37                              | 4                               | 0.6                              |
| Y258F    | 27.3 ± 1.4  | 0.08                              | 6                               | 4                                |
| F259V    | 58.2 ± 4.1  | 0.63                              | 1                               | 2                                |
| T333A    | 30.4 ± 4.9  | 0.61                              | 5                               | 1                                |
| F334A    | 82.1 ± 7.4  | 0.009                             | 40                              | 0.5                              |
| P337A    | 64.8 ± 8.8  | 0.77                              | 2.5                             | 0.5                              |
| K3349A   | 51.4 ± 2.5  | 0.50                              | 5.5                             | 2                                |

<sup>a</sup> Fraction of the NH₃ derived from glutamine hydrolysis that was used for synthesis of PRA. For the wild type enzyme this value was 0.90, as calculated from the Gln-PRA:glutaminase activity ratio. The value of the wild type enzyme was set to 1.0, and values for the mutant enzymes were normalized.

<sup>b</sup> Relative to the value for the wild type enzyme shown in parentheses.

As for the Phε-254 mutants, the increased K<sub>d</sub> value for glutamine binding and reduced glutaminase activity in the Y258F enzyme indicates a signaling defect in this enzyme. The Tyr-258 mutation also decreased the PRPP binding affinity by 4-fold. A low Gln-PRA to glutaminase activity ratio of 0.08 suggests defective function of the NH₃ channel. However, in the case of Tyr-258 mutants, an alternative interpretation of the low Gln-PRA activity must be considered because of a hydrogen bond between the Tyr-258 hydroxyl group and the 02ₕ phosphate of PRPP (3). This interaction does not make a major contribution to PRPP binding, since the K<sub>d</sub> for PRPP was increased by only 4-fold, and the PRPP binding signal activated glutaminase activity in the Y258F enzyme 50% as well as in the wild type. However, it is not known whether the interaction of Tyr-258 with the α phosphate of PRPP has a role in catalysis. If this interaction is important in catalysis, the Gln-PRA activity would not be a reliable monitor of channel function.

**Phe-334**—The F334A channel mutant bound PRPP similarly to the wild type enzyme, yet signaling to the glutamine site was perturbed as shown by the 40-fold elevated K<sub>d</sub> for glutamine. Notwithstanding the signaling defect, glutaminase activity was approximately 35% higher than that of the wild type enzyme. However, virtually none of the NH₃ derived from glutamine hydrolysis was available for synthesis of PRA, as indicated by the low channeling efficiency. In contrast to the L415A enzyme, which has a low channeling efficiency and a leaky channel phenotype, the NH₃-PRA activity of the F334A enzyme was at the lower limit of detection (data not shown). The F334A enzyme thus has the features expected for a blocked or disrupted NH₃ channel. There is no direct interaction between Phe-334 and PRPP to suggest perturbation of a step in the reaction of NH₃ with PRPP.
about the same extent as seen for F254V and F259V channel mutations. Overall, the two enzymes with mutations in the flexible loop exhibit modest perturbations in signaling and channel function.

The flexible loop has three functions in its closed state. It sequesters the PRTase active site from solvent, it signals the glutaminase domain that PRPP is available for reaction with a nucleophile, and it forms a channel for the nucleophile NH₃. Thus it is no surprise that substitutions of conserved residues in the flexible loop impair one or more of these functions. The only physical contact between the flexible loop and glutaminase domain is between Ile-335 and Tyr-74. The importance of Ile-335 and Tyr-74 to signaling was demonstrated in earlier work (7).

Channel Structure and Function—In addition to glutamine PRPP amidotransferase, two other enzymes with physically separated active sites, tryptophan synthase and carbamoylphosphate synthetase, have been structurally defined (11, 12). Two mechanisms are used to couple the partial reactions at the catalytic sites in all three enzymes. First, substrate binding to site 1 activates the partial reaction at site 2. Second, an intermediate product generated at site 2 is transferred through a channel for reaction at site 1. The glutamine PRPP amidotransferase NH₃ channel, in contrast to the tryptophan synthase indole channel, is a transient structure that is formed by the reorganization of a PRTase domain flexible loop upon binding of PRPP. Carbamoylphosphate synthetase, similar to tryptophan synthase, likely maintains channels for NH₃ and for carbamate throughout the catalytic cycle.

The present results along with earlier work (7) emphasize that mutations in residues lining the NH₃ channel perturb not only the transfer of NH₃ derived from glutamine hydrolysis to the PRPP site but also transmission of the PRPP binding signal to the glutaminase site. The structural basis for the signaling deficiency of channel mutants is not obvious. The positions of Phe-254, Tyr-258, and Phe-259 do not change relative to the glutaminase active site when the signaling interaction is established, and Phe-334 does not contact the glutaminase domain.

Modest changes to some of the side chains lining the NH₃ channel (F254Y, F259V) perturbed channeling as did substitutions at other conserved residues near, but not part of, the NH₃ channel (T333A, P337A, K349A, L415A). The effects of channel residues on signaling and of nonchannel residues on channeling may be explained by the unique properties of the NH₃ channel. The NH₃ channel is formed by loosely packed, hydrophobic side chains. However, unlike the hydrophobic interior of proteins, the transient NH₃ channel is not supported by a skeleton of hydrogen-bonded secondary structure. Thus side chain substitutions in the channel or in residues surrounding it are likely to result in a different structure for the flexible loop when it closes over bound PRPP. The transient functions of sequestering, signaling, and channeling require transient structures for the flexible loop and are inconsistent with extensive hydrogen bonding. As a consequence of these structural constraints, channel formation and signaling are linked.

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DUAL ROLE FOR THE GLUTAMINE PHOSPHORIBOSYLPYRROPHOSPHATE AMIDOTRANSFERASE AMMONIA CHANNEL: INTERDOMAIN SIGNALING AND INTERMEDIATE CHANNELING

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