Striking Conformational Change Suspected within the Phosphoribulokinase Dimer Induced by Interaction with GAPDH*

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A multitechnique approach was used to study the [glyceraldehyde-3-phosphate dehydrogenase]2α,4β[phosphoribulokinase]2α,2β multienzymatic complex of the alga Chlamydomonas reinhardtii. On the one hand, each component of the complex was compared with known atomic structures of related enzymes or of similar enzymes originating from different organisms. On the other hand, the overall low-resolution architecture of the whole complex was studied using cryoelectron microscopy and image processing techniques. The dimers of phosphoribulokinase are suspected to undergo a dramatic change in activity during a cycle of binding and detaching from tetramers of glyceraldehyde-3-phosphate dehydrogenase. This is likely supported by strong structural differences between the modeled phosphoribulokinase dimers and the counterpart in the three-dimensional reconstruction volume of the whole complex obtained from cryoelectron microscope images.

There is mounting evidence that in eukaryotic cells most enzymes are associated with cell organelles and with other proteins referred to as multienzyme complexes (1). The main functional advantage for these supramolecular edifices may be a direct metabolite transfer, or channeling, from active site to active site avoiding milieu diffusion, but there is fast (although conflicting) literature about the existence and purpose of these channeling effects (2–5). Moreover, this direct transfer requires that enzymes catalyze consecutive reactions in these complexes. Although numerous multienzyme complexes belong to this category, others do not. In the latter case, the functional advantage of physical association relies on the alteration of intrinsic properties of the enzymes involved in these supramolecular edifices.

We have purified a bi-enzyme complex, glyceraldehyde-3-phosphate dehydrogenase (EC 1.2.1.13) and phosphoribulokinase (EC 2.7.1.19), from the green alga Chlamydomonas reinhardtii (6). This complex is involved in the Benson-Calvin cycle responsible for CO2 assimilation. It has an overall molecular mass of 460 kDa and comprises two (2 × 80 kDa) dimeric molecules of phosphoribulokinase (PRK)1 and two (2 × 150 kDa) tetrameric molecules of glyceraldehyde-3-phosphate dehydrogenase (GAPDH). Whereas PRK catalyzes the ATP-dependent phosphorylation of ribulose-5-phosphate to form ribulose-1,5-biphosphate (the CO2 acceptor in photosynthetic organisms), GAPDH catalyzes the reversible reduction and dephosphorylation of 1,3-biphosphoglyceric acid into glyceraldehyde-3-phosphate using NADPH or NADH. These two enzymes are light-regulated and play a key role in the Benson-Calvin cycle, because this metabolic pathway only operates under light (7, 8). The existence of a multienzyme complex between these two enzymes has been reported in many photosynthetic organisms (6, 9–14), and the association may therefore be a way to act as a control unit of the Benson-Calvin cycle.

At least three forms of PRK may exist (15). The first is embedded in the complex. The second is released from the complex upon high dilution (100-fold) or reduction with a reducing agent such as dithiothreitol. This second form, the designated metastable form, bears an imprint from GAPDH for a while and then slowly relapses into a third form, the stable PRK. The stable enzyme is devoid of activity when oxidized, whereas the form inserted in the complex and the metastable enzyme are active in oxidized state with respective catalytic constants kcat equal to 0.062 s−1/site, 3 s−1/site, and 56.3 s−1/site. The metastable state is very active because it retains the imprint effect exerted by GAPDH, and it is more active than the same enzyme bound to GAPDH, probably because catalysis requires significant mobility that is reduced within the complex. This oxidized metastable form, competent for catalysis, then reaches a stable inactive conformation. The Km of these three oxidized forms are also quite different and higher for the stable form than for the two other forms (15). From these data, it is clear that GAPDH has given to PRK instructions that result in an increase of activity. Another result further supports this contention; mixing stable oxidized inactive PRK with GAPDH to reconstitute the complex in vitro (6) gives rise to an active PRK.

Under the reduced state, the Km for the three forms are nearly equivalent, but the kcat for the reduced metastable form (300 s−1/site) is also higher than for the two others (16). The reaction mechanisms are clearly distinct in the binding mode of the substrates or in the product inhibition type (17), and phosphoribulokinase (inserted into the complex) is more amenable to thioredoxin activation than the stable form (18).

Thus, these data clearly demonstrate the role of protein-protein interactions in the alteration of kinetic properties of enzymes (19). Whereas the functional aspects of this complex are of great importance for a better understanding of the regulation of the metabolic pathway in which it is involved, the structural aspects are of great importance to get the rationale and explanations for all of the observed differences. Nonetheless, although the function of this supramolecular structure is...
at least in part deciphered, the structure of this entity is completely unknown. Only the residue Arg-64 of PRK was identified as playing a major role in the association of the two enzymes (20).

The aim of this study is to obtain for the first time some structural data on the whole active complex using cryoelectron microscopy (cryoEM) and molecular modeling. With information on the quaternary structures of PRK of photosynthetic bacteria Rhodobacter sphaeroides (21) and of tetrmeric glycolytic GAPDH available (22), although showing differences (light for GAPDH, wide for PRK) with the algal counterparts, the similarities between these enzymes are tentatively used to propose a three-dimensional model for the PRK-GAPDH complex.

EXPERIMENTAL PROCEDURES

Sample Preparation and Negative Staining—The bi-enzyme complex made up of PRK and GAPDH was purified from C. reinhardtii cells as previously described (6). The complex (200 μg/ml) was diluted 5–10-fold in 100 mM phosphate buffer, pH 7.4, 0.1 mM NAD, 5 mM cysteine, 10% glycerol. The complex integrity in the presence of 5 mM cysteine and 0.1 mM NAD was checked by electrophoresis (data not shown), but dilution (10-fold) may lead to slight depolymerization of the complex. Sample solution was applied on glow-discharged 400-mesh copper grids coated with a thin carbon film and negatively stained with 1% uranyl acetate. Grids were observed in a Philips CM12 electron microscope (EM) at an accelerating voltage of 100 kV with condenser and objective apertures of 200 and 70 μm, respectively. Each specimen field was recorded at 1-μm defocus, and micrographs were developed for 8 min in full-strength Kodak D19 developer.

Cryoelectron Microscopy—Complex samples were diluted 7-fold in 50 mM acetate buffer, pH 4.5, with tobacco mosaic virus at a concentration of 8 μg/ml as an internal test molecule for quantitative measurement of the magnification. Sample solution was applied on 400-mesh copper grids coated with perforated carbon films and dialyzed twice with acetate buffer (23). After blotting the excess solution, grids were rapidly plunged into liquid ethane (24, 25), and frozen-hydrated samples were transferred with a Gatan 626N cryoholder to a Philips CM12 electron microscope equipped with a Gatan 651N anticontaminator. Images were recorded at an accelerating voltage of 100 kV with condenser and objective apertures of 200 and 70 μm, respectively. A magnification of ×45,000 ± 1% was measured from the tobacco mosaic virus (26). Each specimen field was recorded twice with the grid tilted at 45° and untilted with defocuses of 2.7 and 2.5 μm, respectively. Micrographs were recorded under low dose conditions and developed for 9 min in full-strength Kodak D19 developer. For later refinements, additional untilted-specimen images were recorded at defocuses ranging from 0.8 to 1.4 μm to allow good signal retrieval through correction of the contrast transfer function.

Image Processing and Three-dimensional Reconstruction—Selected micrographs were digitized with an Optronics P1000 drum rotating microdensitometer using an aperture and scanning step of 25 μm corresponding to a pixel size of 5.885 Å on the specimen. All programs used for image processing are part of the SPIDER and WEB software (27).

The three-dimensional reconstruction was carried out using the method of random conical-tilt series (29). Untilted-specimen images were aligned and classified using rotationally invariant K-means classification approach (30). For each selected homogeneous images class, a three-dimensional reconstruction volume was computed from a new series of untitled-specimen images and recorded at low defocus (0.8 to 1.4 μm), using three-dimensional projection alignment (31) and Wiener filtering to correct for the contrast transfer function of the microscope (26, 32, 33).

Resolution was estimated using the Fourier Shell Correlation (FSC) criterion (34, 35) using either a cutting level derived from the 3σ noise curve (FSC₃σ) (36) or a cutting level of 0.5 (FSC₅₀) corresponding to a signal-to-noise ratio of 1 (Penczek and co-workers (Ref. 37, appendix)). The final volume was low-pass-filtered to its resolution limit (FSC₅₀).

and was rescaled with minimum and maximum densities of 0.0 and 1.0, respectively. The volume was explored with the help of IRIS Explorer (Numerical Algorithms Group, Inc., Downers Grove, IL) software. Each surface rendering is characterized by the density selected as a threshold value between protein and ice (between 0 and 1) and by the corresponding volume of protein (in nm³).

Sequence Comparison and Three-dimensional Modeling—Orthologous sequences were first searched using BLAST2 (38), and the resulting multiple alignments were refined using Hydrophobic Cluster Analysis (39). These alignments were then used to generate three-dimensional models using the program Modeler 4 (40). The coordinates of the models were checked using Verify3D (41) and Procheck (42, 43) algorithms.

Attempts to fit atomic models of GAPDH tetramers and PRK dimers into the low resolution three-dimensional cryoEM volume of the whole complex were carried out with the Situs 1.4 software (44, 45) using the vector quantitation algorithm (46) and were visualized using the VMD 1.5 program (47).

RESULTS

Isolated Particles in Negative Stain—Three types of macromolecular assemblies are present within the image fields obtained by the negative staining technique (Fig. 1A). First, most isolated particles have a rod-like shape composed of at least two main masses and some smaller extensions (squares). The overall dimensions of these particles (20 × 10 nm) are in good agreement with the expected size for the GAPDH-PRK complex. To better grasp the features, a set of 2,984 images of rod-like-shaped isolated particles were subjected to rotationally invariant K-means classification (30). Four typical average maps are shown in Fig. 1, B–E. Second, some smaller assemblies (circles) may correspond to partially degraded complexes. Finally, long flexible strings of material (arrow) are visible in most fields of the grid. They seem to contain subassemblies corresponding to the rod-like-shaped particles (squares) or at least part of them (circles) observed in Fig. 1A. When carefully looking at the average maps of the rod-like-shaped particles, they correspond to two main types of views that we designated as 2-fold (Fig. 1, B and C) and asymmetric rod-like (Fig. 1, D and E).

The 2-fold views comprise two antiparallel identical motifs disposed around a central cavity. Each motif comprises a main trapezoidal mass and a small comma-shaped expansion. The name given to this electron microscope view indicates the obvious presence of a central 2-fold symmetry axis in the complex. Although the average maps of Fig. 1, B and C both qualify as 2-fold views, they possess distinct features. First, in Fig. 1B
some dark channels are visible in the main trapezoidal masses, whereas in Fig. 1C these masses are compact, because no stain penetrates into local notches. Second, the small comma-shaped expansions visible near the central part of the complex have different positions. In Fig. 1B they are connected mainly to one trapezoidal mass, and they delineate a central oblique cleft going from the upper left to the lower right edges of the complex. Conversely, in Fig. 1C each comma-shaped expansion equally binds to both main trapezoidal masses, thus closing this central oblique cleft. The overall dimensions of the complex measured on the 2-fold view (Fig. 1B) correspond to 21 ± 3 nm × 14 ± 3 nm.

The asymmetric rod-like views (Fig. 1, D and E) bear some resemblance to the first type of 2-fold view (Fig. 1B) when considering the shape of the large trapezoidal masses. However, only one smaller expansion is clearly visible in the central lower part of the particle, forming a strong spot of stain exclusion. The upper expansion is still slightly visible in Fig. 1D as a gray area, but it disappears almost completely in Fig. 1E. These observations may correspond to a rocking of the particles on the support carbon film.

Cryoelectron Microscopy—For the computation of three-dimensional reconstruction volumes, the GAPDH-PRK complex was observed in vitreous ice with a defocus of 1.9 μm (Fig. 2A) for the first three-dimensional reconstruction using the single exposure random conical-tilt series technique (29). A refined volume was then computed from a set of 6,057 untilted-specimen images selected from 17 micrographs with defocuses ranging from 1.4 to 0.8 μm (Fig. 2B). A unique three-dimensional reconstruction volume was then computed with the Wiener filtering approach (26, 32, 33) using an amplitude contrast of 5%, a source size of 4 Å, an envelope half-width of 9 Å, and a signal-to-noise ratio of 3.

To check the validity of this three-dimensional reconstruction volume, Fig. 2, C–J shows some experimental cryoEM average images (avg) with, next to them, the surface rendering of the three-dimensional reconstruction volume (vol) and the corresponding two-dimensional projection map (prj) mimicking the orientation of the particles in the vitreous ice layer of the EM grid. For example, one can observe four types of cryoEM images resembling the asymmetric rod-like view (Fig. 2, D, E, G, and H) and only one type of 2-fold view (Fig. 2C). Furthermore, some particles produce new types of views in the ice layer that resemble an annulus (Fig. 2F) with two smaller expansions (Fig. 2J). Therefore, we refer to such orientations of the particles in the ice layer as the annular view. Some particles also produce a trapezoidal view with two smaller expansions (Fig.
Fig. 4. Model of the GAPDH-PRK complex. A, alignment of the GAPDH sequence of \textit{C. reinhardtii} (SwissProt identifier, G3PC\_CHLRE) with that of \textit{B. stearothermophilus}, whose structure was used to build the \textit{C. reinhardtii} GAPDH model (G3PC\_BACST; PDB identifier, 4dbv). Amino acids were numbered without considering the signal peptide (G3PC\_CHLRE) or according to the PDB file (G3PC\_BACST). Secondary structures are indicated below the \textit{B. stearothermophilus} GAPDH sequence (arrow, \(\beta\)-strand, bold line, \(\alpha\)-helix). Identical amino acids are shown as white on a black background, whereas similar amino acids are boxed. These are shaded light gray when corresponding to hydrophobic residues (V, I, L, M, F, Y, W) and dark gray (white letters) when corresponding to aromatic residues (F, Y, W, H). B, alignment of the PRK sequence of \textit{C. reinhardtii} (SwissProt identifier, KPPR\_CHLRE) with that of \textit{R. sphaeroides}, whose structure was used to build the \textit{C. reinhardtii} PRK model (SwissProt identifier, KPP1\_RHOSH; PDB identifier, 1a7j). These two sequences were also aligned with several representative members of the PRK family.
Structural Organization of the GAPDH-PRK Multienzyme Complex

2J). Although this last type of cryoEM view is much smaller than the previous one, we see that the volume in a new orientation of the complex can easily produce it.

To better grasp the outer boundaries and the high density zones within the three-dimensional reconstruction volume, two series of surface representations are shown in Fig. 3. The first set of surface renderings was computed with a threshold of 0.44 and corresponds to a volume occupancy of 1102 nm$^3$ (Fig. 3, A, C, E, and G), whereas the second set was computed with a threshold density of 0.64, corresponding to only 326 nm$^3$ (Fig. 3, B, D, F, and H). In each set of surface representation, the volumes are shown as if observing the particle in a cubic box oriented at its top (A and B), bottom (C and D), front (E and F), and profile (G and H) views, respectively. Because the volume was computed with a 2-fold symmetry, the front and back views are identical to the left and right profile views. Furthermore, for the sake of clarity, the lettering L for large masses, P for protrusions, and E for expansions designates the building blocks observed in the volume. Each of them is present in two copies, symmetrically disposed around the 2-fold axis. Therefore, we observe six building blocks in the complex named L1, L2, E1, E2, P1, and P2.

Depending on the threshold used for surface rendering the overall size of the particle may vary significantly. However, the width, height, and depth of the particle can be estimated to be close to 220, 150, and 150 Å, respectively, when measured on the front view and taking a median threshold density value of 0.5 corresponding to a volume of 770 nm$^3$ (Fig. 5B). In the top view (Fig. 3A), the two large lateral masses (L1 and L2) are connected in the front with the two triangular expansions (L1–E1 and L2–E2) and at the back with the two protrusions (L1–P1 and L2–P2). When looking at the high density zones of the volume (Fig. 3B) these masses are totally individuated, and the central smaller expansions form a parallelogram with the longest diagonal oriented in the upper left direction. From Fig. 3 the most probable location for the GAPDH tetromers seems to be the two lateral masses (L1 and L2), whereas the four copies of PRK may correspond to the smaller masses (E1, E2, P1, and P2).

In the front orientation (Fig. 3, E and F), the hollow nature of the complex is clearly visible, and a central void space is limited at each side by the large lateral masses (L1 and L2) and above and below by the small high density zones E1/E2 and P1/P2, respectively. In this orientation, the E1/E2 expansions appear as oblong bodies, whereas the lower protrusions P1/P2 are less elongated. However, they are located in close proximity to the lower edge of the lateral masses so that it is difficult to point to the exact boundaries between the two types of masses. The striking feature is the overall distribution of the high density zones within an ellipsoid that is clearly reminiscent of the annular view (Fig. 2, F and I). Even the large lateral masses that appear as bulky material in all other views take a curved shape resembling a baseball glove in this specific orientation. Finally, in the profile view (Fig. 3, G and H) one can see the large gap between the E1/E2 expansions, whereas the lower protrusions P1/P2 appear in closer vicinity.

Sequence Comparison and Modeling of C. reinhardtii GAPDH and PRK—We next tried to correlate these low resolution structural data of the complex with the atomic structures of each of its components for which experimental atomic structures are available in other species. Three-dimensional models of the C. reinhardtii GAPDH and PRK were thus generated by homology using the known structures of the Bacillus stearothermophilus and R. sphaeroides enzymes, respectively.

Modeling of C. reinhardtii GAPDH using the B. stearothermophilus structure as template (PDB identifier, 3DBV) indicates a very similar structure (0.4 Å root mean-squared deviation between the 666 superimposable Cα atoms) supported by a high level of sequence identity (58% in Fig. 4A). Because the B. stearothermophilus GAPDH (similar to the C. reinhardtii GAPDH) is organized as a tetramer, and regions involved in the tetramer contacts are highly conserved, we then reproduced this quaternary structure by fitting our model onto each of the subunits of the C. reinhardtii oligomer (Fig. 5–A–F). The fitting of this tetrameric model of GAPDH within the EM density was satisfactory (see “Discussion”).

Modeling of the C. reinhardtii PRK structure was more difficult to perform, given the low level of sequence identity shared with the R. sphaeroides PRK sequence (below 25%), which is the only sequence with a known three-dimensional structure and could thus be used as a template (21) (PDB identifier, 1A7J). In the alignment procedure we thus especially took into consideration information about the secondary structure, which is currently much more conserved than the primary structure. This information was gained through the use of Hydrophobic Cluster Analysis (see the Fig. 4 legend for details), a two-dimensional method of sequence analysis adding to the one-dimensional lexical comparison an analysis of secondary structures (regular secondary structures are mainly centered on the hydrophobic clusters displayed on the two-dimensional net used by this method) (39). The consideration of the whole PRK family also helped the alignment procedure by giving valuable information about conserved positions essential to the fold and/or function (e.g., the positions that are always occupied by hydrophobic amino acids, highlighted by stars on Fig. 4B). Thus, although the R. sphaeroides and C. reinhardtii enzymes share as low as 22% of identity as determined after optimized alignment using Hydrophobic Cluster Analysis (see Fig. 4 legend for details), most of the hydrophobic
PRKs, exist as octamers that consist of two layers of four PRK molecules. However, the dimeric organization created by the 2-fold symmetry that relates the two layers within the \( R. \text{ sphaeroides} \) octamer is supposedly conserved throughout evolution (21). Indeed, regions located at the interface between the two monomers are much more conserved than other parts of the sequence (especially helices E and F/F’ and strand 5, boxed in Fig. 4B). Consequently, it is probable that the dimeric interface existing in \( R. \text{ sphaeroides} \) PRK structure within the octamer is similar to that existing within the \( C. \text{ reinhardtii} \) structure (Fig. 4C). The presence of an additional sequence in the \( C. \text{ reinhardtii} \) PRK, distant from the dimeric interface and the active site but in the vicinity of helix G, which defines the opening to the center of the \( R. \text{ sphaeroides} \) octamer, would therefore prevent the formation of octameric structures in \( C. \text{ reinhardtii} \) and limit the quaternary arrangement to dimers. This dimeric organization predicted by homology should define the most compact volume of the PRK dimer, which can be used to explore EM density after subtraction of the GAPDH tetramer volume (see “Discussion”).

**DISCUSSION**

Interactions between proteins are fundamental to a broad spectrum of biological functions. Whether or not two proteins will bind to form a stable complex that is required for biological function is dependent on the three-dimensional conformation of the proteins. Because in biology it is widely postulated that sequence specifies conformations, modeling of PRK and GAPDH structures has been performed. As these two proteins from the green alga \( C. \text{ reinhardtii} \) have a large propensity to interact and mainly exist as a bi-enzyme complex, this entity was then studied using negative staining and cryoEM.

Previous reports have shown that a mutant PRK produced by site-directed mutagenesis of Arg-64 is not capable of reforming the complex (20). Therefore the basis of the interaction between GAPDH and PRK was supposed to reside in the Arg-64 region (Fig. 4, B and C). The PRK model supports the contention that this residue (and the helix B to which it belongs) may be a good candidate, because it is exposed to the solvent in the molecule. This model also shows that the Gln-189 residue (helix F”) is buried in the molecule and therefore is in good agreement to unpublished experimental data, which indicate that a mutant PRK produced by site-directed mutagenesis of Gln-189 was still able to reconstitute the complex in vitro. It was then tempting to fit the structures of PRK and its partner (GAPDH) into the model obtained by cryoEM and negative staining.

Dimensions (20 × 10 nm) of the observed particles are in good agreement with the expected size 460 kDa of GAPDH-PRK complex (6). Smaller assemblies may correspond to the partially degraded complex; this is possibly explained by the 10-fold dilution of the complex required for the negative staining, because it has been shown previously that the complex could depolymerize upon dilution. The rod-like structures may be the result of aggregated GAPDH. Indeed, GAPDH has been described as aggregated forms in plants (48, 49). Although the C-terminal extension of the protein that is missing in the algal enzyme seems to be responsible for the self-aggregation (48), the rod-like structures observed here may also be the result of such an aggregation. The study of this possible aggregation is under investigation.

The overall matrix obtained by cryoEM was tentatively used to fit the modeled structures of GAPDH and PRK. The fitting of two tetrameric GAPDH within the whole complex was straightforward (Fig. 5, A–F) and allowed the computation of a three-

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2 B. Gontero, personal communication.
dimensional difference map (Fig. 5, G–I) corresponding to the space occupied by the PRK dimers (Fig. 5, J–L). In this three-dimensional subtraction map we observe four main masses (E1, E2, P1, and P2) that may each correspond to a PRK monomer. However, the scattered disposition of these masses is not compatible with the dimeric conformation of the PRK as presented in Figs. 4C and 5, J–L. Hence, from the top view orientation of the whole complex (Fig. 5H) masses E1-E2 and P1-P2 seem to form two dimers, but in fact they are located far apart when observed from the front (Fig. 5I) and profile views (Fig. 5J). Similarly, a dimeric disposition E2-P1 and E1-P2 could be inferred from Fig. 5G but not clearly from Fig. 5, H and I. Therefore, our attempts to fit two dimers of PRK (Fig. 5, J–L) in the remaining space of the three-dimensional subtraction map (Fig. 5, G–I) were unsuccessful. One should of course keep in mind that it was not possible to model the C terminus of the algal PRK and that the most likely explanation was that within the complex, PRK quaternary structure had undergone a conformation change. Hence, a strong structural deformation is most likely the molecular basis for the activation of the PRK with the complex. These results are in good agreement with those presented in a recent review from Janin and co-workers. In this work, several examples illustrate large changes in conformations occurring within oligomeric complexes with large interfaces between components (interface area > 2000 Å² per contact) (50).

Finally, the presence of additional material clearly distinct from E and P masses in the subtraction maps of Fig. 5, G–I may suggest the presence of another protein within the bi-enzyme complex. Quite recently, in C. reinhardtii, the bi-enzyme complex was shown to be associated with a third component, the so-called CP12, a protein not easily detected (14). This protein is therefore a good candidate to fill at least in part the space observed by the cryoEM technique, and the search of this protein is now under investigation.

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