A Drosophila melanogaster G Protein α Subunit Gene Is Expressed Primarily in Embryos and Pupae*

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A G protein α subunit gene has been isolated from a Drosophila melanogaster genomic library using a combination of bovine rod and cone transducin α subunit cDNAs as a probe under reduced stringency conditions. The gene, DGal1, encodes a protein with an amino acid sequence 78% identical to bovine Gα1. However, unlike all reported Gα subunits the DGα1-encoded protein is not expected to be a pertussis toxin substrate, because it lacks a cysteine at the appropriate site. The protein coding region of the gene is split by four introns. The sequence of a head tissue cDNA clone, as well as amino acid similarities to mammalian G proteins, confirms this exon/intron structure. Northern blots of total cellular RNA reveal a major 2.3-kilobase transcript and a less abundant 1.7-kilobase transcript. These transcripts are most abundant in RNA from embryos and pupae. The DGα1 gene is located on band 65C on the left arm of the third chromosome, on the basis of in situ hybridizations to Drosophila salivary gland polytene chromosomes.

Guanine nucleotide binding proteins (G proteins) are a family of membrane-associated intracellular proteins which relay signals between activated membrane receptors and intracellular effector enzymes (Gilman, 1987; Stryer and Bourne, 1986). Many G proteins are now well characterized. G, interacts with hormone-bound βγ-adrenergic receptor and stimulates intracellular adenyl cyclase. Transducins, G proteins found only in photoreceptors, carry the light-stimulated flow of information from bleached rhodopsin to a cGMP phosphodiesterase. The binding of a variety of hormones to their specific receptors activates G, and causes inhibition of adenyl cyclase. G proteins are also implicated in phosphoinositide breakdown and turnover (Kikuchi et al., 1987; Logothetis et al., 1987; Yatani et al., 1987), and olfactory signal transduction (Pace and Lancet, 1986).

G proteins are heterotrimeric which consist of an α subunit associated with a tight complex of β and γ subunits. They exist in two activity states, determined by the type of guanine nucleotide bound to the α subunit. In its active state the α subunit binds GTP, dissociates from the βγ complex, and interacts directly with an effector enzyme. A slow GTPase activity intrinsic to the α subunit hydrolyzes the bound GTP to GDP, and promotes the reassociation of α with βγ, converting the G protein to its inactive state. Cholera and pertussis toxins catalyze covalent ADP-ribosylation of G protein α subunits, thereby altering G protein inactivation and activation kinetics, respectively.

Much of the biochemical characterization of G proteins has focused on vertebrate signal transduction systems. While these systems are useful for protein characterization studies, they are in general limited by the difficulty of generating and characterizing G protein mutants. In addition, the behavioral and neuronal impact of G protein function is difficult to study in vitro. For these reasons we have chosen to embark on a study of G proteins in Drosophila melanogaster, a species amenable both to genetic manipulation and neurobiochemical study.

We describe here the isolation and characterization of a gene encoding a D. melanogaster G protein α subunit. Isolated from a D. melanogaster genomic library by virtue of its cross-hybridization to a bovine transducin α subunit cDNA probe, this Drosophila G protein gene encodes an amino acid sequence 78% identical to that of mammalian Gα. We also present data demonstrating that transcripts from this gene are most abundant in RNA from early embryos and pupae.

**EXPERIMENTAL PROCEDURES**

*Fly Culture—*Wild type Canton S strain D. melanogaster flies were maintained at room temperature on cornmeal/molasses/agar medium (Roberts, 1986), collected at various developmental stages, and frozen in liquid nitrogen prior to use for DNA or RNA preparation.

*Phage Library Screening—*Approximately 13 genomic equivalents, 1.35 × 10⁹ phage, from a D. melanogaster Canton S genomic library in phage λ Charon 4 (Maniatis et al., 1982) were screened with nick-translated restriction fragments from bovine cone and rod transducin α subunit cDNAs. The cone transducin α subunit cDNA clone (Locher et al., 1985) contained a full-length insert, while the rod cDNA insert extended approximately from nucleotide 114 to 1095 as designated by Yatsunami and Khorana (1985). Nitrocellulose filter lifts (Maniatis et al., 1992) were prehybridized at 45 °C for 1–5 h in a solution consisting of 6 × SSC (1 × SSC = 150 mM NaCl, 15 mM sodium citrate), 10 × Denhardt's (5 × Denhardt's = 1 mg/ml each Ficoll, bovine serum albumin, and polyvinylpyrrolidone), 100 μg/ml sheared salmon sperm DNA (Sigma), 10 mM EDTA. The library lifts were hybridized for 12–24 h at 45 °C in 6 × SSC, 50% deionized formamide, 5 × Denhardt's, 100 μg/ml sheared salmon sperm DNA, 1–4 × 10⁶ dpm/ml nick-translated probe. After hybridization, filters were washed for 20 min in 2 × SSC, 1% SDS 1 at room temperature, then for 1–2 h in 0.1 × SSC, 1% SDS at 45, 55, 65, or 70 °C. An adult D. melanogaster Canton S head cDNA library in λGT11 (Paul Salvaterra, City of Hope, Duarte, CA) and an Oregon R 0–3-h embryo cDNA library in λGT10 (kindly provided by S. Poole, L.

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The nucleotide sequence(s) reported in this paper has been submitted to the GenBank™/EMBL Data Bank with accession number(s) J03002.

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1 The abbreviations used are: SDS, sodium dodecyl sulfate; kb, kilobase pair.
were screened using a nick-translated 0.35-kb EcoRI genomic fragment from the DGa1 gene (Fig. 1). Hybridization conditions were identical to those described for the genomic library except that 30% formamide was used in the hybridization solution, and the hybridization was carried out at 30 °C. Library lifts were washed in 2× SSC, 1% SDS at 48 °C.

Isolation of RNA and Northern Blot Analysis—Total RNA was isolated by the method of Cathala et al. (1983), with the following modifications: pelleted RNA was solubilized in 3 M LiCl, 1 M guanidinium isothiocyanate and the solution sheared by several passages through an 18-gauge needle; solubilization buffer contained 1% SDS; the crude RNA solution was extracted three times with 1 volume of phenol, two times with 1 volume of chloroform: i-butanol (4:1, v/v); RNA was precipitated with 2 volumes of ethanol and 0.1 volume of 3 M sodium acetate.

Total RNA (15 μg/lane) was electrophoresed on a 1.0% agarose, 2.2 M formaldehyde gel as described in Maniatis et al. (1982). 32P end-labeled DNA molecular weight standards (λ HindIII digest, Bethesda Research Laboratories) and RNA molecular weight standards (RNA ladder, Bethesda Research Laboratories) were treated in the same manner as RNA samples and run on adjacent lanes of the agarose gel. Electrophoresed RNA was transferred to Nytran (Schleicher & Schuell) in 20× SSC. Filters were prehybridized as described above for library lifts and lifted at 63 °C in the same hybridization solution as that used to screen the head cDNA library. A 0.35-kb EcoRI genomic fragment (Fig. 1) was used as a probe for gene expression, and a ribosomal protein 49 probe, pGRP49 (O'Connell and Rosbash, 1984), was used as a probe for RNA integrity. After hybridization, filters were washed in 2× SSC, 1% SDS at room temperature for 20 min, then were washed in 0.1× SSC, 0.05% SDS at 65 °C for 1 h. Autoradiography was performed with x-ray film and an intensifying screen at -70 °C.

DNA Sequencing—The DNA sequences of the genomic and cDNA clones were determined using the chain termination method of Sanger et al. (1977) and Hattori and Sakaki (1986). Restriction fragments were subcloned into double-stranded plasmid vectors pUC 19 (Bethesda Research Laboratories) and PBS (Stratagene, La Jolla, CA). Sequence was determined from both strands using specific oligonucleotide probes synthesized by an Applied Biosystems Model 380B automated DNA synthesizer. Sequencing reactions employed either Sequenase (United States Biochemical Corp., Cleveland, OH) or Escherichia coli DNA polymerase Klenow fragment (Bethesda Research Laboratories) and labeling was accomplished with either [α-32P]dATP or α-32P-dATP.

Genomic DNA Isolation and Southern Blot Analysis—Isolation of Drosophila genomic DNA from frozen fly tissues was performed as described in Maniatis et al. (1982) except that RNase digestion preceded dialysis of the genomic DNA. Genomic DNA (5 μg/lane) was digestion with BamHI and electrophoresed on a 1% agarose gel. DNA was transferred to Nytran as described (Maniatis et al., 1982). Blots were prehybridized as described for library lifts and hybridized at 45 °C in the same hybridization solution as that used for screening the cDNA library. High stringency washes were performed in 0.1× SSC, 0.05% SDS at 65 °C for 1-2 h. Low stringency wash conditions were 0.5× SSC, 0.5% SDS at 45 °C for 1-2 h.

In Situ Hybridizations to Polytenie Chromosomes—A nick-translated biotinylated 0.35-kb EcoRI genomic restriction fragment (Fig. 1) was hybridized to polytene chromosomes in situ according to the method of Engels et al. (1986).

RESULTS

A D. melanogaster genomic library was screened with two bovine transducin cDNA clones at reduced stringency. Fourteen positively hybridizing plaques were isolated from the initial screening. Two clones were purified and their inserts found to be overlapping. One of these clones was studied in detail. Fig. 1A shows the restriction pattern of this clone, designated A4'. Several cDNA clones corresponding to A4' were isolated using a 0.35-kb EcoRI fragment of clone A4' (Fig. 1) to screen a Drosophila Canton S adult head cDNA library and a Drosophila Oregon R embryo cDNA library. Fig.

![A](image1)

![B](image2)

**Fig. 1.** Restriction map and sequencing strategy of genomic clone λ4' (A) and head cDNA ASD7110 (B). Hatched boxes indicate protein coding regions of the gene. Arrows indicate sequencing strategy. The 0.35-kb EcoRI fragment designated by an asterisk (*) was used as a probe in cDNA library screening and in the experiments described in Figs. 4-6. Restriction site abbreviations are: E, EcoRI; H, HindIII; B, BamHI.
Fig. 2. Partial DNA sequence and conceptual translation product of the genomic clone and head cDNA. The DNA sequence is indicated below the genomic DNA sequence; *dashed lines* signify identities. The single amino acid difference is shown in parentheses below the genomic conceptual translation product.

1B shows the restriction pattern of one such clone derived from the adult head cDNA library, aSD7110. DNA restriction fragments of M4 and aSD7110 were subcloned into plasmids for sequence analysis (Fig. 1, A and B). The sequences of the protein coding regions of the gene and the adult head cDNA (Fig. 2) were identical save for one base difference. Base 8, a guanosine in the genomic clone, is changed to an adenosine residue in the head cDNA, causing the amino acid sequence to change from a cysteine (TGT) to tyrosine (TAT) at codon 3. There were also minor differences in the sequences near the extreme 5' end of the cDNA which we attributed to cloning artifacts (data not shown). The one base difference in the protein coding region may be either a cloning artifact or a strain polymorphism, since a different cDNA, isolated from a 0–3 h Drosophila Oregon R strain embryo cDNA library, is identical to the gene at base 8 but differs at bases 177 and 751 (data not shown). The gene appears to code for a G protein subunit, and therefore we have designated it DGa1 (for Drosophila G protein α subunit 1).

The DGa1 conceptual translation product was compared with different bovine G protein α subunit sequences (Fig. 3A). Several peptide sequences common to all G protein α subunits are present in DGa1. These conserved amino acids are thought to be necessary for GTP binding and hydrolysis (Masters et al., 1986). DGa1 appears to be most similar to bovine Gαs, the α subunit of the G protein which inhibits adenyl cyclase. A comparison of the proteins encoded by DGa1 and Gαs cDNAs derived from three different mammalian genes (Fig. 3B) reveals the highest degree of amino acid identity between DGa1 and bovine Gαs. Seventy-eight percent of the corresponding amino acids in DGa1 and Gαs are identical. Despite this high degree of similarity, there is a major difference between the DGa1 gene product and mammalian Gαs. All mammalian Gαs contain a cysteine 4 residue from the carboxyl terminus which serves as a substrate
**A**  
**DGa1 vs. % Amino Acid Identity**

|        | BGa1 | BGa2 | BGa3 | BTa1 | BGa3 |
|--------|------|------|------|------|------|
| DGa1   | 78%  | 66%  | 61%  | 44%  |      |

**B**  
**DGa1:**

| Amino Acid Sequence | Genes          |
|---------------------|----------------|
| 1                   |                |
| MCAVSTARKESAISKWIDRAERGASAENKLILLLAGEGSKSTIHKMK1 | BGa1 (bovine) |
|                  |                |
| DGal:             |                |
|                  |                |
|                  |                |
|                  |                |
|                  |                |

**Fig. 3. Comparison of DGa1 amino acid sequence with mammalian G protein α subunit amino acid sequences.**

A, conceptual translation product of DGa1 compared to amino acid sequences of bovine α subunits. Black vertical lines indicate amino acid identities. Abbreviations are: BGa1, bovine DGa1 (Nukada et al., 1986); BGa2, bovine DGa2, (Van Meurs et al., 1987); BTa1, bovine rod transducin α (Yatsunami and Khorana, 1985); BGa3, bovine DGa3 (Robishaw et al., 1986). B, DGa1 conceptual translation product compared to bovine DGa1 (Nukada et al., 1986), human DGa2 (Beals et al., 1987), and human DGa3 (Beals et al., 1987). Amino acid identities are indicated by dashed lines.
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**BAM DIGEST**

**FIG. 4. Southern blot analysis of Drosophila genomic DNA.** Drosophila genomic DNA was digested with BamHI, transferred to nylon membranes, and probed with the 0.35-kb EcoRI fragment of DGal under high and low stringency conditions (see "Experimental Procedures"). *Arrows* indicate DNA fragments not present in the DGal gene, indicating possible cross-hybridization between DGal and other genes in the *Drosophila* genome.

For pertussis toxin-catalyzed ADP-ribosylation. The DGal gene product, however, contains an isoleucine at this position.

In order to determine if there are other G protein α subunit genes within the *Drosophila* genome, a probe from the DGal gene was tested for cross-hybridization with other *Drosophila* genes. Fig. 4 shows a Southern blot of BamHI-digested *Drosophila* genomic DNA probed with the 0.35-kb EcoRI fragment from clone $\lambda^4$. The DNA within this probe encodes a polypeptide sequence (amino acids 34–58 in Fig. 3B) which is conserved among all G proteins. Under high stringency conditions only the 6-kb BamHI fragment predicted from the DGal gene structure is detected. However, a low stringency wash of the Southern blot reveals several additional bands (designated by *arrows*) which do not correspond to the DGal gene, indicating cross-hybridization. The faint high molecular weight bands present on the high stringency genomic blot may represent partially digested genomic DNA.

Developmental expression of DGal was examined by Northern blot analysis of total cellular RNA using the 0.35-kb EcoRI genomic fragment as a probe (Fig. 5A). The predom-
intranscript, 2.3 kb long, is present in RNA from embryos, pupae, and (less abundantly) in adult heads. A 1.9-kb transcript was also detected in RNA from 0–3-h embryos. Because the DGa1 probe hybridized poorly with adult body RNA, we probed the DGal probe hybridized with RNA in all the lanes, indicating intact RNA was present.

Drosophila salivary gland polytene chromosomes were probed in situ with the 0.35-kb EcoRI fragment from DGa1. Fig. 6 shows the gene-specific probe hybridized to a region on the left arm of chromosome 3 near region 65C. This was the only band which hybridized to the DGa1 probe.

**DISCUSSION**

Many recent reports (Blumenfeld et al., 1985; Fein, 1986; Tsuda et al., 1986; Dietzel and Kurjan, 1987; Miyajima et al., 1987) have suggested that invertebrates use G proteins for signal transduction. Nonhydrolyzable guanine nucleotides have produced phototransduction effects in limulus (Fein, 1986), squid (Tsuda et al., 1986), and house flies (Blumenfeld et al., 1985). In addition, pertussis toxin ADP-ribosylates proteins in squid retinas (Tsuda et al., 1986) and Drosophila heads (Hopkins et al., in press). Two groups have also isolated a G protein gene from *Saccharomyces cerevisiae* which may be important for mating pheromone response (Dietzel and Kurjan, 1987; Miyajima et al., 1987). The isolation of the DGa1 gene confirms and extends these findings.

The isolation and characterization of DGa1 also provides further evidence that the nervous system of *D. melanogaster* utilizes molecular signal transduction mechanisms similar to those of higher eukaryotes. The identification of ion channels (Salkoff et al., 1987; Papazian et al., 1987), visual pigments (O'Tousa et al., 1985; Zuker et al., 1985), adenyl cyclase (Chen et al., 1986), and G protein β subunit (Yarfitz et al., 1988) and α subunit (this work) reaffirms the choice of *D. melanogaster* as a model neurobiological system for higher eukaryotes.

The amino acid sequence of the DGa1 gene product is most similar to mammalian Ga1 (78% identical), and slightly less similar to Ga2 and Ga3 (77% identical). A value for the estimated evolutionary distance (K, between DGa1 and each of the three mammalian Ga3 (based on the number of third base substitutions at synonymous codons) was calculated by the method of Kimura (1981). The K value for DGa1 versus human Ga2 was 0.61 ± 0.09, as compared to values much greater than 1 for DGa1 versus bovine Ga1 or human Ga3. Thus, despite the fact that the DGa1 amino acid sequence is most similar to bovine Ga1, these calculations indicate that DGa1 is likely to have evolved from the gene that became Ga2.

Pertussis toxin catalyzes the covalent attachment of an ADP-ribose moiety to a cysteine residue near the carboxyl terminus of many G proteins. In the DGa1 gene product an isoleucine has been substituted for this conserved cysteine. Since the biological function of endogenous ADP-ribosylation is unknown, the significance of a missing pertussis toxin recognition site in the DGa1 gene product is unclear. Nonetheless, other pertussis toxin substrates are present in Drosophila tissues (Hopkins et al., in press). Perhaps a regulatory mechanism reflected by the ADP-ribosylation phenomenon has been evaded by the DGa1 gene product.

Although the function of the DGa1 gene product remains unknown, it is probably not a phototransduction enzyme. The northern blots in Fig. 6 show that the most abundant transcripts are present in cellular RNAs isolated from embryos and pupae, and very little signal was found in head RNA. If this gene product were important in signal transduction primarily within Drosophila photoreceptors, a much stronger hybridization signal from head RNA might be expected. It also seems unlikely that a phototransduction-specific G protein would be found in early embryos, since photoreceptors are lacking at this stage of development. The presence of cross-hybridizing bands on genomic Southern blots (Fig. 4), evidence for pertussis toxin and cholera toxin substrates in Drosophila heads (Hopkins et al., in press), and light-dependent GTPase activity in house flies (Blumenfeld et al., 1985) all suggest that Drosophila may utilize more than one type of G protein in signal transduction.

DGa1 transcripts were detected in the earliest staged embryo RNA isolated. Since very few genes are zygotically transcribed in the first 3 h after fertilization (Edgar and Schubiger, 1986), this result suggests that the DGa1 gene may be maternally transcribed and packaged into the unfertilized egg. If this is so, DGa1 could join the growing list of genes which are important in early Drosophila development (Scott and O'Farrell, 1986). It is noteworthy that improper regulation of cAMP levels is associated with infertility, developmental defects, and learning defects in Drosophila (Bellen et al., 1987).

There are no reports of mutants at the cytological locus of DGa1 on the third chromosome. Therefore the identification of the function of this new G protein awaits localization, tissue-specific expression, and mutagenesis experiments.

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