The Primary Structure of Rat Liver Glycogen Synthase Deduced by cDNA Cloning

ABSENCE OF PHOSPHORYLATION SITES 1a AND 1b*

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The cDNA for rat liver glycogen synthase was isolated by screening a rat liver cDNA library constructed in λgt11. The cDNA was 2.4 kilobases in length and encoded a protein of 703 amino acid residues with a molecular mass of 80.5 kDa. Comparison of the rat liver and the human muscle sequences show that the amino- and carboxyl-terminal regions are quite divergent as compared to the internal sequences which show an 80% identity. The rat liver carboxyl-terminal region is truncated by 33 residues and has only 46% identity with the muscle sequence but retains the common feature of a low content of hydrophobic amino acids (13%). Phosphorylation sites 1a and 1b, which are the primary targets for phosphorylation by cAMP-dependent protein kinase, are absent in the liver sequence. The presence of these divergent, structurally anomalous carboxyl-terminal regions in liver and muscle glycogen synthase suggests the absence of the requirement that they possess a tertiary structure that is integral to that of the protein core. A model is proposed in which this region interacts with a catalytic core to maintain the I state, and in which phosphorylation serves to uncouple this interaction.

Glycogen synthase (EC 2.4.1.11) is the enzyme responsible for the synthesis of 1,4-α-linked glucose chains in glycogen, the primary storage form of glucose in higher eukaryotes (for reviews see Refs. 1-4). Glycogen synthases from muscle and liver are oligomeric proteins of subunits of ~85,000. The liver enzyme has been isolated as a dimer (5, 6) and is a distinct gene product from the muscle enzyme as shown by partial amino acid sequence analyses (7-9) and by immunochemical studies (10, 11). In an interesting parallel with glycogen phosphorylase, glycogen synthase was originally shown to exist in I (dephospho) and D (phospho) forms, these representing interconvertible forms which differed in their dependence on the allosteric effector, glucose 6-phosphate (12-14). The I to D interconversion was demonstrated to be mediated by cAMP-dependent protein kinase (15, 16), the effects of phosphorylation being to increase the dependence of the enzyme activity on glucose 6-phosphate (1-4). It later became evident that muscle glycogen synthase was, at least in vitro, the target of a number of different protein kinases and that it possessed multiple phosphorylation sites (1-4, 17-22).

The identity of the phosphorylation sites and the in vitro site specificity of various protein kinases has been well defined in rabbit skeletal muscle glycogen synthase (1-3). There are at least 10 phosphorylation sites, which are located at the amino and carboxyl termini of the protein (Fig. 1). These sites have been located at the extreme ends of the molecule by sequence analysis of two CNBr fragments, CB-1, a M, = 9,000 amino-terminal fragment and CB-2, a M, = 24,000 fragment consisting of the 124 carboxyl-terminal residues (1, 20). CB-1 contains site 2 (Ser-7) at the amino-terminal sequence PSRLTSVSS (1-3); Ser-3 and Ser-10 can also be phosphorylated (23). The carboxyl terminus contains sites 3a, 3b, 3c, 4, and 5 which are spaced at intervals of 4 amino acids in the sequence SVPPSPSLRHHSSPQ, and sites 1a and 1b, both of which exhibit optimal substrate recognition sequences for cAMP-dependent protein kinase (RRXS, KRSNS). Site 1a is the major phosphorylation site recognized by cAMP-dependent protein kinase, which also phosphorylates site 2 and 1b but at slower rates (1-3); at higher protein kinase concentrations sites 3 and 4 are also phosphorylated (24). Phosphorylase kinase specifically phosphorylates site 2 (22, 25). Site 5 is phosphorylated by casein kinase II (20) but this does not affect the activity ratio of glycogen synthase. This phosphorylation at site 5 has a synergistic effect on the phosphorylation of glycogen synthase at sites 3a, 3b, and 3c by glycogen synthase kinase-3 (19, 20, 26). This effect has been explained by the formation of the recognition site Ser-X-X-X-Ser(P) for glycogen synthase kinase-3, which then sequentially phosphorylate sites 4, 3c, 3b, and 3a (26). In addition to the protein kinases already mentioned, phosphorylation of glycogen synthase by at least seven other protein kinases has been demonstrated in vitro (see Refs. 1 and 2 for review). Despite this complexity, it can be generalized that phosphorylation of site 2, site 3a, 3b, 3c, and 1a are the major determinants for inactivation of muscle synthase in vitro. The placement of these phosphorylation sites within the complete primary structure of muscle glycogen synthase has recently become possible by the cloning of the cDNA of human muscle synthase (27).

Liver glycogen synthase is also subject to phosphorylation by various protein kinases at multiple sites, and gives rise to CNBr fragments analogous to rabbit muscle CB-1 and CB-2 (2, 7, 28-33). Partial sequence analysis has demonstrated the
The appropriate antibody dilutions for the screening process. The procedure used was described by Tan and Nuttall (34).

Screening of a Rat Liver cDNA Library—The antisera to rat liver glycogen synthase was used in these studies was prepared and characterized as described by Tan and Nuttall (34).

RESULTS AND DISCUSSION

Isolation and Characterization of a cDNA for Rat Liver Glycogen Synthase—The initial antibody screening resulted in the isolation of a partial cDNA of ~1.4 kb which was positively identified by sequence comparison with the human muscle glycogen synthase. The partial cDNA contained an internal EcoRI site, and gave rise to two fragments (A and B, “Experimental Procedures”). Rescreening of the library with nick-translated fragment A led to the isolation of five cDNA clones of ~2.4 kb (“Experimental Procedures”). These λgt11 clones yielded two fragments on cleavage with EcoRI (C and B) because of the internal EcoRI site. DNA sequencing showed that these clones all harbored the complete coding region for glycogen synthase.

The cDNA sequence and the deduced primary structure of rat liver glycogen synthase are shown in Fig. 2. The cDNA consists of 2386 bp, with the internal EcoRI site at nucleotide 1483. There is an open reading frame of 2109 nucleotides (nucleotides 46–2154), encoding a protein of 703 residues with a molecular mass of 80.5 kDa. This is smaller than expected from most reports of the size of isolated rat liver synthase.

The abbreviations used are: bp, base pair(s); kb, kilobase(s); SDS, sodium dodecyl sulfate.
FIG. 2. The nucleotide and deduced amino acid sequences of the cDNA of rat liver glycogen synthase. Nucleotides underlined are the translation initiation site, the termination codon, and the polyadenylation signal site.

The GC content of the cDNA was 49.5%. The codon usage in the third positions was found to be 27% G, 31% C, 23% T, and 19% A. A high usage of G + C has been previously noted for a number of muscle proteins (44), including phosphorylase (45), the catalytic subunit of phosphorylase phosphatase (46, 47), and human muscle glycogen synthase (27). However, the G + C codon usage in the liver cDNA is only 58% as compared to the value of 77% for the human muscle glycogen synthase cDNA (27).

The coding region (nucleotides 46-2154) of the rat liver glycogen synthase cDNA has a 68% identity with the nucleotide sequence of the only other reported glycogen synthase cDNA which was isolated from human muscle (27). A search for related sequences in the National Biomedical Research Foundation data bank by the FASTP program (48) of the Protein Information Resource failed to reveal any related sequences.

Alignment of the Deduced Amino Acid Sequences of Rat Liver and Human Muscle Glycogen Synthases—The two sequences show a 70% overall identity (Fig. 4). They can be aligned by the inclusion of a single gap in the muscle sequence following residue 21, and two single gaps in liver sequence following residues 173 and 555 (Fig. 4). Alignment at the carboxyl terminus requires a gap of 6 residues in the liver sequence after residue 661. The last 19 amino acid residues of the liver sequence show little identity with the remaining 46

Consistent with the values obtained by the in vitro translation studies of Bahnak and Gold (40) but not with those of 93 kDa obtained for rat liver and heart glycogen synthase by Rulfs et al. (41). Previous studies have provided indications that glycogen synthase behaves anomalously on sodium dodecyl sulfate-polyacrylamide gel electrophoresis systems. This has been variously attributed to the effects of proteolytic modification, phosphorylation (2, 3), or the presence of the carboxyl-terminal region (1). The calculated molecular mass of the rat liver CB-2 carboxyl-terminal fragment is 19.2 kDa and can be compared with the reported M, of 28,000 (29), a difference of 8,800.

The -1 to -5 sequence (GAAGA) upstream of the proposed translational initiation site (nucleotide 46) differs considerably from the translational initiation consensus sequence (CCA/GCC) (42), but there has been at least one other such sequence reported, that for the Torpedo acetylcholine receptor pre-a-subunit (43). There is a polyadenylation signal (nucleotide 2365), 210 bp downstream from the stop codon; one of the isolates which was sequenced contained a poly(A) tail of 29 bases, indicating that we had obtained the complete 3' untranslated region. The short stretch of the 5' untranslated region suggests that we have only isolated a portion of this region. Northern blotting of rat liver mRNA with nick-translated probes (either fragment C or A + B) showed the presence of a single band of ~2.4 kb, which suggests that the liver isoform is expressed in brain, in apparent conflict with immunohistochemical data which shows that liver and brain synthases are different (10, 11).

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FIG. 3. Northern blotting of rat liver and rabbit muscle poly(A) mRNA. Northern blotting of rat liver and rabbit skeletal muscle mRNA was performed as described under "Experimental Procedures." Lanes 1 and 1', rat liver ribosomal mRNA; lanes 2 and 2', 4 μg of rat liver mRNA; lanes 3 and 3', 2 μg of rat liver mRNA; lanes 4 and 4', 4 μg of rabbit muscle mRNA. Lanes 1-4 were hybridized against a nick-translated probe consisting of fragment C, the 5' half of the cDNA clone. Lanes 1'-4' were hybridized against a nick-translated probe consisting of fragments A + B from the 3' half of the cDNA. (The rabbit muscle mRNA was checked by hybridization to a probe derived from the rabbit muscle cDNA for the catalytic subunit of phosphorylase phosphatase; Ref. 47.)

Muscle 3'-untranslated region of 1.2 kb (27). Browner et al. (27) have indicated that Northern blotting of rat liver and brain with the human muscle glycogen synthase cDNA probe revealed smaller bands of ~2.4 kb, which suggests that the liver isoform is expressed in brain, in apparent conflict with immunohistochemical data which shows that liver and brain synthases are different (10, 11).

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The first 200 residues of the rat liver amino acid sequence was aligned with the sequence of human fetal muscle glycogen synthase (27) using the ALIGN program (50) of the Protein Identification Resource, National Biomedical Research Foundation. Washington, D. C. Identities with the rat liver sequence are shown as solid dots. Gaps are shown as dashes. The human muscle sequence includes corrections between residues 175 and 189 (M. F. Romner and R. J. Fletterick, personal communication).

![Fig. 5. Comparison of the amino-terminal sequence containing phosphorylation site 2 of rat liver glycogen synthase with those of glycogen synthases from other tissues.](image)

residues of the muscle sequence, but we have inserted an arbitrary gap of 5 residues after residue 185 (Fig. 4). This was done since there is a corresponding gap of 14 nucleotides in the alignment of the liver and muscle nucleotide sequences.

The first 200 residues of the rat liver amino acid sequence have a 55% identity with the human muscle sequence, the next 400 residues have an identity of 80%, and the final 103 residues have an identity of 46%. It is thus evident and surprising that the regulatory domains at the amino and carboxyl termini containing the phosphorylation sites are conserved in both the human muscle and rat liver sequences.

The most obvious difference between liver and muscle glycogen synthase is that the liver sequence is truncated at the carboxy terminus, being 34 residues shorter and encoding a protein of 80.5 kDa by comparison to 83.6 kDa for the human muscle (27). A difference of significant consequence is that the primary site for cAMP-dependent protein kinase in muscle, site 3a in human or rabbit skeletal muscle is not conserved and the methionine residue closest to the carboxy terminus is Met-598, so that the rat liver CNBr fragment would be 165 residues long, as compared to 124 for rabbit muscle.

The major difference between liver and muscle glycogen synthase is that the liver sequence is truncated at the carboxy terminus, being 34 residues shorter and encoding a protein of 80.5 kDa by comparison to 83.6 kDa for the human muscle (27). A difference of significant consequence is that the primary site for cAMP-dependent protein kinase in muscle, site 3a in human or rabbit skeletal muscle is not conserved and the methionine residue closest to the carboxy terminus is Met-598, so that the rat liver CNBr fragment would be 165 residues long, as compared to 124 for rabbit muscle.
1a, as well as site 1b, are absent. It can be speculated that the loss of site 1a is due to a deletion event which removed the residues comprising the recognition site as well as causing a reading frame shift which removes site 1b. The present work confirmed earlier \textit{in vitro} studies based on the examination of phosphorylated peptides derived from rabbit liver glycogen synthase which suggested the absence of phosphorylation sites 1a and 1b (7). This absence explains studies which showed that liver glycogen synthase is largely phosphorylated \textit{in vitro} by cAMP-dependent protein kinase in the CNBr peptide corresponding to CB-1, \textit{i.e.} that containing site 2 at the amino terminus (7, 30, 31), in sharp contrast to the muscle enzyme, where site 1a in CB-2 at the carboxyl terminus is the most rapidly phosphorylated. However, studies of the \textit{in vivo} phosphorylation of liver glycogen synthase show that both CB-1 and CB-2 are extensively phosphorylated after the actions of glucagon or hormones which act via \textit{\alpha}-adrenergic mechanisms (2, 29-31). This is a situation similar to that in the muscle, where \textit{in vivo} phosphorylation of the various sites of glycogen synthase cannot be predicted by simple consideration of the activation of specific protein kinases, and in particular where \textit{\beta}-adrenergic agents have been shown also to increase phosphorylation of sites 3 (a + b + c) and serine 10 (1, 2, 32). It should be noted that to date there are no analyses of the \textit{in vivo} phosphorylation of the individual sites 3a, 3b, and 3c, so that the \textit{in vivo} contributions of cAMP-dependent protein kinase (24) or glycogen synthase kinase-3 (1, 2) to the phosphorylation of this region remains open to debate.

The greater variation between the liver and muscle glycogen synthases in the regions containing the phosphorylation sites as compared to the internal sequences indicates that they are under lesser constraints for the structural integrity of the protein, and may reflect evolutionary changes in the regulation of the two enzymes as well as implications for the structural interactions involved in regulatory mechanisms (see below). The viewpoint that the existence of a distinct liver isoform can be rationalized from the different functions of glycogen in liver as a source of glucose for the purpose of homeostasis, as opposed to its function as a source of glycolytic fuel in other tissues, has been previously raised in relation to immunochemical evidence that liver has a distinct synthase while muscle, heart, fat, kidney, and brain share a similar isoform (10, 11). While the present comparison is between liver and muscle glycogen synthases of two different species, it is likely that these differences will be confirmed when sequences from the same species are available.

\textbf{Anomalous Nature of the Carboxyl-terminal Regulatory Domain—}Brown et al. (27) have noted that human glycogen synthase exhibits an asymmetric charge distribution with the amino- and carboxyl-terminal regions bearing net negative charges if the contributions of Arg, Lys, Glu, and Asp alone are considered, and is particularly pronounced at the carboxyl terminus. The strongly charged nature, as well as the low occurrence of hydrophobic residues in this region (9%), all indicate that these residues are likely to be solvent exposed and are anomalous by comparison to the internal sequences (27). The liver amino-terminal sequence is less charged than the corresponding sequence in muscle (−2 compared to −8 in the first 35 residues). The carboxyl-terminal 100 residues of the liver sequence (Fig. 6) carry a net negative charge of −6 compared to −8 for the muscle (27), and also has a low content of hydrophobic amino acids (13%). However, if the examination is extended to the preceding 30 amino acid residues, the net charge is +2 and it is seen that the striking feature is not only an asymmetric negative charge distribution in the carboxyl terminus compared to the whole, but an asymmetric charge distribution \textit{within} this region which can be arbitrarily divided into four segments. These are (Fig. 6): 1) a positively charged region (+8) of 43 residues (574-616); 2) a neutral proline-serine-rich region of 40 residues (617-656, 25% Pro, 23% Ser) which harbors phosphorylation sites 3a1, 3a2, 3c, 4, and 5 (659-656) and which in the fully phosphorylated state would have added negative charge of −12; 3) a negatively charged region (−12) of 21 residues (657-677) in which there are 9 aspartate and 5 glutamate residues, and 4) a second positively charged (+6) region of 26 residues. It is striking that the charged residues in the first three regions are highly conserved between the human muscle and rat liver sequences, and while region 4 is quite divergent from the human muscle sequence, the latter also carries a net positive charge in this region in the unphosphorylated state. Thus the features of this region are not only the asymmetric charge distribution but the well conserved separation of negatively and positively charged regions and a common low content of hydrophobic amino acid residues. The juxtaposition of negatively and positively charged regions provides structural elements which have the potential to interact with each other or with another regulatory domain, and such interactions could provide a basis for the regulation of the activity of glycogen synthase by phosphorylation.

\textbf{Possible Mechanisms for the Role of the Carboxyl-terminal Region in the Regulation of Glycogen Synthase—}The comparison of the carboxyl-terminal regions of the liver and muscle enzymes provide important clues to the nature of the structural mechanisms involved in regulation of synthase activity by phosphorylation. Their hydrophilic compositions argue against the possession of specific tertiary structures, while the greater divergence of the two carboxyl-terminal sequences (by comparison to the core enzyme) suggests the absence of the requirement that they possess a tertiary structure that is integral to that of the protein core. This suggests a structural
model for glycogen synthase in which there is a catalytic core with a regulatory domain which is involved in an interaction with a less structurally constrained carboxy-terminal domain. This view of a globular structure is supported by findings that limited proteolytic digestions of rabbit muscle (1) and rabbit liver synthases (28, 30, 32, 33) generate catalytically active products as small as 70 kDa with the loss of some of the carboxy-terminal phosphorylation sites. Two hypothetical models for the regulation of synthase by phosphorylation are shown, and they are in their simplest form in Fig. 7. In the first model the unphosphorylated carboxy-terminal region is involved in the maintenance of the I state by interaction with the core enzyme, and phosphorylation uncouples this interaction (Fig. 7A). In the second model, it is the phosphorylated carboxy-terminal region which is involved in interaction with the core protein. In this case it is involved in the maintenance of the D state and the effect of phosphorylation is to promote the interaction of the carboxy terminus with the core protein (Fig. 7B). The model involving a less structured carboxy-terminal is also consistent with the requirement for multiple phosphorylation to achieve regulation.

Scission of the carboxy-terminal domain would give rise to two different catalytically active cores (I' and D') according to the models given in Fig. 7, A and B, which would be expected to behave like synthase I and D, respectively, and thereby provide an experimental means for distinguishing the two. Studies by Tan and Nuttall (28) provide general support for the regulatory model given in Fig. 7A, since chymotryptic treatment was found to convert rabbit liver glycogen synthase I to a glucose 6-phosphate-dependent form with no loss in total activity, whereas treatment of the D form had no effect on its glucose 6-phosphate dependence and little effect on its kinetic properties. It should be noted that the chymotryptic products obtained from synthase I and D, respectively, by Tan and Nuttall (28) did not have identical kinetic properties. However, the chymotryptsin-treated enzymes were not subsequently isolated, leaving open the possibility that the cleaved nonphosphorylated carboxy-terminal region is independently capable of interaction with the core. Different findings have been reported for the effects of tryptic digestion (28, 33), which, however, do not lead to changes that can be readily interpreted according to this model. Deletion mutagenesis of glycogen synthase is therefore likely to provide further insights into the mechanisms by which phosphorylation of the carboxy-terminal regulates glycogen synthase.

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