Architectural Principles for the Structure and Function of the Glucocorticoid Receptor 1 Core Activation Domain*

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A 58-amino acid region mediates the core transactivation activity of the glucocorticoid receptor 1 core domain. This 1 core domain is unstructured in aqueous buffers, but in the presence of trifluoroethanol three α-helical segments are induced. Two of these putative structural modules have been tested in different combinations with regard to transactivation potential in vivo and binding capacity to the coactivators in vitro. The results show that whereas single modules are not transcriptionally active, any combination of two or three modules is sufficient, with trimodular constructs having the highest activity. However, proteins containing one, two, or three segments bind Ada2 and cAMP-response element-binding protein with similar affinity. A single segment is thus able to bind a target factor but cannot transactivate target genes significantly. The results are consistent with models in which activation domains are comprised of short activation modules that allow multiple interactions with coactivators. Our results also suggest that an increased number of modules may not result in correspondingly higher affinity but instead that the concentration of binding sites is increased, which gives rise to a higher association rate. This is consistent with a model where the association rate for activator-target factor interactions rather than the equilibrium constant is the most relevant measure of activator potency.

Transcriptional regulatory proteins are often composed of domains that can function independently of the other parts of the protein. It is generally accepted that these proteins can be subdivided into fully functional DNA-binding domains and activation domains. In the case of activation domains, the concept of modularity has been extended to suggest that these domains are themselves built up of short peptide modules that contribute to gene activation independently of each other but in a synergistic manner (1–5). These ideas lead to the suggestion that even though the subdomains could employ distinct mechanisms, they may be functionally redundant and that it would be the number rather than the composition of the submodules in an activation domain that is of importance for its gene activation potential.

The glucocorticoid receptor (GR)1 belongs to the large family of ligand-inducible nuclear receptors that function by modulating the transcription of target genes (6, 7). The transactivation activity of the human GR is mainly mediated by two domains, 1 core (residues 77–262), which resides at the N terminus of the protein, and 2 core (residues 526–556), which is localized just C-terminally of the DNA-binding domain (DBD) (8, 9). A small region at the C terminus of the receptor may also play a role in GR-mediated transcription (10). The 1 core constitutes the major transactivation function in the GR, and this domain represents the only autonomous activation region within the GR N terminus (9). When fused to a DNA-binding domain, 1 core constitutively activates transcription both in vivo and in vitro (11, 12). A 58-amino acid segment that represents the core activation domain (the 1 core) has been localized to residues 187–244 (13). This domain retains 60–70% of the activity conferred by the intact 1 core domain (13). The 1 core domain belongs to the group of acidic activators because of its relative abundance of acidic amino acid residues. Mutagenesis studies of the 1 core domain (14) and of acidic activation domains in VP16 (15–17), GCN4 (5, 18), NF-κB p65 (2), p53 (19), and HNF-4 (20) have shown that hydrophobic amino acids are important for transactivation activity of both isolated activation domains and intact activator proteins.

Similar to the transactivation domains of VP16 (21, 22) and NF-κB p65 (23), purified 1 core and 1 core core proteins have been shown to be unstructured in aqueous solution as measured by circular dichroism and NMR spectroscopy (24). However, in trifluoroethanol, the 1 core forms α-helices, which is also consistent with studies of the VP16 (21) and NF-κB p65 (23) transactivation domains. Three putative α-helical regions in the 1 core have been identified by NMR spectroscopy (25). Proline substitution mutants within two of the putative helical regions reduce the transactivation activity of the 1 core and also its ability to form α-helices in trifluoroethanol (24). α-Helix formation may thus be an important step in 1 core-mediated gene activation, and it is possible that target factor interactions induce or stabilize a structured conformation in the activation domain similar to the situation that has been demonstrated for activation domains of p53 (26) and VP16 (27, 28).

If this model is correct for the 1 core, the α-helices that can be induced in the 1 core peptide can be considered as structural modules. In this study we wanted to further address whether the 1 core domain is composed of modules with distinct and independent functions or whether it should be viewed as a structurally integrated protein domain. The results reported here provide evidence for a model in which the 1 core activation domain is built up of small modules with acidic and hydrophobic character, each of which interacts with target DNA-binding domain; GST, glutathione S-transferase; PCR, polymerase chain reaction; CBP, cAMP-response element-binding protein; MOPS, 4-morpholinepropanesulfonic acid.

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‡ The abbreviations used are: GR, glucocorticoid receptor; DBD,

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10514 This paper is available online at http://www.jbc.org
protein(s) to give efficient activity of transcription. Furthermore, the ability of constructs consisting of duplicated and triplicated modules of the same type to activate transcription suggests that the individual segments do not carry determinants absolutely critical for transactivation function.

EXPERIMENTAL PROCEDURES

Strains and Plasmids

Strains—The Saccharomyces cerevisiae strain W303–1A (MATa, ade2–1, can1–100, his3–11, 15, leu2–3, 112, trp1–1, 1, ura3–1) was used as the yeast host cell for all experiments in the study. The E. coli strains BL21(DE3)pLysS (Novagen) was used for GST and GST fusion protein expression.

Plasmids—pKVBB-GRDBD-r core and pKVBB-GRDBD-r (187–227) express r core and r (187–227), respectively, fused to the GR DBD. The plasmid pKVBB-GRDBD was generated from plasmid pKV-XE (11) by destroying the existing BamHI site in the insert and inserting a linker containing a BamHI and a BglII site in the SacI site. BamHI-BglII fragments corresponding to r core-H1 and r core-H2 were amplified by PCR using the following primers: 5′-CAGCAAGATCAGATCGACATC-3′ and 5′-CCACCAAGATCTATGGCTCTCTTATGCGATG-3′ for the H1 fragment and 5′-CACAGGAGATCCCTTGGAGATCAGACCTGTTGATC-3′ and 5′-CCACCAAGATCTATGGCTCTCTTATGCGATG-3′ for the H2 fragment. In this way acid amino sequence GSKT (from the region following the H1 segment) is joined to the end of the H2 module, thus giving a similar linker sequence between any two segments in the different combinations. Plasmid pKVBB-GRDBD expressing GR DBD was cleaved with BamHI and BglII, and the PCR fragments were inserted, resulting in plasmids pKVBB-GRDBD-H1 and pKVBB-GRDBD-H2, respectively. To obtain pKVBB-GRDBD-H1-H1, H1-H2, -H2-H2, and -H2-H1, pKVBB-GRDBD-H1 and pKVBB-GRDBD-H2 were linearized by BglII, and the BamHI-BglII PCR fragments were inserted. The following trisegment plasmid constructs were made using the same strategy: pKVBB-GRDBD-H1-H1-H1, -H1-H2-H1, -H1-H1-H2, -H1-H2-H1, and -H2-H2-H2. The GR-responsive lacZ reporter gene contains two glucocorticoid response elements from the rat tyrosine aminotransferase promoter cloned upstream of a basal CYC1-lacZ promoter and is contained in the vector pLGZ-2xTAT, described previously (29). GST fusion plasmids pGEX-Ada2 and pGEX-CBP-C2 (amino acids 1678–1868) have been described previously (30).

Transactivation Assay in Yeast

Plasmids were transformed into the yeast strains using a spheroplast procedure (31). Several colonies from each transformation were checked on 5-bromo-4-chloro-3-indolyl-β-galactopyranoside (X-gal) plates for homogeneity of transactivation activity (32). Representative cultures were diluted to an absorbance of 0.1 at 600 nm, and 600 μl of 0.2 in minimal media was added to each well. After 16 h of growth, the plates were stained with X-gal and subsequently washed. Several colonies from each transformation were linearized by NotI, and the PCR fragments were inserted, resulting in plasmids pKVBB-GRDBD-H1 and pKVBB-GRDBD-H2, respectively. To obtain pKVBB-GRDBD-H1-H1, H1-H2, -H2-H2, and -H2-H1, pKVBB-GRDBD-H1 and pKVBB-GRDBD-H2 were linearized by BglII, and the BamHI-BglII PCR fragments were inserted. The following trisegment plasmid constructs were made using the same strategy: pKVBB-GRDBD-H1-H1-H1, -H1-H2-H1, -H1-H1-H2, -H1-H2-H1, and -H2-H2-H2. The GR-responsive lacZ reporter gene contains two glucocorticoid response elements from the rat tyrosine aminotransferase promoter cloned upstream of a basal CYC1-lacZ promoter and is contained in the vector pLGZ-2xTAT, described previously (29). GST fusion plasmids pGEX-Ada2 and pGEX-CBP-C2 (amino acids 1678–1868) have been described previously (30).

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RESULTS

H1 and H2 Segments Function as Interchangeable Modules That Contribute Synergistically to Gene Activation—A schematic representation of the r core transactivation domain of human GR is shown in Fig. 1A. The location of segments with propensity for a-helical formation as identified by NMR is also shown. The amino acid sequences of the r core, r (187–227), H1, and H2 are shown in Fig. 1B. To investigate whether the putative helical segments in the r core are interchangeable and to see how the transactivation activity is affected by both the order and number of segments, different combinations of H1 and H2 were fused to the GR DBD (Fig. 2). Previous mutagenesis and deletion studies (13, 14) of the r core domain have indicated a less important role for H3 compared with H1 and H2. Because of this and for practical reasons in the experimental design, the H1 and H2 segments were used in this study. The different proteins were expressed in yeast cells in which expression of β-galactosidase is controlled by two glucocorticoid-responsive elements. The β-galactosidase data obtained from yeast strain W303–1A (Fig. 2) show that one segment only is not enough for significant activation but that any combination of two segments is sufficient to give transcriptional activation. The level of activation achieved with two segments is lower than for r (187–227) but still significant. Constructs containing three segments showed a transactivation potential comparable with the wild type r core. The exceptions are constructs containing only one type of module, i.e., the H1-H1-H1 and H2-H2-H2 proteins, which both had a lower transactivation activity than did the wild type r core. Both these criteria, the H1 and H2 segments appear to function as interchangeable modules that contribute synergistically to gene activation. However, to be able to draw firm conclusions from the transactivation activity data, the expression levels of the different proteins were analyzed by Western blotting using an antibody against GR DBD. Data in Fig. 3 show protein levels to be very similar except for constructs
containing only H1 segments, which were expressed at a much lower level. With longer exposure times, however, bands of the predicted size of H1, H1-H1, and H1-H1-H1 could be detected (data not shown).

Low Expression of Constructs Containing Only H1 Modules Is Not Due to Differences at the mRNA Level—Because gene expression is often regulated at the level of transcription, it is necessary to investigate whether the observed differences in protein levels are due to differences at the mRNA level. The transcript levels of selected constructs were assayed by Northern blotting of total RNA extracted from W303–1A yeast cells expressing the corresponding constructs using probes that hybridize to GR DBD and actin (internal control) mRNA. The results show that very similar amounts of mRNA were produced by the different constructs (Fig. 4). Consequently, the differences seen in protein expression levels for the H1, H1-H1, and H1-H1-H1 constructs cannot be accounted for by differences at the level of transcription but must originate at the level of protein synthesis or protein stability.

Binding of Cofactors Ada2 and CBP to Mono-, Di-, and Trimodular Constructs—Ada2 and CBP proteins are coactivators known to bind to the \(t1\) core (30, 37). To test whether the binding capacity of the \(t1\) core to coactivators correlates with the demonstrated transcriptional activity, an in vitro protein-protein interaction assay was performed using GST-Ada2 and GST-CBP-C2 fusion proteins and the \[^{35}S\]methionine-labeled in vitro translated \(t1\) core and different \(H\) segment proteins. As shown in Fig. 5A, proteins containing one, two, or three \(H2\) segments resulted in similar binding to both Ada2 and CBP-C2, but no binding to GST alone was seen. Furthermore, several constructs containing combinations of \(H1\) and \(H2\) modules did not show significantly higher binding affinity (Fig. 5B). The \(t1\) core included in the experiment as a control showed a similar binding affinity to that of the other constructs. Thus, the substantially higher activity seen in the transactivation experiments for the multisegment constructs is not due to a dramatically higher affinity for target factor binding.

DISCUSSION

The \(t1\) core activation domain of GR contains three putative \(\alpha\)-helical structural segments (25) that have been shown previously to have an important role in the transcriptional activation function of the GR receptor (30). In this study we have used a hybrid protein approach involving different combinations of the \(H1\) and \(H2\) activation submodules of the \(t1\) core to analyze the functional dependence on the modular structure. The purpose of the study was to address whether the \(t1\) core region should be viewed as a structurally integrated domain or as composed of redundant submodules. We have demonstrated that isolated \(H1\) and \(H2\) segments do not have significant residual activities on their own (Fig. 2). We have further shown that duplication of \(H1\) and \(H2\) segments in different combinations is sufficient for transcriptional activation. Results obtained with the duplication constructs also showed that neither segment carries unique determinants absolutely critical for transactivation function. In addition, trimodular constructs gave rise to higher transactivation activity than the duplication constructs, reaching levels comparable with the wild type \(t1\) core. These results support the model, mentioned in the intro-

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**FIG. 1.** Domain structure of GR and amino acid sequences of the \(t1\) fragments used. A, schematic representation of the human glucocorticoid receptor. \(t1\) and \(t2\) transactivation domains, the DBD, and the steroid-binding domain (SBD) of the GR are indicated. The \(t1\) core is indicated by a shaded box. The locations of segments with propensity for \(\alpha\)-helical conformation identified by NMR are shown as cylinders. B, the amino acid sequence of the \(t1\) core, \(t1\)-(187–227), \(H1\), and \(H2\). The \(BamHI\) site in the single \(H1\) and \(H2\) constructs gives rise to amino acids Gly and Ser in the \(H1\) and \(H2\) proteins, whereas the \(BglII/BamHI\) site that connects the different \(H1\) and \(H2\) modules in the other constructs gives rise to amino acids Arg and Ser.

**FIG. 2.** Transactivation potential of the \(t1\) core, \(t1\)-(187–227), and different \(H1\) and \(H2\) combinations in yeast cells. All activities were normalized to that of the \(t1\) core. The results represent mean values (± S.D.) obtained from at least three independent experiments for each construct tested.
binding affinity to target factors. Thus, large deletions in the modular constructs is therefore not due to an increased overall struct (of different combinations) compared with the monomodularly higher transactivation observed for the trimodular construct, Ada2 or CBP, with similar affinity (Fig. 5). The dramatic results show that the different constructs bind each target struct described here, which differ widely in activity. The most important to show whether this is also true for the constructs in which it is contained. Presumably, it either facilitates production or perhaps more likely stabilizes these proteins. In addition, H1 may have higher activation potential than H2 because a comparably high transactivation was observed for the relatively low protein levels of the H1-only constructs.

Previous studies have shown an exquisite proportionality between binding affinity and transcription potential for different 1 core amino acid substitution mutants (30). It was therefore important to show whether this is also true for the constructs described here, which differ widely in activity. The results show that the different constructs bind each target factor, Ada2 or CBP, with similar affinity (Fig. 5). The dramatically higher transactivation observed for the trimodular constructs (of different combinations) compared with the monomodular constructs is therefore not due to an increased overall binding affinity to target factors. Thus, large deletions in the 1 core do not change target factor binding affinity but severely affect transactivation potential so that the previously observed proportionality between binding affinity and transactivation activity is lost. An explanation probably lies in the fact that the number of binding modules was kept constant in the previous study (with the full-length 1 core) whereas it was varied in the present study.

It has been shown that different components of the transcription initiation complex (e.g. TATA-binding protein, Ada2, and CBP) are able to bind to the 1 core domain (30, 37, 39). That several transcription factors and coactivators are molecular targets for acidic activators has also been shown for activators such as VP16, NF-κB, and HNF-4. Examples of targets include TATA-binding protein, TFIIB, TFIIF1, TFIIH1, TFIIH80, CBP, Ada2, and PC4 (20, 40-42). Protein-protein in vitro interaction assays monitor binding affinity for one target factor at a time, whereas transactivation assays measure transcription activity in vivo where many different target factors/coactivators are present. Our results could therefore imply that multiple interactions are required for efficient transactivation. The stoichiometry of the binding of the 1 core to target proteins has not been determined. The presence of multiple redundant modules would also increase the concentration of binding sites that can interact with the target factors and thereby give rise to a higher association rate. The requirement for multiple modules, as demonstrated in this study, thus suggests that the

Aromatic and hydrophobic amino acids are known to be important for activity, as indicated by mutagenesis studies of acidic domains of GR (14), VP16 (15–17), NF-κB p65 (2), and HNF-4 (20). Furthermore, α-helical structure formation of acidic activator domains upon binding to putative target factors has been demonstrated in circular dichroism studies of the c-Myc activation domain bound to TATA-binding protein (38), crystal structure studies of the p53 activation domain bound to MDM2 (26), fluorescence analyses of the interaction of the VP16 activator domain with TATA-binding protein (27), and NMR studies of the VP16 activator domain upon interaction with TAF31 (28). These studies are consistent with an induced fit model for the folding of an otherwise unstructured activator domain. These findings together with the ability of the H1-only or H2-only proteins (e.g. H1-H1 and H2-H2) to activate transcription, shown here, suggest that secondary structure formation and/or formation of hydrophobic surfaces are likely to be more important for transcriptional activation than the primary amino acid sequence as such. However, our study also indicates that the two modules H1 and H2 are functionally distinct, at least in part. First, combinations of H1 and H2 are always better activators than H1-only or H2-only alternatives. Second, the H2 module has a positive effect on the protein levels of the constructs in which it is contained. Presumably, it either facilitates production or perhaps more likely stabilizes these proteins. In addition, H1 may have higher activation potential than H2 because a comparably high transactivation was observed for the relatively low protein levels of the H1-only constructs.

Protein-protein interactions of the 1 core and different H1 and H2 combinations with Ada2 and CBP-C2. Binding of the [35S]methionine-labeled in vitro translated 1 core or different H1 and H2 combinations to GST, GST-Ada2, or GST-CBP-C2 The input lanes represent 10% of the amount of labeled protein used in each pull-down. A, the effect of the number of H2 segments is shown. B, the effect of including H1 in different combinations with H2 is shown.
modular architecture of the activation domain may underlie its ability to activate gene transcription by influencing the kinetics through changes in association rate of its interaction with one or more target factors. This model would be consistent with our previous results showing proportionality between activation potential and binding affinity in r1 core mutants if the affinity changes observed for these mutants are also accompanied by changes in target factor interaction kinetics. In the future, direct association and dissociation measurements have to be made to test this model.

The similar properties in terms of hydrophobicity, acidic amino acid content, propensity for α-helical formation, and modular structure of the r1 core and other acidic activation domains could reflect a general mechanism for such activators, which would involve complex and dynamic interactions with different target factors acting synergistically to achieve efficient activation of transcription.

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