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Plasma membrane guanylate cyclase is a multimodule transduction system

Minireview Article

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Summary. This minireview highlights the studies which suggest that guanylate cyclase is a single-component transducing system, containing distinct signaling modules in a single membrane-spanning protein. A guanylate cyclase signaling model is proposed which envisions the following sequential events: (1) a signal is initiated by the binding of the hormone to the ligand binding module; (2) the signal is potentiated by ATP at ARM; and (3) the amplified signal is finally transduced at the catalytic site. All of these signaling steps together constitute a switch, which when turned on, generates the second messenger cyclic GMP.

Keywords: Amino acids – Guanylate cyclase – ATP-Regulatory Module – Atrial natriuretic factor receptor – Type C natriuretic factor receptor

Introduction

The discovery of a plasma membrane guanylate cyclase, which was also an atrial natriuretic factor receptor (Paul et al., 1987; Kuno et al., 1986, Meloche et al., 1988, Takayanagi et al., 1987), suggested a new transmembrane signaling concept which was radically different from the prevailing well-established concept for the adenylate cyclase system. In the hormone-dependent adenylate cyclase there is an assemblage of individual components – hormone receptor, GTP-binding protein, and cyclase catalytic moiety – for signal transduction; in contrast, the presence of dual activities, receptor binding and enzymic, on a single peptide chain indicated that the guanylate cyclase transmembrane protein contained both the information for signal recognition and its transduction into a second messenger (Paul et al., 1987). In addition, unlike the adenylate cyclase

and phosphatidylinositol systems which are G-protein-driven, the guanylate cyclase transduction system is a single component, multimodule system in which G proteins have no direct regulatory role.

Characterization of the surface receptor guanylate cyclase revealed another surprising aspect. The nature of the existence of the adenylate and guanylate cyclases is different in mammalian cells. In contrast to adenylate cyclase, which exists almost exclusively in a membrane-bound form, guanylate cyclase occurs in two forms: membrane-bound and soluble. Both the soluble and membrane guanylate cyclase forms occur ubiquitously in almost all mammalian cell types, and may be intimately involved in regulation of the central and peripheral related activities.

The current thinking is that the primary regulator of soluble guanylate cyclase is the nitric oxide gas, which acts through the heme-containing portion of the cyclase (reviewed in: Snyder, 1992). This present, brief, review is totally focused on the membrane guanylate cyclases, and discusses only the most recent developments, primarily from the authors' laboratories, which show: (1) the expanding nature of the cyclase family; (2) the molecular and biochemical features of the cyclases that may allow their classification into subfamilies; and (3) the regulatory mechanisms that govern the events of transmembrane signaling. The reader is referred to several excellent recent reviews which cover earlier studies in this field in a more exhaustive and general fashion (Sharma et al., 1988a, b; Needleman, et al., 1989; Brenner et al., 1990; Rosenzweig et al., 1991; Yuen and Garbers, 1992; history of the discovery of atrial natriuretic factor is reviewed in: deBold, 1985).

Receptor guanylate cyclase family

The initial study showed that the polyclonal antibody to the biochemically characterized atrial natriuretic factor receptor guanylate cyclase (ANF-RGC) only partially inhibited the crude membrane guanylate cyclase activity. The antibody inhibition increased with the increasing purity of the enzyme, fully inhibiting the homogeneous guanylate cyclase (Paul et al., 1987). Less than complete antibody inhibition of the cyclase activity suggested possible heterogeneity of the cyclases, only one of which was antibody-specific. At the time, the identity of membrane guanylate cyclase subtypes was not known. Later, immunological studies confirmed heterogeneity of the membrane cyclase system by showing antibody cross-reactivity to 3 proteins that were membrane guanylate cyclases and were also natriuretic factor receptors (Marala and Sharma, 1992). The antibody cross-reactivity characteristic suggested that these cyclase receptors were structurally similar. These immunological studies reflected the existence of a surface receptor guanylate cyclase family, a concept also supported by molecular cloning studies.

First, ANF-RGC was cloned (Chang et al., 1989; Chinkers et al., 1989). This was followed by a series of other cloning studies: Type C natriuretic factor receptor guanylate cyclase (CNP-RGC) (Koller et al., 1991); enterotoxin receptor

guanylate cyclase (STa-RGC) (Schulz et al., 1990; de Sauvage et al., 1991); GCα (Duda et al., 1991); and a retinal guanylate cyclase (RetGC) (Shyjan et al., 1992). The endogenous ligand of STa-RGC is probably guanylin (Currie et al., 1992), while the receptors for GCα and RetGC are not known.

Cloning studies had indicated a discrepancy in assignment of the molecular mass value to the wild type ANF-RGC. The predicted value of ANF-RGC from the amino acid sequence data was 115,852 (Chinkers et al., 1989), but the expressed protein, based on its [^{125}I]ANF crosslinking studies was 130 kDa (Chinkers et al., 1989). Because the crosslinking studies were not done on the pure protein, it was not possible to show that the 130 kDa ANF-cross-linked protein is also a guanylate cyclase.

These conflicting issues were resolved by the combined tools of biochemistry, immunology and recombinant DNA (Marala et al., 1992).

GCα was genetically tailored to create the ANF-RGC (Duda et al., 1991) which was structurally and functionally identical to the wild type cloned ANF-RGC. Expression studies indicated that this protein in its purified form was immunologically and functionally identical to the ANF-RGC biochemically characterized earlier (Marala et al., 1992). Thus, the identity of the wild type ANF-RGC to the cloned ANF-RGC was established.

These studies with the genetically-tailored ANF-RGC also demonstrated that the discrepancy in the predicted and observed values of the expressed protein is most probably due to the post-translational modification, such as the glycosylation state of ANF-RGC, because the genetically-tailored protein migrated as the 130 kDa protein.

Topographic model of receptor guanylate cyclase

The primary amino acid sequence of the cloned membrane guanylate cyclases suggested their identical topography. They contain a single membrane-spanning helical domain which divides the protein into two roughly equal portions; the N-terminal is extracellular and the C-terminal is intracellular. The receptor domain lies in the extracellular portion while the intracellular portion contains two domains: the one adjacent to the transmembrane is termed the "kinase-like" domain due to its sequence similarity to the tyrosine kinase family, and the C-terminal region contains the catalytic domain (Thorpe and Morkin, 1990; Chinkers et al., 1989).

Support for this "Topographic Model" came from site-directed (Goraczniak et al., 1992; Marala et al., 1992) and deletion-mutagenesis studies on ANF-RGC (Goraczniak et al., 1992; Chinkers and Garbers, 1989), in which the truncated-receptor cyclase showed basal guanylate cyclase activity, but no ANF-binding and ANF-dependent cyclase activity. The truncated-cyclase receptor, which migrated as a 70 kDa protein, bound ANF. The 70 kDa molecular mass closely resembles the predicted mass of the extracellular domain of ANF-RGC (Marala et al., 1992). Localization of the catalytic domain sequence motif in the carboxyl region of ANF-RGC was resolved through studies with the bacterial expression system (Thorpe and Morkin, 1990).

Receptor guanylate cyclase subfamilies

Primary amino acid sequence comparisons of the cloned ANF-RGC and CNP-RGC show about 80% identity in the intracellular segment of the proteins; there is, however, only about 40% identity in the extracellular domain (Chinkers et al., 1989; Lowe et al., 1989). With the exception of two amino acids, GCα is structurally identical to ANF-RGC. Both variant amino acids are located in the extracellular domain (Duda et al., 1991). This high degree of sequence identity between ANF-RGC, CNP-RGC and GCα suggests that these cyclases represent three subtypes of the natriuretic factor receptor sub-family, although the ligand for GCα is, as yet, unknown.

STa-RGC (de Sauvage et al., 1991) and RetGC (Shyjan et al., 1992) show far less sequence similarity between each other and to the natriuretic factor receptor cyclase subfamily. There is approximately 10 to 15% sequence similarity between the extracellular domains of STa-RGC and ANF-RGC or CNP-RGC, and about 15% identity between the extracellular domains of STa-RGC and RetGC. There is, however, a relatively high degree of sequence similarity, ranging from 40 to 45% among their intracellular regions, the catalytic region showing the most identity, from 50 to 55% (Shyjan et al., 1992).

It appears that the cloned RetGC (Shyjan et al., 1992) is a distinct cyclase subfamily, the other subfamily member being the biochemically characterized 112 kDa guanylate cyclase, termed ROS-GC (Margulis et al., 1993), present in the rod outer segments of bovine retina (Krishnan et al., 1978; Fleichman et al., 1980; Hakki and Sitaramayya 1990; Hayashi, and Yamazaki, 1991; Koch, 1991). The N-terminal and two internal peptide sequences of purified ROS-GC have about 90% similarity with the corresponding sequences of RetGC; the sequence identity with the natriuretic factor receptor cyclases is about 30% (Margulis et al., 1993). A 19 amino acid long sequence from a tryptic peptide of ROS-GC had no corresponding sequence to any of the known receptor cyclases (Margulis et al., 1993).

These results suggest that ROS-GC and RetGC are two members of the same cyclase subfamily, and this subfamily is distinct from the other subfamily of natriuretic factor receptor cyclases, and also from the subfamily comprising the enterotoxin receptor/s.

Thus, to date, structural studies have suggested the existence of three distinct subfamilies of receptor guanylate cyclases, which are: (1) the natriuretic factor receptor; (2) the enterotoxin receptor; (3) and the retinal guanylate cyclase. With time, members of these subfamilies and the subfamilies by themselves are bound to increase.

Signaling modules in guanylate cyclases

ANF-binding module

Site-directed (Goraczniak et al., 1992; Marala et al., 1992) and deletion-mutagenesis studies (Goraczniak et al., 1992; Chinkers and Garbers, 1989) showed that the ligand binding site resides in the extracellular region of ANF-

RGC (*vide supra*). Localization of this site was accomplished through GCα remodeling studies.

GCα is a plasma membrane guanylate cyclase, that, with the exception of two amino acids, is structurally identical to ANF-RGC (Duda et al., 1991). The two amino acid changes are the substitutions $Gln^{338} \rightarrow$ His and $Leu^{364} \rightarrow$ Pro, involving single nucleotide changes, CAG → CAC and CTG → CCG, respectively. GCα cyclase activity is independent of ANF (and other natriuretic peptides), and GCα is not an ANF-receptor (Duda et al., 1991). By oligonucleotide-directed mutagenesis, the GCα cDNA regions encoding amino acid residues 338 and 364 were remodeled to (1) create a double mutant encoding Gln^{338} and Leu^{364}; (2) a single-substitution mutant encoding Leu^{364}; and (3) a deletion mutant lacking residue 364. The double mutant and the single-substitution mutant expressed both ANF binding and ANF-dependent cyclase activities, but the deletion mutant did not express either of the above activities (Duda et al., 1991).

These results established that Leu-364 is a critical site of ANF signaling.

It is noted, however, that this study did not conclude in absolute terms a direct interaction between the ligand (ANF) and Leu-364. It is possible that the configurational arrangement of Leu-364 provides a three-dimensional structure for ANF binding. In the situation where it is replaced by Pro, the Pro residue may alter the binding site drastically and eliminate ANF binding.

ATP regulatory module (ARM)

ANF binds to the receptor domain and increases the catalytic activity of the enzyme, causing production of the second messenger, cyclic GMP. But this binding-signal by itself is not sufficient to stimulate the cyclase activity; the presence of ATP and Mg^{2+} is necessary (Chinkers et al., 1991; Marala et al., 1991). Thus, between the two domains, i.e. ligand-binding and catalytic, there appeared to be a module in the guanylate cyclase molecule which was allosterically regulated by ATP, and this putative ATP-regulated module bridges the binding-signal with the signal transduction.

There are two mechanisms, direct and indirect, by which ARM could mediate the ATP effect. In the indirect mechanism, interaction between ATP and cyclase would be through a separate ATP-binding protein (Chang et al., 1990); in the direct mechanism, ATP regulates guanylate cyclase activity by directly binding to it (Kurose et al., 1987).

Principal support for the direct mechanism comes from two observations. One, the homogeneous ANF-RGC specifically binds ATP (Marala et al., 1991). Two, an ANF-RGC-mutant, in which the kinase-like domain is deleted, is not stimulated by ATP (in the presence or absence of ANF) (Chinkers and Garbers, 1989). This interpretation implies that the ATP binding site of guanylate cyclase resides in the kinase-like domain, although no direct evidence for this conclusion was provided (Chinkers and Garbers, 1989).

Through a program in which a variety of mutants of GCα were created by site-directed and deletion mutagenesis and then the expression studies were conducted on them, a structural motif (Gly^{503}-Arg-Gly-Ser-Asn-Tyr-Gly^{509})

was identified that bound ATP and amplified the ANF-dependent cyclase activity; this, therefore, represented an ARM of the enzyme, which plays a pivotal role in ANF signaling (Goraczniak et al., 1992).

Like ANF-RGC, the mere ligand (CNP) binding to the receptor domain of CNP-RGC is not enough to maximally stimulate the cyclase activity. In this case also, obligatory to this activation process is an intervening step, which is regulated by ATP (Duda et al., 1993a, b). Through genetic remodeling techniques, a sequence motif (Gly^{499}-Ser-Ser-Tyr-Gly^{503}) was identified that bound ATP and amplified the CNP-dependent cyclase activity. This, therefore, represented an ARM of CNP-RGC.

These studies did not prove that the Gly-Xa-Xa-Xa-Gly motif is the direct ATP binding site. But a "predicted nucleotide-binding-protein model" indicates that the second glycine in the structural motif Gly-Xa-*Gly*-Xa-Xa-Xa-Gly is crucial in the direct GTP binding to p^{21} protein (Wirenga and Hol, 1983). This suggests a parallel between the structural motifs of GTP-binding proteins and the ATP-binding receptor guanylate cyclases. It is, therefore, a good possibility that the middle glycine in the ARM sequence – Gly-Xa-*Gly*-Xa-Xa-Xa-Gly – is the direct binding site of ATP. As has been suggested for the "nucleotide-binding-protein model" (Wirenga and Hol, 1983), it does not mean that the modification of the middle glycine will result in the complete elimination of the nucleotide binding to the protein. Such a change may merely result in the "altered mode of binding of the nucleotide" (Wirenga and Hol, 1983). This interpretation fits the findings where the disruption of the middle glycine in the glycine cluster did not result in the complete elimination of ATP binding with the ANF-RGC and CNP-RGC mutants (Duda et al., 1993a, b).

In conclusion, these findings provided a unified mechanism for the operation of both ANF and CNP signaling processes, and supported the multi-module concept of the guanylate cyclase transduction system (Goraczniak et al., 1992).

In addition to the stimulatory-ARM of guanylate cyclase, there also appears to be an inhibitory-ARM of ANF-RGC, because ATP in the presence of Mn^{2+} inhibits the ANF-dependent guanylate cyclase activity (Marala et al., 1991).

The ATP-regulated stimulatory mode of cyclase operation appears to be a unique characteristic of the natriuretic factor receptor subfamily. In contrast, ATP inhibits rod outer segment guanylate cyclase activity (Sitaramayya et al., 1991), and this ATP-inhibitory characteristic may be a typical feature of the ROS-GC subfamily. The identity of this inhibitory site is not known.

Putative protein kinase C (PKC) regulatory module

Studies with vasopressin in smooth muscle cells (Nambi et al., 1986; Nambi et al., 1987; Ballermann and Neuser, 1988), and in a variety of other cell systems (Jaiswal et al., 1988; Ballermann et al., 1988; Duda and Sharma, 1990) show that PKC-linked receptor signals negate the ANF-dependent guanylate cyclase activity and the cyclic GMP formation (Jaiswal et al., 1988; Duda and Sharma, 1990; Ballermann et al., 1988; Iwata et al., 1991). Based on these studies a hypothetical model was proposed which depicted an interaction of ANF and PKC-linked signaling pathways; interaction was such that ANF activated the

guanylate cyclase activity and PKC terminated the activated cyclase activity (Sharma et al.; 1988a, b, 1989a, b). Further support for this model has now come from a study with endothelin (ET-1). ET-1 stimulates membrane PKC activity and inhibits the ANF-dependent cyclic GMP formation in pulmonary aortic endothelial cells (Marala et al., 1993). PKC phosphorylates ANF-RGC directly or indirectly (Sharma et al., 1989a, b; Larose et al., 1992). Thus, it appears that ANF-RGC contains a PKC-regulatory inhibitory module.

The above mechanism of PKC regulation of ANF signal transduction may be unique to the natriuretic factor receptor cyclase family; because the PKC-activators, phorbol esters, stimulate enterotoxin-dependent cyclase activity (Crane et al., 1992). The stimulation parallels an increase in the enterotoxin binding activity, and may be mediated by phosphorylation of the cyclase or a closely related protein. This differential PKC regulation of the enterotoxin receptor cyclase and of the natriueric factor receptor cyclases may provide a biochemical marker differentiating the two cyclase subfamilies.

Guanylate cyclase signal transduction model

In contrast to the cAMP and phosphatidylinositol signaling pathways, in which three membrane components (receptor, G-protein and catalyst) participate to transduce the hormonal signal, guanylate cyclase is a single-component transducing system, containing distinct signaling modules in a single membrane-spanning protein. Two decisive modules, the ligand binding motif (Duda et al., 1991) and the ARM (Goraczniak et al., 1992, Duda et al., 1993a, b) of the protein have been identified, and the third, the cyclase catalytic module, lies on the distal

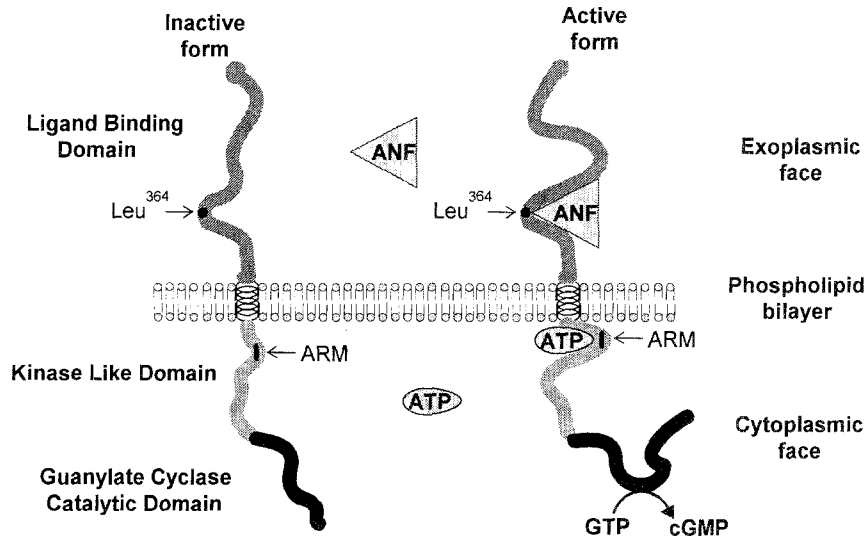

Fig. 1. ANF-RGC signal transduction model

carboxyl portion (Thorpe and Morkin, 1990). The possibility also exists for a fourth, the ATP-Mn inhibitory module (Marala et al., 1991), and for a fifth module, the PKC regulatory inhibitory module (Marala et al., 1993).

Based on these observations, a guanylate cyclase signaling model has been proposed which envisions the following sequential events: (1) a signal is initiated by the binding of the hormone to the ligand binding module; (2) the signal is potentiated by ATP at ARM; and (3) the amplified signal is finally transduced at the catalytic site. All of these signaling steps together constitute a switch, which when turned on, generates the second messenger cyclic GMP (Goraczniak et al., 1992). This multimodule signaling model is schematically represented in Fig. 1.

Recent findings show that ATP causes inhibition of ANF binding to ANF-RGC (Larose et al., 1992; Jewett et al., 1993). In such a case, upon binding ATP, ARM performs two functions at two opposite ends of the ANF-RGC molecule. One function occuring at the extracellular domain, transforms the high affinity ANF receptor to the lower affinity, and the other function occurring at the catalytic domain causes the signal transduction event to occur.

It is anticipated that this ANF-RGC signal transduction model will serve as a prototype for all natriuretic factor signaling processes, and some features of this model will be applicable to the other membrane guanylate cyclase subfamilies.

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