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ATP-regulated module (ARM) of the atrial natriuretic factor receptor guanylate cyclase

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Abstract

ATP is an obligatory agent for the atrial natriuretic factor (ANF) and the type C natriuretic peptide (CNP) signaling of their respective receptor guanylate cyclases, ANF-RGC and CNP-RGC. Through a common mechanism, it binds to a defined ARM domain of the cyclase, activates the cyclase and transduces the signal into generation of the second messenger cyclic GMP. In this presentation, the authors review the ATP-regulated transduction mechanism and refine the previously simulated three-dimensional ARM model (Duda T, Yadav P, Jankowska A, Venkataraman V, Sharma RK. Three dimensional atomic model and experimental validation for the ATP-regulated module (ARM) of the atrial natriuretic factor receptor guanylate cyclase. Mol Cell Biochem 2000;214:7–14; reviewed in: Sharma RK, Yadav P, Duda T. Allosteric regulatory step and configuration of the ATP-binding pocket in atrial natriuretic factor receptor guanylate cyclase transduction mechanism. Can J Physiol Pharmacol 2001;79: 682–91; Sharma RK. Evolution of the membrane guanylate cyclase transduction system. Mol Cell Biochem 2002;230:3–30). The model depicts the ATP-binding dependent configurational changes in the ARM and supports the concept that in the first step, ATP partially activates the cyclase and primes it for the subsequent transduction steps, resulting in full activation of the cyclase.

Keywords: ATP-regulated module; Atrial natriuretic factor; Guanylate cyclase

1. Introduction

With the landmark discoveries of atrial natriuretic factor (ANF) [13] and the atrial natriuretic factor-receptor guanylate cyclase (ANF-RGC) [61,78,84,85,111] dawned a new era of cellular signal transduction. They showed that the research fields of cardiovascular biology and membrane guanylate cyclase transduction are intertwined; and most significantly, the finding that the ANF-RGC activity is hormonally-dependent profoundly impacted the membrane guanylate cyclase field in many ways (recently reviewed in: [103]; some of the material from this reference has been reproduced in the present review; for essays covering almost all the guanylate cyclase area up to the year 2001, the readers are referred to a special volume "Guanylate Cyclase" *Mol Cell Biochem* 230: 2002). This finding: (1) settled the then ongoing debate, which questioned the independent existence of a peptide hormone-dependent guanylate cyclase transduction system in mammalian systems; (2) It established cyclic GMP as a bona fide hormonal second messenger; (3) It showed that guanylate cyclase exists in two distinct forms, the soluble and the membrane bound. Prior to the finding, the soluble form was presumed to be the sole form of the guanylate cyclase. The finding established that the soluble form is a transducer of the nitric oxide signal, and the membrane bound form is a transducer of the peptide hormone signal. The nitric oxide signal is generated inside the cell and the peptide hormone (ANF) signal outside the cell.

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The original report disclosing the discovery noted, 'coexistence of the ANF receptor and guanylate cyclase activities on a single peptide chain indicates that the mechanism of trans-membrane signal transduction involving second messenger, cyclic GMP, is different from the well-established adenylate cyclase system. In hormone-dependent adenylate cyclase there is an assemblage of individual components – receptor, GTP binding protein, and catalytic moiety – for signal transduction. In contrast, the presence of dual activities – receptor binding and enzymic – on a single polypeptide chain indicates that this trans-membrane protein contains both the information for signal recognition and its translation into a second messenger' [84]. Thus, the discovery defined a new paradigm of cellular signaling in which cyclic GMP was a second messenger of the peptide hormone; the production of the second messenger was directly through the predicted single membrane spanning protein guanylate cyclase; and the new paradigm was remarkably unlike the previous known paradigms of the cyclic AMP and IP_3 signaling systems whose origins occurred through the signaling of G-protein coupled seven trans-membrane spanning receptors. At the time of the discovery of ANF-RGC [61,78,84,85,111], it was just being realized that the G-protein coupled receptors are serpentine receptors (reviewed in: [3,11,67]), and as yet none of the G-protein coupled IP_3 receptors was cloned.

Presently, there are three known members of the ANF family. They are termed ANF (alternatively called ANP), brain natriuretic peptide (BNP) and type C natriuretic peptide (CNP) (reviewed in: [81,95]). The residential sites of ANF and BNP are in the atrial and the ventricular granules of the heart. With each atrial stretch, defined doses of these peptides are pulsated into the blood stream, and carried to their target tissues where they exhibit their biological activities. This mode of action was first demonstrated for ANF by deBold's group [13], which classified the heart as an exocrine gland, and, thereby, showed that it is not merely a blood pump [13].

In contrast to ANF and BNP, CNP does not exist in the heart granules. Its primary residence is in the vascular endothelial cells [35,109,118], and may also be in the localized regions of the central nervous system. To varying degrees, all three natriuretic factors exhibit vasodilatory activities and lower blood pressure by accelerating the renal sodium and water excretion (reviewed in: [2,4,43]). Gene knock-out studies link ANF with salt-sensitive hypertension [54]. And ANF-RGC has been linked with the salt-resistant form [68]. There is, however, some reservation regarding this conclusion [56,82,108]. Some studies link BNP with skeletal growth [110] and CNP with bone cartilage growth [5]. It is, therefore, likely that besides being common vasodilator agents, the individual natriuretic peptides also possess biological activities, which are unique to them.

Subsequent to its biochemical characterization, ANF-RGC and its homologue, CNP-RGC, were cloned [7,8,23,25,69,83,98]. The identities between the cloned and the native ANF-RGCs were established through the specific polyclonal antibody probe against native ANF-RGC [72]. Both the cloned and the native forms showed identical immunoaffinity [72].

Antibody studies also suggested ubiquity of the ANF-RGC presence in the mammalian cells because the cyclase was present in all the tested tissues of the rat adrenal gland, the testes and in the bovine aortic endothelial cells [74]. Subsequent studies showed that besides being positively regulated by the parent hormone, ANF, ANF-RGC activity is also negatively regulated by phorbol-12-myristate 13 acetate (PMA), an activator of protein kinase C (PKC), and directly by PKC [30,51,66,101]. Similarly, the vasoconstrictors – endothelin, angiotensin II and arginine-vasopressin – which act through PKC, also inhibit activities of ANF-RGC and CNP-RGC [1,52,73,86,96]. In a model of ANF-RGC (GC-A) transfected NIH3T3 cells protein kinase C mediates the negative regulation of ANF-RGC through the activation of a hypothetical phosphatase, which lowers the ANF-dependent cyclic GMP level [86]. Thus, through protein kinase C, the vasorelaxant system of ANF-RGC appears to be internetted with the vasoconstrictor systems of endothelin, angiotenisn II and arginine-vasopressin.

The present studies show that besides being regulated by ANF, ANF-RGC is also regulated by BNP [7], suggesting that the cyclase is a receptor for both ANF and BNP. ANF-RGC and CNP-RGC, together with another cloned membrane guanylate cyclase, enterotoxin receptor guanylate cyclase (STa-RGC), constitute the peptide hormone receptor guanylate cyclase family. STa-RGC is a receptor for the bacterial enterotoxin [15,97,106,119] and also for the endogenous peptide hormones – guanylin and uroguanylin ([12,44,55,121]; reviewed in: [37,38,99,124]). A central feature of this guanylate cyclase family is that all its members are peptide hormone receptors. These receptors, by binding to their specific ligands, transduce the signal generated outside the cell into production of the second messenger cyclic GMP inside the cell. The membrane guanylate cyclase protein solely carries out the entire signal transduction operation. Thus, in the first chapter of the membrane guanylate cyclase transduction field story, this transduction mechanism was shown to be strikingly different from that of the G-protein coupled receptor signal transduction mechanism, and the membrane guanylate cyclase family was classified as a surface receptor family.

Because the first three characterized membrane guanylate cyclases were surface receptors, the concept evolved that the membrane guanylate cyclase form is solely a surface receptor; that is, it is regulated exclusively by peptide hormone signals (reviewed in: [103]). Implicit in this concept was that the family is designed to transduce only the signals generated outside the cell. With the discovery of a Ca^{2+}-modulated membrane guanylate cyclase subfamily, this concept has now been revised (reviewed in: [91,103]). The first member of this subfamily was cloned from retina based on the sequence of the protein purified from the rod outer segments (ROS) of the photoreceptor cells [41,76], hence, it bore the name ROS-GC and its homologues constitute the ROS-GC sub-