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Review

Phosphodiesterase 9: Insights from protein structure and role in therapeutics

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ABSTRACT

This review focuses on the development of drugs targeting phosphodiesterase 9A (PDE9A). PDE9A normally regulates cGMP (cyclic guanosine monophosphate) levels, which in turn regulate signal transduction. However, in pathological conditions, PDE9A inhibition is required to treat diseases that lower the level of cGMP. Hence, there is a need for specific PDE9A inhibitors. Aligning the 3D structure of PDE9A with other phosphodiesterases reveals residues crucial to inhibitor selectivity. GLU406 is unique to PDE9A and stabilizes the side chain of an invariant glutamine (GLN453). TYR424 is another relevant residue, unique only to PDE9A and PDE8A. Therefore, TYR424 could discriminate between PDE9A and all other PDEs except PDE8A. TYR424 should also be considered in the design of selective inhibitors because PDE8A has low expression levels in the brain. Hence, GLU406 and TYR424 are important target residues in the design of PDE9A-selective inhibitors.

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Contents

Introduction

Cellular communication is important for coordinating multitudinous activities between various cells and their extracellular environment. In mammalian cells, signal transduction is carried out by various signaling molecules. Among these molecules, the second messengers cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) act as mediators in transmitting a wide variety of external signals through membrane-bound receptors, which in turn regulate many intracellular metabolic processes (Kim and Park, 2003; Wang et al., 2010). Fig. 1 illustrates signal transduction through the second messengers cAMP and cGMP along with their associated metabolic activities.

cGMP is involved in a myriad of cellular functions, including neurotransmission, smooth muscle relaxation, platelet aggregation inhibition, blunting cardiac hypertrophy, protection against ischemia/reperfusion injury of the heart, and improvement in cognitive function (Francis et al., 2011). The cGMP signaling pathway mainly involves three enzymes: guanylyl cyclases (GC), phosphodiesterases (PDEs) and protein kinase G (PKG). cGMP synthesis is initiated by the activation of soluble membrane-bound guanylyl cyclase. Three major targets of cGMP are cGMP-dependent protein kinase (PKG), cGMP-dependent phosphodiesterases, and cGMP-gated ion channels (CNG) (Lucas et al.,

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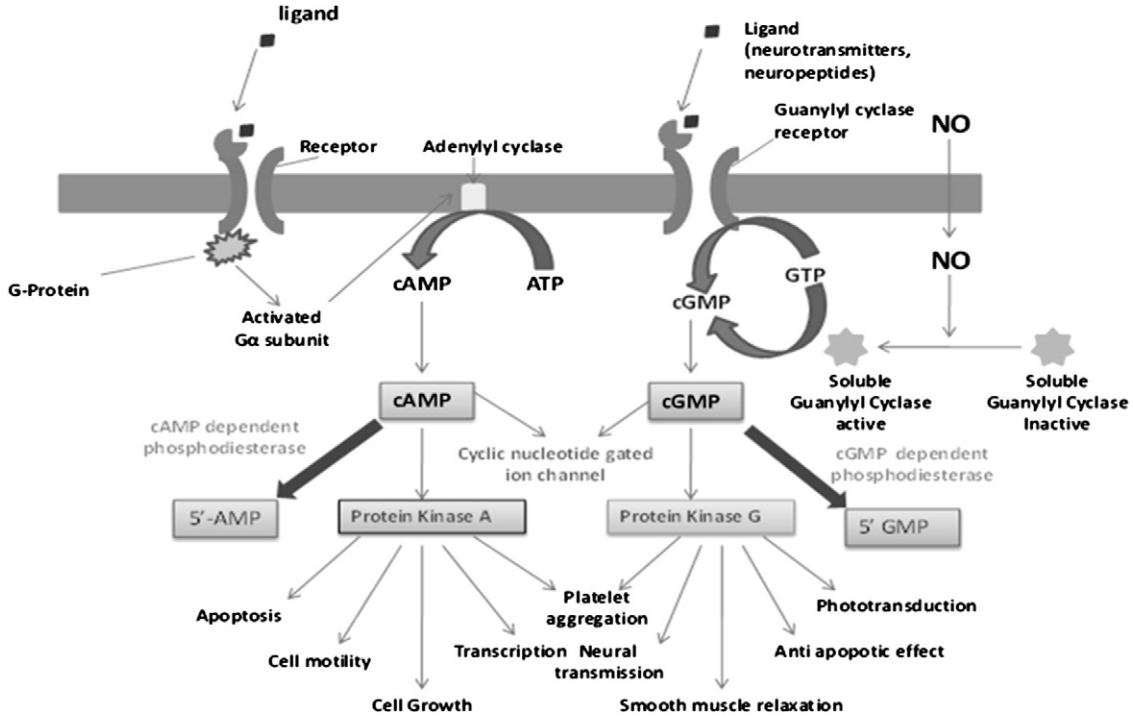

Fig. 1. Pathway of signal transduction in the cell.

2000; Friebe and Koesling, 2003; Mullershausen et al., 2004; de Vente, 2004). Among these targets, cGMP-specific phosphodiesterases play important roles in regulating cellular signals by controlling the intracellular cGMP level. However, in various pathophysiological conditions, cGMP-specific phosphodiesterases act as a potential biomarker. These conditions include male erectile dysfunction, neurodegenerative disease (including Alzheimer's disease, schizophrenia, Parkinson's disease (PD), Creutzfeldt–Jakob disease (CJD), diabetes, obesity, chronic obstructive pulmonary disease (COPD), and certain cardiovascular diseases (Oeckl et al., 2012)). Thus, cGMP-dependent phosphodiesterase inhibition has become the routine choice in drug development for such diseases. Its inhibition leads to persistent signaling by increasing the level of cGMP (Reneerkens et al., 2009). Several inhibitors are available against various PDEs. Sildenafil (synthesized by a group of pharmaceutical chemists at Pfizer's research facility in Sandwich, Kent, England), is a phosphodiesterase 5 (PDE5) inhibitor widely used to treat male erectile dysfunction (Goldstein et al., 1998). However, the search for specific inhibitors against a particular PDE member still remains a challenge due to the scarcity of available knowledge on this subject (Wang et al., 2007; Liu et al., 2008; Hou et al., 2011). Therefore, very few drugs that specifically inhibit this particular member of the phosphodiesterase superfamily have successfully reached the market.

A plethora of reviews have been published on the phosphodiesterase superfamily (Card et al., 2004; Zhang et al., 2004; Lugnier, 2006; Bender and Beavo, 2006; Halpin, 2008; Francis et al., 2011; Keravis and Lugnier, 2012). However, very few reviews exist on one particular PDE family. This review emphasizes the details of PDE9, including its structure, mechanism of action, inhibition pattern and drug development. Furthermore, this review summarizes research progress on PDE9 with the intent to develop PDE9-specific inhibitors.

Overview of cyclic nucleotide phosphodiesterase enzyme

Phosphodiesterases are the most prominent family of enzymes that degrade cAMP and cGMP by hydrolysis to 5′-AMP and 5′-GMP, respectively (Braumann et al., 1986; Trong et al., 1990). Figs. 1 and 2 depict phosphodiester bond cleavage by phosphodiesterase enzymes, resulting in cell signal disruption.

PDEs can be divided into three classes: class I, class II and class III. Mammalian PDEs belong to class III (Omori and Kotera, 2007). The human genome contains genes that encode 21 PDEs from 11 different families (1–11). This classification is based on amino acid sequence, a conserved C-terminal catalytic domain of ~270–300 amino acids, and a regulatory domain present between the N-terminal splicing region and the C-terminal catalytic domain. Each family contains several isoforms generated by using various transcriptional start sites and alternate mRNA splicing (Bender and Beavo, 2006; Lugnier, 2006; Ke and Wang, 2007). The regulatory domain is the most diverse region of the phosphodiesterase enzyme structure and is therefore the basis for classification within the superfamilies (Fig. 3).

PDE members also differ in terms of substrate affinity, specificity, and subcellular localization. These differences can be exploited in the development of specific inhibitors (Russell et al., 1973). Table 1 provides complete details of the PDE families, including the various subtypes, Km values for cGMP/cAMP, site of localization, available inhibitors, and the cellular activities influenced by the inhibition of PDE.

On the basis of substrate specificity, phosphodiesterases are divided into three groups: (1) cAMP specific-PDE 4, 7 and 8; (2) cGMP specific-PDE 5, 6 and 9; and (3) both cAMP and cGMP specific-PDE 1, 2, 3, 10 and 11 (Mehats et al., 2002; Conti and Beavo, 2007). While these specificities are determined by the highly conserved catalytic domain, the specific mechanism of substrate recognition remains a question (Ke et al., 2011; Hou et al., 2011). According to Zhang et al. (2004), a "glutamine switch mechanism" may be important for selectivity. This is because the γ-amino group of a conserved or invariant glutamine in the PDE active site can adopt two different orientations. In one orientation, the hydrogen bond network supports guanine binding, resulting in cGMP selectivity. In the second orientation, the network supports adenine binding, resulting in cAMP selectivity. In contrast, in the dual-specificity PDEs, the side chain of glutamine can switch between the two orientations, resulting in specificity towards both the cyclic nucleotides (Zhang et al., 2004; Jeon et al., 2005). Binding patterns of the invariant glutamine of different phosphodiesterases are shown in Fig. 4.

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