Functional characteristics and research trends of PDE11A in human diseases (Review)

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Received March 26, 2022; Accepted June 15, 2022

DOi: 10.3892/mmr.2022.12814

Abstract. cAMP and cGMP are important secondary messengers involved in cell regulation and metabolism driven by the G protein-coupled receptor. cAMP is converted via adenylyl cyclase (AC) and activates protein kinase A to phosphorylate intracellular proteins that mediate specific responses. cAMP signaling serves a role at multiple steps in tumorigenesis. The level of cAMP is increased in association with cancer cell formation through activation of AC-stimulatory G protein by mutation. Phosphodiesterases (PDEs) hydrolyze cAMP and cGMP to AMP and GMP. PDEs are composed of 11 families, and each can hydrolyze cAMP and cGMP or both cAMP and cGMP. PDEs perform various roles depending on their location and expression site, and are involved in several diseases, including male erectile dysfunction, pulmonary hypertension, Alzheimer's disease and schizophrenia. PDE11A is the 11th member of the PDE family and is characterized by four splice variants with varying tissue expression and N-terminal regulatory regions. Among tissues, the expression of PDE11A was highest in the prostate, and it was also expressed in hepatic skeletal muscle, pituitary, pancreas and kidney. PDE11A is the first PDE associated with an adrenocortical tumor associated genetic condition. In several studies, three PDE11A mutations have been reported in patients with Cushing syndrome with primary pigmented nodular adrenocortical disease or isolated micronodular adrenocortical disease without other genetic defects. It has been reported that an increase in PDE11A expression affects the proliferation of glioblastoma and worsens patient prognosis. The present mini-review summarizes the location of PDE11A expression, the impact of structural differences and disease relevance.

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1. Introduction

Molecular and genetic studies of the endocrine system have progressed rapidly over the past few decades. Cyclic adenosine monophosphate (cAMP) is the most important secondary messenger involved in endocrine system development and function. Dysregulation of cAMP expression and signaling perturbs the endocrine physiology and causes disease. cAMP production and degradation is mediated by ACs and phosphodiesterases (PDEs) respectively (1-5). PDEs hydrolyze the phosphate bonds of cyclic nucleotides; 11 PDE gene families have been identified based on amino acid sequences, biochemical properties, and inhibitor profiles (6,7). PDEs may share a catalytic function but differ in subcellular localization and tissue expression status (7). PDEs hydrolyze cAMP and cyclic guanosine monophosphate (cGMP) to AMP and GMP. PDEs may degrade cAMP (PDE4, 7, 8), cGMP (PDE5, 6, 9), or both.
PDEs perform various roles depending on their location and expression status. For example, inhibitors of PDE5 serve as therapeutic agents for male erectile dysfunction and pulmonary hypertension (11,12). PDE9A and PDE10A are widely distributed throughout the central nervous system (CNS); modulation of their expression usefully treats Alzheimer's disease (13) and schizophrenia (14-16). PDE11A degrades both cAMP and cGMP (17-21). PDE11A features four splice variants (1-4) varying in terms of tissue expression and the N-terminal regulatory regions. The N-terminal domain is regulatory in nature and the C-terminal domain catalytic. The longest isoforms of PDE11A in the mouse and human share ~95% protein sequence homology. The PDE11A level is highest in the prostate (22) of the various splice variants, PDE11A1 and PDE11A3 are found in the spleen (23,24) and PDE11A4 in the hippocampus (25). PDE11A is also expressed in the liver, skeletal muscle, pituitary gland, pancreas, and kidneys (18,19,22). Thus, PDE11A expression and structural characteristics vary by tissue location. This mini-review summarizes the locations of PDE11A expression, the effects of structural differences, and disease involvement.

2. cAMP/cGMP-dependent signaling

cAMP and cGMP are important secondary messengers involved in cell regulation and metabolism (6) driven by the GPCR. AC catalyzes conversion of ATP (Adenosine triphosphate) to cAMP and inorganic pyrophosphate; cAMP activates cellular proteins that mediate specific responses (26). cAMP induces dissociation of the Gs subunit (encoded by the GNAS gene) from G-protein, AC activation, cAMP generation, and PKA activation. PKA is a tetrameric complex of two regulatory subunits (PRKACA and PRKACB). The latter is responsible for phosphorylation of various enzymes and transcription factors, including the cAMP response element-binding protein (CREB) (Fig. 1). cAMP signaling plays roles during several steps of tumorigenesis. Inactivation of germline mutations in the alpha regulatory subunit gene of PKA induces the Carney complex (27-32) (an autosomal-dominant disease characterized by cardiac myxoma, schwannoma, and endocrine tumors; Carney complex is one of the most common types of primary pigmented crystalline adrenocortical disease associated hyperplasia) (33). Such mutations are also implicated in cancer cell formation via activation of the stimulatory G protein of AC, increasing the cAMP level (34). Similar to cAMP, cGMP is degraded by class I phosphodiesterase in metazoans, some of which are activated by cGMP binding to the GAF domain (35). Cyclic GMP signaling is not observed in eubacteria, plants, and yeast but is found in vertebrates. Besides that, it was also found in Drosophila and Caenorhabditis elegans with cGMP signaling, which is mediated by cGMP regulatory protein kinase G, possibly Ras guanine nucleotide exchange factor, and ion channels, is similar to that of vertebrates. Furthermore, these regulators contain the cyclic nucleotide-binding domain instead of the GAF domain (36,37). In metazoans, cGMP is synthesized by two guanylyl cyclases, one membrane-bound and the other soluble, and has a common phylogenetic precursor. Although no close homologs of this protein have been found in Dictostelium, Dictostelium guanylyl cyclases (38), guanylyl cyclases A and soluble guanylyl cyclases are similar to AC. guanylyl cyclases A has a dozen ubiquitous topologies on metazoan AC, whereas soluble guanylyl cyclases is just homologous to a small family of soluble AC present in vertebrates and bacteria (39,40). Upregulation of cGMP levels by PDEs induces activation of PKG, which promotes vasodilation and increases blood flow, particularly in the brain (41). cAMP also contributes to tumorigenesis via PDE (6), which increases cAMP and cGMP levels (1.8-10), resulting in sustained activation of the cAMP/PKA cascade. PDE is expressed in many different cancer cells, which may also host PDE mutations (examples PDE11A R804H, and R867G (6,42,43). An association between PDE genetic changes and tumorigenesis has been noted, particularly in the prostate, testis, and adrenal cortex (44,45). Hence, mutations in PDE and circulation of cAMP and cGMP are essential not only for human development but also for cancer and many diseases.

3. Phosphodiesterase family

PDEs regulate cAMP and cGMP production and are essential enzymes. PDEs are found in various tissues where they perform different roles. PDE features 11 different isoforms (Fig. 2). The four PDE1 isoforms (PDE1A, PDE1B, PDE1B1-2, and PDE1C1-2) are found in the brain, sperm, kidney, liver, pancreas, and thyroid gland (46-48); the heart (49); immune cells (50); and the olfactory epithelium (51) respectively, and regulate both cAMP and cGMP action. The PDEs play roles in vascular smooth muscle contraction and proliferation, sperm function, dopamine signaling, and immune cell activation. The common PDE1 subtype inhibitors include Vinpocetine, IC224 (PDE1A), SCH51866, 8-MeoM-IBMX (PDE1B), Zaprinast (PDE1B1-2), and Sildenafil (PDE1C1-2). PDE2A1-3 is expressed in the adrenal glomerulosa (52). The PDE2 proteins regulate both cAMP and cGMP actions and control aldosterone and ACTH secretion and long-term memory. Common PDE2A inhibitors include EHNA, BAY60-7550, PDP, and IC933. PDE3 includes PDE3A1-3 and PDE3B. The former is expressed in the heart (53), adipocytes, oocytes, cardiac and vascular smooth muscle, myocardium, and platelets (54). PDE3B is expressed in heart muscle (55), the immune system (56), endothelial cells (mediating permeability and cell proliferation) (57), the brain (58) and the liver (59). PDE3A and PDE3B regulate both cAMP and cGMP production; PDE3A controls cardiac contraction, platelet aggregation, vascular smooth muscle contraction, cell maturation, and renin release. PDE3B modulates lipolysis, glycogenolysis, insulin secretion, and heart function. Common PDE3 inhibitors include amrinone, cilostazol, milrinone, and enoximone. In addition, many inhibitors have been reported to modulate PDEs (Table 1). PDE4 includes PDE4A, PDE4B, PDE4C, and PDE4D. PDE4 is expressed in the heart and small intestine (60), immune cells (61), and the brain (62). Unlike PDEs 1, 2, and 3, PDE4 exhibits a higher affinity for cAMP than cGMP and controls brain function, monocyte and macrophage activation, neutrophil infiltration, vascular smooth muscle proliferation, fertility, and heart β-adrenergic signaling and excitatory/contract coupling. PDE5 includes PDE5A1-3 expressed in the lung,
Figure 1. General cyclic AMP signaling pathway. cAMP is a nucleotide that acts as an important secondary transporter in numerous signal transmission pathways. The generation of cAMP is regulated by AC in a G-protein-dependent manner. The decomposition of cAMP is regulated by PDE. cAMP is involved in several signal transmission pathways, including controlling ion channel operation and PKA activity. When PKA is activated, phosphorylation of CREB activates the transcription of various target genes. This regulates various cell functions, including cell proliferation and differentiation, gene transcription, and protein expression. AC, adenylyl cyclase; CREB, cAMP reactive element binding protein; GPCR, G-protein-coupled receptor; PDE, phosphodiesterase; PKA, protein kinase A.

Figure 2. Structure and function of the PDE family. All PDEs regulate the levels of cAMP and cGMP or cAMP/cGMP. There are ~21 PDE classes in humans and mice. Based on structural similarities, such as sequence homogeneity, protein substrate specificity, dynamic properties, endogenous resection, and enzyme properties, it is classified into 11 different isoforms based on sensitivity to inhibitors. PDE shares a catalytic domain with a common COOH end. Different domains (CaM, cGMP binding, UCR, PAS and target domains) exist for each family. PDE, phosphodiesterase; CaM, calmodulin; PAS, Per-Arnt-Sim; UCR, upstream conserved region.
penis, smooth muscle (28), platelets (63), brain (64) and cardiac muscle (65). Both PDE5 enzymes regulate cGMP; the nitrous oxide (NO)/cGMP effects in vascular smooth muscle, platelets, and the lower urinary tract; and the cardiac stress response. PDE6 includes PDE6A, PDE6B, and PDE6C expressed in photoreceptors (66) and the pineal gland (67). PDE6 regulates cGMP action, controls the cGMP concentrations of rod and cone photoreceptors, and is the primary effector enzyme of the phototransduction cascade. PDE7 features PDE7A1‑2 and PDE7B1‑3 found in immune cells (68), skeletal and cardiac muscles (69) and the brain (70). PDE7 modulates the cAMP activity and plays an important role in the regulation of human T cell function. PDE8 includes PDE8A1‑5 and PDE8B1‑3 found in immune cells (71), the heart (72), the ovary and testes (73), the thyroid gland (74), placenta, brain (75) and the adrenal gland (76). Both PDE8s regulate cAMP activation and TSH levels, adrenal steroid production, luteinizing hormone signaling, and steroidogenesis in Leydig cells, and activate T cells. PDE9 includes PDE9A1‑6 expressed in the kidney, spleen, gut, and prostate (77). PDE9 regulates cGMP activation to play a role in energy balance. PDE10 includes PDE10A1‑2 expressed in the brain, testis, and thyroid (78). PDE10 regulates both cAMP and cGMP actions and plays roles in striatal activation and behavioral activity. PDE11 includes PDE11A1‑4 of the testis, pituitary gland, heart, kidney, liver (18,19), prostate, adrenal gland, and colon (22), but only the A4 splice mutant is expressed in adrenal tissue. PDE11A regulates both cAMP and cGMP actions and is involved in spermatogenesis. PDE11A4 was recently found in the hippocampus (23,79). Besides that, all PDEs are expressed somewhere in the CNS and hydrolyze cAMP and cGMP to perform their respective roles (Fig. 3A) (80). However, when the central nervous system is damaged, the increase of PDEs expression activates immune cells and decreases the regeneration of neuronal cells, resulting in the death of neural cells (Fig. 3B) (81). Therefore, all PDE families can perform their respective roles depending on the expression site, and all PDEs also can contribute to the growth and development of nerve cells and cancer cells.

### 4. PDE11A and tumors

cAMP and cGMP are important GPCR-driven secondary messengers controlling cellular regulation and metabolism. cAMP is formed by the actions of AC and PDE and mediates cellular responses by activating PKA to phosphorylate intracellular proteins (4,5). In addition, the cAMP has been implicated in various tumorigenesis due to either increasing expression levels by activating the stimulatory G protein of AC or degraded by PDE11A. PDE11A encoded on chromosome 2q31.2 is highly polymorphic and was also the first PDE

| Table I. Inhibitors commonly used for PDEs. |
|---------------------------------------------|
| **Family** | **Type** | **Commonly used inhibitors** |
| PDE1       | PDE1A    | Vinpocetine, IC224, SCH51866, 8-MeOM-IBMX |
|            | PDE1B    | Zaprinast |
|            | PDE1B1-2 | Sildenafil |
| PDE2       | PDE2A1-3 | EHNA, BAY60-7550, PDP, IC933 |
| PDE3       | PDE3A1-3 | Milrinone, Tolafentrine, Cilostazol, Cilostamide, Trequinsin, OPC-33540, Dihydropyridazinone, Lixazinone |
|            | PDE3B    | |
| PDE4       | PDE4A    | Cilomilast, Rolipram, Ro20-1724, Roflumilast, AWD12281, V11294A, SCH35159, Denbufylline, Arofylline, Tolafentrine, Zardaverine |
|            | PDE4B    | |
|            | PDE4C    | |
|            | PDE4D    | |
| PDE5       | PDE5A1-3 | Sildenafil, Tadalafil, DA8159, E402, Vardenafil, Zaprinast, DMPPO, Dipyridamole |
| PDE6       | PDE6A    | Zaprinast, Dipyridamole, Sildenafil, Verdenafil, Tadalafil |
|            | PDE6B    | |
|            | PDE6C    | |
| PDE7       | PDE7A1-2 | BRL 50481, IC242, Dipyridamole, BMS-586353, Thiadiazoles |
|            | PDE7B1-3 | |
| PDE8       | PDE8A1-5 | Dipyridamole |
|            | PDE8B1-3 | |
| PDE9       | PDE9A1-6 | BAY 73-669, SCH51866, Zaprinast |
| PDE10      | PDE10A1-2| Papaverine, Zaprinast, Dipyridamole, PQ-10 |
| PDE11      | PDE11A1-4| Dipyridamole, Zaprinast |

PDE, phosphodiesterase.
associated with an adrenocortical tumor-associated genetic condition. Furthermore, PDE11A degrades not only cAMP but also cGMP (82). Besides, several previous studies found that PDE11A mutations were mainly expressed in abnormal adrenal glands (19,83). Three PDE11A mutations have been reported in Cushing syndrome patients with a primary pigmented nodular adrenocortical disease or isolated micronodular adrenocortical disease without other genetic defects. An association between the GWA single-nucleotide polymorphism (SNP) of PDE11 and adrenocortical tumors has also been confirmed (43). Mutations and relationships of PDE11A have been reported in numerous types of cancer, as well as the most studied adrenal cortical tumors (https://www.cbioportal.org/).

The heterozygous inactivation strains of Pde11a in patients were identified in non-secreting adrenal cortical adenoma, and heterozygous missense strains were more common in Primary bilateral macronodular adrenal hyperplasia (24%) and adrenocortical carcinomas (19%) compared to control group (5.7%) (84). Furthermore, the p.R867G PDE11A mutation was found in one patient with familial Primary bilateral macronodular adrenal hyperplasia (85). In a Primary bilateral macronodular adrenal hyperplasia cohort, the frequency of all PDE11A variants was significantly higher in Primary bilateral macronodular adrenal hyperplasia patients (28%) than in controls (7.2%). The inactivating PDE11A mutation (p.R307) was also found in adrenocortical cancer-associated genetic condition patients (19). Not only that, in the New York Cancer Project, Horvath et al (43,86) studied 745 patients with adrenocortical tumors and found PDE11A sequence changes including three truncation mutations (c.171Tdel/fs41X, c.919C>T/p.R307X and c.1655_1657TCTdelICIns/fs15X) and two missense substitutions [c.2411G>A(R804H) and c.2599C>(R867G)] (Fig. 4). Mutations in PDE11A have also been reported in testicular germ cell tumors. In 259 patients with testicular German cell tumors, 55 Pde11a strains (20 missense, 4 splice sites, 2 non-sense sites, 7 synonyms, 22 introductions, 10 missense strains, 9 transcriptions) were identified. Among them, rare mutations (p.F258Y, p.G291R, p.V820M, p.R545X, p.K568R) were found. Mutations in PDE11A testicular germ cell tumors degrade PDE11A function, ultimately increasing the cAMP/cGMP level (87). Mutation of PDE11A was also observed in Carney complex, somatic dystrophy and various endocrine tumors (kidney, prostate, colon, lung and breast) (22,44,82,88,89). In addition, mutations in Y727C and E840K of PDE11A have been reported to be extremely high expressed in prostate cancer (90). Moreover, the role of PDE11A in brain tumors has recently been studied and reported due to the brain belongs to an essential part of the human body and is responsible for a critical part of the CNS (91). All brain cancers are graded from 1 to 4 based on how the cancer cells look under the microscope and how well they reproduce. The most aggressive and fast-growing malignant Grade 4 tumor is called glioblastoma (92). Currently open surgery, radiation therapy (93), and chemotherapy (94)

Figure 3. Effects of PDEs on the CNS through cAMP/cGMP regulation. Each protein in the PDE family has a unique location expressed in human tissues, but all PDEs are expressed in the CNS. (A) In the CNS, each PDE is involved in angiogenesis and neurogenesis by hydrolyzing cAMP/cGMP, and serves a role in lowering the activity of macrophages and T cells. (B) PDE expression increases when the CNS is damaged by disease or injury. Increased PDE causes inflammation and neuronal cell death. CNS, central nervous system; PDE, phosphodiesterase.
are all using for the treatment of glioblastoma. However, they are ineffective or have a very high probability of side effects. Therefore, to develop an effective treatment strategy for glioblastoma, the studies of analytical methods using molecular targeting are necessary. Besides, with the increase of studies on the association between PDE11A and the brain, it was found in the brain's hippocampus (62), and the deletion of PDE11A in the brain has been shown to increase microglial activation (25). More specifically, recently, PDE11A was also found to be highly expressed in glioblastoma. Lee et al (95) found that the PDE11A expression level in glioblastomas was higher than in normal brains and PDE11A knockout reduced cancer cell proliferation. This suggests that the expression of PDE11A can regulate the development of glioblastoma in patients. Other PDEs (PDE5, PDE8, and PDE10) are also involved in cancer cell proliferation; various mutations have been described (96-98). Therefore, PDE11A and other PDEs fail to act as regulators of cAMP and cGMP, affecting the growth and development of cancer cells. Furthermore, it is thought that alternatives to PDEs related to such mutation can play a clear role in CNS and testicular cancer, where PDEs are highly expressed.

5. Other diseases cause by PDE11A

PDE11A is expressed in the human testis, pituitary gland, heart, kidney, liver, prostate, adrenal gland, colon, and hippocampus (18,19,22,23,79), and is associated with tumors and other diseases. Adrenocorticotropic hormone (a hypothalamic hormone) is required for the development and function of the adrenal gland. Adrenocorticotropic hormone is produced by the anterior pituitary gland and acts on the adrenal cortex to stimulate the production of cortisol and other steroid hormones. These hormones are essential for maintaining blood pressure, regulating metabolism, and supporting the immune system.

6. Further focus for PDE11A

PDE11A hydrolyzes cAMP and cGMP to AMP and GMP (82). cAMP and cGMP are essential secondary messengers involved in the development and function of the immune and endocrine systems (82). cAMP signaling is mediated by AC activity triggered by the GPCR; PKA is activated and phosphorylates intracellular proteins (4,5), controlling cellular responses, development, and function. cAMP and cGMP signaling pathways are closely associated with tumors (31,32). Germline mutational inactivation of the alpha regulatory subunit gene of Protein Kinase CAMP-Dependent Type I Regulatory Subunit Alpha triggers Carney complex (27,28) (an autosomal-dominant genetic disorder).
disease characterized by cardiac myxomas and endocrine tumors). cAMP and cGMP contribute to tumorigenesis by affecting PDE action. PDEs degrade the intracellular levels of cAMP and cGMP, resulting in sustained activation of the cAMP and cGMP/PKA cascade. PDE expression is high in several types of cancer cells; PDE mutations were observed. The PDE isoforms fall into 11 families that share catalytic functions but differ in terms of subcellular localization and tissue expression. For example, PDEs that degrade both cAMP and cGMP include PDE1, 2, 3, 10, and 11; PDEs that degrade only cAMP include PDE4, 7, and 8; and PDEs that degrade only cGMP include PDE5, 6, and 9 (1,8-10) The roles of the various PDE isoforms vary in different human tissues. PDE11A features four splice variants. PDE11A expression is highest in the prostate, but the enzyme is also expressed in the spleen, hippocampus, liver, skeletal muscle, pituitary, pancreas, and kidney (18,19). PDE11A regulates both cAMP and cGMP levels (82), is expressed in many cancer cells, and several mutations have been defined. Three PDE11A truncations and two substitution mutations were identified in 745 patients (43,86). In addition, the PDE11A level was enhanced in glioblastomas and PDE11A knockdown inhibited cancer proliferation. High-level PDE11A expression (and mutations) have been observed in various endocrine tumors in the kidney, prostate, colon, lung, and breast. The relationships between genetic PDE11A changes and tumors of the prostate, testis, and adrenal glands are under study. It is already clear that PDE11A and other PDEs are expressed by many cancers and are essential for cancer cell growth. Thus, the identification of PDE11A and other PDE-related targets may aid the treatment of refractory cancers. Moreover, the expression of PDE11A in sperm affects sperm production, motility, and survival. This suggests that PDE11A and all other PDE families may be involved in physiology and development in various tissues by regulating cAMP and cGMP depending on the location and intensity of expression. Besides, the effect of PDE11A on the development of cancer cells also has sufficient potential as a new therapeutic strategy in brain tumors and other cancers.

Acknowledgements

The authors would like to thank Prof. Guang-Ho Cha (Chungnam National University, South Korea) and Dr Sung-Jin Park (National Institute of Health, USA) for fruitful discussions.

Funding

This work was financially supported by a research fund of Chungnam National University (2020) (grant no. CNU-2020SHK) and by the National Research Foundation of Korea (NRF) grant funded by the Korea Government (MEST) (grant nos. NRF-2021R1A2C1008492, NRF-2020R1F1A1049801 and NRF-2021R1C1C2008456).

Availability of data and materials

Not applicable.

Authors’ contributions

GK and JoP conceived the present study. GK and HL analyzed the PDE11A literature and made substantial contributions to finalization of this manuscript. TTV, UJ, JIP and SHK assessed and analyzed the oncogene database (https://www.cbioportal.org/). SHK, JIP, JoP and SK commented on previous versions of the manuscript. JoP and SK were involved in data interpretation and writing the discussion. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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