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REVIEW ARTICLE

Temporal and spatial regulation of cAMP signaling in disease: role of cyclic nucleotide phosphodiesterases

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ABSTRACT

Since its discovery, cAMP has been proposed as one of the most versatile second messengers. The remarkable feature of cAMP to tightly control highly diverse physiological processes, including metabolism, homeostasis, secretion, muscle contraction, cell proliferation and migration, immune response, and gene transcription, is reflected by millions of different articles worldwide. Compartmentalization of cAMP in space and time, maintained by mainly phosphodiesterases, contributes to the maintenance of equilibrium inside the cell where one signal can trigger many different events. Novel cAMP sensors seem to carry out certain unexpected signaling properties of cAMP and thereby to permit delicate adaptations of biologic responses. Measuring space and time events with biosensors will increase our current knowledge on the pathophysiology of diseases, such as chronic obstructive pulmonary disease, asthma, cognitive impairment, cancer, and renal and heart failure. Further insights into the cAMP dynamics will help to optimize the pharmacological treatment for these diseases.

INTRODUCTION

The spatial organization and temporal regulation of intracellular signaling pathways have emerged as a key issue in normal physiology and pathology. One example is the cyclic adenosine 3′,5′-monophosphate (cAMP) signaling pathway, which is now recognized to transduce signals in a compartmentalized way such that individual stimuli only engage a subset of the whole pathway physically constrained within defined subcellular locations, leading to a precise functional outcome. Thus, local manipulation of cAMP signals may offer a different approach to treat specific diseases.

cAMP is one of the most known second messenger systems involved in several cellular processes. Memory formation [1–3], metabolism [4], immune reactions [5], insulin secretion [6,7], gene expression [8,9], and regulation of heart rate [10,11] are some of the critical physiological events where cAMP is involved. High level of complexity in this signaling pathway leads to diverse pleiotropic effects when cAMP signaling is deregulated [12,13]. Therefore, the cAMP homeostasis directly dependent on its spatiotemporal dynamics plays a critical role in coordinating the signals provided by the different physiological events [14,15]. The so-called cAMP microdomains may explain how the spatiotemporal dynamics organize this complex communication [16].

cAMP is synthesized by adenylyl cyclases (ACs) from adenosine triphosphate (ATP). Most ACs are activated downstream of G-protein-coupled receptors (GPCRs), when specific hormones or neurotransmitters bind

their GPCR and activate the α-subunit of the heterodimeric Gs protein [17,18].

Once produced inside the cell, cAMP exerts its action on a limited number of effectors: cAMP-gated ion channels, exchange protein directly activated by cAMP (EPAC), and protein kinase A (PKA) [19,20]. Moreover, the intracellular cAMP levels are regulated by cyclic nucleotide phosphodiesterases (PDEs), a group of specific cyclic-nucleotide-degrading enzymes involved in control of homeostasis [21–23]. It is recognized that the action of phosphodiesterases is essential for the spatiotemporal regulation of cAMP levels [24].

PHOSPHODIESTERASES

Since the discovery of cAMP [25], research has been absorbed by cAMP-hydrolyzing PDEs. Analysis of the human genome has identified 21 genes for cyclic nucleotide PDEs, and structural and regulatory properties of these proteins have been described [26–28]. Based on their molecular sequence, regulation, and pharmacological properties, mammalian PDEs have been classified into 11 families, denoted by an Arabic numeral 1–11. Some of these families have more than one member each encoded by different genes, and these are denoted by a capital letter after the numeral, for example, PDE4A, PDE4B, PDE4C, and PDE4D. In addition, several genes encoding PDEs have multiple promoters, and the transcripts are subject to alternative splicing, resulting in nearly one hundred PDE messenger RNAs [29].

All PDEs contain three functional domains: a C-terminal domain [29–31], a conserved catalytic core, and a regulatory N-terminal domain. The C-terminal is similar in all the PDE families except PDE6, with 18%–46% sequence identity overall. Although there is some evidence that the C-terminal region of PDE4 may be involved in dimerization [32] and may also be a target for regulatory phosphorylation [33], its physiological function remains unclear.

The catalytic domain containing about 270 amino acids shows a high degree of amino acid conservation between the 11 PDE families (25%–49%). However, the families themselves and the isoforms within the respective family possess varying substrate preferences for cAMP and cGMP. In mammals, PDE4, PDE7, and PDE8 hydrolyze cAMP selectively; PDE5, PDE6, and PDE9 hydrolyze cGMP; and the remaining five PDEs (PDE1, 2, 3, 10, and 11) hydrolyze both cAMP and cGMP. Current evidence suggests that substrate specificity is conferred by the orientation of a single glutamine residue within the catalytic site, which can form hydrogen bonds with cAMP, cGMP, or both depending on its fixed orientation or ability to rotate [34].

The N-terminal region shows high diversity between PDE families, and the differences in this region are crucial to understand the regulation and subcellular localization of different PDEs. Within this region, there are essential domains that are essential for ligand binding, oligomerization, kinase recognition, and phosphorylation that regulate PDE function. The regulatory domains include the calmodulin-binding domain found in PDE1; the cGMP-binding (GAF) domains found in PDE2, 5, 6, 10, and 11; and the so-called upstream conserved regions 1 and 2 (UCR1 and UCR2) found in PDE4. Regarding dimerization, it appears likely that PDEs function as dimers or oligomers in several cells, where dimerization is an essential structural element that determines the regulatory properties and inhibitor sensitivities, that is, PDE4 [35]. In addition, the spatial location of PDEs within cells is crucial to define their intracellular effects. This appears to be partially determined by the presence of different targeting domains in the N-terminal domain [36]. One explanation for the existence of multiple isoforms is their targeting to different subcellular locations.

Scaffolding molecules such as A-kinase anchoring proteins (AKAPs) dynamically assemble cAMP effector molecules, such as PKA, EPAC, and PDEs, into signaling complexes, which regulate the temporal and spatial effects of cAMP [37]. In particular, PDE4D3 and PKA are related to muscle mAKAP, where phosphorylation of PDE4D3 by PKA in these complexes enhances its PDE activity, thus forming a negative feedback control system to limit the activation of PKA and regulate local cAMP levels [38]. Under resting conditions, PDE4D3 maintains local cAMP levels below the threshold required for PKA activation, and when cAMP levels rise following receptor stimulation, phosphorylation of PDE4D3 by activated PKA increases its activity, returning cAMP levels to baseline [39]. Additionally, PDEs themselves may function as scaffolding for the assembly of macromolecular complexes, which compartmentalize the effects of cAMP. PDE4D3 interacts with EPAC, a guanine nucleotide exchange factor for the Ras-like small GTPases Rap1 and Rap2 [40], and ERK5, an extracellular-signal-regulated kinase [41]. These intermolecular interactions facilitate the dissemination of distinct cAMP signals through each effector protein. ERK phosphorylation of PDE4D3 decreases the

phosphodiesterase activity, thereby favoring local accumulation of cAMP and subsequent EPAC activation [39]. PDE4 also forms another macromolecular signaling complex with β-arrestin to regulate cAMP diffusion from activated receptors. Arrestins bind specifically to active (phosphorylated) G-protein-coupled receptors (GPCRs) and arrest or reduce signaling by these receptors. Specifically, β-arrestin binds to the β-adrenergic receptor and recruits PDE4. This results in the local regulation of cAMP levels and PKA activity, which phosphorylates the β-receptor switching its predominant coupling from stimulatory guanine nucleotide regulatory protein (Gs) to inhibitory guanine nucleotide regulatory protein (Gi) [42]. A summary of different PDE families is given in *Table* I, which is discussed in more detail below.

Table I Phosphodiesterases enzymatic properties, inhibitors and tissue distribution.

PDE family	Genes	Subfamilies	Substrate specificity	Inhibitor	Tissue distribution	References
PDE1	*PDE1A*, *PDE1B*, *PDE1C*	PDE1A PDE1B PDE1C	cAMP < cGMP cAMP < cGMP cAMP = cGMP	Nimodipine Vinpocetine IC224 SCH51866	Heart, kidney, lung, smooth muscle, sperm, olfactory epithelium, lymphocytes, brain – such as hippocampus and cerebral cortex – and also in male and female urogenital tract	[165–176]
PDE2	*PDE2A*	PDE2A	cAMP = cGMP	EHNA BAY 60-7550 PDP IC933	Adrenal medulla, brain, heart, platelet, brown adipose tissue, liver, olfactory epithelium	[51,175,177–184]
PDE3	*PDE3A*, *PDE3B*	PDE3A	cAMP > cGMP PDE3B	Cilostamide Milrinone Trequinsin Cilostazol OPC-33540	Heart, platelet, vascular smooth muscle, cardiovascular tissues, kidney, oocytes, adipocytes, hepatocytes, spermatocytes, T lymphocytes, and macrophages	[185–191]
PDE4	*PDE4A*, *PDE4B*, *PDE4C*, *PDE4D*	PDE4A PDE4B PDE4C PDE4D	cAMP	Rolipram Ro 20-1724 Roflumilast Cilomilast AWD 12-281 SCH351591 V-11294A	Brain, lung, testis, and immune cells such as neutrophils, eosinophils, dendritic cells, macrophages, $CD8^+$ lymphocytes	[192–205]
PDE5	*PDE5A*	PDE5A	cGMP	Zaprinast DMPPO E4021 Sildenafil Vardenafil Tadalafil DA-8159	Platelets, vascular and visceral smooth muscle, skeletal muscle, placenta, brain, liver, pancreas, lung, heart, kidney, and cerebellum	[71,72,74–79, 206–214]
PDE6	*PDE6A*, *PDE6B*, *PDE6C*, *PDE6D*	PDE6A/B PDE6C PDE6D	cGMP	Zaprinast DMPPO E4021 Sildenafil	Pineal gland and in the outer segments of the retinal photoreceptor neurons	[84–86,215–217]
PDE7	*PDE7A*, *PDE7B*	PDE7A PDE7B	cAMP	BRL 50481 IC242	Lung, spleen, brain, thymus, and immune cells	[89–92,218–223]
PDE8	*PDE8A*, *PDE8B*	PDE8A PDE8B	cAMP	Dipyridamole	Brain, thyroid, pancreas, and adrenal cortex	[98,99,224,225]
PDE9	*PDE9A*	PDE9A	cGMP	BAY 73-6691 PF-04447943	Brain, prostate, kidney, spleen, and gastrointestinal tissues	[105,226–229]
PDE10	*PDE10A*	PDE10A	cAMP < cGMP	Papaverine	Brain, testis, heart, and thyroid	[230–232]
PDE11	*PDE11A*	PDE11A	cAMP = cGMP	BC11-38	Liver, prostate, testis, skeletal muscle, thyroid, and salivary gland	[109,233,234]

PDE FAMILIES

One of the first families identified was the Ca^{2+}/calmodulin-dependent PDE, now known as phosphodiesterase 1 family (**PDE1**) [43]. This family comprises three isoforms, PDE1A, PDE1B, and PDE1C, which are expressed in different cell types and specific tissues. In early studies, a postsynaptic localization of PDE1 in diverse brain areas was proposed [44]. Currently, PDE1 has been also described in the heart and in blood vessels, macrophages, T lymphocytes [45], testis, and spermatozoa [46]. These enzymes are mainly found in the cytosol, but are also located in specific subcellular regions such as the spermatozoon tail [47].

The **PDE2** family includes a dual-substrate enzyme, which hydrolyzes both cAMP and cGMP. A key feature of this family is its allosteric activation by cGMP, which stimulates cAMP degradation [48,49]. Although only one gene has been described (PDE2A), three splice variants are known, cytosolic and membrane-bound forms [50]. The protein was firstly purified from bovine and calf tissues, such as heart, liver adrenal gland, and platelets [51,52]; moreover, it has been found in endothelial cells, macrophages, and brain [53,54]. Platelet aggregation [55], aldosterone secretion [56], and regulation of calcium channels [57] are processes that require cAMP hydrolysis by PDE2. Recently, a particular variant of PDE2A with a mitochondrial targeting sequence has been reported [58]. This variant seems to regulate the respiratory chain, which opens the possibility of using specific PDE-targeting drugs to regulate mitochondrial function.

The **PDE3** family also hydrolyzes cAMP and cGMP, having a relatively high affinity for cGMP, and is often referred to as cGMP-inhibited PDE. Two isoforms have been described, PDE3A and PDE3B. PDE3A is highly expressed in cardiomyocytes, oocytes, vascular smooth muscle, and platelets. PDE3B is found in pancreas, liver, and adipose tissue [59]. PDE3A regulates myocardial contractility through interaction with the sarcoplasmic reticulum Ca++ ATPase (SERCA2a pump) [60]; thus, PDE3A inhibitors have been used to treat heart failures in spite of chronic use leading to adverse effects [18,61]. PDE3B seems to be involved in energy metabolism; thus, it is an interesting target to treat metabolic disorders, but the interplay between the different tissues that express this isoform must be taken into account to develop novel therapeutic strategies [62,63].

PDE4 is one of the best-studied phosphodiesterase families. It has a low Km and cAMP-specific PDE activity. This activity was initially characterized by the fact that it can be selectively inhibited by the drug rolipram, and the enzymes were once named RoI-PDEs (rolipram-inhibited PDEs) based on this property. One consequence of the early discovery of PDE4 is that its biochemistry, genetics, and physiological functions have been extensively described. This family is expressed in many different tissues and cell types, playing a role in a large number of physiological processes [35,64]. There are four isoforms (PDE4A–PDE4D), each with multiple variants. Diverse variants may be generated by alternative splicing, such as 'long', 'short', and 'super-short' variants [23,65]. Currently, at least 25 splice variants have been described [66]. In this family of phosphodiesterases, a conserved module termed upstream conserved region (UCR) has been described in the region N-terminal to the catalytic core, which has been associated with several processes including subcellular localization and catalytic activity as previously mentioned [23,67,68]. Interactions between UCRs and several proteins can confer PDE4 precise subcellular locations. For instance, interactions between one of the UCRs of PDE4D3 with myomegalin [69] and AKAP450 [70] confer this isoform a Golgi/centrosomal location. For PDE4A5, perinuclear location is also mediated by the UCR domain while targeting to membrane ruffles and cell periphery is mediated by a discrete sequence in the N-terminal region that possesses an SH3 interaction site [36].

The **PDE5** family is known as cGMP-specific phosphodiesterase based on their substrate specificity. It was initially isolated and characterized from platelets and lung [71,72]. PDE5A is the only isoform described; however, three variants have been identified [73–75]. It is located in vascular and visceral smooth muscle, skeletal muscle, placenta, brain, liver, and greatly in pancreas, kidney, heart, lung, and cerebellum [76–79].

PDE5 inhibitors such as sildenafil are currently used to treat erectile dysfunctions [80] and have also shown effects in treating pulmonary hypertension [81]. In both cases, the mechanism involves the cGMP-mediated relaxation of the vascular smooth muscle cells [82].

The **PDE6** family, also called photoreceptor PDE, is composed of three isoforms, PDE6A, PDE6B, and PDE6C, plus two regulatory subunits (PDE6γ and PDE6δ) [83]. They are mainly expressed in the outer segments of the retinal photoreceptor neurons, where

they are key participants in the visual response to light [84–86]. Some forms of retinitis pigmentosa and stationary night blindness are related to genetic mutations affecting the protein subunits of the PDE6 complex [87,88].

The **PDE7** family, such as PDE4, has high selectivity for cAMP as substrate. It was described by a genetic screening in yeast [89]. This family is composed of two isoforms, PDE7A and PDE7B. For PDE7A, A1, A2, and A3 variants have been described [90]. PDE7 has been detected in lung, spleen, brain, thymus, and immune cells [90–93] where it participates in T-lymphocyte activation [94–96] through the Golgi apparatus [97].

PDE8 family is cAMP specific and shows great affinity by their substrate. This family is composed of two isoforms, PDE8A and PDE8B [98,99], and it has been associated with T-cell adhesion [100] and lymphocyte chemotaxis [101]. In addition, PDE8A has a role in cardiac muscle where it is implicated in the regulation of Ca++ movement in the cardiomyocyte [102]. PDE8B mutations have been found in patients with adrenocortical hyperplasia [103].

PDE9 family has only one gene product identified, PDEA9A; however, there are at least 20 splice variants of this isoform [104]. This isoform possesses the highest affinity for cGMP [105]. Splice variants have been found in different intracellular localization, such as cytosol and nucleus [106].

The **PDE10** family is composed of only one member, PDE10A, although four variants (PDE10A1–4) have been described. These phosphodiesterases possess a domain, which has higher specificity for cAMP than for cGMP [107]. The gene product is mainly expressed in the striatal medium spiny neuron, and at low levels in the brain and other tissues [108].

PDE11 family was the last family discovered. Like PDE10 family, only one gene product has been identified, PDE11A, and four splicing variants have been described (PDE11A1–4). This family regulates both cGMP and cAMP [109]. The function of this family has not yet been described; however, its activity has been associated with adrenal and testicular tumorigenesis [110,111].

COMPARTMENTALIZED CAMP SIGNALING AND DISEASES

Extensive studies of the role of cAMP signaling in many diseases have been performed, reporting the involvement of up/downregulated genes, genetic mutations, and changes in AC and PDE activity. Additionally, the current evidence strongly supports that compartmentalized and anchored PDE pools are also required for spatiotemporal regulation of cAMP signaling in both physiological and disease conditions [112–115].

Accordingly, the role of cAMP-degrading PDE isoforms 3 and 4 in several diseases, including certain types of heart diseases, has been extensively studied by use of 'cAMP sensors' based on fluorescence resonance energy transfer (FRET) [23,112,113,116]. In cardiomyocytes, PDE3 and PDE4 variants account for the majority of cAMP degradation [83,117]. Both PDEs also are localized to distinct compartments of cardiomyocytes and also regulate distinct pools of cAMP [117]. However, their role in heart diseases (hypertrophy and heart failure) and the underlying mechanisms are slightly different. While heart disease is associated with downregulation of PDE3 gene expression by ICERs (inducible cAMP early repressors) [118–120], PDE4D isoforms have been reported in the rat ventricular myocytes to be involved in altered cAMP-compartmented signaling and heart failure [113,121]. In the case of PDE4D3, this isoform binds to the muscle A-kinase anchoring protein mAKAP, a scaffold protein that also binds to the protein kinase A (PKA) and EPAC1 [39]. Some AKAPs are also induced in hypertrophic cardiomyocytes, which leads to redistribution of PDE4D3 from the cytosol to a perinuclear compartment by an unknown mechanism, thereby alters the cAMP signaling for cardiac contractility [38,122].

It has been reported that during cardiac hypertrophy there is a downregulation of PDE3A, PDE4A, and PDE4B, which in the short term can compensate a decrease in cAMP synthesis, but in the long term may cause a loss of compartmentalized cAMP signaling and chronic activation of downstream effectors (PKA, EPAC) that are involved in pathological hypertrophy [123].

Recently, also a role for PDE2 has been suggested during heart failure. In this condition, PDE2 is upregulated and protects against hypertrophic stimuli, suggesting that PDE2 activation can be used as a therapy for heart failure [124].

Glomerular diseases are also associated with changes in PDE localization and thus altered cAMP-compartmented signaling [125]. The main feature of glomerular failure (acute and chronic glomerulonephritis) is the excessive proliferation of mesangial cells, a specialized type of smooth muscle cell localized at the center

of glomerulus with a critical role in glomerular pathophysiology [126,127]. In the mesangium, PDE3 and PDE4 are both involved in compartmentalized intracellular pools of cAMP with different effects in mesangial cells: While the PDE3-linked cAMP-PKA pathway accounts for mitogenesis, the PDE4-linked cAMP-PKA pathway modulates generation of reactive oxygen species (ROS) [128–130]. Modified mesangial mitogenesis has been associated with changes in cAMP pools due to an altered PDE3 interaction with Raf-1 kinase and ERK, which belong to the MAPK signaling pathway [131–134]. Moreover, ROS generation has been widely described in development of glomerulonephritis pathology [135], and they can be suppressed by use of PDE4 inhibitors [134–137], which might be correlated with modification in PDE4 activity and subcellular localization and thus compartmentalized cAMP.

Deregulated cAMP signaling by PDE4 isoform may also play an important role in mental disorders such as depression [138] and schizophrenia [139]. Recently, it has been reported that DISC1, a genetic susceptibility factor for schizophrenia and related severe psychiatric conditions that acts as multifunctional scaffold protein, directly interacts with PDE4B isoform through its UCR2 domain in the human neuroblastoma cell line SH-SY5Y [140,141]. This interaction leads to a subsequent dissociation of PDE4B from DISC1 and increased cAMP levels, which is involved in neuronal migration and brain development [140,142,143]. Deregulation of cAMP levels by disruptions in the DISC1-PDE4B interaction has been involved in brain alteration, affect, and cognition. However, deciphering the DISC1–PDE4 interactions and how it can regulate cAMP signaling is a complex task. DISC1 contains five PDE4D binding sites acting as a multifunctional scaffold protein, but the specificity of each binding site remains to be clear [141]. In addition, studying deregulated DISC1–PDE4 interaction in patients is complicated by factors including tissue availability, drug therapy, and others [138,143]. Therefore, mouse models will be useful to reveal the role of DISC1–PDE4 interaction and cAMP signaling in psychiatric disorders.

The concept of cAMP compartmentalization involved in disease also includes other cAMP-processing proteins such as soluble adenylyl cyclase (sAC), which is responsible for cAMP synthesis. This protein is highly expressed in testis [144] and diffusely expressed in epidermal cells (keratinocytes and melanocytes) and other cell types (eccrine ductal cells, mononuclear cells, and cutaneous nerves) [145,146]. Inside cells, sAC is found in the cytoplasm, plasma membrane, mitochondria, centriole, and nucleus [130]. However, in certain hyperproliferative disorders of the skin, including psoriasis, sAC in keratinocytes is predominately found at the nucleus of differentiated cells induced to reenter to the cell cycle [145]. In the nucleus, sAC activates the cAMP-response-element-binding (CREB) transcription factor [130,145], which increased activity has been previously reported in psoriasis pathogenesis [147]. The fact that the keratocyte cAMP signaling is involved in this disease by modulating nuclear gene expression highlights the importance of a proper cAMP compartmentalization and localization of cAMP-modulating enzymes in health and disease.

CANCER AND PDE

Targeting tumor cells with chemotherapy agents is, so far, the gold standard in cancer treatment. Phosphodiesterases (PDEs) are activated by different signaling pathways disrupted in numerous types of tumors and might play an important role not only in the pathogenesis but also in the development of novel drugs targeting cell cycle.

Gastrointestinal tumors, such as colorectal cancer, are the fourth leading cause of cancer and cancer-related mortality in the world, primarily affecting patients in developed countries [148,149]. Although the epidemiology of this disease remains poorly understood, there is an inverse relationship between the incidence of colorectal cancer and enterotoxigenic *Escherichia coli* (ETEC) infections [150]. ETEC produce heat-stable enterotoxins (STs), a principle cause of secretory diarrhea in endemic populations, travelers, and agriculturally important animal herds. STs are plasmid-encoded small peptides that bind to guanylyl cyclase C (GC-C), specifically expressed in intestinal epithelial cells [150]. STs inhibit DNA synthesis in human colon cancer cells expressing GC-C but not in GC-C-deficient tumor cells. This inhibition on cell proliferation is due to the accumulation of intracellular cGMP. Yet, selective inhibitors of PKG, which disrupt ST induction of intestinal secretion, do not prevent the antiproliferative action of the enterotoxins. Moreover, inhibitors of cAMP-dependent protein kinase or cGMP-regulated PDE3 do not influence inhibition of proliferation by ST [151]. Thus, the antiproliferative effects of ST on human colon carcinoma cells are not mediated by classical downstream effectors of cGMP [152,153].

According to public datasets of gene expression analysis, PDE4B expression levels are higher in clinical tumor samples from patients with colorectal cancer (CLC) in comparison with those from healthy control [153]. PDE4B is specifically upregulated among other PDE4 isoforms, and re-expression of oncogenic KRAS in HKe3 cells (isogenic human colon cancer cells that lack the mutant KRASG13D allele) [154] induces PDE4B overexpression [153]. In addition, increased expression of PDE4B mRNA is correlated with relapsed CRC, which suggests PDE4B as a promising candidate for a therapeutic target and as prognostic molecular marker in CRC [153]. As reported for patients with colon cancer, PDE4D is overexpressed in human prostate cancer, showing variations in isoform expression. In fact, PDE4D knockdown reduces the growth and proliferation rate of prostate cancer xenografts in vivo [155].

Chronic obstructive pulmonary disease (COPD) is an inflammatory lung disease associated with decreased expiration of CO_2 and upregulation of the nicotinic receptor A7nAChR. Although the tobacco carcinogen NNK normally binds to B-adrenergic receptors in the healthy lung, it binds preferentially to the sensitized A7nAChR in the COPD lung. In addition, the COPD lung typically overexpresses PDE4, leading to a deficiency of intracellular cAMP, thus deprives lung cells of their defense against hyperactive RAF1-mediated signaling [156,157]. Therefore, PDE4 may be an attractive therapeutic target.

As PDE4, PDE5 displays a role in cancer. In melanoma cells, oncogenic BRAF induces invasion through downregulation of PDE5A [158,159]. Nevertheless, PDE5 inhibition is responsible for the breast tumor cell growth inhibitory activity in addition to apoptosis, suggesting that PDE5 is another promising therapeutic target in this type of cancer [160].

Concerning specific mutations on PDE genes, several mutations have been described as predisposing to bilateral adrenal hyperplasia and other adrenal tumors [161]. PDE11A and PDE8B mutations have been found in patients with this type of cancer. In these studies, it has been defined that PKA and/or cAMP acts as a coordinator of growth and proliferation in the adrenal cortex. Mouse models where the respective genes have been knocked out support this notion [162].

These evidences confirm that dysregulation of cAMP homeostasis can be linked to tumorigenesis, both directly and indirectly [163]. Impaired cAMP (and/or cGMP) generation upon overexpression of PDE isoforms has been described in several cancer pathologies. Inhibition of specific PDE isoforms may induce apoptosis and cell cycle arrest in a broad spectrum of tumor cells. Hence, the development and clinical application of specific PDE isoenzyme inhibitors may selectively restore normal intracellular signaling, providing an antitumor therapy with reduced adverse effects [164].

Due to complex cross talk among signaling pathways, predicting the impact and efficacy of signaling inhibitors is difficult because they produce a weak growth inhibition. Thus, inhibition of multiple pathways will be certainly required to substantially affect tumor cell growth. Compartmentalization, which is the spatial confinement of multiple elements of the cAMP-signaling pathway, might be the answer. Spatial and time control involves not only the protein components of the pathway but also the cAMP molecule. The best example is cardiomyocytes where spatially segregated signaling domains are the key to regulate the specificity of response. Given the large number of potential targets in cancer therapy, an urgent task is to further investigate the previously identified candidates, which inhibition/activation might provide alternative therapeutic treatment in combination with other targeted therapies.

In summary, involvement of cAMP-processing enzymes in spatial and temporal regulation of cAMP signal propagation is critical. Experimental evidence strongly supports that any perturbation in the tight control of cAMP signaling may lead to altered cAMP response and pathological conditions. Future perspectives of cAMP compartmentalization include not only identification of other pathological disorders associated with the spatiotemporal tuning of cAMP regulators (ACs and PDEs), but also synthesis and characterization of novel PDE inhibitors to contribute to the development of alternative drug therapy. Considerable attention has been given to the development of selective PDE inhibitors, especially after the therapeutic success of PDE5 inhibitors in the treatment of erectile dysfunction. Thus, understanding the molecular basis of cAMP signaling can provide new insights for improved pharmaceutical targeting of cancer cells and other pathologies.

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REFERENCES

1 Abel T., Nguyen P.V. Chapter 6 regulation of hippocampus-dependent memory by cyclic AMP-dependent protein kinase. Prog. Brain Res. (2008) **169** 97–115.
2 Kandel E.R. The molecular biology of memory storage: a dialogue between genes and synapses. Biosci. Rep. (2001) **294** 1030–1038.
3 Kandel E. The molecular biology of memory: cAMP, PKA, CRE, CREB-1, CREB-2, and CPEB. Mol. Brain (2012) **5** 14.
4 Desvergne B., Michalik L., Wahli W. Transcriptional regulation of metabolism. Physiol. Rev. (2006) **86** 465–514.
5 Duan B., Davis R., Sadat E.L. et al. Distinct roles of adenylyl cyclase VII in regulating the immune responses in mice. J. Immunol. (2010) **185** 335–344.
6 Holz G.G. Epac: a new cAMP-binding protein in support of glucagon-like peptide-1 receptor-mediated signal transduction in the pancreatic β-cell. Diabetes (2004) **53** 5–13.
7 Seino S., Takahashi H., Fujimoto W., Shibasaki T. Roles of cAMP signalling in insulin granule exocytosis. Diabetes Obes. Metab. (2009) **11** 180–188.
8 Gerlo S., Kooijman R., Beck I., Kolmus K., Spooren A., Haegeman G. Cyclic AMP: a selective modulator of NF-κB action. Cell. Mol. Life Sci. (2011) **68** 3823–3841.
9 Jin T. Mechanisms underlying proglucagon gene expression. J. Endocrinol. (2008) **198** 17–28.
10 DiFrancesco D., Borer J. The funny current. Drugs (2007) **67** 15–24.
11 Mangoni M.E., Nargeot J. Genesis and regulation of the heart automaticity. Physiol. Rev. (2008) **88** 919–982.
12 Raymond D.R., Carter R.L., Ward C.A., Maurice D.H. Distinct phosphodiesterase-4D variants integrate into protein kinase A-based signaling complexes in cardiac and vascular myocytes. Am. J. Physiol. Heart Circ. Physiol. (2009) **296** H263–H271.
13 Terrin A., Di Benedetto G., Pertegato V. et al. PGE1 stimulation of HEK293 cells generates multiple contiguous domains with different [cAMP]: role of compartmentalized phosphodiesterases. J. Cell Biol. (2006) **175** 441–451.
14 Feinstein W.P., Zhu B., Leavesley S.J., Sayner S.L., Rich T.C. Assessment of cellular mechanisms contributing to cAMP compartmentalization in pulmonary microvascular endothelial cells. Am. J. Physiol. Cell Physiol. (2012) **302** C839–C852.
15 Gesellchen F., Stangherlin A., Surdo N., Terrin A., Zoccarato A., Zaccollo M. Measuring spatiotemporal dynamics of cyclic AMP signalling in real-time using FRET-based biosensors. Methods Mol. Biol. (2011) **746** 297–316.
16 Arora K., Sinha C., Zhang W. et al. Compartmentalization of cyclic nucleotide signaling: a question of when, where, and why? Pflügers Arch. (2013) **465** 1397–1407.
17 Sassone-Corsi P. The cyclic AMP pathway. Cold Spring Harb. Perspect. Biol. (2012) **4** pii:a011148.
18 Landry Y., Gies J.-P. Drugs and their molecular targets: an updated overview. Fundam. Clin. Pharmacol. (2008) **22** 1–18.
19 Beavo J.A., Brunton L.L. Cyclic nucleotide research [mdash] still expanding after half a century. Nat. Rev. Mol. Cell Biol. (2002) **3** 710–718.
20 Shabb J.B. Physiological substrates of cAMP-dependent protein kinase. Chem. Rev. (2001) **101** 2381–2411.
21 Conti M. Phosphodiesterases and cyclic nucleotide signaling in endocrine cells. Mol. Endocrinol. (2000) **14** 1317–1327.
22 Lefkowitz R.J. Historical review: a brief history and personal retrospective of seven-transmembrane receptors. Trends Pharmacol. Sci. (2004) **25** 413–422.
23 Houslay M.D., Adams D.R. PDE4 cAMP phosphodiesterases: modular enzymes that orchestrate signalling cross-talk, desensitization and compartmentalization. Biochem. J. (2003) **370** 1–18.
24 De Arcangelis V., Liu S., Zhang D., Soto D., Xiang Y.K. Equilibrium between adenylyl cyclase and phosphodiesterase patterns adrenergic agonist dose-dependent spatiotemporal cAMP/protein kinase A activities in cardiomyocytes. Mol. Pharmacol. (2010) **78** 340–349.
25 Sutherland E.W., Rall T.W. The properties of an adenine ribonucleotide produced with cellular particles, ATP, Mg++, and epinephrine or glucagon. J. Am. Chem. Soc. (1957) **79** 3608.
26 Conti M., Jin S.-L.C. The molecular biology of cyclic nucleotide phosphodiesterases. Prog. Nucleic Acid Res. Mol. Biol. (1999) **63** 1–38.
27 Soderling S.H., Beavo J.A. Regulation of cAMP and cGMP signaling: new phosphodiesterases and new functions. Curr. Opin. Cell Biol. (2000) **12** 174–179.
28 Francis S.H., Turko I.V., Corbin J.D. Cyclic nucleotide phosphodiesterases: relating structure and function. Prog. Nucleic Acid Res. Mol. Biol. (2001) **65** 1–52.
29 Conti M., Beavo J. Biochemistry and physiology of cyclic nucleotide phosphodiesterases: essential components in cyclic nucleotide signaling. Annu. Rev. Biochem. (2007) **76** 481–511.
30 Thompson W.J. Cyclic nucleotide phosphodiesterases: pharmacology, biochemistry and function. Pharmacol. Ther. (1991) **51** 13–33.
31 Bolger G.B. Molecular biology of the cyclic AMP-specific cyclic nucleotide phosphodiesterases: a diverse family of regulatory enzymes. Cell. Signal. (1994) **6** 851–859.
32 Kovala T., Sanwal B.D., Ball E.H. Recombinant expression of a type IV, cAMP-specific phosphodiesterase: characterization and structure–function studies of deletion mutants. Biochemistry (1997) **36** 2968–2976.
33 Lenhard J.M., Kassel D.B., Rocque W.J. et al. Phosphorylation of a cAMP-specific phosphodiesterase (HSPDE4B2B) by mitogen-activated protein kinase. Biochem. J. (1996) **316** 751–758.
34 Maurice D.H., Palmer D., Tilley D.G. et al. Cyclic nucleotide phosphodiesterase activity, expression, and targeting in cells of the cardiovascular system. Mol. Pharmacol. (2003) **64** 533–546.
35 Richter W., Conti M. The oligomerization state determines regulatory properties and inhibitor sensitivity of type 4

cAMP-specific phosphodiesterases. J. Biol. Chem. (2004) **279** 30338–30348.
36 Beard M.B., Huston E., Campbell L. et al. In addition to the SH3 binding region, multiple regions within the N-terminal noncatalytic portion of the cAMP-specific phosphodiesterase, PDE4A5, contribute to its intracellular targeting. Cell. Signal. (2002) **14** 453–465.
37 McConnachie G., Langeberg L.K., Scott J.D. AKAP signaling complexes: getting to the heart of the matter. Trends Mol. Med. (2006) **12** 317–323.
38 Dodge K.L., Khouangsathiene S., Kapiloff M.S. et al. mAKAP assembles a protein kinase A/PDE4 phosphodiesterase cAMP signaling module. EMBO J. (2001) **20** 1921–1930.
39 Dodge-Kafka K.L., Soughayer J., Pare G.C. et al. The protein kinase A anchoring protein mAKAP coordinates two integrated cAMP effector pathways. Nature (2005) **437** 574–578.
40 Bos J.L. Epac: a new cAMP target and new avenues in cAMP research. Nat. Rev. Mol. Cell Biol. (2003) **4** 733–738.
41 Zhou G., Bao Z.Q., Dixon J.E. Components of a new human protein kinase signal transduction pathway. J. Biol. Chem. (1995) **270** 12665–12669.
42 Baillie G.S., Sood A., McPhee I. et al. β-Arrestin-mediated PDE4 cAMP phosphodiesterase recruitment regulates β-adrenoceptor switching from Gs to Gi. Proc. Natl Acad. Sci. USA (2003) **100** 940–945.
43 Cheung W.Y. Cyclic 3′,5′-nucleotide phosphodiesterase: demonstration of an activator. Biochem. Biophys. Res. Commun. (1970) **38** 533–538.
44 Ludvig N., Burmeister V., Jobe P.C., Kincaid R.L. Electron microscopic immunocytochemical evidence that the calmodulin-dependent cyclic nucleotide phosphodiesterase is localized predominantly at postsynaptic sites in the rat brain. Neuroscience (1991) **44** 491–500.
45 Essayan D.M. Cyclic nucleotide phosphodiesterases. J. Allergy Clin. Immunol. (2001) **108** 671–680.
46 Yan C., Zhao A.Z., Sonnenburg W.K., Beavo J.A. Stage and cell-specific expression of calmodulin-dependent phosphodiesterases in mouse testis. Biol. Reprod. (2001) **64** 1746–1754.
47 Vasta V., Sonnenburg W.K., Yan C., Soderling S.H., Shimizu-Albergine M., Beavo J.A. Identification of a new variant of PDE1A calmodulin-stimulated cyclic nucleotide phosphodiesterase expressed in mouse sperm. Biol. Reprod. (2005) **73** 598–609.
48 Mumby M.C., Martins T.J., Chang M.L., Beavo J.A. Identification of cGMP-stimulated cyclic nucleotide phosphodiesterase in lung tissue with monoclonal antibodies. J. Biol. Chem. (1982) **257** 13283–13290.
49 Martinez S.E., Wu A.Y., Glavas N.A. et al. The two GAF domains in phosphodiesterase 2A have distinct roles in dimerization and in cGMP binding. Proc. Natl Acad. Sci. USA (2002) **99** 13260–13265.
50 Yang Q., Paskind M., Bolger G. et al. A novel cyclic GMP stimulated phosphodiesterase from rat brain. Biochem. Biophys. Res. Commun. (1994) **205** 1850–1858.
51 Martins T.J., Mumby M.C., Beavo J.A. Purification and characterization of a cyclic GMP-stimulated cyclic nucleotide phosphodiesterase from bovine tissues. J. Biol. Chem. (1982) **257** 1973–1979.
52 Yamamoto T., Manganiello V.C., Vaughan M. Purification and characterization of cyclic GMP-stimulated cyclic nucleotide phosphodiesterase from calf liver. Effects of divalent cations on activity. J. Biol. Chem. (1983) **258** 12526–12533.
53 Bender A.T., Ostenson C.L., Giordano D., Beavo J.A. Differentiation of human monocytes in vitro with granulocyte–macrophage colony-stimulating factor and macrophage colony-stimulating factor produces distinct changes in cGMP phosphodiesterase expression. Cell. Signal. (2004) **16** 365–374.
54 Juilfs D.M., Soderling S., Burns F., Beavo J.A. Cyclic GMP as substrate and regulator of cyclic nucleotide phosphodiesterases (PDEs). Rev. Physiol. Biochem. Pharmacol., **vol. 135**, Springer, Berlin Heidelberg, 1999.
55 Dickinson N.T., Jang E.K., Haslam R.J. Activation of cGMP-stimulated phosphodiesterase by nitroprusside limits cAMP accumulation in human platelets: effects on platelet aggregation. Biochem. J. (1997) **323** 371–377.
56 MacFarland R.T., Zelus B.D., Beavo J.A. High concentrations of a cGMP-stimulated phosphodiesterase mediate ANP-induced decreases in cAMP and steroidogenesis in adrenal glomerulosa cells. J. Biol. Chem. (1991) **266** 136–142.
57 Simmons M.A., Hartzell H.C. Role of phosphodiesterase in regulation of calcium current in isolated cardiac myocytes. Mol. Pharmacol. (1988) **33** 664–671.
58 Acin-Perez R., Russwurm M., Günnewig K. et al. A phosphodiesterase 2A isoform localized to mitochondria regulates respiration. J. Biol. Chem. (2011) **286** 30423–30432.
59 Shakur Y., Holst L.S., Landstrom T.R., Movsesian M., Degerman E., Manganiello V. Regulation and function of the cyclic nucleotide phosphodiesterase (PDE3) gene family. Prog. Nucleic Acid Mol. Biol. (2001) **66** 241–277.
60 Beca S., Ahmad F., Shen W. et al. Phosphodiesterase type 3A regulates basal myocardial contractility through interacting with sarcoplasmic reticulum calcium ATPase type 2a signaling complexes in mouse heart. Circ. Res. (2013) **112** 289–297.
61 Packer M., Carver J.R., Rodeheffer R.J. et al. Effect of oral milrinone on mortality in severe chronic heart failure. N. Engl. J. Med. (1991) **325** 1468–1475.
62 Choi Y.H., Park S., Hockman S. et al. Alterations in regulation of energy homeostasis in cyclic nucleotide phosphodiesterase 3B–null mice. J. Clin. Invest. (2006) **116** 3240–3251.
63 Degerman E., Ahmad F., Chung Y.W. et al. From PDE3B to the regulation of energy homeostasis. Curr. Opin. Pharmacol. (2011) **11** 676–682.
64 Norambuena A., Metz C., Jung J.E. et al. Phosphatidic acid induces ligand-independent epidermal growth factor receptor

endocytic traffic through PDE4 activation. Mol. Biol. Cell (2010) **21** 2916–2929.
65 Houslay M.D., Sullivan M., Bolgerz G.B. The multienzyme PDE4 cyclic adenosine monophosphate-specific phosphodiesterase family: intracellular targeting, regulation, and selective inhibition by compounds exerting anti-inflammatory and antidepressant actions. Adv. Pharmacol. (1998) **44** 225–342.
66 Richter W., Menniti F.S., Zhang H.-T., Conti M. PDE4 as a target for cognition enhancement. Expert. Opin. Ther. Targets (2013) **17** 1011–1027.
67 Bushnik T., Conti M. Role of multiple cAMP-specific phosphodiesterase variants. Biochem. Soc. Trans. (1996) **24** 1014–1019.
68 Houslay M.D. The N-terminal alternately spliced regions of PDE4A cAMP-specific phosphodiesterases determine intracellular targeting and regulation of catalytic activity. Biochem. Soc. Trans. (1996) **24** 980–986.
69 Verde I., Pahlke G., Salanova M. et al. Myomegalin is a novel protein of the Golgi/centrosome that interacts with a cyclic nucleotide phosphodiesterase. J. Biol. Chem. (2001) **276** 11189–11198.
70 Taskén K.A., Collas P., Kemmner W.A., Witczak O., Conti M., Taskén K. Phosphodiesterase 4D and protein kinase A type II constitute a signaling unit in the centrosomal area. J. Biol. Chem. (2001) **276** 21999–22002.
71 Coquil J.-F., Franks D.J., Wells J.N., Dupuis M., Hamet P. Characteristics of a new binding protein distinct from the kinase for guanosine 3′:5′-monophosphate in rat platelets. Biochim. Biophys. Acta (1980) **631** 148–165.
72 Francis S.H., Lincoln T.M., Corbin J.D. Characterization of a novel cGMP binding protein from rat lung. J. Biol. Chem. (1980) **255** 620–626.
73 Kotera J., Fujishige K., Imai Y. et al. Genomic origin and transcriptional regulation of two variants of cGMP-binding cGMP-specific phosphodiesterases. Eur. J. Biochem. (1999) **262** 866–873.
74 Lin C.-S., Lau A., Tu R., Lue T.F. Expression of three isoforms of cGMP-binding cGMP-specific phosphodiesterase (PDE5) in human penile cavernosum. Biochem. Biophys. Res. Commun. (2000) **268** 628–635.
75 Loughney K., Hill T.R., Florio V.A. et al. Isolation and characterization of cDNAs encoding PDE5A, a human cGMP-binding, cGMP-specific 3′,5′-cyclic nucleotide phosphodiesterase. Gene (1998) **216** 139–147.
76 Giordano D., De Stefano M.E., Citro G., Modica A., Giorgi M. Expression of cGMP-binding cGMP-specific phosphodiesterase (PDE5) in mouse tissues and cell lines using an antibody against the enzyme amino-terminal domain. Biochim. Biophys. Acta - Mol. Cell. Res. (2001) **1539** 16–27.
77 Kotera J., Fujishige K., Omori K. Immunohistochemical localization of cGMP-binding cGMP-specific phosphodiesterase (PDE5) in rat tissues. J. Histochem. Cytochem. (2000) **48** 685–693.
78 Stacey P., Rulten S., Dapling A., Phillips S.C. Molecular cloning and expression of human cGMP-binding cGMP-specific phosphodiesterase (PDE5). Biochem. Biophys. Res. Commun. (1998) **247** 249–254.
79 Yanaka N., Kotera J., Ohtsuka A. et al. Expression, structure and chromosomal localization of the human cGMP-binding cGMP-specific phosphodiesterase PDE5A gene. Eur. J. Biochem. (1998) **255** 391–399.
80 Palit V., Eardley I. An update on new oral PDE5 inhibitors for the treatment of erectile dysfunction. Nat. Rev. Urol. (2010) **7** 603–609.
81 Galiè N., Ghofrani H.A., Torbicki A. et al. Sildenafil citrate therapy for pulmonary arterial hypertension. N. Engl. J. Med. (2005) **353** 2148–2157.
82 Rybalkin S.D., Yan C., Bornfeldt K.E., Beavo J.A. Cyclic GMP phosphodiesterases and regulation of smooth muscle function. Circ. Res. (2003) **93** 280–291.
83 Bender A.T., Beavo J.A. Cyclic nucleotide phosphodiesterases: molecular regulation to clinical use. Pharmacol. Rev. (2006) **58** 488–520.
84 Baehr W., Devlin M.J., Applebury M.L. Isolation and characterization of cGMP phosphodiesterase from bovine rod outer segments. J. Biol. Chem. (1979) **254** 11669–11677.
85 Gillespie P.G., Beavo J.A. Characterization of a bovine cone photoreceptor phosphodiesterase purified by cyclic GMP-sepharose chromatography. J. Biol. Chem. (1988) **263** 8133–8141.
86 Deterre P., Bigay J., Forquet F., Robert M., Chabre M. cGMP phosphodiesterase of retinal rods is regulated by two inhibitory subunits. Proc. Natl Acad. Sci. USA (1988) **85** 2424–2428.
87 Gal A., Orth U., Baehr W., Schwinger E., Rosenberg T. Heterozygous missense mutation in the rod cGMP phosphodiesterase [beta]-subunit gene in autosomal dominant stationary night blindness. Nat. Genet. (1994) **7** 64–68.
88 McLaughlin M.E., Sandberg M.A., Berson E.L., Dryja T.P. Recessive mutations in the gene encoding the [beta]-subunit of rod phosphodiesterase in patients with retinitis pigmentosa. Nat. Genet. (1993) **4** 130–134.
89 Michaeli T., Bloom T.J., Martins T. et al. Isolation and characterization of a previously undetected human cAMP phosphodiesterase by complementation of cAMP phosphodiesterase-deficient *Saccharomyces cerevisiae*. J. Biol. Chem. (1993) **268** 12925–12932.
90 Han P., Zhu X., Michaeli T. Alternative splicing of the high affinity cAMP-specific phosphodiesterase (PDE7A) mRNA in human skeletal muscle and heart. J. Biol. Chem. (1997) **272** 16152–16157.
91 Bloom T.J., Beavo J.A. Identification and tissue-specific expression of PDE7 phosphodiesterase splice variants. Proc. Natl Acad. Sci. USA (1996) **93** 14188–14192.
92 Lugnier C. Cyclic nucleotide phosphodiesterase (PDE) superfamily: a new target for the development of specific therapeutic agents. Pharmacol. Ther. (2006) **109** 366–398.
93 Smith S.J., Brookes-Fazakerley S., Donnelly L.E., Barnes P.J., Barnette M.S., Giembycz M.A. Ubiquitous expression of phosphodiesterase 7A in human proinflammatory and

immune cells. Am. J. Physiol. Lung Cell. Mol. Physiol. (2003) **284** L279–L289.
94 Glavas N.A., Ostenson C., Schaefer J.B., Vasta V., Beavo J.A. T cell activation up-regulates cyclic nucleotide phosphodiesterases 8A1 and 7A3. Proc. Natl Acad. Sci. USA (2001) **98** 6319–6324.
95 Li L., Yee C., Beavo J.A. CD3- and CD28-dependent induction of PDE7 required for T cell activation. Science (1999) **283** 848–851.
96 Nakata A., Ogawa K., Sasaki T. et al. Potential role of phosphodiesterase 7 in human T cell function: comparative effects of two phosphodiesterase inhibitors. Clin. Exp. Immunol. (2002) **128** 460–466.
97 Asirvatham A.L., Galligan S.G., Schillace R.V. et al. A-kinase anchoring proteins interact with phosphodiesterases in T lymphocyte cell lines. J. Immunol. (2004) **173** 4806–4814.
98 Fisher D.A., Smith J.F., Pillar J.S., St Denis S.H., Cheng J.B. Isolation and characterization of PDE8A, a novel human cAMP-specific phosphodiesterase. Biochem. Biophys. Res. Commun. (1998) **246** 570–577.
99 Hayashi M., Matsushima K., Ohashi H. et al. Molecular cloning and characterization of human PDE8B, a novel thyroid-specific isozyme of 3′,5′-cyclic nucleotide phosphodiesterase. Biochem. Biophys. Res. Commun. (1998) **250** 751–756.
100 Vang A.G., Ben-Sasson S.Z., Dong H. et al. PDE8 regulates rapid Teff cell adhesion and proliferation independent of ICER. PLoS One (2010) **5** e12011.
101 Dong H., Osmanova V., Epstein P.M., Brocke S. Phosphodiesterase 8 (PDE8) regulates chemotaxis of activated lymphocytes. Biochem. Biophys. Res. Commun. (2006) **345** 713–719.
102 Patrucco E., Albergine M.S., Santana L.F., Beavo J.A. Phosphodiesterase 8A (PDE8A) regulates excitation–contraction coupling in ventricular myocytes. J. Mol. Cell. Cardiol. (2010) **49** 330–333.
103 Horvath A., Mericq V., Stratakis C.A. Mutation in PDE8B, a cyclic AMP–specific phosphodiesterase in adrenal hyperplasia. N. Engl. J. Med. (2008) **358** 750–752.
104 Rentero C., Monfort A., Puigdomènech P. Identification and distribution of different mRNA variants produced by differential splicing in the human phosphodiesterase 9A gene. Biochem. Biophys. Res. Commun. (2003) **301** 686–692.
105 Fisher D.A., Smith J.F., Pillar J.S., St Denis S.H., Cheng J.B. Isolation and characterization of PDE9A, a novel human cGMP-specific phosphodiesterase. J. Biol. Chem. (1998) **273** 15559–15564.
106 Wang P., Wu P., Egan R.W., Billah M.M. Identification and characterization of a new human type 9 cGMP-specific phosphodiesterase splice variant (PDE9A5): differential tissue distribution and subcellular localization of PDE9A variants. Gene (2003) **314** 15–27.
107 Gross-Langenhoff M., Hofbauer K., Weber J., Schultz A., Schultz J.E. cAMP is a ligand for the tandem GAF domain of human phosphodiesterase 10 and cGMP for the tandem GAF domain of phosphodiesterase 11. J. Biol. Chem. (2006) **281** 2841–2846.
108 Yang S.-W., Smotryski J., McElroy W.T. et al. Discovery of orally active pyrazoloquinolines as potent PDE10 inhibitors for the management of schizophrenia. Bioorg. Med. Chem. Lett. (2012) **22** 235–239.
109 Fawcett L., Baxendale R., Stacey P. et al. Molecular cloning and characterization of a distinct human phosphodiesterase gene family: PDE11A. Proc. Natl Acad. Sci. USA (2000) **97** 3702–3707.
110 Libé R., Horvath A., Vezzosi D. et al. Frequent phosphodiesterase 11A gene (PDE11A) defects in patients with Carney complex (CNC) caused by PRKAR1A mutations: PDE11A may contribute to adrenal and testicular tumors in CNC as a modifier of the phenotype. J. Clin. Endocrinol. Metab. (2011) **96** E208–E214.
111 Vezzosi D., Libé R., Baudry C. et al. Phosphodiesterase 11A (PDE11A) gene defects in patients with ACTH-independent macronodular adrenal hyperplasia (AIMAH): functional variants may contribute to genetic susceptibility of bilateral adrenal tumors. J. Clin. Endocrinol. Metab. (2012) **97** E2063–E2069.
112 Francis S.H., Blount M.A., Corbin J.D. Mammalian cyclic nucleotide phosphodiesterases: molecular mechanisms and physiological functions. Physiol. Rev. (2011) **91** 651–690.
113 Omori K., Kotera J. Overview of PDEs and their regulation. Circ. Res. (2007) **100** 309–327.
114 Martin A.C., Cooper D.M. Layers of organization of cAMP microdomains in a simple cell. Biochem. Soc. Trans. (2006) **34** 480–483.
115 Zaccolo M., Pozzan T. Discrete microdomains with high concentration of cAMP in stimulated rat neonatal cardiac myocytes. Science (2002) **295** 1711–1715.
116 Herget S., Lohse M.J., Nikolaev V.O. Real-time monitoring of phosphodiesterase inhibition in intact cells. Cell. Signal. (2008) **20** 1423–1431.
117 Mongillo M., McSorley T., Evellin S. et al. Fluorescence resonance energy transfer-based analysis of cAMP dynamics in live neonatal rat cardiac myocytes reveals distinct functions of compartmentalized phosphodiesterases. Circ. Res. (2004) **95** 67–75.
118 Movsesian M.A., Bristow M.R. Alterations in cAMP. Mediated signaling and their role in the pathophysiology of dilated cardiomyopathy. Curr. Top. Dev. Biol. (2005) **68** 25–48.
119 Yan C., Miller C.L., Abe J. Regulation of phosphodiesterase 3 and inducible cAMP early repressor in the heart. Circ. Res. (2007) **100** 489–501.
120 Zaccolo M., Movsesian M.A. cAMP and cGMP signaling cross-talk: role of phosphodiesterases and implications for cardiac pathophysiology. Circ. Res. (2007) **100** 1569–1578.
121 Houslay M.D., Baillie G.S., Maurice D.H. cAMP-specific phosphodiesterase-4 enzymes in the cardiovascular system: a molecular toolbox for generating compartmentalized cAMP signaling. Circ. Res. (2007) **100** 950–966.

122 Dodge-Kafka K.L., Bauman A., Mayer N. et al. cAMP-stimulated protein phosphatase 2A activity associated with muscle A kinase-anchoring protein (mAKAP) signaling complexes inhibits the phosphorylation and activity of the cAMP-specific phosphodiesterase PDE4D3. J. Biol. Chem. (2010) **285** 11078–11086.
123 Abi-Gerges A., Richter W., Lefebvre F. et al. Decreased expression and activity of cAMP phosphodiesterases in cardiac hypertrophy and its impact on β-adrenergic cAMP signals. Circ. Res. (2009) **105** 784–792.
124 Mehel H., Emons J., Vettel C. et al. Phosphodiesterase-2 is up-regulated in human failing hearts and blunts β-adrenergic responses in cardiomyocytes. J. Am. Coll. Cardiol. (2013) **62** 1596–1606.
125 Abboud H.E. Growth factors in glomerulonephritis. Kidney Int. (1993) **43** 252–267.
126 Schlöndorff D., Banas B. The mesangial cell revisited: no cell is an Island. J. Am. Soc. Nephrol. (2009) **20** 1179–1187.
127 Cheng J., Thompson M.A., Walker H.J. et al. Differential regulation of mesangial cell mitogenesis by cAMP phosphodiesterase isozymes 3 and 4. Am. J. Physiol. Renal Physiol. (2004) **287** F940–F953.
128 Chini C.C., Grande J.P., Chini E.N., Dousa T.P. Compartmentalization of cAMP signaling in mesangial cells by phosphodiesterase isozymes PDE3 and PDE4 regulation of superoxidation and mitogenesis. J. Biol. Chem. (1997) **272** 9854–9859.
129 Zippin J.H., Chen Y., Nahirney P. et al. Compartmentalization of bicarbonate-sensitive adenylyl cyclase in distinct signaling microdomains. FASEB J. (2003) **17** 82–84.
130 Bokemeyer D., Ostendorf T., Kunter U., Lindemann M., Kramer H.J., Floege J. Differential activation of mitogen-activated protein kinases in experimental mesangioproliferative glomerulonephritis. J. Am. Soc. Nephrol. (2000) **11** 232–240.
131 D'Angelo G., Lee H., Weiner R.I. cAMP-dependent protein kinase inhibits the mitogenic action of vascular endothelial growth factor and fibroblast growth factor in capillary endothelial cells by blocking Raf activation. J. Cell. Biochem. (1997) **67** 353–366.
132 Häfner S., Adler H.S., Mischak H. et al. Mechanism of inhibition of Raf-1 by protein kinase A. Mol. Cell. Biol. (1994) **14** 6696–6703.
133 Sevetson B.R., Kong X., Lawrence J.C. Increasing cAMP attenuates activation of mitogen-activated protein kinase. Proc. Natl Acad. Sci. USA (1993) **90** 10305–10309.
134 Chini C.C., Chini E.N., Williams J.M., Matousovic K., Dousa T.P. Formation of reactive oxygen metabolites in glomeruli is suppressed by inhibition of cAMP phosphodiesterase isozyme type IV. Kidney Int. (1994) **46** 28–36.
135 Gwinner W., Gröne H. Role of reactive oxygen species in glomerulonephritis. Nephrol. Dial. Transplant. (2000) **15** 1127–1132.
136 Millar J.K., Mackie S., Clapcote S.J. et al. Disrupted in schizophrenia 1 and phosphodiesterase 4B: towards an understanding of psychiatric illness. J. Physiol. (2007) **584** 401–405.
137 Tsuboi Y., Shankland S.J., Grande J.P. et al. Rapid publication by inhibitors of cAMP phosphodiesterase isozymes types III and IV, 1996.
138 Reierson G.W., Guo S., Mastronardi C., Licinio J., Wong M.-L. cGMP signaling, phosphodiesterases and major depressive disorder. Curr. Neuropharmacol. (2011) **9** 715–727.
139 Millar J.K., Pickard B.S., Mackie S. et al. DISC1 and PDE4B are interacting genetic factors in schizophrenia that regulate cAMP signaling. Science (2005) **310** 1187–1191.
140 Murdoch H., Mackie S., Collins D.M. et al. Isoform-selective susceptibility of DISC1/phosphodiesterase-4 complexes to dissociation by elevated intracellular cAMP levels. J. Neurosci. (2007) **27** 9513–9524.
141 Mackie S., Millar J.K., Porteous D.J. Role of DISC1 in neural development and schizophrenia. Curr. Opin. Neurobiol. (2007) **17** 95–102.
142 Thomson P.A., Malavasi E.L., Grünewald E., Soares D.C., Borkowska M., Millar J.K. DISC1 genetics, biology and psychiatric illness. Front. Biol. (Beijing) (2013) **8** 1–31.
143 Zippin J.H., Chadwick P.A., Levin L.R., Buck J., Magro C.M. Soluble adenylyl cyclase defines a nuclear cAMP microdomain in keratinocyte hyperproliferative skin diseases. J. Invest. Dermatol. (2010) **130** 1279–1287.
144 Buck J., Sinclair M.L., Schapal L., Cann M.J., Levin L.R. Cytosolic adenylyl cyclase defines a unique signaling molecule in mammals. Proc. Natl Acad. Sci. USA (1999) **96** 79–84.
145 Zippin J.H., Farrell J., Huron D. et al. Bicarbonate-responsive "soluble" adenylyl cyclase defines a nuclear cAMP microdomain. J. Cell Biol. (2004) **164** 527–534.
146 Feng Q., Zhang Y., Li Y., Liu Z., Zuo J., Fang F. Two domains are critical for the nuclear localization of soluble adenylyl cyclase. Biochimie (2006) **88** 319–328.
147 Ferlay J., Shin H.-R., Bray F., Forman D., Mathers C., Parkin D.M. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int. J. Cancer (2010) **127** 2893–2917.
148 Parkin D.M., Bray F., Ferlay J., Pisani P. Estimating the world cancer burden: Globocan 2000. Int. J. Cancer (2001) **94** 153–156.
149 Pitari G.M., Zingman L.V., Hodgson D.M. et al. Bacterial enterotoxins are associated with resistance to colon cancer. Proc. Natl Acad. Sci. USA (2003) **100** 2695–2699.
150 Vaandrager A.B., Bot A.G., De Jonge H.R. Guanosine 3′,5′-cyclic monophosphate-dependent protein kinase II mediates heat-stable enterotoxin-provoked chloride secretion in rat intestine. Gastroenterology (1997) **112** 437–443.
151 Forte L.R. Guanylin regulatory peptides: structures, biological activities mediated by cyclic GMP and pathobiology. Regul. Pept. (1999) **81** 25–39.
152 Vaandrager A.B., Bot A.G., Ruth P., Pfeifer A., Hofmann F., De Jonge H.R. Differential role of cyclic GMP–dependent protein kinase II in ion transport in murine small intestine and colon. Gastroenterology (2000) **118** 108–114.
153 Tsunoda T., Ota T., Fujimoto T. et al. Inhibition of phosphodiesterase-4 (PDE4) activity triggers luminal

apoptosis and AKT dephosphorylation in a 3-D colonic-crypt model. Mol. Cancer (2012) **11** 46.
154 Shirasawa S., Furuse M., Yokoyama N., Sasazuki T. Altered growth of human colon cancer cell lines disrupted at activated Ki-ras. Science (1993) **260** 85–88.
155 Rahrmann E.P., Collier L.S., Knutson T.P. et al. Identification of PDE4D as a proliferation promoting factor in prostate cancer using a sleeping beauty transposon-based somatic mutagenesis screen. Cancer Res. (2009) **69** 4388–4397.
156 Wang D., Cui X. Evaluation of PDE4 inhibition for COPD. Int. J. Chron. Obstruct. Pulmon. Dis. (2006) **1** 373–379.
157 Zhang W.-H., Zhang Y., Cui Y.-Y. et al. Can β2-adrenoceptor agonists, anticholinergic drugs, and theophylline contribute to the control of pulmonary inflammation and emphysema in COPD? Fundam. Clin. Pharmacol. (2012) **26** 118–134.
158 Arozarena I., Sanchez-Laorden B., Packer L. et al. Oncogenic BRAF induces melanoma cell invasion by downregulating the cGMP-specific phosphodiesterase PDE5A. Cancer Cell (2011) **19** 45–57.
159 Houslay M.D. Hard times for oncogenic BRAF-expressing melanoma cells. Cancer Cell (2011) **19** 3–4.
160 Tinsley H.N., Gary B.D., Keeton A.B. et al. Sulindac sulfide selectively inhibits growth and induces apoptosis of human breast tumor cells by phosphodiesterase 5 inhibition, elevation of cyclic GMP, and activation of protein kinase G. Mol. Cancer Ther. (2009) **8** 3331–3340.
161 Stratakis C.A. cAMP/PKA signaling defects in tumors: genetics and tissue-specific pluripotential cell-derived lesions in human and mouse. Mol. Cell. Endocrinol. (2013) **371** 208–220.
162 Stratakis C.A. New genes and/or molecular pathways associated with adrenal hyperplasias and related adrenocortical tumors. Mol. Cell. Endocrinol. (2009) **300** 152–157.
163 Kim M.J., Lee J.H., Park S.Y. et al. Protection from apoptotic cell death by cilostazol, phosphodiesterase type III inhibitor, via cAMP-dependent protein kinase activation. Pharmacol. Res. (2006) **54** 261–267.
164 Savai R., Pullamsetti S.S., Banat G.-A. et al. Targeting cancer with phosphodiesterase inhibitors. Expert Opin. Investig. Drugs (2009) **19** 117–131.
165 Sharma R.K., Adachi A.M., Adachi K., Wang J.H. Demonstration of bovine brain calmodulin-dependent cyclic nucleotide phosphodiesterase isozymes by monoclonal antibodies. J. Biol. Chem. (1984) **259** 9248–9254.
166 Sonnenburg W.K., Seger D., Kwak K.S., Huang J., Charbonneau H., Beavo J.A. Identification of inhibitory and calmodulin-binding domains of the PDE1A1 and PDE1A2 calmodulin-stimulated cyclic nucleotide phosphodiesterases. J. Biol. Chem. (1995) **270** 30989–31000.
167 Snyder P.B., Florio V.A., Ferguson K., Loughney K. Isolation, expression and analysis of splice variants of a human $Ca2^{+}$/calmodulin-stimulated phosphodiesterase (PDE1A). Cell. Signal. (1999) **11** 535–544.
168 Sharma R.K., Wang J.H. Calmodulin and $Ca2^{+}$-dependent phosphorylation and dephosphorylation of 63-kDa subunit-containing bovine brain calmodulin-stimulated cyclic nucleotide phosphodiesterase isozyme. J. Biol. Chem. (1986) **261** 1322–1328.
169 Bender A.T., Ostenson C.L., Wang E.H., Beavo J.A. Selective up-regulation of PDE1B2 upon monocyte-to-macrophage differentiation. Proc. Natl Acad. Sci. USA (2005) **102** 497–502.
170 Hansen R.S., Charbonneau H., Beavo J.A.. Purification of calmodulin-stimulated cyclic nucleotide phosphodiesterase by monoclonal antibody affinity chromatography. Methods Enzymol. (1988) **159** 543–557.
171 Loughney K., Martins T.J., Harris E.A.S. et al. Isolation and characterization of cDNAs corresponding to two human calcium, calmodulin-regulated, 3′,5′-cyclic nucleotide phosphodiesterases. J. Biol. Chem. (1996) **271** 796–806.
172 Yan C., Zhao A.Z., Bentley J.K., Beavo J.A. The calmodulin-dependent phosphodiesterase gene PDE1C encodes several functionally different splice variants in a tissue-specific manner. J. Biol. Chem. (1996) **271** 25699–25706.
173 Epstein P.M., Fiss K., Hachisu R., Andrenyak D.M. Interaction of calcium antagonists with cyclic AMP phosphodiesterases and calmodulin. Biochem. Biophys. Res. Commun. (1982) **105** 1142–1149.
174 Hagiwara M., Endo T., Hidaka H. Effects of vinpocetine on cyclic nucleotide metabolism in vascular smooth muscle. Biochem. Pharmacol. (1984) **33** 453–457.
175 Snyder P.B., Esselstyn J.M., Loughney K., Wolda S.L., Florio V.A. The role of cyclic nucleotide phosphodiesterases in the regulation of adipocyte lipolysis. J. Lipid Res. (2005) **46** 494–503.
176 Vemulapalli S., Watkins R.W., Chintala M. et al. Antiplatelet and antiproliferative effects of SCH 51866, a novel type 1 and type 5 phosphodiesterase inhibitor. J. Cardiovasc. Pharmacol. (1996) **28** 862–869.
177 Rosman G.J., Martins T.J., Sonnenburg W.K., Beavo J.A., Ferguson K., Loughney K. Isolation and characterization of human cDNAs encoding a cGMP-stimulated 3′,5′-cyclic nucleotide phosphodiesterase. Gene (1997) **191** 89–95.
178 Podzuweit T., Nennstiel P., Müller A. Isozyme selective inhibition of cGMP-stimulated cyclic nucleotide phosphodiesterases by erythro-9-(2-hydroxy-3-nonyl) adenine. Cell. Signal. (1995) **7** 733–738.
179 Boess F.G., Hendrix M., van der Staay F.-J. et al. Inhibition of phosphodiesterase 2 increases neuronal cGMP, synaptic plasticity and memory performance. Neuropharmacology (2004) **47** 1081–1092.
180 Seybold J., Thomas D., Witzenrath M. et al. Tumor necrosis factor-α–dependent expression of phosphodiesterase 2: role in endothelial hyperpermeability. Blood (2005) **105** 3569–3576.
181 Yanaka N., Kurosawa Y., Minami K., Kawai E., Omori K. cGMP-phosphodiesterase activity is up-regulated in response to pressure overload of rat ventricles. Biosci. Biotechnol. Biochem. (2003) **67** 973–979.

182 Coudray C., Charon C., Komas N. et al. Evidence for the presence of several phosphodiesterase isoforms in brown adipose tissue of Zucker rats: modulation of PDE2 by the fa gene expression. FEBS Lett. (1999) **456** 207–210.
183 Juilfs D.M., Fülle H.-J., Zhao A.Z., Houslay M.D., Garbers D.L., Beavo J.A. A subset of olfactory neurons that selectively express cGMP-stimulated phosphodiesterase (PDE2) and guanylyl cyclase-D define a unique olfactory signal transduction pathway. Proc. Natl Acad. Sci. USA (1997) **94** 3388–3395.
184 Meyer M.R., Angele A., Kremmer E., Kaupp U.B., Müller F. A cGMP-signaling pathway in a subset of olfactory sensory neurons. Proc. Natl Acad. Sci. USA (2000) **97** 10595–10600.
185 Grant P.G., Colman R.W. Purification and characterization of a human platelet cyclic nucleotide phosphodiesterase. Biochemistry (1984) **23** 1801–1807.
186 Harrison S.A., Reifsnyder D.H., Gallis B., Cadd G.G., Beavo J.A. Isolation and characterization of bovine cardiac muscle cGMP-inhibited phosphodiesterase: a receptor for new cardiotonic drugs. Mol. Pharmacol. (1986) **29** 506–514.
187 Degerman E., Belfrage P., Newman A.H., Rice K.C., Manganiello V.C. Purification of the putative hormone-sensitive cyclic AMP phosphodiesterase from rat adipose tissue using a derivative of cilostamide as a novel affinity ligand. J. Biol. Chem. (1987) **262** 5797–5807.
188 Ruppert D., Weithmann K.U. HL 725, an extremely potent inhibitor of platelet phosphodiesterase and induced platelet aggregation in vitro. Life Sci. (1982) **31** 2037–2043.
189 Tanaka T., Ishikawa T., Hagiwara M., Onoda K., Itoh H., Hidaka H. Effects of cilostazol, a selective cAMP phosphodiesterase inhibitor on the contraction of vascular smooth muscle. Pharmacology (1988) **36** 313–320.
190 Hidaka H., Hayashi H., Kohri H. et al. Selective inhibitor of platelet cyclic adenosine monophosphate phosphodiesterase, cilostamide, inhibits platelet aggregation. J. Pharmacol. Exp. Ther. (1979) **211** 26–30.
191 Sudo T., Tachibana K., Toga K. et al. Potent effects of novel anti-platelet aggregatory cilostamide analogues on recombinant cyclic nucleotide phosphodiesterase isozyme activity. Biochem. Pharmacol. (2000) **59** 347–356.
192 Wang P., Myers J.G., Wu P., Cheewatrakoolpong B., Egan R.W., Billah M.M. Expression, purification, and characterization of human cAMP-specific phosphodiesterase (PDE4) subtypes A, B, C, and D. Biochem. Biophys. Res. Commun. (1997) **234** 320–324.
193 Salanova M., Jin S.-L.C., Conti M. Heterologous expression and purification of recombinant rolipram-sensitive cyclic AMP-specific phosphodiesterases. Methods (1998) **14** 55–64.
194 Rena G., Begg F., Ross A. et al. Molecular cloning, genomic positioning, promoter identification, and characterization of the novel cyclic AMP-specific phosphodiesterase PDE4A10. Mol. Pharmacol. (2001) **59** 996–1011.
195 Wallace D.A., Johnston L.A., Huston E. et al. Identification and characterization of PDE4A11, a novel, widely expressed long isoform encoded by the human PDE4A cAMP phosphodiesterase gene. Mol. Pharmacol. (2005) **67** 1920–1934.
196 Huston E., Lumb S., Russell A. et al. Molecular cloning and transient expression in COS7 cells of a novel human PDE4B cAMP-specific phosphodiesterase, HSPDE4B3. Biochem. J. (1997) **328** 549–558.
197 Schwabe U., MiyakeI M., Ohga Y., Daly J.W. 4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidone (ZK 62711): a potent inhibitor of adenosine cyclic 3′,5′-monophosphate phosphodiesterases in homogenates and tissue slices from rat brain. Mol. Pharmacol. (1976) **12** 900–910.
198 Hatzelmann A., Schudt C. Anti-inflammatory and immunomodulatory potential of the novel PDE4 inhibitor roflumilast in vitro. J. Pharmacol. Exp. Ther. (2001) **297** 267–279.
199 Barnette M.S., Christensen S.B., Essayan D.M. et al. SB 207499 (Ariflo), a potent and selective second-generation phosphodiesterase 4 inhibitor. In vitro anti-inflammatory actions. J. Pharmacol. Exp. Ther. (1998) **284** 420–426.
200 Sheppard H., Tsien W.H. Alterations in the hydrolytic activity, inhibitor sensitivity and molecular size of the rat erythrocyte cyclic AMP phosphodiesterase by calcium and hypertonic sodium chloride. J. Cyclic Nucleotide Res. (1975) **1** 237–242.
201 Schmidt D.T., Watson N., Dent G. et al. The effect of selective and non-selective phosphodiesterase inhibitors on allergen- and leukotriene C(4)-induced contractions in passively sensitized human airways. Br. J. Pharmacol. (2000) **131** 1607–1618.
202 Billah M., Cooper N., Cuss F. et al. Synthesis and profile of SCH351591, a novel PDE4 inhibitor. Bioorg. Med. Chem. Lett. (2002) **12** 1621–1623.
203 Gale D.D., Landells L.J., Spina D. et al. Pharmacokinetic and pharmacodynamic profile following oral administration of the phosphodiesterase (PDE)4 inhibitor V11294A in healthy volunteers. Br. J. Clin. Pharmacol. (2002) **54** 478–484.
204 Houslay M.D., Sullivan M., Bolger G.B. The multienzyme PDE4 cyclic adenosine monophosphate-specific phosphodiesterase family: intracellular targeting, regulation, and selective inhibition by compounds exerting anti-inflammatory and antidepressant actions. Adv. Pharmacol. (1998) **44** 225–342.
205 Stoclet J.-C., Keravis T., Komas N., Lugnier C. Section review: cardiovascular & renal: cyclic nucleotide phosphodiesterases as therapeutic targets in cardiovascular diseases. Expert Opin. Investig. Drugs (1995) **4** 1081–1100.
206 Zoraghi R., Corbin J.D., Francis S.H. Phosphodiesterase-5 Gln817 is critical for cGMP, vardenafil, or sildenafil affinity: its orientation impacts cGMP but not cAMP affinity. J. Biol. Chem. (2006) **281** 5553–5558.
207 Lugnier C., Schoeffter P., Le Bec A., Strouthou E., Stoclet J.-C. Selective inhibition of cyclic nucleotide phosphodiesterases of human, bovine and rat aorta. Biochem. Pharmacol. (1986) **35** 1743–1751.
208 Boolell M., Allen M.J., Ballard S.A. et al. Sildenafil: an orally active type 5 cyclic GMP-specific phosphodiesterase inhibitor

for the treatment of penile erectile dysfunction. Int. J. Impot. Res. (1996) **8** 47–52.
209 Bischoff E., Niewoehner U., Haning H., Es Sayed M., Schenke T., Schlemmer K.H. The oral efficacy of vardenafil hydrochloride for inducing penile erection in a conscious rabbit model. J. Urol. (2001) **165** 1316–1318.
210 Padma-Nathan H., McMurray J.G., Pullman W.E. et al. On-demand IC351 (Cialis) enhances erectile function in patients with erectile dysfunction. Int. J. Impot. Res. (2001) **13** 2–9.
211 Oh T.Y., Kang K.K., Ahn B.O., Yoo M., Kim W.B. Erectogenic effect of the selective phosphodiesterase type 5 inhibitor, DA-8159. Arch. Pharm. Res. (2000) **23** 471–476.
212 Coste H., Grondin P. Characterization of a novel potent and specific inhibitor of type v phosphodiesterase. Biochem. Pharmacol. (1995) **50** 1577–1585.
213 Miyahara M., Ito M., Itoh H. et al. Isoenzymes of cyclic nucleotide phosphodiesterase in the human aorta: characterization and the effects of E4021. Eur. J. Pharmacol. (1995) **284** 25–33.
214 Saeki T., Adachi H., Takase Y., Yoshitake S., Souda S., Saito I. A selective type V phosphodiesterase inhibitor, E4021, dilates porcine large coronary artery. J. Pharmacol. Exp. Ther. (1995) **272** 825–831.
215 Gillespie P.G., Beavo J.A. Inhibition and stimulation of photoreceptor phosphodiesterases by dipyridamole and M&B 22,948. Mol. Pharmacol. (1989) **36** 773–781.
216 D'Amours M.R., Granovsky A.E., Artemyev N.O., Cote R.H. Potency and mechanism of action of E4021, a type 5 phosphodiesterase isozyme-selective inhibitor, on the photoreceptor phosphodiesterase depend on the state of activation of the enzyme. Mol. Pharmacol. (1999) **55** 508–514.
217 Cote R.H. Characteristics of photoreceptor PDE (PDE6): similarities and differences to PDE5. Int. J. Impot. Res. (2004) **16**(Suppl 1) S28–S33.
218 Hetman J.M., Soderling S.H., Glavas N.A., Beavo J.A. Cloning and characterization of PDE7B, a cAMP-specific phosphodiesterase. Proc. Natl Acad. Sci. USA (2000) **97** 472–476.
219 Sasaki T., Kotera J., Omori K. Novel alternative splice variants of rat phosphodiesterase 7B showing unique tissue-specific expression and phosphorylation. Biochem. J. (2002) **361** 211–220.
220 Sasaki T., Kotera J., Yuasa K., Omori K. Identification of human PDE7B, a cAMP-specific phosphodiesterase. Biochem. Biophys. Res. Commun. (2000) **271** 575–583.
221 Lee M.E., Markowitz J., Lee J.-O., Lee H. Crystal structure of phosphodiesterase 4D and inhibitor complex. FEBS Lett. (2002) **530** 53–58.
222 Lee R., Wolda S., Moon E., Esselstyn J., Hertel C., Lerner A. PDE7A is expressed in human B-lymphocytes and is up-regulated by elevation of intracellular cAMP. Cell. Signal. (2002) **14** 277–284.
223 Smith S.J., Cieslinski L.B., Newton R. et al. Discovery of BRL 50481 [3-(N, N-dimethylsulfonamido)-4-methyl-nitrobenzene], a selective inhibitor of phosphodiesterase 7. In vitro studies in human monocytes, lung macrophages, and $CD8^+$ T-lymphocytes. Mol. Pharmacol. (2004) **66** 1679–1689.
224 Gamanuma M., Yuasa K., Sasaki T., Sakurai N., Kotera J., Omori K. Comparison of enzymatic characterization and gene organization of cyclic nucleotide phosphodiesterase 8 family in humans. Cell. Signal. (2003) **15** 565–574.
225 Hayashi M., Shimada Y., Nishimura Y., Hama T., Tanaka T. Genomic organization, chromosomal localization, and alternative splicing of the human phosphodiesterase 8B gene. Biochem. Biophys. Res. Commun. (2002) **297** 1253–1258.
226 Soderling S.H., Bayuga S.J., Beavo J.A. Identification and characterization of a novel family of cyclic nucleotide phosphodiesterases. J. Biol. Chem. (1998) **273** 15553–15558.
227 Soderling S.H., Bayuga S.J., Beavo J.A. Cloning and characterization of a cAMP-specific cyclic nucleotide phosphodiesterase. Proc. Natl Acad. Sci. USA (1998) **95** 8991–8996.
228 Wunder F., Tersteegen A., Rebmann A., Erb C., Fahrig T., Hendrix M. Characterization of the first potent and selective PDE9 inhibitor using a cGMP reporter cell line. Mol. Pharmacol. (2005) **68** 1775–1781.
229 Hutson P.H., Finger E.N., Magliaro B.C. et al. The selective phosphodiesterase 9 (PDE9) inhibitor PF-04447943 (6-[(3S,4S)-4-methyl-1-(pyrimidin-2-ylmethyl)pyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d] pyrimidin-4-one) enhances synaptic plasticity and cognitive function in rodents. Neuropharmacology (2011) **61** 665–676.
230 Fujishige K., Kotera J., Michibata H. et al. Cloning and characterization of a novel human phosphodiesterase that hydrolyzes both cAMP and cGMP (PDE10A). J. Biol. Chem. (1999) **274** 18438–18445.
231 Kotera J., Fujishige K., Yuasa K., Omori K. Characterization and phosphorylation of PDE10A2, a novel alternative splice variant of human phosphodiesterase that hydrolyzes cAMP and cGMP. Biochem. Biophys. Res. Commun. (1999) **261** 551–557.
232 Weber M., Breier M., Ko D., Thangaraj N., Marzan D.E., Swerdlow N.R. Evaluating the antipsychotic profile of the preferential PDE10A inhibitor, papaverine. Psychopharmacology (2009) **203** 723–735.
233 Yuasa K., Ohgaru T., Asahina M., Omori K. Identification of rat cyclic nucleotide phosphodiesterase 11A (PDE11A): comparison of rat and human PDE11A splicing variants. Eur. J. Biochem. (2001) **268** 4440–4448.
234 Ceyhan O., Birsoy K., Hoffman C.S. Identification of biologically active PDE11-selective inhibitors using a yeast-based high-throughput screen. Chem. Biol. (2012) **19** 155–163.