Published in final edited form as:

Horm Metab Res. 2012 September ; 44(10): 713–715. doi:10.1055/s-0031-1301327.

Cyclic AMP, Protein Kinase A, and Phosphodiesterases: Proceedings of an International Workshop

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Abstract

Cyclic nucleotides cAMP and cGMP are part of almost all major cellular signaling pathways. Phosphodiesterases (PDEs) are enzymes that regulate the intracellular levels of cAMP and cGMP. Protein kinase A or cAMP-dependent protein kinase mediates most cAMP effects in the cell. Over the last 25 years, various components of this group of molecules have been involved in human diseases, both genetic and acquired. Lately, the PDEs attract more attention. The pharmacological exploitation of the PDE's ability to regulate cGMP and cAMP, and through them, a variety of signaling pathways, has led to a number of new drugs for diverse applications from the treatment of erectile dysfunction to heart failure, asthma, and chronic obstructive pulmonary disease. We present the abstracts (available online) and selected articles from the proceedings of a meeting that took place at the National Institutes of Health (NIH), Bethesda, MD, June 8–10, 2011.

Cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) are important second messengers in signaling, involved in cell proliferation, cell cycle regulation, and metabolic function. Intracellular cAMP and cGMP levels are controlled both at their production, from the catalysis of ATP and GTP by activated adenylyl-cyclase and guanylyl-cyclase, and at their break down, by phosphodiesterases (PDEs) [1]. Phosphodiesterases are enzymes that act catalyzing the hydrolysis of the 3' cyclic phosphate bond of cyclic nucleotides. To date, 11 families and several isoforms of PDEs have been identified based on their amino acid sequence, biochemical, and inhibitors profiles. Different PDEs can share the same catalytic function, but may differ in tissue expression and intracellular localization [2]. Elevation of cAMP induces cAMP-dependent protein kinase A (PKA) activation. PKA is a heterotetramer formed by 2 catalytic subunits (C) and 2 regulatory subunits (R) [3]. In the absence of cAMP, PKA is inactive. Upon cAMP binding to the PKA Rs, the catalytic subunits are released and phosphorylate different targets, including the cAMP response element binding (CREB) protein, a transcription factor that regulates genes involved in metabolism and proliferation [4,5]. cGMP activates protein kinase G (PKG), which catalyzes the phosphorylation of downstream proteins involved in

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several physiologic functions, such as glycogenolysis, ion channel conductance, and apoptosis [6].

Dysregulation of the cAMP homeostasis has been linked to tumor formation [7]. Some tumor cells overexpress phosphodiesterases and exhibit lower cAMP levels [8], whereas other tumor types have increased cAMP levels [9]. Understanding the molecular involvement of cAMP in cancer can lead to better treatments as demonstrated by several studies [10,11]. Alterations in the cAMP signaling pathway have also been linked to tumors: activating mutations of the stimulatory G protein of adenylyl cyclase (*GNAS* gene) lead to endocrine and non-endocrine lesions in McCune Albright syndrome (MAS) [12]; inactivating germline mutations in the 1-alpha regulatory subunit gene of the PKA gene (*PRKARIA*) lead to a multiple neoplasia syndrome, Carney complex (CNC) [13,14]. More than 120 *PRKARIA* mutations have been described, some in the somatic state in mostly endocrine tumors [13,15–20]. Inactivating molecular defects in PDEs lead to high cAMP that in turn lead to PKA activation, not unlike *GNAS* or *PRKARIA* mutations: *PDE11A* mutations were described in adrenocortical hyperplasia [21]. Although germline *PDE11A* protein-truncating mutations are seen in the general population, they are significantly more common among patients with adrenal hyperplasia [22]. Mutations are frequently found in other adrenocortical tumors, testicular, and prostatic cancer [23–25]. A *PDE8B* missense mutation (p.H305P) was described in a young girl with isolated micron-odular adrenocortical disease (iMAD); a *PDE8B* knock-out mouse model was also reported with Cushing syndrome due to iMAD-like histopathology [26–28]. Subsequently, another 3 novel mutations in *PDE8B* were described in patients with adrenal tumors [29]. Cortisol-producing adenomas without *GNAS*, *PRKARIA*, *PDE11A*, or *PDE8B* mutations were found to have high cAMP levels and decreased PDE activity suggesting additional PDEs or other members of the cAMP signaling pathway to be involved [30]. *PDE8B* is highly expressed in the thyroid and pituitary glands [31]. A strong association between high TSH levels and polymorphisms in the *PDE8B* gene was described in a genome-wide association study [32]. Hyperthyrotropinemia was also linked to *PDE11A* in a smaller, regional population [33]. An association between upregulation of PDEs in a growth hormone (GH)-producing pituitary adenoma carrying a *GNAS* mutation has been investigated: increased PDE4C and PDE4D expression and activity were discussed as a possible protective mechanism against *GNAS*-dependent activation of the cAMP pathway [34].

The continuous interest in cAMP/PKA/PDE research goes hand in hand with the development of pharmaceutical substances that are used, first to biologically characterize PKA/PDEs in different tissues and, second to selectively target PKA/PDEs in the treatment of diseases. The second international workshop on “cAMP, PKA and PDEs” or PDE2011 was held at the NIH main campus in Bethesda, MD on June 8–10, 2011; the first one, or PDE2009, had also been held at the NIH in June 2009. This editorial note is followed by a number of selected reviews by some of the participants [35–44]; they are reflective of the science presented in this extraordinary meeting. We certainly hope that this volume provides a significant addition to the literature in the field; we also hope that it will lead to an expanded meeting in 2013!

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Figure 1.

Commemorative picture of the participants of the International Workshop on 2nd Cyclic AMP, Protein Kinase and Phosphodiesterases, June 2011. The organizers, Drs. Anna Spada (Italy), Constantine A. Stratakis (USA), Vincent Manganiello (USA) and Jerome Bertherat (France) are shown first, second and third in the front row from the left, and second in the second row from the right, respectively. Dr. Susan Taylor, a member of the U.S. National Academy of Sciences, professor of Chemistry and Biochemistry and Pharmacology at the University of California, San Diego, and a Howard Hughes Medical Investigator, delivered the plenary lecture on the crystal structure of PKA subunits; she is shown third from the right in the first row. The picture is used with kind permission of Jeremy Swan (photographer), National Institutes of Health, Bethesda, MD, USA.