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Review

# $Ca^{2+}$-calmodulin-dependent phosphodiesterase (PDE1): Current perspectives

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**Abstract**

$Ca^{2+}$-calmodulin-dependent phosphodiesterases (PDE1), like $Ca^{2+}$-sensitive adenylyl cyclases (AC), are key enzymes that play a pivotal role in mediating the cross-talk between cAMP and $Ca^{2+}$ signalling. Our understanding of how ACs respond to $Ca^{2+}$ has advanced greatly, with significant breakthroughs at both the molecular and functional level. By contrast, little is known of the mechanisms that might underlie the regulation of PDE1 by $Ca^{2+}$ in the intact cell. In living cells, $Ca^{2+}$ signals are complex and diverse, exhibiting different spatial and temporal properties. The potential therefore exists for dynamic changes in the subcellular distribution and activation of PDE1 in relation to intracellular $Ca^{2+}$ dynamics. PDE1s are a large family of multiply-spliced gene products. Therefore, it is possible that a cell-type specific response to elevation in $[Ca^{2+}]_i$ can occur, depending on the isoform of PDE1 expressed. In this article, we summarize current knowledge on $Ca^{2+}$ regulation of PDE1 in the intact cell and discuss approaches that might be undertaken to delineate the responses of this important group of enzymes to changes in $[Ca^{2+}]_i$.


*Keywords:* Phosphodiesterase; Adenylyl cyclase; Cyclic AMP; Lipid raft; Calcium

**Contents**



## 1. Introduction

Cyclic nucleotide phosphodiesterases are a diverse group of enzymes that effectively terminate intracellular cAMP and cGMP signalling by converting the nucleotides to the inactive 5′AMP and 5′GMP, respectively. Their ubiquitous expression in organisms as diverse as *Trypanosoma* [1,2], *Dictyostelium* [3], *Saccharomyces* [4],

*Abbreviations:* AC, Adenylyl cyclase; $[Ca^{2+}]_i$, cytosolic $Ca^{2+}$ concentration; CaM, calmodulin; CaMKII, $Ca^{2+}$-CaM-dependent kinase II; CCE, capacitative $Ca^{2+}$ entry; CNG, cyclic nucleotide-gated channel; InsP3, inositol trisphosphate; PDE, cyclic nucleotide phosphodiesterase; PKA, cAMP-dependent protein kinase.

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Table 1
Kinetic properties of PDE1 isoforms

| PDE isoform | Tissue source | Molecular weight (kDa) | $K_m$ cAMP (μM) | $K_m$ cGMP (μM) | $K_{CaM}$ (nM) | $EC_{50}$ for CaM (nM) | References |
|---|---|---|---|---|---|---|---|
| bPDE1A1 | Lung | 58 | 42 (88) | 2.75 (15) | | 3–5 | [30,42] |
| bPDE1A2 | Brain | 60–61 | 32 (68) | 2.7 (17) | 1 | 5–10 | [30,42,134] |
| bPDE1A1 | Heart | 59 | 40 | 3.2 | 0.1 | | [134,135] |
| bPDE1B1 | Brain | 63 | 12 | 1.2 | 1 | 9.3 | [37,134,135] |
| bPDE1A2 | Expressed in COS-7 cells | 61 | 113 | 5.2 | | | [87] |
| bPDE1B1 | Expressed in COS-7 cells | 63 | 24 | 2.7 | | | [87] |
| mPDE1C1 | Expressed in COS-7 cells | 72 | 3.5 | 2.2 | | | [35] |
| mPDE1C4/5 | Expressed in COS-7 cells | 74 | 1.1 | 1.0 | | | [35] |
| rPDE1C2 | Expressed in COS-7 cells | | 1.2 | 1.1 | | | [87] |
| dPDE1A1 | Heart | 68 | 2.8 (1.2) | 2.1 (0.53) | | 0.28 | [136] |
| hPDE1A3 | Expressed in yeast | 61 | 51 | 3.5 | | | [32] |
| hPDE1C3 | Expressed in yeast | 72 | 0.57 | 0.33 | | | [32] |

The numbers in parenthesis represents values determined in the absence of $Ca^{2+}$-CaM. b: bovine, m: mouse, r: rat, d: dog, h: human, $K_{CaM}$: association constant for CaM.

*Drosophila* [5] and *Homo sapiens* [6,7] highlights their importance in signal transduction. Cloning and functional characterization has identified 11 members of the PDE superfamily, which consist of more than 20 different gene products, with a staggering number of splice variants [8]. Despite this heterogeneity, there is a surprising degree of homology within their catalytic domains; however, slight structural differences in these domains determine whether the PDE is cAMP-specific (PDE4, PDE7, PDE8), cGMP-specific (PDE5, PDE6, PDE9) or has dual substrate specificity (PDE1, PDE2, PDE3, PDE10, PDE11) [9,10]. Divergent N- and C-termini allow differential regulation of PDEs by other intracellular signalling pathways. The regulation of $Ca^{2+}$-calmodulin-dependent PDEs (PDE1) by changes in intracellular [$Ca^{2+}$] ([$Ca^{2+}$]$_i$) represents a good example of such 'cross-talk'.

In intact cells, PDE1 is almost exclusively activated by $Ca^{2+}$ entering the cell from the extracellular space [11–17]. However, a number of $Ca^{2+}$ entry pathways exist in eukaryotic cells. Physiological agonists that trigger the generation of $Ca^{2+}$ mobilizing second messengers (e.g. $InsP_3$) also trigger $Ca^{2+}$ entry secondary to the depletion of $Ca^{2+}$ from intracellular stores. This depletion-dependent $Ca^{2+}$ influx is termed capacitative $Ca^{2+}$ entry (CCE) [18]. Alternatively, $Ca^{2+}$ can enter the cell through other channels, such as voltage-gated-$Ca^{2+}$-channels [19] or channels that are activated by various extracellular [20–22] and intracellular [23–26] messengers. $Ca^{2+}$-sensitive adenylyl cyclases (AC) are exclusively regulated by CCE in non-excitable cells [27]. However, not a great deal is known about whether PDE1 is similarly discriminating as to the source of $Ca^{2+}$ to which it responds. Given the complexity of intracellular $Ca^{2+}$ signals and the multiplicity of PDE1 isoforms, the regulation of PDE1 by these $Ca^{2+}$ signals could provide dynamic spatial and temporal changes in cAMP levels in selected subcellular compartments. Here, we review current opinions on $Ca^{2+}$ regulation of PDE1 and approaches that we might take to further our understanding of this important group of enzymes.

## 2. Diversity of the PDE1 subfamily

PDE1 was first identified in 1970 in the rat brain, together with its endogenous regulator, calmodulin (CaM) [28,29]. The PDE1 subfamily consists of three distinct gene products (PDE1A, PDE1B and PDE1C) which differ in their regulatory properties, substrate affinities, specific activities, activation constants for CaM, tissue distribution and molecular weights (Table 1) [30–38]. The heterogeneity of this group of enzymes is further increased by alternative splicing, creating divergent N- and C-termini [32,35,39–41]. This heterogeneity is clearly illustrated when comparing the observed $K_m$ values of the different isoforms. For example, in bovine brain, PDE1A2 and PDE1B1 have $K_m$ values of 32 and 12 μM, respectively, for cAMP (Table 1). Furthermore, PDE1C isoforms have the highest substrate affinities, with $K_m$ values for cAMP ranging between 0.57 and 3.5 μM (Table 1). Isoforms also exhibit large differences between their affinity for CaM, which highlights the diversity in their $Ca^{2+}$sensitivity (Table 1). Despite this heterogeneity, the overall structure of PDE1 isoforms is well conserved, consisting of four domains; two CaM-binding domains (hereafter referred to in the text as CaM1 and CaM2), an inhibitory domain and a catalytic domain [42,43] (Fig. 1). The conserved core region of ~250 amino acid residues that contains the catalytic domain is highly conserved across the PDE1 subfamily [43]. However, the variation in the N- and C-

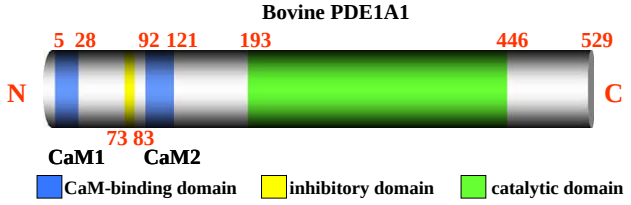


Fig. 1. Bovine PDE1A1 showing the CaM binding domains (CaM1 and CaM2), inhibitory domain and the catalytic domain. The numbers indicate the amino acid residue positions. Adapted with permission from [42].