Pharmacologic activity of phosphodiesterases and their inhibitors

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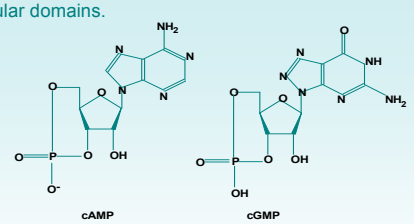
The phosphodiesterases (PDE)

Phosphodiesterases (PDE) are enzymes that **hydrolyze the cyclic nucleotides adenosine 3',5'-cyclic monophosphate (cAMP) and guanosine 3',5'-cyclic monophosphate (cGMP), in their inactive form (5'nucleotide) and, therefore they play an essential role in the cellular enzyme systems.**

The cyclic nucleotide phosphodiesterases (PDE) **degrading the phosphodiester bond in the second messenger molecules cAMP and cGMP** (fig.1).

They **regulate** the localization, duration, and amplitude of cyclic nucleotide signalling within sub cellular domains.

Fig. 1. Spatial structure of cAMP and cGMP



The enzyme systems effectors that are known are:

- **calmodulin system (CaM),**
- **protein kinase;**
- **AC-cAMP system**
- **GC-cGMP system and**
- **PI system (phosphatidyl-inositol)**

Legend

PDE	– *phosphodiesterase*
AMPc	– *cyclic adenosine monophosphate*
ATP	– *adenosine triphosphate*
cGM	– *cyclic guanosine monophosphate*
GT	– *guanosine triphosphate*
AC	– *adenilate cyclase*
GC	– *guanylate cyclase*
I	– *inositol*
PI (IP)	– *phosphatidyl-inositol*
PIP2	– *phosphatidyl-inositol 4, 5-biphosphate*
IP3	– *inositol 1, 4, 5-triphosphate*
DAG	– *diacilglicerol*
CaM	– *calmodulin Y7*
TXA2	– *thromboxanes*
NO	– *nitrogen monoxide*
EDRF	– *the endothelial relaxing factor*
PA	– *the phosphatidic acid*
AA	– *the arahidonic acid*
PG	– *prostanoide*
VOC	– *the voltage-dependent channels*
ROC	– *the receptor-dependent channels*
MLCK	– *the light chain kinase of the myosin*
RE	– *endoplasmic reticulum*
CaP	– *calponine*
CaD	– *caldesmone*
PCI2	– *prostacilin*

PDE,s implication in the enzyme systems work

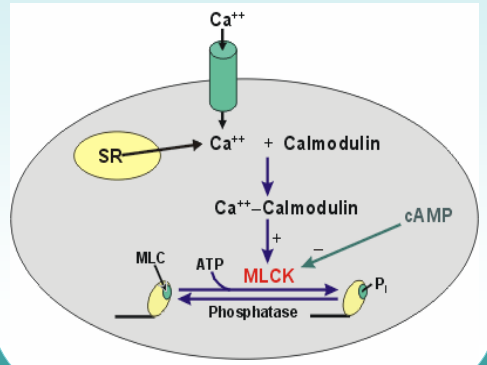
cAMP is a 2 order messenger, who translates the external stimuli into cell internal stimuli, and who is degraded into AMP (*adenosine 5'-monophosphate*) by an cAMP-dependent PDE. An increase in free intracellular calcium can result from either increased flux of calcium into the cell through calcium channels or by release of calcium from internal stores (e.g., sarcoplasmic reticulum; SR).

The free calcium binds to a special calcium binding protein called ***calmodulin.***

Calcium-calmodulin activates ***myosin light chain kinase*** **(MLCK),** an enzyme that is capable of phosphorylating myosin light chains (MLC) in the presence of ATP.

Myosin light chains are 20-kD regulatory subunits found on the myosin heads. MLC phosphorylation leads to cross-bridge formation between the myosin heads and the actin filaments, **and hence smooth muscle contraction** (figure 2).

The PDE enzymes are classified into 11 families, namely PDE1-PDE11, in mammals.



The PDE inhibitors

The phosphodiesterase inhibitors have stimulatory effects on the growth of microtubules in many cell types. It seems that the cAMP-dependent phosphorylation of the tubulin or of the proteins associated with the microtubules stimulates the polymerization of the microtubules

PDE type	Specific activity	Selective inhibitors	Specific activity
PDE1	activated by Ca^{2+}/ calmodulin,	*Vinpocetine Nimodipine*	It is implicated in the level adjustment of the cGMP in the vascular smooth muscle cells, it is considered as important in the control of the action of some vasoconstrictor which growing the intracellular calcium concentration.
PDE2	stimulated by cGMP	*EHNA(erythro-9-(2-hydroxy-3-nonyl) adenine)* *EHNA analogues: BAY 60-7550 PDP (9-(6-Phenyl-2-oxohex-3-yl)-2-(3,4-dimethoxybenzyl)-purin-6one* *Oxindole Anagrelide*	May act in synergy to mediate diverse pharmacological responses including anti-viral, anti-tumour and anti-arrhythmic effects. It has been successfully used with the proper controls as a tool to probe PDE2 functions.
PDE3	cGMP inhibited,	*Enoximone, Milrinone, Inamrinone* (formerly amrinone) *Cilostazol*	Used clinically for short-term treatment of cardiac failure, these drugs mimic sympathetic stimulation and increase cardiac output.
PDE4	AMPc - dependent/ specific	*Mesembrine,* (Sceletium tortuosum alkaloid) *Rolipram, Ibudilast, Piclamilast, Luteolin,*	Inhibitors have proven potential as anti-inflammatory drugs, especially in inflammatory pulmonary diseases such as asthma, COPD, and rhinitis. They suppress the release of cytokines and other inflammatory signals, and inhibit the production of reactive oxygen species. PDE4 inhibitors may have antidepressive effects and have also recently been proposed for use as antipsychotics
PDE5	cGMP	*Sildenafil, Tadalafil, Vardenafil, Udenafil Avanafil*	Selectively inhibit PDE5, which is cGMP-specific and responsible for the degradation of cGMP in the *corpus cavernosum.* These phosphodiesterase inhibitors are used primarily as remedies for erectile dysfunction, as well as having some other medical applications such as treatment of pulmonary hypertension.
PDE6	Ca2+/ cGMP-signalling HPC1	*Dipyridamole Zaprinast*	After activation by rhodopsin, the GDP of the heterotrimer is exchanged for GTP and the Gαt-GTP diffuses and binds to a membrane-associated photoreceptorspecific cGMP PDE.
Non selective inhibitors			
PDE	intracellular cAMP activity, PKA- ,	*Methylated xanthines and derivatives: Caffeine, Aminophylline, IBMX(3-isobutyl-1-methylxanthine),* *Paraxanthine, Pentoxifylline, Theobromine Theophylline,*	Drugs have the potential to enhance circulation and may have applicability in treatment of diabetes, fibrotic disorders, peripheral nerve damage, and microvascular injuries or as bronchodilators. Methylated xanthines act as both competitive nonselective phosphodiesterase inhibitors, inhibit TNF-alpha and leukotriene synthesis, and reduce inflammation and innate immunity and nonselective adenosine receptor antagonists.

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Conclusions

A phosphodiesterase inhibitor is a drug that **blocks one or more of the five subtypes of the enzyme phosphodiesterase** (PDE), therefore preventing the inactivation of the intracellular second messengers' cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) by respective PDE subtype (s).

As is purified, this PDE partially lose his activity. This suggests the existence of a **specific PDE activation factor**, which is removed by the purification processes. **This protein factor is calmodulin (CaM).**

The PDE inhibition, **change the intracellular response to extra cellular data signals** by affecting the mediated processes of the cyclic nucleotides.

The PDE selective inhibition has various therapeutic applications. The **smooth muscle from the most organs**, except the intestine, shrinks under the influence of a *α*-adrenergic stimulation.

The contraction is produced under the action of the MLCK (*myosin light chain kinase*) which is dependent by the CaM. At the smooth muscle stimulation a PA accumulation occurs.

The agonists that causes the contraction of the smooth muscle (*α-adrenomimetics*, M *cholinomimetics*, *histamine* or *serotonin* 5HT) leads to the PI increased division:

The relationship between the PI and the citosol Ca2 + can be seen from two perspectives: the PI hydrolysis from the membranes leads to the opening of some doors for the Ca2 +, the PI changes can lead to the formation of a second intracellular chemical messenger, which release the Ca2 + from the deposits