Pharmacologic activity of phosphodiesterases and their inhibitors

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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 loses its 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 α2-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 PAI 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 hydrolizes 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

Legend

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 (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.

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

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 specific 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 CAM-dependent phosphorylation of the tubulin or of the proteins associated with the microtubules stimulates the polymerization of the microtubules

PDE type Specific inhibitors

PDE1 activated by cAMPCaM

Guanosine Nucleotides

PDE2 stimulated by cAMPCaM

Sildenafil, Tadalafil, Vardenafil

PDE3 cAMPCaM

Vardenafil, Tadalafil, Sildenafil, Olestra, Fosinopril

PDE4 cAMPCaM depressed activity

Indomethacin, Piroxicam, Ibuprofen, Indomethacin

PDE5 cAMPCaM

Sildenafil, Tadalafil, Vardenafil, Mexiletine

PDE6 CaM

Diphenidine, Zaprinast

Non selective inhibitors

Phosphodiesterases

Benzopyran derivatives and Dipyridamole

Methylxanthines, Phosphodiesterases inhibitors

PDE intracellular cAMP activity, PDE5

Clometacin, Tapatinan, Thalidomide, Cyclosporine, Thyronine, Theophylline,

Dapsone have the potential to enhance circulation and may have applicability in treatment of diabetes, cardiac disorders, peripheral nerve damage, and microvascular injuries or as treatment of pulmonary thromboembolism phosphodiesterase inhibitors, Dapsone, TNF-α and interleukin-6, systemic, and reduce inflammation and tissue immunity and connective adhesion receptor antagonists.