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Short Communication

Phosphodiesterases: Biological Activities of Chemical Compounds that Antagonize these Enzymes

Chika J Mbah*

Department of Pharmaceutical and Medicinal Chemistry, Faculty of Pharmaceutical Sciences, University of Nigeria, Nsukka, Enugu State, Nigeria

***Corresponding Author:** Chika J Mbah, Department of Pharmaceutical and Medicinal Chemistry, Faculty of Pharmaceutical Sciences, University of Nigeria, Nsukka, Enugu State, Nigeria.

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Abstract

Phosphodiesterases (PDEs) are enzymes whose primary function is to terminate signaling of cyclic nucleotides by catalyzing the hydrolysis of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) respectively. Invariably, these enzymes are considered to be critical regulators of the intracellular concentrations of cAMP and cGMP including their signaling pathways and accompanied biological effects. The levels of these cyclic nucleotides are maintained through a balance between production (done by adenyl cyclase and guanyl cyclase from adenosine triphosphate and guanosine triphosphate, respectively) and breakdown, (carried out by phosphodiesterases) resulting in the formation of the inactive forms 5'AMP and 5'GMP respectively. A number of extracellular stimuli, namely cytokines, light, growth factors, neurotransmitters and peptide hormones are generators of these signals to be carried by cyclic nucleotides. Cyclic nucleotides (signal-transducing molecules) modulate a number of biological processes, including apoptosis, myocardial contractility, platelet aggregation, proliferation and vascular smooth muscle relaxation. Various therapeutic agents block the unique phosphodiesterases function by increasing cyclic nucleotide concentration levels. In the present article, general information of phosphodiesterases will be given as well as presentation of a number of chemical compounds that target these enzymes.

Keywords: *Phosphodiesterases; Phosphodiesterases Antagonists; Biological Activities*

Introduction

Phosphodiesterases (PDEs) are enzymes that destroy the phosphodiesteric bond of the cyclic nucleotides that regulate many biological processes [1,2]. Such cyclic nucleotides are adenosine monophosphate (cAMP) and guanosine monophosphate (cGMP) respectively. Adenylyl and guanylyl cyclases catalyze formation of cAMP and cGMP from adenosine triphosphate (ATP) and guanosine triphosphate (GTP), respectively. The cAMP and cGMP are intracellular second messengers that have vital responsibility in signal transduction cascades in various biological systems. They activate intracellular targets such as kinases, ion channels, and transcription factors that trigger the cellular response to the message. They also transfer extracellular signals (neurotransmitters, hormones, olfactive and luminous signals) to one of the effector proteins namely protein kinase A (PKA) and protein kinase G (PKG) respectively.

Signaling function of intracellular second messengers regulates various necessary physiological and pathophysiological processes such as cardiac function, calcium ion (Ca^{2+})- dependent signaling, cellular growth, differentiation and proliferation, inflammation, reproduction, tumour development and vision [3].

The regulation of the concentrations of cAMP and/or cGMP by the enzymes can be achieved through: (i) calcium ion (Ca^{2+})/calmodulin (CaM) activation [4], (ii) activation or inhibition of cGMP by PDE2, PDE6 or PDE3 respectively [5,6], (iii) insensitization of cGMP by PDE4 [7], (iv) phosphorylation of PKA and PKG by PDE5 [6].

Three main mechanisms control phosphodiesterases and they include: (i) regulation of the intracellular signal by extracellular signals; (ii) stimulation of the enzyme activity following rise in the levels of cyclic nucleotides, (iii) feedback regulation [1,8].

Phosphodiesterases contain eleven PDE gene families (PDE1 to PDE11), comprising of 21 genes that generate approximately 100 or more proteins [9,10].

Although, the families of these enzymes are structurally related and highly regulated, they differ in their (a) subcellular localization, (b) primary structures, (c) catalytic properties, (d) responses to specific inhibitors and modulators. The intracellular locations of these enzymes might include: (i) cytosol of tissues/organs such as brain, kidney, liver, pancreas, and thyroid [11,12]. Typical examples are PDE1, PDE2, PDE4, PDE5, PDE6, PDE7, PDE11 respectively, (ii) membranes of tissues/organs such as adrenal gland, brain, heart, liver, macrophages, neurons, platelets, and smooth muscles [13-15]. Typical examples are PDE2, PDE3, PDE4, PDE8 respectively (iii) nuclei of tissues/organs such as brain, small intestine, spleen, and testis [16,17]. Typical examples are PDE9 and PDE10 respectively.

Based on substrate specificity, the eleven phosphodiesterases families can be grouped into three main categories namely, (a) PDE4, PDE7, and PDE8-these selectively hydrolyze cAMP; whereas (b) PDE5, PDE6, PDE9 selectively hydrolyze cGMP, (c) PDE1, PDE2, PDE3, PDE10, and PDE11 possess dual specificity by acting on both cAMP and cGMP with varying affinities.

Due to the vital physiological roles of cyclic nucleotides and the hydrolyzing properties of phosphodiesterases, several chemical compounds containing one or more rings that mimic the purine ring were synthesized and investigated for their inhibitory properties against phosphodiesterases. The syntheses were based on the findings that theophylline and 1-Methyl-3-isobutylxanthine (IBMX) inhibited virtually all phosphodiesterases with the exception of PDE8 and PDE9 respectively [18]. The outcome of the syntheses, were numerous chemical compounds that antagonize (inhibited) these enzymes. In this context, the study will enumerate these chemical compounds and their antagonist properties towards phosphodiesterases.

Antagonists (inhibitors) of phosphodiesterases and their biological activities

(i) Inhibitors of phosphodiesterases 1 (PDE1):

a. Nimodipine- Activity against hypertension [19].

b. Vinpocetine- Activity against inflammation, vasodilation, acute ischemic stroke, and urge incontinence [20].

(ii) Inhibitors of phosphodiesterases 3 (PDE3):

a. Olprinone- Activity against inflammation after cardio pulmonary bypass and acidosis [21].

b. Milrinone, cilostamids, amranone, enoxinone- Activity against pulmonary hypertension and vulvular disease [22].

(iii) Inhibitors of phosphodiesterases 4 (PDE4):

a. Ibudilast- Activity against broncho-constriction, vasoconstrictor, platelet aggregation and stroke [23].

b. Cilomilast- Activity against bronchitis, emphysema [24].

c. Mesembrine- Activity against convulsion, depression, age-related dementia and debilitative mental disorders [25].

d. Etazolate- Activity against Alzheimer;s disease [26].

e. Roflumilast- Activity against asthma, chronic obstructive pulmonary disease [27].

f. Rolipram- Activity against multiple sclerosis [28].

(iv) Inhibitors of phosphodiesterases 5 (PDE5):

a. Sildenafil- Mostly used to treat erectile dysfunction and pulmonary hypertension. It also has activity against endothelial dysfunction, ischemic stroke, diabetes mellitus, schizophrenia, gastroparesis and sickle cell anaemia [29].

b. Tadalafil- Mostly used to treat erectile dysfunction. Also has activity against benign prostatic hyperplasia, pulmonary hypertension and prostate cancer [30].

c. Udendafil- Mostly used to treat erectile dysfunction. It also has activity against chronic obstructive pulmonary disease [31].

d. Dipyridamole- Mostly used to treat erectile dysfunction. Has activity also against atherosclerosis, breast cancer, ischemia-reperfusion injury, rheumatoid arthritis and stroke [32].

e. Avanafil, lodenafil and vardenafil- Mostly used to treat erectile dysfunction [29].

(v) Inhibitors of phosphodiesterases 6 (PDE 6):

a. Dipyridamole, sildenafil and vardenafil- Activities similar to those stated under phosphodiesterases 5 inhibitors [29].

b. Zaprinast- Activity against erectile dysfunction [21].

(vi) Inhibitors of phosphodiesterases 10 (PDE 10):

a. Papaverine- Activity against sexual dysfunction and infertility [33].

(vii) Inhibitors of phosphodiesterases 11 (PDE 11):

a. Tadalafil - Activity similar to those stated under phosphodiesterases 5 inhibitors [34].

In addition to above phosphodiesterases antagonists, numerous other chemical compounds are currently undergoing screening as PDE2, PDE 6, PDE 7, PDE 8, and PDE 9 inhibitors.

Conclusion

Phosphodiesterases provide very vital role in the regulation of cellular function by hydrolyzing cyclic nucleotides. The localization, expression levels and regulation of phosphodiesterases 4 (PDE 4) are considered to be very vital in maintaining healthy brain function. Inhibitors of phosphodiesterases 5 (PDE 5) have become first-line therapy for erectile dysfunction as well as being very effective therapeutic

agents for pulmonary hypertension. They are potent and selective therapeutic agents that provide safe and effective method of improving erectile dysfunction. Finally, because of subcellular localization and structure diversity of these enzymes, each phosphodiesterase variant regulates compartmentalized cyclic nucleotide signaling pathways thus defining specific cell responses in an integrated fashion.

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