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Review

Phosphodiesterase Inhibitors: A Review

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ABSTRACT

Phosphodiesterase Inhibitors are class of drugs, actively inhibiting the specific target Phosphodiesterase Enzymes (PDE).FDA approved to be used in myriad of disorders such as Chronic Obstructive Pulmonary Disease (COPD), Erectile Dysfunction (ED), Benign Prostatic Hyperplasia (BPH), Pulmonary Artery Hypertension (PAH), Bronchial Asthma (BA) etc. The primary mechanism of PDE Inhibitors is smooth muscle relaxation and bronchodilation by inhibiting Cyclic Guanosine Monophosphate (cGMP) and Cyclic Adenosine Monophosphate (cAMP) degradation by acting on Nitric Oxide (NO) led pathway. This role of PDE Inhibitors is beneficial in so many conditions, as cGMP and cAMP pathways are present in numerous areas. We present a review on current state uses of PDE Inhibitors and their potential future therapy of experimental uses having off label effects utilising the Nitric Oxide led pathways as the core basis.

KEYWORDS: Phosphodiesterase Enzyme (PDE), cAMP, cGMP, Nitric Oxide, Platelet aggregation, Sildenafil, Tadalafil.

INTRODUCTION

Henry Hyde Salter was a British physician who is considered to be the first to document Phosphodiesterase (PDE) inhibitor. In his book on asthma, he advised having a strong cup of coffee empty stomach in the morning to control asthmatic attack, which actually denoted the weak PDE inhibitory effect of caffeine[1].

It is understood that PDE Inhibitors are the drugs which acts by blocking the PDE Enzyme and its five subtypes. This in turn ceases the inactivation of the Cyclic Adenosine Monophosphate (cAMP) and Cyclic Guanosine Monophosphate (cGMP) which are the secondary messengers in the intracellular compartment.

HISTORY

The first documentation for the isolation of these enzymes are found in the year of 1970, which was done from rat brains[2]. Weiss and Hait first identified the pharmacological and therapeutic properties of PDE in 1977[3].

Beavo identified and classified the multiple subtypes of PDE and placed them under the PDE Super family umbrella. (Table – 1)[4]

Given the widespread tissue expression of PDE, a wide range of drugs are available targeting various conditions.

Table 1: Phosphodiesterase Inhibitors and Drug Examples

Group	Expressive Tissue	Inhibiting Drugs
PDE-1	Smooth muscles, lung, brain, heart	KS-505a, Vinpocetine
PDE-2	Platelets, Liver, Lung, Adrenal Gland	EHNA
PDE-3	Adipose tissue, Inflammatory precursors, Cardiac Cells	Milrinone, Cilostazol, Anagrelide
PDE-4	Sertoli cells, renal cells, nervous cells	Roflumilast, Cilomilast
PDE-5	Smooth muscle cells, vascular cells, platelets	Sildenafil, Zaprinast
PDE-6	Photoreceptor cells	Dipyridamole
PDE-7	Skeletal tissue, cardiac cells, pancreatic cells, T Immune cells (Lymphocytes)	IC242
PDE-8	Testicular cells, hepatic cells, ovarian cells	Zaprinast
PDE-9	Renal, hepatic, nervous, lung	BAY-73-6691
PDE-10	Testicular cells	-
PDE-11	Salivary glands, pituitary cells	-

INDIVIDUAL SUBTYPES AND MECHANISMS

The primary mechanism of the PDE is to isolate the phosphate molecule from the target ell and reduce the amount of cAMP / cGMP. Now when this enzyme is inhibited through selective blockade it stops from cAMP and cGMP to degrade further and in turn preserving their primary effect such as bronchodilation, vasodilation, smooth muscle relaxation etc.

PDE-3

PDE-3 inhibitors specifically target the cardiac cells, they increase the cAMP volume in the peripheral vasculature as well as myocardial cells and platelets, resulting in peripheral vasodilation, increased ionized calcium in myocardial cells and preventing platelet aggregation. These properties are effective in treatment of Peripheral Vascular Disease (Arterial) and heart failure. Milrinone, Cilastazole, Anagrelide are commonly employed[5].

PDE-4

PDE-4 has a degradative impact on the cAMP substrate. They are the most abundant of all the PDE subtypes. There are around 20 subtypes of PDE-4 Inhibitors. PDE-4 target hydrolyzation of cAMP in both nervous and immune cells[6]. PDE-4 inhibitors have multiple uses. Their cognition benefits are well known to improve long term memory[7] along with numerous other cognition benefits such as alertness[8]. They also prevent excitotoxic damage to neuronal cells[9]

There are distinct subvariants of PDE-4 inhibitors, differentiated on the basis of target action and mechanism.The prototype examples of PDE -4 Inhibitors:

- Cilomilast
- Crisaborole
- Ibudilast
- Roflumilast
- Rolipram

Apart from constitutional adverse effects such as vomiting, nausea, Roflumilast is notorious to cause urinary tract and upper respiratory tract disorders[10].

Table 2: Sub Variants of PDE 4

Sub Variants	Expression, Action
PDE4A, PDE4 D	Antidepressant
PDE4 -B	Antipsychotic
PDE4 -C	Expressed in peripheral circulation (Anti-Inflammatory), alcohol de-addiction
PDE4 -D	Area postrema – Potent emetic

PDE-5

The fifth subtype of PDE Inhibitors, PDE-5 is a cGMP related variant. It was first isolated from platelets in rat blood in the year of 1978, termed as cGMP-PDE[11]. The first PDE-5 Inhibitor to be given in humans was Zaprinast. It was given in patients suffering from exercise induced asthma, it was given for its bronchodilator effect[12]. PDE-5 Inhibitors were also considered as a promising agent in cardiovascular medicine due to their effects on vaso-relaxation and smooth muscle relaxation[13]. After being studied it's effect in rat blood, in 1992 Rajfer et al[14]. studied that similarly as in rat blood, the Nitric Oxide (NO) formation was stimulated by Electrical Field Stimulation (EFS) in human corpus cavernosum also, which in turn bringing relaxation. This effect was particularly diminished, or if not then it's reduced in impotent males. He further studied Zaprinast and demonstrated that it further stimulates the relaxation of corpus cavernosum induced by Nitric Oxide, giving us the most widely employed use of PDE-5 – Impotency[14].

PDE-5 Inhibitor agents such as Sildenafil Tadalafil and Vardenafil are used in the treatment of erectile dysfunction[15]. Due to their affinity for cGMP and effect on Nitric Oxide reducing pathway, PDE-5 inhibitors are also used in treating some variants of pulmonary hypertension and benign prostatic hyperplasia. In patients suffering from PAH, PDE-5 inhibitors have significant effect on mortality and also on substantial improvement in quality of life, more so in patients suffering from PAH due to right heart failure[16].

PDE-5 was initially discovered by a British physician named Henry Salter, who discovered the bronchodilator effects of caffeine when a bronchial asthma patient got relief from his symptoms after having a strong cup of coffee[17]. And for the beneficial effects of Angina, initial pre-clinical work was started by Pfizer. Current available marketable agents are Sildenafil, Tadalafil, Zaprinast, Vardenafil, Icaria etc[18].

PDE- 7, 9, 10

Quinazoline a type of PDE-7 inhibitor has been used for it's neuroprotective and anti-inflammatory effects[19].

The primary metabolite of caffeine – Paraxanthine, inhibits the PDE-9 receptor whose primary affinity is with cGMP. It is almost similar to PDE-5 in expression, especially in corpus cavernosum[20].

A common opioid alkaloid derivative – Papaverine is proven to inhibit the PDE-10 receptor. The PDE-10 is seen exclusively in the striatum, and they increase cAMP and cGMP following

inhibition by agents such as Papaverine. It was documented that PDE10-A inhibition increases the cAMP level, this effect correlates to the hypoactivity in brain. The determinant of this action is mainly related to the elevation in cAMP levels by the inhibitors and its capacity to do so[21].

improve attention, cognition, memory registration, inhibition, and processing information. The Long Term Potentiation (LTP) is a favourable property of these PDE Inhibitors. Hope lies on a potential isotope of PDE Inhibitor that helps in aged brain such as in Alzheimer which has acceptable rate of side effects[24].

Table 2: Summary of various PDE - Inhibitors

PDE Group	Disease Target
PDE – 2	Acute Respiratory Distress Syndrome, Sepsis[22]
PDE – 3	PVD, Heart failure etc.
PDE – 4	Depression, Alzheimer's disease, Memory Loss etc.
PDE – 5	Erectile Dysfunction, Pulmonary Hypertension, Premature Ejaculation, Renal Failure
PDE – 7	Anti – Inflammatory
PDE – 9	Psychostimulant
PDE – 10	Antipsychotic

NOVEL POTENTIAL USE

Neuroprotective Role

Numerous disquiets related to the central nervous system over the period of time end up tarnishing the structural format of the architecture. This leads to dysfunctional CNS and also a dysregulated and curtailed repair. To counteract the damage by nervous system disorders and trauma, the intracellular signals comprising mainly of cGMP and cAMP which regulates the inflammation, cell death (neuronal), immune response, neuroplasticity has to be altered. As we discussed earlier, PDEs have an inhibitory effect on these regulators.

In an event of neurotrauma or pathology, PDEs hydrolyse the cGMP and cAMP to 5'GMP and 5'AMP. This inhibits the ongoing process and promotes inflammation and destruction. Inhibiting this PDEs effect has a potential role in neuroprotective and repair process[23].

Out of the entire family, PDEs 2,4,5,9,10 has been proven to

Pleiotropism and Cardiovascular Medicine

The PDE-5 inhibitor Tadalafil, Sildenafil has been also proven to improve the left ventricular function when given with Doxorubicin (Anthracycline derivative – chemotherapeutic agent) and it also has an inhibitory effect in LV dysfunction and apoptosis caused by Doxorubicin. Inhibition has been led by the same cGMP and cAMP upregulation along with the reactive oxygen species (ROS) superoxide dismutase (SOD). This effect does not hamper the chemotherapeutic effect of the agent[25,26,27].

The ROS (Mitochondrial) has been reported to improve killing of neoplastic cells. Doxorubicin acts by increased production of ROS in cancer cells[26]. When combined with sildenafil, this production is further increased exponentially. This killings are independent of p53[28].

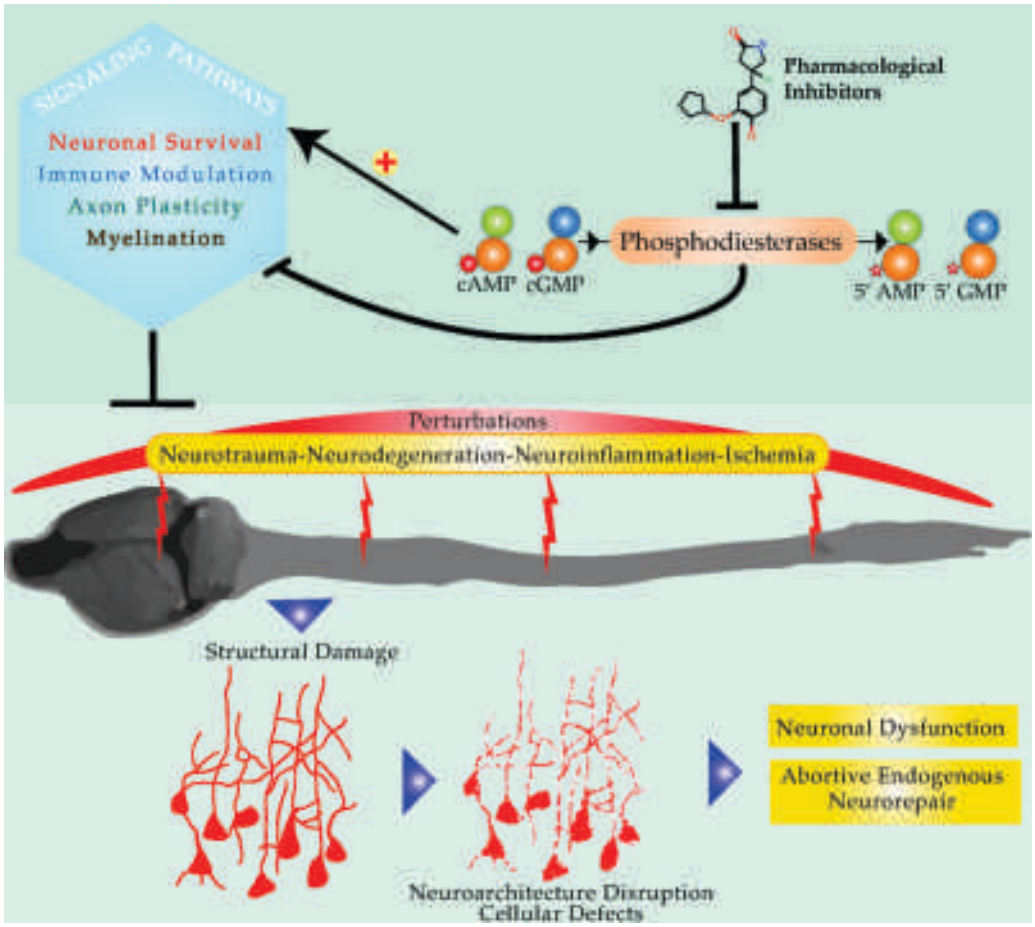

Figure 1: Role of PDEs in Neurodegeneration and therapeutic role of PDE Inhibitors [23]
(Image re-used under creative commons licence)

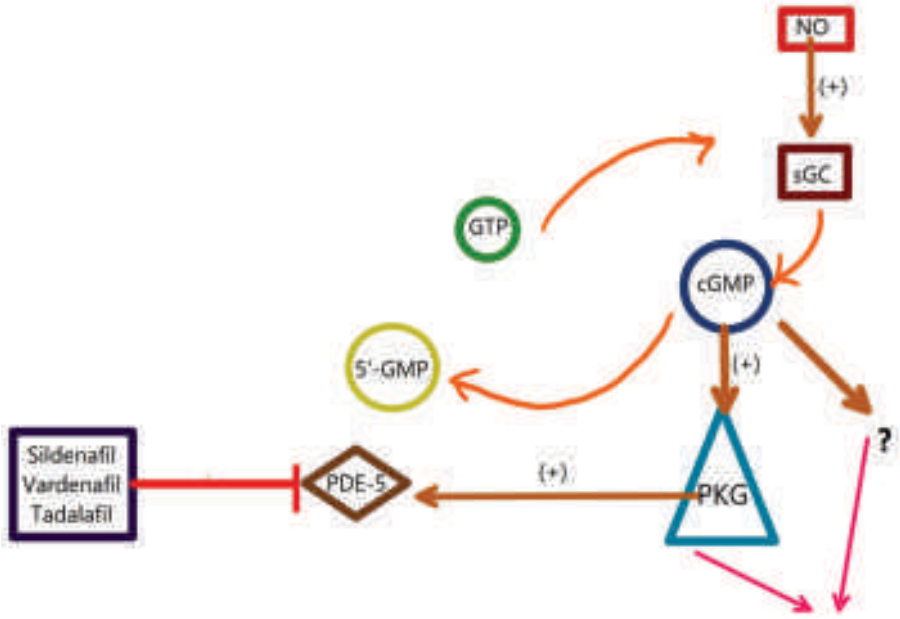

Figure 2: cGMP – PDE 5 Site of action Pathway
(Image redrawn from Gross G[29].)

The increase in cAMP could potentially affect cardiac function, vascularity of heart and the tonicity. They have been proven useful also in stroke (cerebral and cardiac), peripheral vascular disorders and severe heart failure[30]. Pentoxifylline was the first PDE inhibitor to be approved in treatment of limb claudication. However, studies were inconclusive for the same[31,32] The most recent addition in the similar use-case is Cilastazole. The therapeutic benefits are much better compared to Pentoxifylline[33]. It is reported that Cilastazole reduces plasma triglyceride (TGL) levels, and upsurges High Density Lipoproteins (HDL)[34]. Cilastazole has also been shown to reduce the occurrence of coronary restenosis post Percutaneous Transluminal Coronary Angioplasty (PTCA)[35]. Current state of PDE Inhibitors in cardiovascular disease is limited to two approved agents. Pentoxifylline and Cilastazole for intermittent claudication in oral form and Milrinone for acute congestive heart failure intravenously[36].

shown to reduce the serum Lactate Dehydrogenase (LDH) levels with substantial increase lymphocyte count[39]. Milrinone has also shown to improve cardiac function and beneficial in immune dysregulation in septic conditions when given with Esmolol[40]. Reduction in pulmonary arterial pressure and mean arterial pressure is seen in early stages of ARDS induced by severe COVID-19 with Sildenafil[41].

The world entered in a stage of Pandemic because of the havoc created by the deadly SARS CoV -2. The viral pneumonia caused by SARS CoV -2 virus led to severe immune response and dysregulated cytokine recruitment leading to severe ARDS and residual deadly fibrosis. The effect on NO led cGMP cAMP axis of PDE-5 is being studied as a phase three trial given the fact that PDE5 primarily has pulmonary expression. They reduce the cytokine recruitment and alveolar necrosis[42].

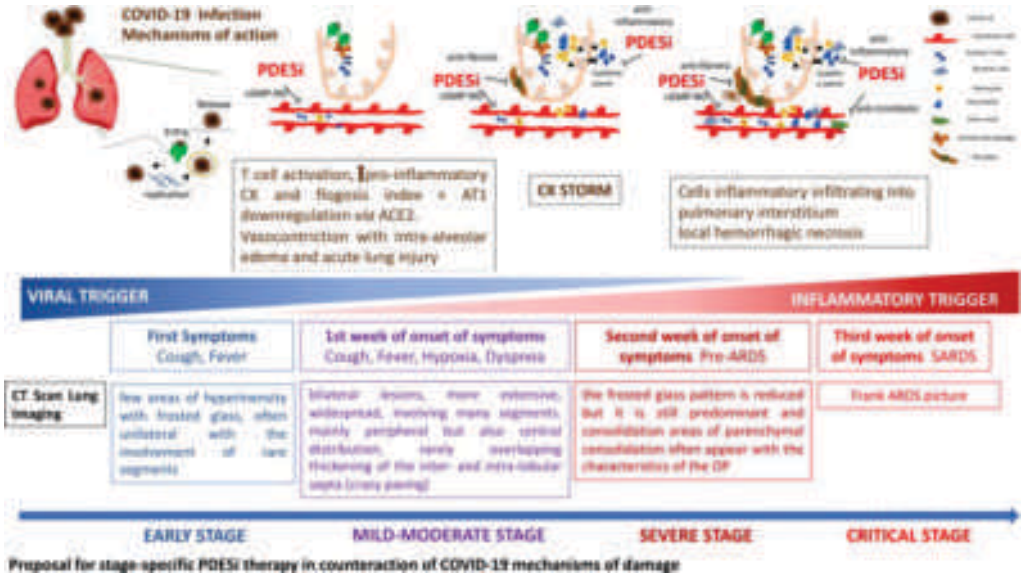

Figure 3: A proposal for PDE Inhibitor in COVID -19
(Image re-used under public health emergency permission. Image by Isadora AM *et al*[42])

Acute Lung Injury and COVID -19

The story of PDE Inhibitor started with beneficial effect of caffeine in bronchial asthma patients due to its bronchodilator properties[1]. But in Acute Lung Injury especially such as ARDS, pneumonia or acute exacerbations of COPD, the pathology is mainly due to dysregulated immune response and cytokine recruitment. In a study done by Salari et al. it was reported that Aminophylline significantly reduced Epidermal Growth Factor Levels (EGF) when introduced in mechanically ventilated patients with PEEP. Both in conjunction reduced the overall Acute Physiology and Chronic Health Evaluation (APACHE) Pi score[37]. Experimental evidence shows that Pentoxifylline improves the oxygen transport and hemodynamic stability in critically ill patients suffering from septic shock[38]. Pentoxifylline was also

Anti-Platelet Therapy

Platelet aggregation is a vital step in the coagulation cascade. The pivotal messengers cAMP and cGMP do exert a robust inhibition on the essential platelet function. The basic principle behind the potential role of PDE Inhibitors in platelet aggregation inhibition is increasing the platelet activating nucleotide which in turn interferes with the cytoskeletal fibrinogen activation, recruitment of pro-inflammatory mediators and degranulation. This affect can be achieved by activating the quintessential cAMP and cGMP pathways[47].

Caffeine was administered as a 250mg oral dose thrice a day for a week in healthy volunteers, they all showed reduced platelet aggregation, upregulation of platelet adenosine receptors and increased cAMP[48]. This characteristic of caffeine as a platelet

inhibitor was first seen in 1967[49]. Only PDE2, PDE3 and PDE5 have been seen being secreted from platelets[50].

- **PDE-2**

PDE-2 acts by hindering the thrombin led platelet aggregation due to nitroprusside[51].

Currently numerous thienylacyl hydrazone derivatives are studied as a PDE-2 representative for their platelet aggregating characteristic[52].

- **PDE-3**

PDE3A is the primary subtype of PDE3 exerted by platelets.[53] Anagrelidehas been found to be causing thrombocytopaenia in humans[54] even though it is a platelet aggregator inhibitor[55]. Another agent Cilastazole also hinders platelet aggregation. It more commonly acts on platelet aggregation led by ADP, collagen fibres and arachidonic acid[56,57]. An enhanced antiplatelet effect was seen when Cilastazole was given in combination with aspirin plusclopidogrelin primary PTCA patients of Myocardial Infarction[58,59]. Along with this Cilostazol has been used in preventing stent restenosis also[60].

Cilastazole has been widely lauded as an excellent agent to prevent stroke and myocardial infarction. Numerous studies including Cilastazole Stroke Prevention Study (CSPS 1&2) shows that Cilastazole reduces the stroke risk significantly along with that it is proven better than Aspirin prophylaxis alone[61,62].

After being discovered to inhibit platelet aggregation in rabbits,[63] all eyes turned to Dipyridamole as another potential antithrombotic element of PDE3 + PDE5 inhibitor especially in stent restenosis[64]. Dipyridamole enhances the Nitric Oxide inhibition on rabbit as well as human platelets[65]. However, there is scarce clinical literature to support the evidence that Dipyridamole can be used as a singular anti platelet agent. But combination use has been promising. The two large scale ESPS2 & ESRIT trial concluded that when used with low-dose of aspirin in cerebrovascular stroke patients, the outcome is more favourable than aspirin alone[66,67]. The American College of Chest Physicians (ACCP) took charge over these studied and in 2008 started recommending dual Anti-platelet therapy with Dipyridamole in stroke or ischaemic event patients[68]. Not just with aspirin, dipyridamole has been proven to be more efficacious in thrombus prevention in patients with artificial heart valves with warfarin prophylaxis[69].

- **PDE -5**

A very potent PDE-5 inhibitor Sildenafil is widely used in treatment of Erectile Dysfunction. But along with this, there is promising role of Sildenafil as anti platelet agent. Very few clinical studies have been employed for the use-case. In a clinical study of healthy volunteers, sildenafil hindered the collagen led platelet aggregation (in doses of 100mg), with enhanced effect if given in conjunction with nitrates[70].

In a study of 30 healthy male volunteers Sildenafil was administered in doses of 50 and 100mg in two randomised groups to see platelet aggregation. It was seen that Sildenafil did in fact improve platelet aggregation ex-vivo, more so on 100mg dose. However ADP led platelet aggregation remained unaffected[71].

This led to research gap in PDE-5 Inhibitor's effect on ADP Induced platelet aggregation. Following up on that, In another study done on 30 male healthy individuals, different PDE-5 agent Tadalafil was administered in a single dose of 10/20 mg to observe its effect on platelet aggregation. The study observed that Tadalafil is actually an effective platelet aggregation inhibitor when induced by ADP and Collagen. The 20mg dose proved to be more effective.

CONCLUSION

PDE Inhibitors are diverse class of drugs having significant therapeutic benefit in numerous diseases. Because of its affect on cAMP and cGMP pathways, they do have a promising role in so many new areas, which are still yet unknown. Be it from using it in ED, Acute Lung Injury or Platelet aggregation, the future looks promising for PDE Inhibitors and appropriate clinical backing is required to prove the theoretical claims.

CONFLICTS OF INTEREST: None

FINANCIAL SUPPORT: None

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