PDE4 as Therapeutic Targets in Different Diseases

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Cyclic nucleotides (cAMP, cGMP) play a major role in normal and pathologic signaling. Beyond receptors, cyclic nucleotide phosphodiesterases; (PDEs) rapidly convert the cyclic nucleotide in its respective 5′-nucleotide to control intracellular cAMP and/or cGMP levels to maintain a normal physiological state. However, in many pathologies, dysregulations of various PDEs (PDE1-PDE11) contribute mainly to organs and tissue failures related to uncontrolled phosphorylation cascade. Among these, PDE4 represents the greatest family, since it is constituted by 4 genes with multiple variants differently distributed at tissue, cellular and subcellular levels, allowing different fine-tuned regulations.

cyclic nucleotide phosphodiesterase (PDE)   cAMP   cGMP   diseases

1. PDE4 in Cardiovascular Diseases

PDE4 participates in the control of cardiovascular function at the level of vessels and heart.

1.1. PDE4, and Vessel

PDE4 has been characterized in human, rat, and bovine aortas [1]. It is clearly established that in vascular smooth muscle, PDE4 inhibitors control endothelium-dependent relaxation, opposite to PDE3 inhibitors or nitric oxide (NO) that per se relax the vessels [2][3][4]. This is related to the different kinetic properties of PDE3 and PDE4 (PDE3 K_m < PDE4 K_m, and PDE3 $V_{max/Km}$ > PDE4 $V_{max/Km}$) as illustrated in **Figure 1**. In the presence of endothelium, at low intracellular cAMP concentrations, firstly PDE3 hydrolyses cAMP; therefore, its specific inhibition, or the endothelial NO production, induces an increase in the cAMP level thus allowing PDE4 hydrolytic function. In that condition, the inhibition of PDE4 would be effective by increasing the cAMP level and would therefore relax the whole vessel. Altogether, at the level of vascular smooth muscle, the researchers demonstrated the existence of cAMP/cGMP cross-talk mediated by PDE3 and PDE4 [4][5][6].

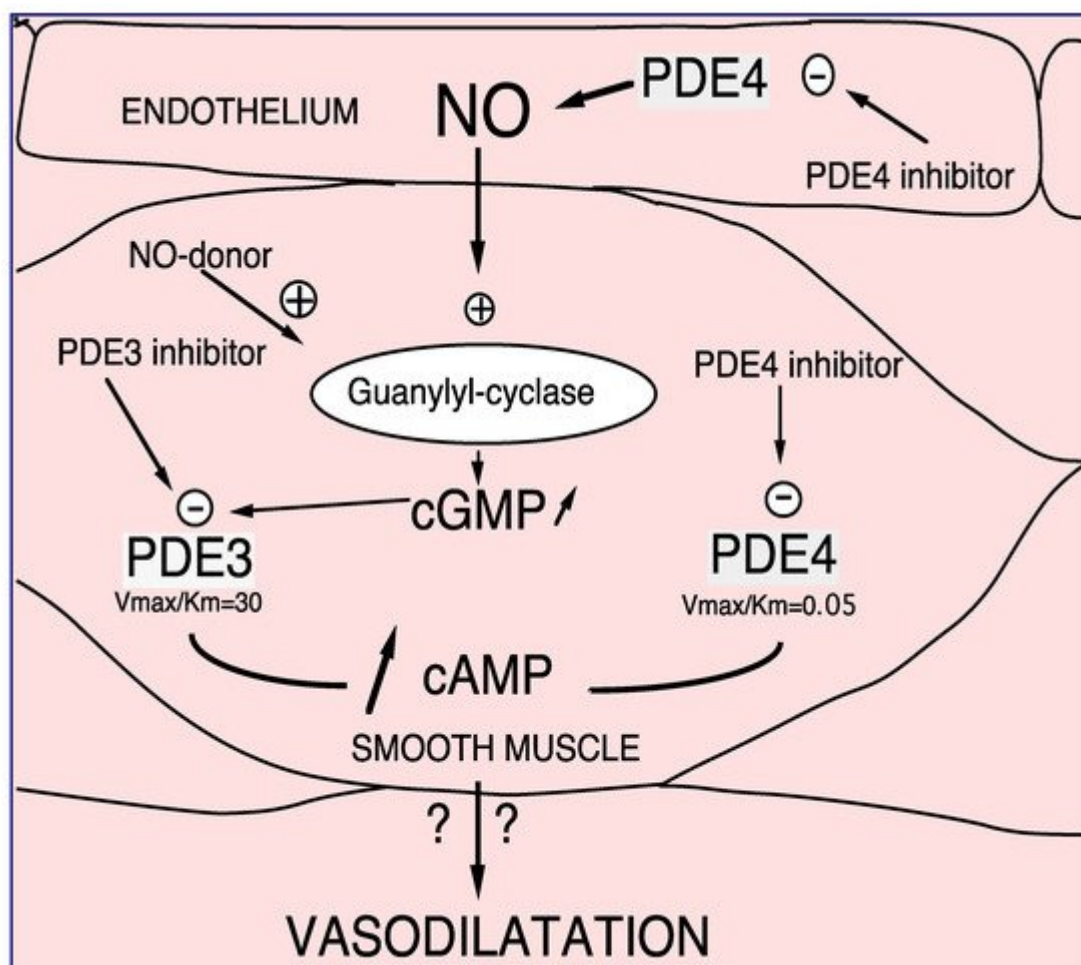**Figure 1.** PDE3 and PDE4 cross-talk in vasodilation. NO or NO donor, by increasing soluble guanylyl cyclase, increases intracellular cGMP level. Therefore, this increase in cGMP induces preferentially PDE3 inhibition and consequently, an increase in cAMP in smooth muscle cells. In that way PDE4 might be able to hydrolyze cAMP in that way, PDE4 inhibitors inhibit PDE4 activity. In the presence of endothelial cells this effect is potentiated. Altogether, increases in cAMP altogether induces vasodilatation which might be potentiated in the presence of endothelium [2][3][4][5].

Moreover, it should be noted that PDE4 is mainly present in human endothelial cells [7][8][9][10]. Surprisingly, in the presence of L-arginine, the PDE4 inhibitor, rolipram, is able to increase cGMP levels by upregulating the L-arginine/NO/cGMP pathway, revealing a cross-talk between PDE4 and cGMP regulation [11] (**Figure 2**).
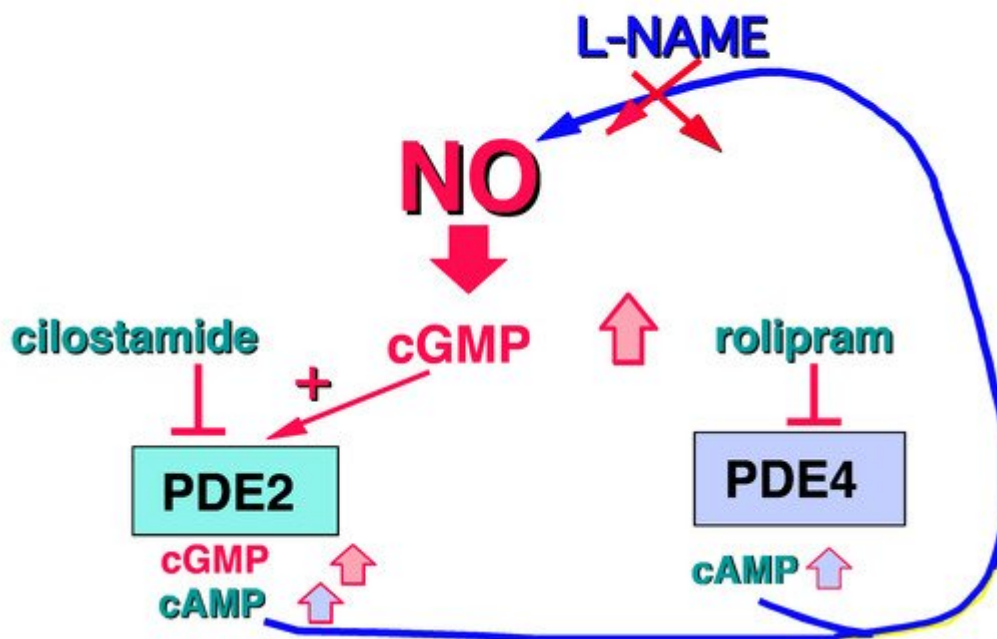
Figure 2. Increase in cGMP in human endothelial cells related to PDE4 inhibition [11].

In particular, PDE4 plays a role in the regulation of endothelial permeability [12]. Notably the PDE4D, by tethering the exchange protein activated by cAMP (EPAC)1 in a vascular endothelial cadherin-based signaling complex (VE-Cad), controls the cAMP-mediated vascular permeability [13]. It should be noted that heart failure in rat induces increases in the PDE4B protein and mRNA expressions in the aorta which could contribute to high blood pressure [14]. Lastly, it was shown that PDE4B, and not PDE4D, was upregulated in inflammatory cells from both experimental and human abdominal aortic aneurism, limiting the progressive increase in the aortic diameter without affecting the blood pressure. Rolipram has strongly mitigated the increase in vascular oxidative stress (superoxide anion) induced by angiotensin II [15]. Clinically, it is important to note that PDE4 inhibition reduces life-sustaining extracorporeal vascular permeability and improves microcirculation in an extracorporeal resuscitation rodent model [16].

1.2. PDE4, and Heart

The cAMP in cardiac muscle is the second intracellular messenger mediating the positive inotrope effects of β-agonists [17]. Thus, PDE3 inhibitors, such as milrinone, SK, and F 94120, were described early in the early 1980s as "new cardiotonic drugs" [18][19]. Consequently, it was clearly established that the positive inotrope effect induced by PDE3 inhibitors was mediated by cAMP [20]. However, due to some mortality in chronic treatment related to tachyarrhythmia and tachycardia, milrinone prescription in humans is now only performed for a short period, beneficially inducing reduced inflammatory and apoptotic signaling [21]. At the same time, a rolipram-sensitive cAMP-PDE has been characterized in the heart. This was carried out by anion exchange chromatography performed on cardiac tissues from the rat heart ventricle [22], as well as from canine left ventricles [23] and from frog

atrial fibers [24]. Furthermore, Komas et al., 1989 [19] isolated by chromatography the rolipram-inhibited cAMP-PDE (PDE4) from dog ventricular and sino-atrial node tissues, pointing out different inhibitory effects of specific inhibitors between the ventricle and sino-atrial node phosphodiesterases (PDEs). Thus, the characterization of PDE4 in cardiac tissues raised the question of its implication in cardiac contraction.

Studies performed on guinea pig cardiac ventricle showed that PDE4 might be implicated differently than PDE3 in the regulation of cardiac contraction, since in opposite to PDE3 inhibitor, PDE4 inhibitor did not per se increase cardiac inotropy, although PDE3 and PDE4 are both cytosolic and membrane bound [25][26]. However, interestingly, PDE4 inhibitors potentiate the effect of PDE3 inhibition, showing that in the presence of cyclic AMP-dependent positive inotropic agents, PDE4 inhibitors exert a positive inotropic effect which probably does not involve enhanced catecholamine release from sympathetic nerve endings [26]. This was confirmed more recently by Eschenhagen, 2013 [27] indicating that rolipram does not affect the positive inotropic effects from β1- or β2-adrenoceptor stimulation. This might also suggest that PDE4 acts in another cAMP compartment.

Thus, the researchers firstly showed in canine and human, purified cardiac microsomal fractions, that PDE3 is associated with the microsomal membranes enriched in vesicles derived from T-tubule and junctional SR membranes; meanwhile, PDE4 is mostly associated with the enriched fraction of sarcolemma membranes, revealing different subcellular compartmentations for PDE3 and PDE4 [28]. To go further, the researchers have canonically demonstrated that PDE4B and PDE4D are associated with the envelope of the nucleus isolated from human cardiac cells [29]. This has only been confirmed very recently by a pharmacological approach, demonstrating that PDE4 insulates a mAKAPβ-targeted PKA pool at the nuclear envelope [30]. In that way, Marco Conti and his colleagues showed that PDE4D isoforms are anchored by myomegalin colocalizing components of the cAMP-dependent pathway to the Golgi/centrosomal region of the cardiac cell [31]. Due to the different physiological and localized contributions of PDE4 in cardiac contraction, its physiopathological role in cardiac pathology could therefore be questioned.

2. PDE4 in Obesity

Obesity is considered the fifth highest cause of death worldwide by the World Health Organization and is associated with pathological conditions and diseases associated with obesity, including hyperlipidemia, heart diseases such as coronary artery disease (CAD) and myocardial infarction, stroke, type 2 diabetes (T2D), hypertension, cancers, low-grade and chronic inflammation, fatty liver disease, osteoarthritis, respiratory problems, and neurodegenerative diseases [32].

Obesity is defined by the body mass index (BMI). It is calculated as weight in kilograms divided by height in meters squared, rounded to one decimal place. Obesity in adults (>20 years old) was defined as a BMI greater than or equal to 30. The prevalence of obesity was 39.8% and affected about 93.3 million US adults in 2015~2016 [33].

Therefore, it was pointed out that caloric restriction might extend lifespan and that the metabolic effect of resveratrol, a mimetic of caloric restriction, might be mediated by inhibiting cAMP phosphodiesterases [34]. In that

way, alterations in PDE activities were firstly reported in omental and subcutaneous adipose tissues in human obesity, i.e., in omental and subcutaneous adipose tissues, it was a significant negative correlation between PDE4 and BMI [35].

Thus, the involvement of PDE4 in obesity has been demonstrated since, under submaximal β-adrenoceptor stimulation of brown adipocytes, the PDE4 inhibitor alone may increase lipolysis [36]. Therefore, it was reported that the PDE4 inhibitor, roflumilast, might be superior to metformin in weight loss in obese women with polycystic ovarian fibrosis [37]. In this way, PDE4B-KO mice had reduced adiposity and adipose-induced inflammation induced by a high-fat diet, highlighting the involvement of PDE4B in adiposity [38].

3. PDE4 in Diabetes

The global prevalence of diabetes among 20- to 79-year-olds is estimated to be about 8.8% in 2015, or 415 million, and approximately 10.4% in 2040, or 642 million [39]. Diabetes is related to alterations in glucose homeostasis governed by insulin. The failure to maintain glucose homeostasis underlies both type 1 diabetes (T1D) and type 2 diabetes (T2D). T1D is an autoimmune disease that originates when β-cells that produce insulin are destroyed. T2D is characterized by insulin resistance and the progressive loss of β-cell function. Although these two forms of diabetes are fundamentally very different, β-cell failure and death play a key role in the pathogenesis of both diseases, leading to hyperglycemia resulting from a reduced capacity to produce insulin [40]. The diagnosis of diabetes and its severity may be determined by measuring blood glycated proteins such as hemoglobin A1c (HbA1c) and glycated albumin (GA) [41]. In the 2000s, it was proposed that inhibiting PDE4 during diabetes may be beneficial against hyperglycemia, oxidative stress, and the production of TNF-α and NFκB [42]. In this way, it has previously been reported that insulin-secreting cells and Langerhans islets contain PDE4 [43]. PDE4C is the main PDE4 subtype expressed at the mRNA level in isolated rat islets. Interestingly, silencing the PDE4C as well as the specific PDE4 inhibitors, roflumilast and compound L-826,141, significantly increases glucose-dependent insulin secretion [44]. PDE4 seemed active only after stimulation with glucose, suggesting some interaction between glucose and PDE4 [45]. Following this, a study in mice showed that roflumilast improves glucose tolerance and insulin sensitivity [45].

4. PDE4 and Ulcerative Colitis and Crohn'Disease

Crohn's disease is a chronic inflammatory condition of the gastrointestinal tract. It can affect any part of the gastrointestinal (GI) tract, but ulcerative colitis affects only the colon. Additionally, while Crohn's disease can affect all layers of the bowel wall, ulcerative colitis (UC) only affects the lining of the colon. Both have been together classified as inflammatory bowel diseases (IBD). In the United States, it is currently estimated that about 1.5 million people suffer from IBD, causing considerable suffering, with a prevalence of Crohn's disease (CD) of 201 per 100,000 population, UC is being equally prevalent [46].

Because Crohn's disease is mainly a chronic inflammation, the inflammatory cytokine productions in intestinal biopsies have been studied in relation to the pathological grade. This research originally shows that TNF-α and IL-1β are significantly increased in endoscopic biopsies, as well as for TNF-α, IL-1β, and IL-6 in the individual culture supernatant of intestinal biopsies, opening a new way of investigation [47]. Thus, the effect of pentoxifylline was investigated on intestinal inflammation in IBD, showing that pentoxifylline downregulates in vitro TNF-α and IL-1β production by PBMCs and by intestinal organ cultures from patients with Crohn's disease and ulcerative colitis [48]. Because pentoxifylline, acting on TNF-α and IL-1β, is a non-selective PDE inhibitor [49], PDE activities were investigated in the human normal mucosa and inflamed mucosa of patients with Crohn's disease. These studies revealed an increase in the % of PDE4 activity (from 42% to 72.5 %, up by $p < 0.05$%) suggesting that the specific PDE4 inhibitor may be effective in Crohn's disease [50]. In that way, the use of OPC-6535 (tetomilast) was suggested for the treatment of a variety of oxidative inflammatory intestinal disorders with an abnormal mucosal barrier such as inflammatory bowel disease [51]. As a result, tetomilast was developed by OTSUKA (phase III) to investigate the treatment of UC [52]. Furthermore, it has been clearly reported that the PDE4 inhibitor, rolipram, prevents and reduces experimental colitis in mice and suppresses TNF-α levels in colonic tissues [53]. Interestingly, rolipram is shown to be superior to methylprednisolone in preventing late collagen deposition [54].

5. PDE4 and Osteoporosis

Osteoporosis is a common disease characterized by reduced bone mineral density (BMD) and increased risk of fragility fractures, which is usually caused by osteoclasts, whereas osteopenia corresponds to a lower bone density than normal and represents the stage before osteoporosis. By 1970, no medications against osteoporosis were being investigated. At the time, fractures were not even recognized as an illness but were considered part of normal aging [55]. Nonetheless, osteoporosis is a public health issue worldwide, affecting over 200 million people. An estimated 30% to 50% of postmenopausal women have this disease. The prevalence (June 2009 to June 2010) of osteoporosis and osteopenia in healthy active workers is 18% [56]. However, it must be pointed out that osteoporosis is an age-associated disease. In the Eastern Mediterranean region, the overall pooled prevalence of osteoporosis was 24.4%, pointing out the necessity of investigating therapeutic approaches [57].

In that way, a study showed that denbufylline, an inhibitor of PDE4 [58][59], was shown to increase the number of mineralized nodules and decrease the number of osteoclast-like cells, suggesting that it should be a therapeutic drug for bone loss [60]. Therefore, this research was reinforced by studying the effect of a new PDE4 inhibitor, XT-44, on mineralized nodule formation, as well as in vivo in ovariectomized female Wistar rats. XT-44 stimulated the formation of mineralized nodules, while it inhibited the formation of osteoclast-like cells in mouse bone marrow culture. Interestingly, in ovariectomized female rats, 1 mg/kg per os (every 2 days for 8 weeks) increased bone mineral density, indicating that XT-44 may be effective in osteoporosis treatment [61].

6. PDE4 and Malignancies

According to MedlinePlus Medical Encyclopedia, "the malignancy" refers to the presence of cancerous cells that have the ability to spread to other sites in the body (https://medlineplus.gov/enc/article/002253.htm, accessed on 13 November 2020). The global cancer incidence and mortality in 2020 were estimated at 19.3 million, almost a million new cases of cancer and 10 million deaths from cancer. The global cancer burden is expected to be 28.4 million cases in 2040 [62].

The use of PDE4-Is in various developing cancers was first investigated in various cancer cell lines as well as on cancer tissues [63][64][65]. Therefore, it was shown that PDE4 protein and mRNA up-regulations are associated in vivo with human endothelial cell proliferation and angiogenesis [9][66] as well as in vivo cancer development in mice [67]. Similarly, there has been reported a phosphodiesterase 4B-dependent interplay between tumor cells and the microenvironment regulating angiogenesis in B-cell lymphoma [68]. Since the PDE4-I, piclamilast, was able to potentiate the cyto-differentiating action of retinoids in myeloid leukemia cells [69], the researchers investigated PDE activity and expression in retinoic acid-resistant cell lines in acute promyelocytic leukemia and showed an increase in PDE4 activity, accompanied by an increase in PDE4D expression [70]. In another area, studies performed in mice, rats, and human tissue revealed that PDE4B protects colon adenomas and is inactivated by epigenetic silencing in colon cancer [71].

7. PDE4 and Fatty Liver Disease

Fatty liver disease, currently named nonalcoholic fatty liver disease (NAFLD) according to the practice guidance commissioned by the American Association for the Study of Liver Diseases (AASLD), is defined by: (1) evidence of hepatic steatosis (HS), either by imaging or histology, and (2) lack of secondary causes of hepatic fat accumulation such as significant alcohol consumption, long-term use of a steatogenic medication, or monogenic hereditary disorders [72]. The overall global prevalence of NAFLD diagnosed by imaging is about 25.24% (95% CI, 22.10–28.65) [73]. NAFLD and alcoholic liver disease (ALD) are the leading causes of liver-related morbidity and mortality and are important causes of liver transplantation [74]. Using bile-duct ligation, as a cholestatic liver injury model, Gobejishvili and colleagues 2013 [75] demonstrated that induction of hepatic PDE4A, B, and D plays a causal role in the development of liver injury and fibrosis. In addition, roflumilast PDE4-I improved glucose tolerance, reduced insulin resistance, and decreased steatohepatitis in mice, increasing the cellular respiratory capacity of hepatocytes [45]. Interestingly, Vonghia et al., 2019 [74] mentioned that the compound tipelukast, also known as MN-001, designed as a leukotriene receptor antagonist, orally bioavailable, being anti-fibrotic and anti-inflammatory in pre-clinical models, interestingly, inhibits PDE3 and PDE4. However, a lack of efficacy of a PDE4-I in phase 1 and 2 trials of patients with non-alcoholic steatohepatitis has already been shown [76].

Overall, these data suggest that today PDE4-Is have failed in the treatment of NAFLD but have induced interesting positive data regarding ALD treatment. Thus, it has been shown that altered PDE4B plays a critical role in alcohol-induced steatosis [77]. A recent review designs PDE4 inhibition as a therapeutic target for ALD as much as, expression of the PDE4 subfamilies is significantly up-regulated in conjunction with markedly decreased cAMP levels in hepatic tissues of patients with severe ALD [78]. It should be noted that inhibition of PDE4 decreases ethanol intake in mice, extending the contribution of PDE4 to liver diseases [79]. Thus, contrary to ALD, one could

speculate that liver PDE4 is not sufficiently induced in NAFLD to demonstrate changes in PDE4 expression and efficiency of PDE4-Is. Nonetheless, overexpression of PDE4 in the mouse liver is sufficient to trigger NAFLD and hypertension and can be avoided and even reversed by roflumilast PDE4-I [80]. A very recent study has supported the clinical use of a novel liposomal rolipram formulation to reduce emesis [81].

8. PDE4 and Depression

Major depression is a common illness that severely limits psychosocial functioning and diminishes quality of life. In 2008, the WHO ranked major depression as the third cause of burden of disease worldwide and projected that the disease will rank first by 2030, the 12-month prevalence of major depressive disorder (MDD) being approximately 6.6%, and the lifetime risk being 15–18% [82].

The potential antidepressant activity of rolipram, as a cAMP phosphodiesterase inhibitor, was canonically demonstrated in mice by Wachtel H, 1983 [83]. In that way, rolipram was first reported as a specific PDE4-I [1]. Rolipram was shown to have antidepressant-like effects on behavior maintained by differential reinforcement of low rat response [84] and to facilitate the establishment of long-lasting long-term potentiation and improve memory [85]. In PDE4D knockout (PDE4D$^{-/-}$) mice, the loss of PDE4D in the cerebral cortex and hippocampus, interestingly, induces an antidepressant-like effect on behavior and reduces sensitivity to rolipram. Furthermore, rolipram potentiated isoproterenol-induced cyclic AMP formation only in the PDE4D$^{+/+}$ mice. Interestingly, the PDE4D-regulated cyclic AMP signaling may play a role in the pathophysiology and pharmacotherapy of depression [86].

9. PDE4, and COVID-19

As previously [87] stated, during the 1990s, PDE4 might participate in viral infections, since the PDE4 inhibitor, rolipram, was canonically shown to inhibit human immunodeficiency virus-1 (HIV-1) replication, and to decrease HIV-1 p24 antigen production in acutely HIV-1 infected PBMCs [88]. This rolipram inhibitory effect on HIV-1 replication in Jurkat and primary T-cells induced by T-cell activation has been confirmed and extended to the production of TNF-α, NFκB, and NFAT activation [89]. Beavo and colleagues showed that infection of CD4+ memory T-cells by HIV-1 requires the expression of PDE4, and that rolipram abolishes HIV-1 DNA nuclear import in memory T cells, pointing out the important contribution of PDE4 in viral infection [90]. Roflumilast inhibits respiratory syncytial virus infection in differentiated human bronchial epithelial cells [91]. However, in the human airway smooth muscle infected by rhinovirus, a non-enveloped RNA virus, surprisingly, inhibition of PDE4 did not overcome cytokine induction [92], opening the hypothesis that the viral envelope is a requisite for cytokine induction and PDE4-I effectiveness. Interestingly, it has been reported that cAMP produced in Tregs is implicated in suppressing the activation and expression of the HIV-1 gene in vivo in humanized mice [93]. Since a relationship between HIV-1 and PDE4 was clearly established, one could wonder whether COVID-19 might modify PDE4 regulation.

Altogether, these data reported for COVID-19 suggest the hypothesis that a PDE4 inhibitor might alleviate both viral infection and tissue inflammation induced by SARS-CoV-2 [87].

Interestingly, a paper published in Nature Medicine (2005), demonstrated that angiotensin-converting enzyme 2 (ACE2) plays a strategic role in SARS-CoV-2-induced lung injury. As expected, the injection of SARS-CoV-2 spikes into mice worsens acute lung failure in vivo which can be alleviated by blocking the renin–angiotensin pathway governed by ACE2 [94]. Furthermore, it has been reported that Ang-II, an AT_1R agonist, induces PDE4 up-regulation, with a 44% increase in the PDE4A protein, mediating cascade inflammation and oxidative stress. Altogether, this opens a new way of PDE interaction with the renin–angiotensin system [95]. More recently, relationships between PDE4, and cytokine storm were discussed for COVID-19 [96][97][98][99]. In this way, a recent in vitro study (phase III) performed with the inhaled PDE4 inhibitor, tanamilast (CHF6001), showed that it blunts proinflammatory dendritic cell activation by SARS-CoV-2 ssRNAs [100].

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