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PDE4 inhibition as a therapeutic strategy for improvement of pulmonary dysfunctions in Covid-19 and cigarette smoking

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ABSTRACT

Angiotensin-converting enzyme 2 (ACE2) is the binding-site and entry-point for SARS-CoV-2 in human and highly expressed in the lung. Cigarette smoking (CS) is the leading cause of pulmonary and cardiovascular diseases. Chronic CS leads to upregulation of bronchial ACE2 inducing a high vulnerability in COVID-19 smoker patients. Interestingly, CS-induced dysregulation of pulmonary renin-angiotensin system (RAS) in part contributing into the potential pathogenesis COVID-19 pneumonia and acute respiratory distress syndrome (ARDS). Since, CS-mediated ACE2 activations is not the main pathway for increasing the risk of COVID-19, it appeared that AngII/AT1R might induce an inflammatory-burst in COVID-19 response by up-regulating cyclic nucleotide phosphodiesterase type 4 (PDE4), which hydrolyses specifically the second intracellular messenger 3′,5′-cyclic AMP (cAMP). It must be pointed out that CS might induce PDE4 up-regulation similarly to the COVID-19 inflammation, and therefore could potentiate COVID-19 inflammation opening the potential therapeutic effects of PDE4 inhibitor in both COVID-19-inflammation and CS.

1. Introduction

The severe acute respiratory syndrome (SARS) started in China 2003, caused by a specific type of coronavirus named SARS-CoV-2, that might be related to emerging infectious diseases leading to economic and health global burden. Later on, Middle East respiratory syndrome (MERS) caused by MERS-CoV was emerged in 2012 [1]. In 2019, a pulmonary infection caused by a novel coronavirus nCoV-19 also called SARS-CoV-2 was started in Wuhan, China led to coronavirus infection disease (COVID-19), which was initially named Wuhan pneumonia, that seems to be originating from bats [2].

The binding site and the entry-point for SARS-CoV-2 is angiotensin-converting enzyme 2 (ACE2), which is highly expressed in the respiratory epithelial cells, lymphocytes, endothelial cell, and renal tubular epithelial cells. The clinical presentations of COVID-19 are mild in 81%, asymptomatic in 50% and 2–4% severe likes acute respiratory distress syndrome (ARDS), acute kidney injury, sepsis and coagulopathy [3]. According to Shurin et al., the immune responses induced by SARS-CoV-2 infection seem to be in two-stages. As most of the infected individuals develop only mild or no clinical symptoms, it is conceivable that during the incubation and non-severe stages, a specific adaptive immune response is required to eliminate the virus and to preclude disease progression to severe stages [4]. The case-fatality rate of COVID-19 patients is higher in patients with underlying comorbidities, including: hypertension, diabetes mellitus and tobacco smoking, which accelerate the viral entry or replication of SARS-CoV-2 [5].

The nicotine smoking, either from cigarette smoking (CS) or from electronic cigarette, is the leading cause of pulmonary and cardiovascular diseases. As well, CS leads to pulmonary hypertension, endothelial dysfunction, congestive heart failure, chronic pulmonary disease, and metabolic complications directly or through dis-regulation of the renin-angiotensin system (RAS) [6]. In another way, it is well known that intracellular signaling, mediated by cyclic nucleotide phosphodiesterases (PDEs, PDE1-PDE11), controls tissue CAMP and cGMP levels in response to receptor activation. Interestingly, it is largely implicated in lung and cardiovascular diseases as well as in inflammation, notably ARDS [7–10]. Therefore, RAS and PDEs together might open new therapeutic approaches in COVID-19, notably in CS.

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2. The Renin-Angiotensin system (RAS)

RAS is composed of different peptides involved in the regulation of blood pressure and homeostasis. The hepatic angiotensinogen is hydrolyzed by renin to produce angiotensin (ANG) I, which is then converted by angiotensin-converting enzyme (ACE) into the biologically active ANG II. More recently, renin- and ACE-independent formation of ANG II have also been reported. By cleaving ANG II into ANG (1–7), ACE2 plays a pivotal role in the compensatory ACE2/ANG-(1–7)/MasR axis of the RAS by counterbalancing the deleterious actions of the ACE/ANG II/AT1R arm. ACE: Angiotensin converting enzyme; ACE2: Angiotensin converting enzyme type 2; MLDAD: mononuclear leukocyte-derived aspartate decarboxylase; MasR: Mass receptor; AT1R: Angiotensin II type 1 receptor; AT2R: Angiotensin II type 2 receptor; APA: Aminopeptidase A; APN: Aminopeptidase N; MrgD: Mas-related G protein-coupled receptor D. Adapted from [11].

3. Renin-Angiotensin system (RAS) and cigarette smoking (CS)

The lung is the first organ which encounters the nicotine. Of interest, Glynos et al. reports that both e-cigarette vaping and conventional CS negatively impact lung biology, triggering inflammatory responses and adversely respiratory system mechanisms [15]. Furthermore, it has been reported that in SARS-CoV-2, that e-cigarette induces pulmonary inflammation and dis-regulated repair and increased SARS-CoV-2 Covid-19 ACE2 receptor (ACE2) [16]. Although, nicotine per se might be beneficial in COVID-19, by inhibiting nicotinic acetylcholine receptor [17] or by decreasing ACE2 expression [18], CS affects pulmonary RAS in different ways. In one way, Lu et al., found that CS increases the expression of ACE and elevates the circulating ANG-II concentrations, which is not sustained following ten days of the effect. However, in healthy human, ACE activity increased for minutes only and returns to the normal after first exposure. As well, both nicotine and its metabolites elevate the in vitro activity of ACE in the cultured endothelial cells [19]. Of interest, it must be pointed out that such consumptions might induce intracellular signaling changes, possibly enzyme expression such as PDE4 expressions [20]. In another way, nicotine, related to CS, reduces the expression of ACE2 in the pulmonary smooth muscle cells, directly or through elevation of ANG-II, contributing to the initiation of pulmonary hypertension. Since, high ANG-II downregulates ACE2 through an AT1R signaling pathway, therefore, Ang-II-receptor blockers might restore the activity of ACE2 of chronic smoker patients [11]. However, chronic CS leads to alveolar septal fibrosis and apoptosis through induction of oxidative stress via AT1R-dependent pathway. This CS induced-pulmonary dysfunction might be attenuated by the administration of Ang1-7, which acts on MasR [21] (see Fig. 1). Therefore, acute CS adversely affects the pulmonary RAS through up-regulation of ACE and AT1R which might be accompanied by down-regulation of ACE2 and AT2R. Podowski et al. showed that in mice losartan may protect lung tissue from cigarette smoke-induced oxidative stress levels and...
normalize AT_{2}R expression in the lung parenchyma, pointing out the beneficial effect of losartan (3–30 mg/kg in mice for 2 months) in oxidative stress [22].

Regarding CS subjects and susceptibility to COVID-19, Berlin et al. found that pulmonary ACE2 gene expression was higher in the former smoker subjects, that may explain the higher vulnerability of smoker patients in the early reported cases of COVID-19 in China [23]. Besides epidemiological studies, it was observed that CS subjects are at a higher risk for SARS-CoV-2 infection and required mechanical ventilation and aggressive interventions [24]. Bai et al. reported that the affected COVID-19 patients were chiefly smokers, 21.2% compared with non-smokers, 14.5%, suggesting that CS is involved in the pathogenesis of COVID-19 due to suppressing of the pulmonary ACE2/Ang₂/₇/MasR axis [25]. It was suggested that individuals ‘nicotine primed’ to have a higher risk because nicotine can directly impact the putative receptor for the virus (ACE2) and lead to deleterious signaling in lung epithelial cells [26]. Therefore, CS induced deregulations of pulmonary RAS may in part contribute to the potential pathogenesis COVID-19 pneumonia and ARDS. CS induced up-regulation of pulmonary ACE2 is not regarded as the main pathway since, ACE2 activators, like xanthone and diminazene, seem to be protective against ALI and COVID-19 pneumonia [27]. Besides the CS induced down-regulation of ACE2, the induction of oxidative stress is involved by ALI [28]. The underlying mechanism of CS induced over-expression of ACE2 is not through direct interaction, but nicotine activates pulmonary epithelia nicotinic receptors, which are co-expressed with pulmonary ACE2. Activation of nicotinic receptors leads to stimulation of signaling pathways, including TNF-α and p38/mitogen activated protein kinase (p38/MAPK) which induce protease activation, inflammatory signaling and apoptosis, which together disturbing pulmonary alveolar cell function with subsequent ACE2 activation [29]. Furthermore, a recent study clearly suggests that smoking may promote cellular uptake mechanisms of SARS-CoV-2 through α7-nAChR signaling with a downstream induction of phospho-AKT and phospho-p42/p44 MAPK [30].

These changes provoke ACE2 expression that has abnormal functions with higher binding affinity to SARS-CoV-2. These findings might explain the higher incidence of COVID-19 in chronic CS [31]. Cui et al. suggest that ACE2 inhibitors like azathioprine, valproic acid, butyrate, sambucus and epoxomicin are effective anti-SARS-CoV-2 through inhibition of its entry via ACE2 [32]. This study concludes that CS-mediated ACE2 activations is not the main pathway for increasing the risk of COVID-19, as ARBs and ACEIs also increase the expression of ACE2 without increasing the risk of COVID-19. Therefore, extensive researches are recommended to explore and clarify the links between CS and RAS in CS at molecular and sub-molecular levels. As much as, a meta-analysis reports that COPD patients with confirmed COVID-19 show a higher mortality rate at 60%, moreover a higher mortality rate of 38.5% was reported in current smokers with confirmed COVID-19 [33]. Moreover, a recent meta-analysis on 11,189 patients reports that smoking doubles the risk of COVID-19, although, this result being non-significant is probably related to different mechanisms, notably acting on immune system and COPD [34]. In that way, lastly and interestingly, a recent review reports for CS that current smokers show a reduced risk of SARS-CoV-2 infection, while former smokers appear to be at increased risk of hospitalization, increased disease severity and mortality from COVID-19 [35]. This might open a new therapeutic approach requiring to differently analyze CS clinical studies.

Nevertheless, beyond AT₂R receptor signaling, it must be of interest of taking into accounts the rapid cyclic nucleotides degradations, governed by PDEs, that play a major role in normal and pathophysiological intracellular signaling, notably in inflammation and oxidative stress, for which new potent and original PDE inhibitors have been developed [9,10].

### 4. The PDE4 subfamily and chronic obstructive pulmonary diseases (COPD)

Since SARS mainly affects pulmonary system, which is the target of chronic obstructive pulmonary diseases (COPD), for which many new compounds have been conceived and some of which are successfully marketed as PDE inhibitors [7,9]. Thus, among the eleven-known PDE families, the PDE4 family, hydrolyzes specifically the cyclic 3′,5′-AMP (cAMP) in 5′-AMP and H⁺. PDE4 was characterized by its specific inhibitor rolipram [36], and was designed as a COPD therapeutic target. This family is pointed out by its great number of subfamilies (A, B, C and D), by its great number of variants (~25 human variants), being distributed in various tissues and subcellular compartments, allowing a fine tuning of compartmentalized intracellular signaling [7]. This family is particularly intricate with intracellular signaling components, including a great variety of kinases as well as peptides, altogether designed signalosomes [7,9,10]. The PDE4 family, early mainly implicated in inflammation, and oxidative stress was recognized as a new target for COPD treatments, for which pharmaceutical industry developed third generations of new very specific and potent PDE4 inhibitors, such as roflumilast with low emetic effects [9]. PDE4, as RAS, is largely involved in inflammation, and oxidative stress was recognized as a new mechanism of CS induced over-expression of ACE2 is not through direct interaction, but nicotine activates pulmonary epithelia nicotinic receptors, which are co-expressed with pulmonary ACE2. Activation of nicotinic receptors leads to stimulation of signaling pathways, including TNF-α and p38/mitogen activated protein kinase (p38/MAPK) which induce protease activation, inflammatory signaling and apoptosis, which together disturbing pulmonary alveolar cell function with subsequent ACE2 activation [29]. Furthermore, a recent study clearly suggests that smoking may promote cellular uptake mechanisms of SARS-CoV-2 through α7-nAChR signaling with a downstream induction of phospho-AKT and phospho-p42/p44 MAPK [30].

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### Table 1

| Substrate  | PDE1  | PDE2 | PDE3 | PDE4 | PDE5 |
|------------|-------|------|------|------|------|
| eGMP/ Ca²⁺ | 0.001 | N.S. | 1.2  | N.S. | N.S. |
| CaM ⁵⁺  | 0.001 | N.S. | 1.2  | N.S. | N.S. |

IC₅₀ determined at 1 μM substrate concentration, N.S.: IC₅₀ > 200 μM. CaM: calmodulin.
Fig. 2. Cross-talk between COV-19 and PDE4 mediated by AT₁R and its potentiation by CS. On one hand, PDE4 inhibitor overcomes HIV-1 infection and infection, and might also inhibit SARS-COV-2 replication and infection. On the other hand, SARS-COV-2 spikes by inhibiting ACE2 regulates ANG-II production, which induces PDE4 up-regulation. Cigarette smoking might up-regulate AT₁R and therefore increases PDE4. The up-regulated PDE4 might produce an increase of 5′-AMP, as well as of H⁺, inducing lung injury and acute lung inflammation. These de-regulations might be related to PDE4B and PDE4C up-regulations, inducing increases in ROS production, as well in TNF-α, IL-1β, IL-6, IL-8, NFXB and p-p38 MAPK. Interestingly, PDE4 is also up-regulated by CS, opening a commune therapeutic approach in COVID-19 and CS. Altogether, the use of specific PDE4 inhibitor or microRNA-124-3p to act on SARS-COV-2 and on PDE4 up-regulation, represents innovative approaches for treating Covid-19 CS.
the lung parenchyma by restoring IκBk detection, reporting a potential buffering of NF-κB signaling. Moreover, this PDE4 inhibitor reduces human distal bronchial hyper-responsiveness by decreasing p-CP1-17, which in turn may be related to a down-regulation of PDE4C, PDE4B, and other intracellular signaling pathways such as p-p38-MAPK [46]. Furthermore, NCS 613 displays anti-inflammatory and anti-proliferative properties on A549 human lung epithelial cells and human lung adenocarcinoma explants [47], and suppresses systemic inflammation and immune complex deposition by increasing CAMP level [48]. These studies, clearly demonstrate the importance of PDE4 participation in the control of human lung responsiveness, inflammation and hyper-responsiveness processes, as well as of the targeted effectiveness of PDE4 inhibitors. Furthermore, NCS 613 treatment is also clearly effective on peripheral blood mononuclear cells (PBMCs) from both healthy donors and lupus patients. This specific PDE4 inhibitor decreased PDE4B whether it up-regulated PDE4C in human PBMCs which mainly control tissue inflammation. NCS 613 decreased p-p38 MAPK as well as NF-κB translocation to the nucleus and abolishes lipopolysaccharide (LPS)-induced inflammation by reducing IL-1β, IL-6, IL-8, and TNF-α cytokines [49]. In accordance, Chen et al., reported that the plasma cytokine levels of IL-6 and TNF-α were significantly increased in severe cases of patients with COVID-19, in comparison with moderate cases [50]. Altogether, these data obtained from human tissues and moreover inflammatory cells, show that PDE4s in lung and inflammatory cells might contribute in pulmonary disease, notably in SARS/ARDS.

It must be pointed out that losartan, used as an AT, R antagonist in the RAS, inhibits the PDE4 activity (IC₅₀ = 26 μM [51]; used at 10 μM to antagonize AT, R [52]). Interestingly, a study reported that Ang-Il, AT, R agonist, induces PDE4 up-regulation and increases by 44% the PDE4A protein expression and mediates inflammation cascade and oxidative stress, opening a new way of interacting with RAS [53]. Altogether, these data clearly show that PDE4 might be an interesting target in COVID-19 inflammation and oxidative stress, as much as PDE4 is mainly present in pulmonary tissues inflammatory cells and endothelial cells [10]. Of interest, it was originally reported that miR-124-3p, which helps to protect against ARDS attenuate the increases in IL-1β, IL-6, and the TNF-α levels induced by LPS, suppressed LPS-induced p65 expression, an essential subunit of NF-κB, and thereby inhibit the inflammatory response in lung tissue and promotes the apoptosis of macrophages in a mouse model of ARDS [54]. Later, it was also reported that miR-124-3p attenuates severe community acquired pneumonia progression in macrophages by targeting TNF receptor-associated factor 6 [55]. In accordance with these anti-inflammatory effects, it was previously reported that miR-124-3p suppresses the activity of mTOR signaling, inhibits neuro-inflammation, mainly through overcoming the expression of PDE4B [56]. Furthermore, another study demonstrated that LPS increased levels of TNF-α, IL-1β, enhanced NF-κB activity and p-p38 MAPK, which were attenuated by miR-124-3p over-expression, suggesting that miR-124-3p may serve as a therapeutic target for severe community-acquired pneumonia [57]. Altogether, these data indicate that miR-124-3p inhibits PDE4 expression which participates in ARDS inflammation, representing a novel therapeutic approach at the RNA level targeting PDE4 for treating ARDS.

Chronic CS-induced pulmonary dysfunction is attenuated by the administration of Ang1–7, which acts on MasR. Therefore, acute CS adversely affects the pulmonary RAS through up-regulation of ACE and with down-regulation of ACE2 and AT, R (see Fig. 1), whether, as shown previously, AT, R up-regulation induces PDE4 up-regulation and consequently inflammatory processes [53]. However, chronic CS leads to up-regulation of the bronchial ACE2 as a compensatory mechanism which returns to the normal following quitting of smoking [58]. Nevertheless, it was reported for smokers with COPD that PDE4A4 is up-regulated in lung macrophages, and that concomitantly in PBMCs, PDE4B2 and PDE4A4 are also up-regulated, indicating that PDE4 inhibitors might be beneficial to smokers [59]. This was attested by Zuo et al. by various studies showing that CS reduces CAMP by activating PDE4 in cultured human bronchial epithelial cells [60] (Fig. 2).

5. PDE4 and viral infection

PDE4, not only participates in human intracellular signaling, but also might participate in viral infection. Since, it was previously shown that TNF-α enhances human immunodeficiency virus (HIV)-1 replication in vitro, the PDE4 inhibitor, rolipram was canonically shown to inhibit HIV-1 replication, and to decrease HIV-1 p24 antigen production in acutely HIV-1 infected PBMCs [61]. Thereafter, this rolipram inhibitory effect on HIV-1 replication was confirmed and extended to TNF-α production, NF-κB and NFAT activation, induced by T-cell activation in Jurkat and primary T cells [62]. Thus, a pivotal role of PDE4 in HIV-1 replication was reported by Gallo and colleagues, showing that rolipram potently inhibited HIV-1 replication in cultures stimulated by anti-CD3/CD28 + TAT. Furthermore, this PDE4 inhibitor also abrogates the Tat-mediated increase in IL-2 production and CD41 T cell proliferation, attesting that rolipram overcomes both viral replication and inflammation [63]. Interestingly, 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 [64]. Thus, it was reported that CAMP produced in Tregs is involved in the suppression of HIV-1 gene activation and expression in vivo in humanized mice [65]. Altogether, these data clearly show that PDE4 is implicated virus replication and T cell activations, designing PDE4 as a possible target in viral infection. Interestingly, an in-silico study allowed to conceive the compound 31 that inhibits TNF-α in vitro (IC₅₀ = 5.14 μM) and which binds with the SARS-CoV-2 N-terminal RNA binding domain residues [66]. Altogether, this opens a promising approach to treat simultaneously the COVID-19 by targeting both SARS-CoV-2 and inflammation related to PDE4.

6. Covid-19, RAS-CS and PDE4

As stated before, during 2013 a new coronavirus issued in China. Thus, it induced ARDS by using their spikes to target pulmonary system. Interestingly, previously in 2005, a paper issued in Nature Medicine demonstrated that angiotensin converting enzyme 2 (ACE2) plays a strategic role in SARS-CoV-2 induced lung injury [67]. This study clearly showed that ACE2 is a crucial SARS-CoV-2 receptor in vivo, and that both SARS-CoV-2 infection and the spike protein of the SARS-CoV-2 reduce ACE2 expression. Therefore, the injection of SARS-CoV-2 spikes into mice worsens acute lung failure in vivo which can be attenuated by blocking the renin-angiotensin pathway (see RAS paragraph, pages 3–5). Thus, it was done by using the AT, R antagonist losartan, being a PDE4 inhibitor, which, as expected, attenuated acute severe lung injury and pulmonary edema in spike-Fc-treated mice. These results provide a molecular explanation why SARS-CoV-2 infections cause severe and often lethal lung failure. They might be extended to COVID-19, to open new therapeutic approaches, by targeting PDE4 which greatly increases in both viral infection [61] and severe lung injury [42] (Fig. 2).

Since, CS-mediated ACE2 activation is not the main pathway for increasing the risk of COVID-19 in CS, beyond the use of Ang-II receptor blockers, which results are not clearly established, it would be of interest to take into accounts the pathological implications of PDE4 at viral and host levels and therefore to investigate the beneficial effects of PDE4 inhibitors in COVID-19 treatment.

Therefore, as stated before, it is clearly established that the PDE4 inhibitor rolipram inhibits HIV-1 replication, which is dependent on PDE4 expression, attesting the crucial role of PDE4 in viral infection. Interestingly, the possible PDE4 inhibitor effect on SARS-CoV-2 infection was addressed in 2021 by conceiving effective compounds, such as compound 31, targeting both SARS-CoV-2 and inflammation related to PDE4 [66].

Nevertheless, the SARS-CoV-2 infection processes targeting ACE2,
include the activation of AT₁R, inducing a pulmonary "inflammatory storm" that can be counteracted by specific AT₁R antagonists which can be considered for treating COVID-19. However, this therapeutic approach might not be so effective in SARS-CoV-2 infection for CS. Therefore, it would be better targeting selectively and potently PDE4 beyond AT₁R, as much as it is well established that PDE4 is up-regulated during inflammatory storm and that new potent and specific PDE4 inhibitors have been developed and marketed by pharmaceutical industries [9,10]. Importantly, losartan was previously shown to inhibit PDE4 activity, strengthening the possible PDE4 implication in COVID-19 [51]. Moreover, in that way, we showed that Ang-II up-regulates PDE4 activity in conjunction with PDE4A expression, supporting a new therapeutic approach [53]. Therefore, the use of specific PDE4 inhibitor should be adapted to selectively cure the pulmonary inflammation storm. In that way, studies performed on human pulmonary tissues [37,38] and PBMCs [49], clearly showed that inflammation up-regulates PDE4B, PDE4C, and subsequently increases TNF-α, IL-1β, IL-6, IL-8, NFκB, p-p38-MAPK, mediators of inflammation. Interestingly, these inflammatory processes have been overcome by a specific PDE4 inhibitor (Fig. 2).

Furthermore, knowing that PDE4 is up-regulated in CS [59], PDE4 inhibitor represents a promising treatment for COVID-19 CS, as much as a PDE4 inhibitor might be also active on virus replication and infection (see section 5: PDE4 and viral infection). In accordance with our present suggestion, a treatment for COVID-19 was proposed by combining antiviral and anti-inflammatory treatments [68]. On our way, a rationale for evaluating PDE4 inhibition for mitigating against severe inflammation in COVID-19 pneumonia was lastly reported [69], as well as suggested in a commentary as a potential adjunct treatment targeting the cytokine storm in COVID-19 [70]. It could not be neglected that previously a company was developing a novel drug candidate against HIV-1 which presents both anti-inflammatory and anti-viral properties, notably by generating miR-124 [71].

Therefore, this review illustrates a great link between PDE4, and RAS in patients with CS, highlighting the potential role of these intricate pathways in the initiation and the propagation of SARS-CoV-2 and the subsequent CS-potentiation of acute lung injury. Besides, the modulation of PDE4 or RAS and CS in COVID-19, PDE4 inhibitors might be a promising way in the attenuation of COVID-19 induced-CS-ARDS.

7. Future directions

Altogether, beneath AT₁R stimulation, up-regulation of PDE4 is associated with H⁺ production, inducing AT₁L, likely potentiated by CS. It should be pointed out that Raoult and colleagues have prone against SARS-CoV-2 the use chloroquine, which mediates anti-inflammatory response, interfere with the pH-dependent endosome-mediated viral entry of enveloped virus which is activated at acidic pH [72]. Interestingly, the use of PDE4 inhibitor might overcome the decrease in pH (see Fig. 2) and consequently might inhibit the release of the viral genome into the cytosol [72]. Interestingly, Kono et al. reported that chloroquine inhibits also the activation of active protein kinase p38-MAPK, which is involved in the multiplication of HCoV-229E [73], similarly to PDE4 inhibitors [46,49].

Therefore, other extensive studies, such as PDE4 implication, are recommended to explore the plausible scenario of CS and risk of COVID-19, as well as new opportunities for its treatment. In that way, it was reported on the 16th of June 2020, by Martin Landray, Professor of
Interestingly, PDE4 inhibitors were pointed out as a therapeutic way for PDE4 inhibitors to cure inflammation and intervene in COVID-19 treatment. Furthermore, PDE4 is also implicated in vascular smooth muscle cell proliferation, since in human pulmonary smooth muscle cells PDE4 inhibitors increase cAMP level and induce anti-proliferative treatment. Furthermore, PDE4 is also implicated in vascular smooth muscle cell proliferation, since in human pulmonary smooth muscle cells PDE4 inhibitors increase cAMP level and induce anti-proliferative effects [84]. However, it must be pointed out that long-term effect (>8h) of PDE4 inhibitors in rat smooth muscle cells [85], as well as in human endothelial cells [86], increases cAMP hydrolysis by PDE4, being in endothelial cells related to PDE4 up-regulated expressions. Therefore, it should be hypothesized that rapid treatment with PDE4 inhibitor might overcome COVID-19 aggression, whether late treatment by PDE4 inhibitor induces up-regulated PDE4 expression, increasing its activity, as does CS (Fig. 3). Hopefully, this increase in PDE4 activity might be overcome in the presence of its specific PDE4 inhibitor opening a new way for treating COVID-19 and CS.

CRediT authorship contribution statement

Claire Lugnier: Conceptualization, Writing - review & editing.
Hayder M. Al-Kurashi: Conceptualization, Writing - original draft.
Eric Rousseau: Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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