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Medical Hypotheses 144 (2020) 110277

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Phosphatidylglycerol and surfactant: A potential treatment for COVID-19?

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ARTICLE INFO

Keywords:
COVID-19
Innate immunity
Phosphatidylglycerol
SARS-CoV-2
Surfactant

ABSTRACT

A hypothesis concerning the potential utility of surfactant supplementation for the treatment of critically ill patients with COVID-19 is proposed, along with a brief summary of the data in the literature supporting this idea. It is thought that surfactant, which is already approved by the Food and Drug Administration for intratracheal administration to treat neonatal respiratory distress syndrome in pre-term infants, could benefit COVID-19-infected individuals by: (1) restoring surfactant damaged by lung infection and/or decreased due to the virus-induced death of the type II pneumocytes that produce it and (2) reducing surface tension to decrease the work of breathing and limit pulmonary edema. In addition, a constituent of surfactant, phosphatidylglycerol, could mitigate COVID-19-induced lung pathology by: (3) decreasing excessive innate immune system stimulation via its inhibition of toll-like receptor-2 and -4 activation by microbial components and cellular proteins released by damaged cells, thereby limiting inflammation and the resultant pulmonary edema, and (4) possibly blocking spread of the viral infection to non-infected cells in the lung. Therefore, it is suggested that surfactant preparations containing phosphatidylglycerol be tested for their ability to improve lung function in critically ill patients with COVID-19.

Introduction

COVID-19, caused by the novel coronavirus SARS-CoV-2, has resulted in massive morbidity and mortality, as well as profound economic difficulties due to the necessity for quarantining to contain and mitigate the pandemic. Although many people who become infected exhibit only mild or moderate symptoms, others develop severe symptoms, and COVID-19 appears to be more deadly than influenza, especially in older individuals and those with pre-existing conditions. Treatment to date is mainly symptomatic supportive care including invasive or non-invasive ventilation. In a recent retrospective study of 52 Chinese patients with COVID-19 requiring intensive care, more than 60% of the patients died [1]. Of the non-survivors about 80% of the patients developed acute respiratory distress syndrome (ARDS) [1], and respiratory failure associated with ARDS is the leading cause of COVID-19 mortality [2].

ARDS is characterized by lung inflammation and pulmonary edema, which reduces gas exchange and leads to hypoxemia and dyspnea, often requiring mechanical ventilation to provide sufficient oxygenation. ARDS is also accompanied by enhanced secretory phospholipase A_2 ($sPLA_2$) activity in the lungs [3,4]; $sPLA_2$ degrades the phospholipids that are components of surfactant, including phosphatidylglycerol (PG) (reviewed in [5]). Indeed, a recent study has demonstrated an increase in the activity of an sPLA2 that preferentially hydrolyzes PG, as well as a significant decrease in PG in the bronchoalveolar lavage fluid of ARDS patients versus normal control subjects [3]. The impairment of surfactant function not only can increase surface tension and reduce lung compliance but may also further exacerbate pulmonary edema, since surfactant helps to reduce fluid infiltration into the alveoli through its reduction of surface tension [6,7]. Knowledge about this sequence of events has led to studies in humans testing the efficacy of exogenous surfactant in the treatment of ARDS, and some results have been promising [8–11], although *meta*-analyses have largely failed to show an effect of exogenous surfactant administration on the survival of adult ARDS patients (e.g., [12;13]). On the other hand, another *meta*-analysis determined a benefit of surfactant administration on oxygenation levels

Abbreviations: ARDS, acute respiratory distress syndrome; DAMP, danger- or damage-associated molecular pattern; IL, interleukin; NFκB, nuclear factor kappa-light-chain-enhancer of activated B cells; PAMP, pathogen-associated molecular pattern; PG, phosphatidylglycerol; $sPLA_2$, secretory phospholipase A_2; TLR, toll-like receptor; TNFα, tumor necrosis factor-alpha

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https://doi.org/10.1016/j.mehy.2020.110277
Received 1 July 2020; Received in revised form 11 August 2020; Accepted 12 September 2020
Available online 16 September 2020
0306-9877/ Published by Elsevier Ltd.

and mortality in those patients with severe ARDS caused by pneumonia or aspiration of gastric contents [14], suggesting that co-morbidities other than ARDS may potentially determine the effect (or lack thereof) of surfactant administration on survival.

In contrast, the pulmonary failure induced by COVID-19 seems to differ in many respects from other types of ARDS [15,16]. For example, many COVID-19 patients initially present with hypoxemia with maintained lung compliance and low elastance, termed the L type presentation [17]. These L-type patients can often be treated with oxygen supplementation and prone positioning, or if they are intubated due to worsening hypoxia, mechanical ventilation at low positive end expiratory pressures (PEEP). However, L-type patients often transition into the second or H-type clinical presentation [17], in which they exhibit high elastance and low compliance and usually require mechanical ventilation at higher PEEP [18]; low pulmonary compliance portends worsening lung disease manifested by atelectasis and increasing hypoxia. Therefore, only the H-type mimics the lung parameters observed in pre-term infants that produce minimal surfactant, suggesting that at least in the early stages, COVID-19 patients exhibiting L-type disease may retain some pulmonary surfactant activity.

A key role of pulmonary surfactant is to reduce surface tension and prevent alveolar atelectasis at end expiration. In the absence of active surfactant, high surface tension at the air-liquid interface in the alveoli creates collapsing forces [19]. In addition, since surface tension draws fluid from the capillaries into the alveolar spaces, surfactant decreases pulmonary fluid accumulation by reducing surface tension to maintain airway dryness [20]. Increased surface tension related to surfactant dysfunction also alters alveolar capillary shape and pulmonary blood flow to exacerbate hypoxemia [19]. On the other hand, during severe respiratory distress with mechanical ventilation, the role of higher PEEP is to keep the alveoli “recruited” or, in other words, to prevent end-expiratory alveolar collapse. However, mechanical ventilation and high PEEP represent a double-edged sword: maintaining or improving oxygenation while causing alveolar lung injury. Mechanical ventilation with high PEEP may also reduce the ability of surfactant to lower surface tension, since compression of surfactant to an area of less than 50% of its original surface area by higher pressures can result in rupturing of the film on re-expansion, resulting in compromised surface tension-reducing capacity [21,22]. In addition, the stresses of mechanical ventilation also stimulate the inflammatory response [21].

Thus, it seems likely that another function of surfactant may be important: its ability to dampen the inflammatory response to microbial components. Thus, at least one of the surfactant phospholipids, PG, has been shown to inhibit activation of toll-like receptors (TLR) of the lung innate immune system by microbial components (reviewed in [23]). Voelker and colleagues have shown that PG inhibits TLR2 and TLR4 activation by microbial components, also known as pathogen-associated molecular patterns (PAMPs), such as acylated lipopeptides and lipopolysaccharide [23]. This inhibition then results in reduced production of inflammatory mediators and decreased lung inflammation and damage [24–26]. These results are also consistent with the results of Wu at al. [27], who demonstrated that PG inhibits endotoxin-stimulated activation of nuclear factor-kappaB (NFκB), a transcription factor associated with inflammation, to reduce Type IIA secretory phospholipase A_2 levels/activity in macrophages. The mechanism of action of PG seems to be related to the ability of the TLR2 and TLR4 co-receptor CD14 to bind this phospholipid and somehow prevent TLR activation [26,28]. Indeed, Martin et al. [29] have recently suggested blocking CD14, but with inhibitory antibodies, to control inflammation in COVID-19.

Of note, PAMPs are not the only molecules that can activate TLRs. TLR activation can also be induced by endogenous proteins that are released by damaged or stressed cells, the so-called danger- or damage-associated molecular patterns (DAMPs) (reviewed in [30]). Many such TLR-stimulating DAMPs have been identified (reviewed in [31]), including several heat shock proteins, high mobility group B1 (HMGB1) and fibrinogen [31], and these can be released extracellularly upon cell damage. We recently showed that PG can inhibit DAMP-induced inflammatory mediator production [32] and skin inflammation [32,33]. Specifically, PG inhibits TLR2 and TLR4 activation by the DAMPs S100A9 and beta-defensin-2 [32]. PG can also inhibit TLR2 and TLR4 activation in response to PAMPs in several cell types and in TLR2 and TLR4 reporter cell lines [34], with minimal effects on the activation of, or stimulation of inflammatory mediator expression by, other pattern recognition receptors, such as the TLR7/8 that recognizes single-stranded RNA. In addition, supplementation of surfactant with additional PG (to a molar percentage of 6%) preserves lung function and prevents alveolar epithelial injury and the expression of pro-fibrotic mediators in a neonatal pig triple injury model of ARDS [35]. The ability of PG to protect against cell injury would be expected to be beneficial in COVID-19 ARDS. Furthermore, COVID-19 patients have been reported to exhibit elevated levels of tumor necrosis factor-alpha (TNFα) [2], and drugs targeting pro-inflammatory mediators, such as interleukin (IL)-1 and IL-6 have been proposed or are in use for the treatment of COVID-19 [36,37]. PG has been shown to inhibit the expression of IL-1α, IL-1β, IL-6, and/or TNFα, as well as IL-8, interferon-gamma and/or macrophage inflammatory protein-2, in response to TLR activation by PAMPs and DAMPs [24–26,28,32,34,38,39]. In turn, several of these inflammatory mediators (e.g., IL-6 and TNFα) are also known to increase the levels of certain $sPLA_2$s, in particular that encoded by the gene PLA2G2A [3], which would decrease PG levels even further. Finally, excessive inflammation (e.g., markedly increased C-reactive protein and D-dimer levels) is associated with the hypercoagulopathy sometimes seen in COVID-19 patients [40]. Therefore, the ability of PG to inhibit PAMP- and DAMP-induced might also decrease these COVID-19 sequelae as well.

Hypothesis

Collectively, these results have led to the current hypothesis that PG, in the form of exogenous surfactant, might be efficacious in treating the symptoms of COVID-19. By analogy with SARS-CoV [41,42], SARS-CoV-2 is thought to target alveolar type-II cells [43,44], the lung cells that produce surfactant; the resulting release of endogenous molecules by these damaged cells would presumably activate TLRs and stimulate inflammatory mediator production and inflammation. These effects likely would, together with the gradual reduction in surfactant resulting from the death of these type II pneumocytes (and possibly the increased activity of $sPLA_2$) [3–5], promote the pulmonary edema that is a hallmark of COVID-19. The pulmonary edema, in turn, further impairs gas exchange and leads to ARDS with further hypoxemia and dyspnea. However, the initial presentation might be expected to show differences from the respiratory distress seen in pre-term infants: phosphatidylcholine represents approximately two-thirds to three-quarters of pulmonary surfactant lipid content [45,46] and thus provides the majority of its surfactant activity. Therefore, gradual loss of phosphatidylcholine would allow maintenance of compliance despite enhanced inflammation resulting from decreased levels of PG, which comprises only 9–12% of surfactant phospholipid [45,46], and the resultant pulmonary edema. Presumably, loss of the anti-surface tension effects of surfactant would only occur once large numbers of Type II alveolar cells were destroyed and phosphatidylcholine was severely depleted. At this point, then, patients would transition to the H-type clinical presentation, with the low compliance more typical of neonatal respiratory distress syndrome.

Pulmonary administration of exogenous surfactant would be expected to counter this sequence of events in multiple ways: (1) it would restore the levels of surfactant to protect against increased surface tension in the lung; (2) it would inhibit activation of the innate immune system by released DAMPs to reduce inflammation and inflammatory damage; and (3) it would decrease pulmonary edema through the combination of the first two effects. In addition, it is thought that in

Table 1
Surfactant Medications Approved by the Food and Drug Administration for Treatment of Neonatal Respiratory Distress Syndrome.

	Natural Surfactants			Synthetic Surfactants	
Generic Name	Beractant	Calfactant	Poractant alfa	Culfosceril palmitate*	Lucinactant
Brand Name	Survanta	Infasurf	Curosurf	Exosurf	Surfaxin
Company	Abbott	ONY Biotech	Chiesi	GSK[†]	Windtree[f]
Source	Minced bovine lung extract	Calf lung lavage	Minced porcine lung extract	First-generation synthetic	Second generation synthetic
Protein/amount	SP-B and –C (1 to 21 mg/mM PL)	SP-B and –C (13.5 mg/mM PL	SP-B and –C (7 to 15 mg/mM PL)	N/A	SP-B-like sinapultide (0.9 mg/mL)
Phospholipid/amount	30 mg/mL	35 mg/mL	80 mg/mL	13.5 mg/mL	30 mg/mL
PG/amount[§]	3.2% total PL	4–6% total PL	1.2% total PL	N/A	25% total PL
FDA approval	July 1991	July 1998	November 1999	August 1990	March 2012

*Withdrawn from the market due to reduced efficacy relative to other natural surfactant medications.

[f] Discovery Labs became Windtree Therapeutics in 2016.

[†] Abbreviations: FDA, Food and Drug Administration; GSK, GlaxoSmithKline; N/A, not applicable; PG, phosphatidylglycerol; PL, phospholipid; SP-B, surfactant protein-B; SP-C, surfactant protein-C.

[§] The values for protein and PG amounts were obtained from references [49,71–73].

some individuals, COVID-19-related morbidity and mortality may be related to an over-reaction of the immune system and a "cytokine storm" [2,37,47,48]. By inhibiting innate immune system activation and release of pro-inflammatory mediators that recruit and activate additional immune cells, including those of the adaptive immune system, PG would likely interrupt this process of immune system hyper-responsiveness, acting as a dampening mechanism, or rheostat, to regulate lung inflammation [23]. Finally, it is known that pulmonary surfactant can facilitate recruitment of collapsed airways and offer protection from mechanical ventilation-induced lung injury. Thus, exogenous surfactant therapy may restore or replenish insufficient or dysfunctional endogenous surfactant activity and improve outcomes in COVID-19. Thus, we are proposing that PG-containing surfactant medications that are already approved by the Food and Drug Administration for the treatment of neonatal respiratory distress syndrome (Table 1) be administered intratracheally via bronchoscopy to COVID-19 patients with severe acute respiratory distress syndrome. It should be noted that natural and second-generation synthetic surfactant preparations have been found to exhibit increased efficacy for improving neonatal respiratory distress syndrome relative to first-generation protein-free surfactant medications like Exosurf®. These results are consistent with data indicating the importance of certain surfactant proteins to improve the effect of surfactant on surface tension [49] and others to reduce microbial infection ([50,51] and reviewed in [52]).

Additional considerations

The histologic description of COVID 19 pathology at autopsy shows diffuse alveolar damage with cellular fibromyxoid exudates, acute fibrinous, hyaline membrane formation, organizing pneumonia and desquamation of pneumocytes, all consistent with ARDS [53,54]. Hyaline membrane formation has been observed in histological samples at both the early and later stages of the disease, suggesting early type II pneumocyte injury with surfactant dysfunction [53]. Although not all COVID-19 patients progress to a low-compliance phenotype, evidence in histological specimens highly suggests that there is surfactant dysfunction and hyaline membrane formation comparable to that observed in the non-COVID-19 ARDS-mediated alveolar damage described by Matthay and Zemans [55]. One approach to improve the dysfunctional surfactant in this disease is to treat with exogenous surfactant, thereby allowing maintenance of its function in the alveoli. Indeed, it seems likely that COVID-19-affected lungs will require functioning surfactant to fully recover. Exogenous bronchial surfactant instillation has been a feasible and safe approach in infants, although a higher dose and repeated administration may be required to restore dysfunctional alveoli impacted by COVID-19.

It should also be noted that despite its ability to inhibit TLR activation and inflammation, PG in surfactant does not seem to be globally immunosuppressive. In fact, in animal models *in vivo* it protects against infection resulting from several viruses, including respiratory syncytial virus, influenza A (H3N2) and H1N1 [38,39,56], by inhibiting the interaction of these viruses with their receptors on host cells (Fig. 1). Although it is not known whether PG has a similar inhibitory effect on the infectious capacity of SARS-CoV-2, a positive-sense single-strand RNA virus, the minimal effect of PG on the activation of TLR7/8 [32,34] would suggest that this phospholipid would likely not suppress innate immune system responses to the virus. Therefore, surfactant might be useful in preventing the spread of SARS-CoV-2 viral infection between infected and naïve cells within the lung without affecting the response to this infection, in addition to protecting against the damage caused by excessive inflammation and edema and the increased surface tension that eventually results from loss of surfactant. On the other hand, the surfactant lipids phosphatidylcholine, in particular disaturated phosphatidylcholine (dipalmitoyl-phosphatidylcholine), and phosphatidylserine are reported to potentially promote infection by viral pathogens [57]. However, the mechanisms are thought to involve facilitation of viral entry via the ability of the virus to bind lipid and co-opt reuptake/recycling pathways in the case of PC and promotion of viral fusion by mimicking of an apoptotic signal in the case of PS [57]. Since SARS-CoV-2 purportedly gains entry into cells through angiotensin-converting enzyme 2 (ACE2) [40], these mechanisms used by other viruses seem unlikely to be relevant to SARS-CoV-2 and COVID-19 pneumonia.

It should also be noted that certain conditions that increase the risk of a severe response to SARS-CoV-2 infection are also known to reduce surfactant and/or surfactant phospholipid levels or to impair surfactant function. Thus, phospholipid levels inversely correlate with age, at least in horses [58]. Smoking also reduces phospholipid levels in pulmonary surfactant [59] and is thought to increase the risk of adverse outcomes from COVID-19 [48]. Diabetes causes increased serum levels of high mobility group-B1 (HMGB1) [60], a known DAMP [31] that activates TLR4 [31], which would be expected to enhance inflammation. Similarly, in some cases hypertension has also been proposed to result from enhanced serum DAMP levels (reviewed in [61]), which again could possibly lead to a chronic low-level inflammation. Obesity is also thought to be accompanied by inflammation (reviewed in [62]). Indeed, serum levels of C-reactive peptide, a marker of inflammation, have been observed to correlate well with SARS-CoV-2 viral load and the Murray score, which assesses the severity of lung injury in individuals with ARDS [63]. Diabetes, hypertension and obesity have been suggested to predispose individuals to worse outcomes from COVID-19 [64]. In addition, serum levels of angiotensin II, which is also reported to increase inflammation through TLR4 [31,65], are reported to be elevated in patients with COVID-19 [63]. Finally, a recent report

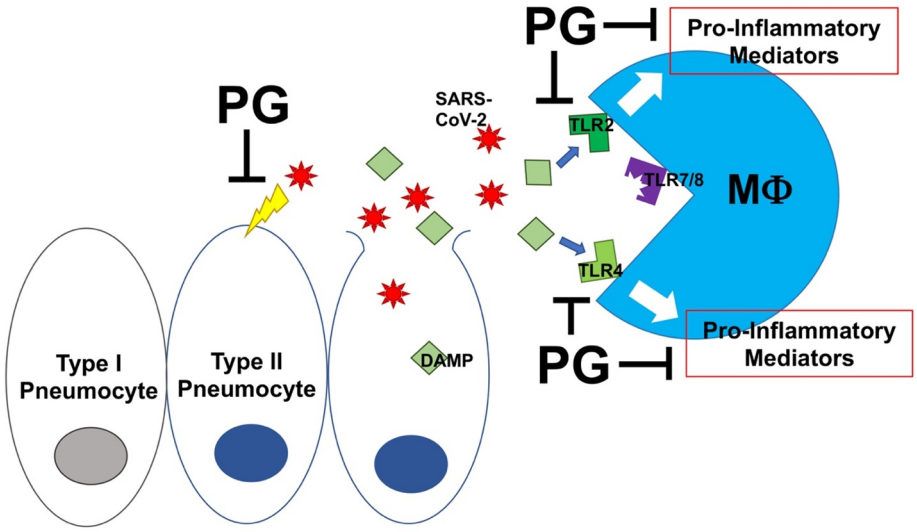

Fig. 1. Phosphatidylglycerol in surfactant inhibits toll-like receptor-2 (TLR2) and TLR4 activation in response to damage-associated molecular patterns (DAMPs). SARS-CoV-2, the virus that causes COVID-19, is thought to infect type II pneumocytes, the cells in the lung responsible for surfactant production. Propagation of the virus results in pneumocyte death and the release of viral particles and endogenous intracellular molecules, some of which can serve as DAMPs. These DAMPs, as well as pathogen-associated molecular patterns (PAMPs) derived from microorganisms and viruses (reviewed in [74]), activate the innate immune system through TLR2 and TLR4 on alveolar macrophages (Mϕ), triggering pro-inflammatory mediator production and inflammation. Phosphatidylglycerol (PG) in surfactant inhibits PAMP- and DAMP-induced TLR2 and TLR4 activation thereby reducing inflammatory mediator production and inhibiting inflammation. PG also may inhibit SARS-CoV-2's ability to infect naïve cells. It is hypothesized that restoration or supplementation of surfactant PG by administration of exogenous surfactant will improve the respiratory failure characteristic of COVID-19 pneumonia.

has suggested that the corticosteroid dexamethasone may improve survival in patients with severe COVID-19 [66]. If confirmed, this result would be consistent with the hypothesis described here, since glucocorticoids are known not only to suppress inflammation but also to increase lung surfactant synthesis [67,68]. By stimulating any remaining Type II alveolar cells to produce more surfactant phospholipids including PG, dexamethasone could both directly and indirectly decrease lung inflammation.

Implications

Surfactant has already been used in studies to treat ARDS [8–11] in adult patients, although with less than impressive results. It should be noted that Walmrath et al. [9] discussed the likelihood that higher doses and/or more frequent administration of surfactant might be necessary in the case of ARDS (versus neonatal respiratory distress syndrome) to overcome the ongoing surfactant-inactivating conditions (increased $sPLA_2$ levels, inflammation and oxidative stress) often present in ARDS lungs. We would also like to point out that not all surfactant medications contain PG (for example, Exosurf® does not), which could potentially be another explanation, in addition to potentially inadequate dosing and inactivation of surfactant function by shearing [13], for why not all studies of surfactant administration in ARDS have found a benefit [12]. Despite the mixed results concerning exogenous surfactant medication in adult ARDS [12,13], it is approved by the Food and Drug Administration for intratracheal administration to pre-term *infants* to treat neonatal respiratory distress syndrome. In infants there are few side effects, and infants who receive surfactant have shorter hospital stays and better survival [69]. Similarly, eleven clinical trials in adults have indicated that surfactant therapy is both feasible and safe, with no significant adverse effects reported [70]. Therefore, it is postulated that because SARS-CoV-2 is thought to target and damage/destroy surfactant-producing type II pneumocytes, COVID-19 may be more like neonatal ARDS than are other types of ARDS. Indeed, like preterm infants, patients with COVID-19 have been found to exhibit hyaline membrane formation [53]. Therefore, it is proposed that investigative studies to administer PG-containing surfactant, either synthetic (e.g., Surfaxin®) or isolated from bovine (Alveofact®, Survanta®, Beraksurf® and Infasurf®) or porcine lungs (Curosurf®), to critically ill COVID-19 patients be initiated, particularly in view of the fact that few therapies for severe COVID-19 have been shown to be effective to date [37], and such treatments are actively being sought.

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.

Acknowledgements

The authors would like to acknowledge and thank Dr. William Davis (Augusta University) for helpful feedback on this work. This work received no specific funding. WBB was supported in part by Veterans Affairs Merit Award #CX001357 and in part by National Institutes of Health/National Eye Institute award #R01EY030576. These sponsors had no role in the research, the writing of the manuscript or the decision to publish. The contents of this article do not represent the official views of the Department of Veterans Affairs or the United States Government.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2020.110277.

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