Aerosolized hyaluronic acid and its applications

V. Raia, A. Sepe, A. Tösco, F. De Gregorio, F. Amato
Department of Translational Medical Sciences University “Federico II” of Naples, Italy

Abstract. Although the interaction of low MW HA fragments with surface receptors such as TLRs may explain how HA can favor the inflammatory response, some physical and chemical properties, such as high MW HA, may increase its capability to retain water and to preserve the distensibility of elastic fibers that is dependent on the interaction with water molecules, thus enhancing pulmonary ventilation. Encouraging clinical results provide the beneficial effect of inhaled HA in CF patients who have previously shown poor tolerance to aerosolized hypertonic saline solution. (www.actabiomedica.it)

Key words: hyaluronic acid, respiratory disease, inhaled therapy

Introduction

Cystic Fibrosis (CF), the most common lethal genetic disorder in the Caucasian population, is caused by mutations of the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which encodes for a cAMP-dependent chloride channel expressed in secretory epithelia of the body. High morbidity and mortality are due to chronic obstructive lung disease resulting from airway surface dehydration and im paired mucociliary clearance that lead to airway mucus obstruction, neutrophilic inflammation and bacterial infection. As a consequence, early onset of bronchiectasis and progressive emphysema are a characteristic feature of CF lung disease and their severity contributes to progressive loss of lung function and disease burden in patients with CF. While the imbalance between chloride secretion and sodium absorption in submucosal glands and airway epithelium in the lung is responsible for detrimental airway dehydration, cells lacking functional CFTR display several other constitutive dysfunctions such as unregulated activation of the nuclear factor kappa-light chain-enhancer of activated B cells (NF-κB) pathway (hyper-inflammation) (Fig 1) (1), decreased anti-inflammatory responses, and oxidative stress that is a hallmark in CF lung disease and represents an inducer of the pro-inflammatory status, upon stimulation with either Toll-like receptor (TLR) ligands or Pseudomonas aeruginosa. Bacterial products such as lipopolysaccharide (LPS), which trigger the recruitment of macrophages and
neutrophils, and increase secretion of elastolytic pro-
tases, such as macrophage elastase and neutrophil
elastase, may also play an important role in emphy-
sema formation in CF (2). Elevated levels of interleu-
kine-8 (IL-8) signaling mediated by the NF-κB result
in chronic infection, neutrophilic inflammation, and
progressive structural lung damage. This pathogenetic
cascade indicates that additional rehydration strategies
may be required for effective treatment of airway mucus
obstruction in CF with secondary consequences also
on inflammation (1).

Discussion

Glycosaminoglycans (GAGs) play key struc-
tural roles in the lung where they are distributed in
the extracellular matrix that fills the interstitial space
lying between the capillary endothelium and the al-
veolar epithelium (Fig. 2) (3), in the subepithelial tis-
sue, bronchial walls, and airway secretions. GAGs are
also involved in a number of biological activities me-
diated by specific receptors including cell migration
and differentiation, antigen recognition, cell adhesion
and communication. Recently (3), the importance of
glycosaminoglycans (GAGs) in CF has been high-
lighted. Increased concentrations of GAGs have been
found in BALF from children with CF, and secretion
of HA is markedly increased in bronchial cells and CF
tissues (4).

Figure 2. Localization of extracellular matrix in the lung from
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Figure 3. Structural formula of HA

HA is a simple linear polysaccharide chain be-
longing to the family of glycosaminoglycans made
of alternating β-1, 4-glucuronic acid and β-1, 3-N-
acetylglucosamine disaccharide units (Fig. 3). It oc-
curs in many tissues and body fluids in vertebrates.
Previous experimental results in animal models have
provided effects of aerosolized HA in preventing ex-
perimentally induced parenchymal emphysema (5). The intratracheal ad-
ministration of hyaluronan prior to the induction of
experimental emphysema developed significantly less
disease than untreated controls.

The use of aerosolized hyaluronan (HA) has been
proposed as an alternative approach to treating em-
physema (6). The protective effect of HA may be re-
lated to its ability to bind to lung elastic fibers, thereby
preventing their breakdown by elastases (7). In partic-
ular, it has been proposed that the special ability of this
polysaccharide to retain water may increase the elastic-
ity of lung elastic fibers, producing a relatively rapid
improvement in pulmonary mechanics. However, the
biological activity of HA is likely related to its mo-
lecular size, with larger polysaccharide chains having
anti-inflammatory properties and smaller ones having
pro-inflammatory activity.

No nebulized formulations including HA have
been provided in patients with chronic obstruction
pulmonary disease in recent clinical studies. Such a
potential beneficial treatment of nebulized HA for re-
spiratory diseases in clinical trials is not expected to
become evident as a measurable effect for at least sev-
eral years, taking into account that pulmonary emphy-
sema progresses at a relatively slow rate.

In CF, early onset and progressive emphysema
is a characteristic feature of lung disease, as recently
shown by non-invasive methods (8), where a pivotal role in the destruction of lung tissue is played by release of proteolytic enzymes that overwhelm the antiprotease defences of the lung. While cytokine- and chemokine-GAGs interactions seem to decrease the plasma clearance and increase the cytokine activity (9) where several fragmentary ECM components are pro-inflammatory such as low molecular weight HA (LMWHA), intact high molecular weight HA (HMWHA) can inhibit TLR-2 signaling in vitro and in vivo (10) playing an active role in the maintenance of immune tolerance (10).

Clinical application of HMWHA has been recently proposed (11) for increasing tolerability of inhaled hypertonic saline solution mucolytic agent. Several studies (12, 13) have further confirmed this data in controlled clinical trials. In addition, both mouse models CftrF508del mice, carrying the most common F508del-CFTR mutation, and Scnn1b-Tg mice, overexpressing the β-subunit of the ENaC channel, were analyzed to evaluate the expression of markers of inflammation in lung homogenates after nebulized HA. In particular, decreased levels of TNFa and MIP-2, the analogous of human IL-8, mainly responsible for neutrophil recruitment into lungs, reducing leukocyte infiltration in the lungs of mice, and decreasing levels of MPO, an enzyme that is most abundantly present in neutrophils, were found (15). The effect of nebulized HA in controlling ROS-mediated effects in CF epithelia induced by the challenge with PA-LPS might help preventing HA degradation, thus avoiding the putative pro-inflammatory effects of small HA fragments.

Conclusion

Aerosol HA administration may have a potential therapeutic impact on respiratory diseases reducing the bronchial hyper-reactivity to muscular exercise in asthmatics and controlling progression of emphysema. Preliminary results in mouse models could pave the way for the implementation of nebulized HA not only as adjuvant in medical devices, but also as a putatively safe, anti-inflammatory medical device for the treatment of patients with CF.

References

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