



Is lipoxin A4 an effective treatment on fat embolism syndrome by attenuating pro-inflammatory response?



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ABSTRACT

Fat embolism syndrome (FES) is characterized by high mortality and lack of effective treatment, the symptomatic therapy is most used to relieve clinical symptoms. Some studies have shown that inflammation is one of the main pathogeneses of FES. Lipoxin A4 is an endogenous-derived anti-inflammatory substance which was discovered recently. It can alleviate inflammatory response and promote inflammation resolution, and is referred as brake signal of inflammation. Therefore we hypothesize that lipoxin A4 may have a remission and therapeutic effect on FES by attenuating FES-induced inflammatory responses.

Introduction

Fat embolism syndrome (FES)

Fat embolism syndrome (FES) is a life-threatening clinical complication caused by systemic dissemination of fat droplets into the circulation [1], leading to a triad of respiratory failure, neurological abnormalities, and petechiae [2,3]. FES occurs most commonly in orthopedic trauma, especially in long bone fractures. Nonorthopedic causes of FES are very rare, including acute or chronic pancreatitis, sickle cell disease and liposuction [1]. The incidence of FES varies from 1% to 11% [1], with the mortality rates of 13–87% [4]. Pulmonary dysfunction-induced hypoxemia is the most common clinical presentation and the main cause of death.

The pathophysiology of FES

The exact pathophysiology of FES remains unclear [3]. Two main theories have been proposed. The mechanical theory postulated by Gassling et al. proposes that fat droplets gain access to the venous system after trauma and deposited in the pulmonary capillary bed. With potent proinflammatory and prothrombotic effects, fat droplets trigger platelets aggregation and fibrin generation acceleration and lead to a systemic inflammatory response [3]. Due to pulmonary capillary obstruction, pulmonary artery pressure elevates and oxygen exchange is impaired [1], which lead to shortness of breath and hypoxia. Fat cells may also escape to the system circulation via a patent foramen ovale or

directly transverse the pulmonary vasculature, causing the characteristic signs on end-organs such as the brain, kidney, and skin of FES.

The biochemical theory proposed by Baker et al. suggests that FES occurs as a result of a proinflammation state [3]. Fat is decomposed into chylomicrons and toxic free fatty acid (FFA) by tissue lipases, exacerbating the underlying proinflammatory physiology and causing damage to pulmonary endothelium and end-organs. Then a pro-inflammatory cytokine cascade is triggered, leading to acute respiratory syndrome. Several pro-inflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF- α) increased in FES.

Actually, the mechanical and biochemical processes are combined in most cases of FES, inflammation plays an important role in both pathophysiology theories of FES. Many previous studies have demonstrated the importance of inflammation in FES [3].

Treatment for FES

By now specific and effective treatment for FES is lack. Due to anti-inflammatory potency, corticosteroids have been proposed to treat FES. Corticosteroids can inhibit complement activated leucocyte aggregation, decrease FFA level and stabilize the membrane [1] by reducing inflammatory response. In addition, corticosteroids can decrease perivascular hemorrhage and edema resulted from lipid metabolites-induced pulmonary injury [2]. Although a meta-analysis about prophylactic use of corticosteroids after the skeletal trauma showed 78% reduction of the risk of FES, there is no difference in mortality between

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the corticosteroids treatment and control group [3]. Additionally, there is an increased risk of infection, wound healing delay in a traumatic patient after the corticosteroids therapy [2,5]. Therefore, there is insufficient evidence to support the routinely use of corticosteroids in FES.

Lipoxin A4 and lipoxin A4 receptor (ALX)

Lipoxins (LXs) are endogenous lipid mediators derived by lipoxygenases from arachidonic acid [6]. The synthesis, structures and functions of lipoxins are different from other arachidonic acid metabolites and lipoxins have potential immunoregulatory and anti-inflammatory abilities. Subtypes of lipoxins include lipoxin A4, lipoxin B4, 15-epi-lipoxin A4, and 15-epi-lipoxin B4. Lipoxins are transcellular synthesized by lipoxygenase. There are three biosynthesis routes of lipoxin that have been proved. In airway epithelial cells, mononuclear macrophage, vascular endothelial cells, and eosinophile granulocyte, arachidonic acid is oxygenated via 15-lipoxygenase type I followed by 5-lipoxygenase to biosynthesize lipoxins [7]. Another route to generate lipoxin is via 5-lipoxygenase in leukocytes within the blood vessels and the intermediate leukotriene A4 is released. Leukotriene A4 is then converted to lipoxin A4 and lipoxin B4 by 12-lipoxygenase within the platelet [7,8]. In addition, aspirin-triggered lipoxin (ATLs) are generated by cyclooxygenase-2 and then modified further by 5-lipoxygenase [9].

Among all lipoxins, lipoxin A4 is the most frequently studied. Lipoxin A4 receptor (ALX) is a G protein-coupled receptor and named ALX/FPR2 due to its high affinity to lipoxin A4. After binding to ALX, lipoxin A4 transduces intracellular signals to ALX and exerts both anti-inflammation and pro-resolving properties [10]. ALX is expressed in a variety of cells [11]. Lipoxin A4 plays a crucial role in many biological functions especially in inflammatory process and has been regarded as the key endogenous “stop signal” for inflammation [12–15].

Endogenous lipoxins are unstable because they degrade rapidly [16]. A number of synthetic analogues of lipoxin A4 such as BML-111 are metabolically stable and commercially available. Moreover, these analogs have been proved to retain the biological activity of native lipoxins [17–20].

Mechanism of anti-inflammation and pro-resolution of lipoxin A4

Lipoxins are synthesized at inflammation sites and has dual anti-inflammatory and pro-resolving bioactions [21–24]. Previous studies have indicated that lipoxin A4 prohibit the recruitment of neutrophil and eosinophil to the inflamed site [25–27], prohibit migration of neutrophil across postcapillary venules [28,29], and promote the apoptotic of neutrophils which suppresses the inflammatory progress [30]. Lipoxin A4 has been implicated in regulating the balance of proinflammatory factors and anti-inflammatory factors. Moreover, lipoxin A4 has been demonstrated to promote the repair and prohibit fibrosis of the damaged tissues.

There are three main signaling pathways that mediate the effect of lipoxin A4 on inflammation response including the mitogen-activated protein kinase (MAPK) pathway, the phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) pathway and transcription factor NF- κ B [11].

Previous research [31] have showed lipoxin A4 can attenuate the activation of spinal ERK, JNK, NF- κ B, decrease pro-inflammatory cytokines (TNF- α and IL-1 β) expression, and promote anti-inflammatory cytokines (TGF- β 1 and IL-10) expression to attenuate inflammatory response that leads to radicular pain. Lipoxin A4 has been shown to inhibit proliferation of human lung fibroblasts via downregulation of ERK and PI3K/AKT [32].

Lipoxin A4 has been demonstrated to attenuate acute lung injury induced by lipopolysaccharide and exert therapeutic effects in acute lung injury (ALI) [33]. Activation and infiltration of neutrophil play key role in development of acute inflammation in the injured lung. The

formation of lipoxin A4 and expression of ALX are up-regulated significantly in the mice model of acute lung injury induced by hydrochloric acid [34]. Furthermore, the incidence of ALI is low in transgenic mice with high ALX expression [34].

Lipoxins generated in respiratory tissues showed to inhibit airway inflammation in the model of asthma [35]. Indomethacin increases the generation of lipoxin A4 by activating 5-lipoxygenase pathway, which resolute the infection-induced inflammation [36]. Lipoxin A4 significantly increases natural killer cell and decreases IL-13 release by type 2 innate lymphoid cells to regulate airway inflammation and the catabasis of eosinophilic inflammation in asthma [37].

Lipoxin A4 also plays anti-inflammatory effect in the endometriosis which is a common inflammatory condition [15]. Lipoxin A4 was reported to reduce neuroinflammation in stroke [38] and demonstrated to reduce the inflammation response by inhibiting NF- κ B and PI3K/Akt signaling pathway to provide a protective effect against experimental autoimmune myocarditis [39]. Moreover, Lipoxin A4 was shown to significantly attenuate renal inflammation and injury induced by high-fat-diet in obesity-related glomerulopathy models [40].

As an endogenous “pro-resolving” mediator, lipoxin A4 plays a crucial role in the resolution of inflammation. Lipoxin A4 has been proved as a major component of two pivotal events during the resolution process including monocytes chemotaxis [41,42] and phagocytosis for apoptotic neutrophil by monocyte-derived macrophages [43].

Hypothesis

We build a novel concept to treat the fat embolism syndrome. We propose that LXA4 may have therapeutic benefits in FES by attenuating pro-inflammatory responses induced by FES via some signaling pathways.

We all know inflammation plays a pivotal role in the process of FES. FES is a result of interstitial and alveolar inflammation triggered by the lipid [2]. Although corticosteroid is used as an anti-inflammation agent in FES, it still has many systemic side effects. Some small randomized, controlled trials have found that corticosteroids can reduce hypothermia without significant difference in mortality of FES [3]. Therefore, regarding the use of corticosteroids in FES, the efficacy and safety of corticosteroids are not strong enough to be proposed as a routine treatment of FES.

Lipoxin A4 is an endogenous lipid mediator with anti-inflammatory and pro-resolution bioactions. Due to the therapeutic effect of lipoxin A4 on different inflammatory situation proved by many previous researches, we hypothesize that lipoxin A4 may probably be a novel treatment for FES. Additionally, compared with corticosteroids, lipoxin A4 has fewer side effects and doesn't disturb normal metabolism.

Our hypothesis links the inflammatory mechanism of FES and the anti-inflammatory/pro-resolution potencies of LXA4 and provides clue to explore new route for the treatment of FES. The present hypothesis implicates the therapeutic potential of lipoxin A4 on FES, and warrants studies to reveal the efficacy and safety of lipoxin A4 for the treatment of FES.

Discussion

The validity of our prediction will be tested *in vivo* in rat model and *in vitro* at cellular level respectively.

The role of lipoxin A4 in the pathological process of FES will be investigated *in vivo*. Allogeneic perirenal fat of the half lethal dose (LD50) will be injected through the tail vein of rats to establish experimental model of FES which is closely related to clinical FES. Healthy adult male Sprague Dawley rats will be randomly assigned into four groups. Besides FES group and control group, lipoxin A4 group and ALX antagonist group will also be included. In lipoxin A4 group, rats will be pretreated with BML-111, which is synthetic analogue of lipoxin A4. In ALX antagonist group, rats will be pretreated with Boc-2, an ALX

antagonist. According to previous literature [38,44,45], we found the most LXA4 is administered intravenously in animal experiment, especially in experiment on lung. There are some alternative routes of LXA4 administration. LXA4 was administrated through intracerebroventricular injection in a study about the effect of LXA4 on cognitive deficits [46]. Intrathecal injection of LXA4 was used to study the effect of LXA4 on radicular pain [31]. So we choose the intravenously route in our animal experiment.

Lung tissue will be harvested for oil red O staining and HE staining to observe the pathological changes. And the changes of wet-to-dry lung weight ratio (W/D) in the lung tissue and total protein concentration in bronchoalveolar lavage fluid (BALF) will be evaluated to detect pulmonary edema in FES. The expression of endogenous lipoxin A4, ALX/FPR2 and ALX/FPR2 mRNA will be determined by ELISA kits, immunohistochemistry and Real-time PCR, respectively. Inflammatory response in FES will be evaluated by counting the number of leukocytes and neutrophils, testing the activity of myeloperoxidase (MPO), level of plasma TNF- α and IL- β . Fat-induced inflammatory response and the severity of pulmonary injury determined by microscopy will be compared between groups.

We will explore the variation of endogenous lipoxin A4 in the process of FES and evaluate the effects of lipoxin A4 on the FES. If our hypothesis works, lipoxin A4 will significantly reduce pro-inflammatory cytokines and improve blood oxygen saturation and survival rate. BML-111 pretreatment will reduce the damage of lung tissue. Lipoxin A4 receptor inhibitors BOC-2 will show reverse effects.

In order to investigate the effect of lipoxin A4 on inflammatory response in FES at the cellular level, we will apply a cellular model in which pulmonary microvascular endothelial cells (PMVECs) from rats will be pretreated with a free fatty acid (FFA) mixture. The concentration of lipoxin A4 and the expression of ALX in PMVECs will be tested. The PMVECs viability will be determined by using methylthiozoyl tetrazolium (MTT) assay and the changes of pro-inflammatory cytokines will also be determined after exposed to lipoxin A4. If hypothesis works, the expression of ALX would be increased by lipoxin A4. The PMVECs apoptosis and the pro-inflammatory cytokines will be reduced after lipoxin A4 application.

Furthermore, we will explore the potential signaling pathway by which lipoxin A4 works on FES in PMVECs. By using agonists and antagonists of MAPK, NF- κ B and PI3K/Akt respectively, the phosphorylation of MAPK (p38, ERK1/2 and JNK), activation of nuclear factor- κ B (NF- κ B) and phosphatidylinositol-3-kinase (PI3K)/Akt after lipoxin A4 exposure will be evaluated.

Conclusion

Inflammation plays an important role in the development of fat embolism syndrome. Assessing the anti-inflammation and pro-resolution potency of lipoxin A4 may shed a light on the new therapy of FES.

Conflict of interest

None declared.

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