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Research Article

Effect of Folic Acid in Sepsis-induced Lung Damage in Rats

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Abstract

Aim: Sepsis-induced lung injury remains a critical concern with significant morbidity and mortality. This study aimed to investigate the potential therapeutic role of Folic Acid in mitigating lung injury induced by sepsis while exploring its interaction with the soluble suppression of tumorigenicity 2 (sST2) protein in an experimental rat model.

Material and Methods: Rats were divided into three groups: a normal control group, a group induced with sepsis and treated with saline, and a group induced with sepsis and treated with Folic Acid (5 mg/kg). Biomarkers of oxidative stress, inflammation, respiratory gas exchange, and lung histopathology were assessed.

Results: Folic Acid administration resulted in significantly decreased Malondialdehyde (MDA) levels ($p<0.01$) and reduced soluble ST2 levels ($p<0.05$) compared to the sepsis-induced saline group. Tumor necrosis factor α (TNFα) levels were markedly reduced ($p<0.001$), and lung histopathology demonstrated decreased alveolar inflammation and septal thickness. Additionally, improved oxygenation (PaO_2) was observed following Folic Acid treatment ($p<0.05$), while $PaCO_2$ remained stable.

Conclusion: These findings suggest that Folic Acid protects against sepsis-induced lung injury, ameliorating oxidative stress, inflammation, and histopathological alterations. The modulation of soluble ST2 levels may implicate Folic Acid's role in immune regulation and potential crosstalk with the IL-33/ST2 pathway. Despite promising results, limitations inherent to animal models and the complexities of clinical translation warrant further investigation. This study highlights the potential of Folic Acid as a therapeutic intervention in sepsis-induced lung injury. It underscores the need for mechanistic studies and clinical trials to validate its effectiveness in human patients.

Keywords: Sepsis, acute lung injury, soluble ST2, folic acid

INTRODUCTION

Sepsis is a clinically significant condition with widespread implications, especially in critical care settings. The mortality rate associated with the hyperactive immune response to infections, specifically the occurrence of multiple organ dysfunction, ranges from 25% to 52% (1). In the initial stages of sepsis, the lungs, kidneys, and liver are among the organs that experience a significant impact. The presence of dysfunction in two or three of these factors exhibits a strong correlation with heightened mortality rates among patients diagnosed with sepsis (2). A "cytokine storm" phenomenon results from an exaggerated immune response directed toward combating and containing an infection (3). Cytokines have a substantial impact as pleiotropic regulators in modulating the immune response and are essential in the complex pathophysiology of sepsis. By demonstrating both pro- and anti-inflammatory properties, they can regulate the immune response in the context of an infection.

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are pathological states that manifest with the abrupt onset of respiratory failure, leading to significant morbidity and mortality (4). According to empirical evidence, individuals who effectively recuperate from ALI encounter an adverse impact on their long-term quality of life (5). Considerable advancements have been achieved in understanding this malady's epidemiological facets, pathogenic mechanisms, and therapeutic strategies. However, further progress is necessary to reduce the rates of mortality and morbidity related to ALI and ARDS (6).

Folic acid (FA), also known as vitamin B9, is an essential

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nutrient that plays a crucial role in DNA synthesis, cell division, and other cellular processes (7). It is essential during rapid cell growth and division, such as pregnancy. While FA is primarily known for its role in cell division and DNA synthesis, it also has anti-inflammatory properties. It has been investigated for its potential to modulate inflammatory responses (8).

ST2, the interleukin-1 receptor-like 1 (IL1RL1), is a protein receptor involved in immune responses and inflammation. ST2L is expressed on the surface of specific immune cells, such as T-helper 2 (Th2) cells, which play a role in allergic responses and immune regulation. When ST2L binds to its ligand, interleukin-33 (IL-33), it can trigger signaling pathways contributing to immune responses and inflammation (9).

Soluble suppression of tumorigenicity 2 (sST2) has been identified as a promising biomarker for heart failure, with potential applications in inflammatory diseases due to its ability to indicate increased serum sST2 concentrations (10). sST2, on the other hand, is a soluble version of the ST2 receptor that is released into the bloodstream. It acts as a decoy receptor, preventing IL-33 from binding to membrane-bound ST2L (10). This IL-33/ST2 pathway modulation has been implicated in various physiological and pathological processes, including immune responses, inflammation, and tissue repair. ST2 and its soluble form might serve as biomarkers of disease severity (10).

This study examines the potential impact of FA on sepsis-induced lung injury (SILI) through the utilization of histopathological examination, assessment of lipid peroxidation (LPO), and immunohistochemistry in a rat model of sepsis.

MATERIAL AND METHOD

Animals

This study utilized a sample of 30 male Wistar albino mature rats with an average weight of 200 to 250 grams. The experiments conducted in this study were executed by the guidelines outlined in the Guide for the Care and Use of Laboratory Animals, as adopted by the National Institutes of Health in the United States. After obtaining approval from the Animal Ethics Committee (Science University, Ethical number: 2023083321), The laboratory rats utilized in the experiment were sourced from the Experimental Animal Laboratory at Science University. The rats were provided with unlimited access to food. They were kept in steel cages under controlled environmental conditions, maintaining a temperature of 22±2°C and a light/dark cycle of 12 hours each.

Experimental Procedures

A study was conducted on a sample of 30 rats. Twenty rats were randomly divided into three groups. The feces intraperitoneal-injection group (FIP) procedure was conducted on these rats to induce a sepsis model. A total of ten rats were divided into two groups: a normal group and a group that did not undergo any experimental procedures. The FIP rat model was established using a methodology previously outlined by Karaali et al. (11). The fecal samples were gathered and subsequently suspended in a saline solution, resulting in the preparation of the fecal saline solution. They were administered intraperitoneal injection at 1 gram per kilogram of body weight. The structure and organization of study groups were devised as follows: Group 1 consisted of 10 individuals who served as the normal control group. These individuals did not undergo any surgical procedures and were orally fed. Group 2, on the other hand, consisted of 10 rats diagnosed with FIP. This group was administered 1 ml/kg of tap water as a placebo via oral gavage. In Group 3, the subjects were administered FIP and 5 mg/kg of FA (specifically, Folbiol tablet 5 mg manufactured by Menarini) via oral gavage. The sample size for this group was 10. All treatments were administered one hour following the FIP procedure. The study was concluded within a 24-hour timeframe. A total of six rats expired within the initial 24-hour period after the procedure, resulting in their exclusion from the study. Specifically, four rats from the placebo group and two from the FA group were among the deceased.

After the study, all animals underwent euthanasia through cervical dislocation, following administration of anesthesia consisting of Ketamine (100 mg/kg, Ketasol, Richterpharma AG Austria) and xylazine (50 mg/kg, Rompun, Bayer, Germany). Subsequently, blood samples were obtained via cardiac puncture for biochemical analysis.

Determination of TNF-a and sST2 in Plasma

Plasma tumor necrosis factor α (TNFα) and sST2 levels were quantified using commercially available enzyme-linked immunosorbent assay (ELISA) kits from Biosciences and Abcam. The measurements were conducted following the guidelines provided by the manufacturer.

Measurement of Lipid Peroxidation

Lipid peroxidation was quantified in plasma samples by assessing malondialdehyde (MDA) concentrations as thiobarbituric acid reactive substances. Concisely, the experimental procedure involved the addition of trichloroacetic acid and TBARS reagent to the plasma samples. Subsequently, the mixture was thoroughly combined and incubated at 100°C for 60 minutes. After cooling on ice, the samples underwent centrifugation at a speed of 3000 revolutions per minute for 20 minutes. Subsequently, the absorbance of the resulting supernatant was measured at a wavelength of 535 nanometers.

Histopathological Examination of Lung

To facilitate histological analysis, anesthesia was administered to all animals via intraperitoneal injection of Ketamine and xylazine. Following that, the subjects were subjected to perfusion using a solution comprising 200 milliliters of 4% formaldehyde in a phosphate-buffered saline (PBS) with a concentration of 0.1 M. Lung sections with a thickness of 5 µm, which had been fixed with formalin, were subjected to staining using the hematoxylin and eosin (H&E) technique. The sections were obtained through an Olympus C-5050 digital camera, securely attached to an Olympus BX51 microscope. The primary histopathological lung damage score was calculated per

the methodology described in prior research. In brief, the histopathological assessment of lung injury encompassed the evaluation of several parameters, namely alveolar congestion (AC), hemorrhage (H), leukocyte infiltration or aggregation in air spaces/vessel walls (AL), perivascular/interstitial edema (PE), and the thickness of the alveolar wall/hyaline membrane formation (TA). The severity of each item was evaluated utilizing a grading scale encompassing a range of values from 1 to 4. Each grade was associated with a particular percentage range: 1 (0-25%), 2 (25-50%), 3 (50-75%), and 4 (75-100%) (12).

Arterial Blood Gas Analysis

The carotid artery blood of rats in each group was sampled (0.2 mL) at 24 h after the operation, and PaO2 and PaCO2 in the blood samples were assayed using a blood gas analyzer.

Statistical Analysis

The data are displayed in the format of mean values and the standard error of the mean (SEM). The data analyses were performed using SPSS version 15.0 for the Windows operating system. The data underwent analysis utilizing the non-parametric Mann-Whitney U test. P-values equal to or less than 0.05 were considered to have statistical significance.

RESULTS

Plasma oxidative stress marker malondialdehyde (MDA) levels exhibited significant differences among the experimental groups. The standard control group measured the plasma MDA level at 14.3±1.02 nM/mg protein. Conversely, the group subjected to FIP induction and saline treatment demonstrated a markedly elevated plasma MDA level of 48.3±1.6 nM/mg protein ($p<0.001$). Notably, the administration of 5 mg/kg FA to the FIP-induced rats resulted in a significant reduction in plasma MDA levels, measuring 33.5±0.8 nM/mg protein ($p<0.01$), compared to the FIP and saline group (Table 1).

Regarding the plasma sST2 levels, the normal control group displayed a 0.85±0.1. In contrast, the FIP-induced rats treated with saline exhibited a significantly higher plasma sST2 level of 2.59±0.2 ($p<0.05$). In the FIP-induced group treated with 5 mg/kg FA, the plasma sST2 level was reduced to 1.24±0.1 (#$p < 0.01$#) in comparison to the FIP and saline group (Table 1).

Measurement of plasma tumor necrosis factor alpha (TNF-α) levels revealed substantial variations across the experimental groups. The normal control group registered a TNF-α level of 15.2±1.8 pg/ml. Remarkably, the FIP-induced rats treated with saline displayed a significantly elevated plasma TNF-α level of 374.3±8.2 pg/ml ($p<0.001$). However, administration of 5 mg/kg FA to FIP-induced rats led to a substantial reduction in plasma TNF-α levels, measuring 228.1±5.5 pg/ml (##$p<0.001$##), in comparison to the FIP and saline group (Table 1).

The levels of various biomarkers in different lung tissues exhibited significant variations among the experimental groups. In the normal control group, the levels of AC, H, AL, PE, and TA were measured at 0.3±0.2, 0.2±0.1, 0.3±0.2, 0.5±0.1, and 0.2±0.2, respectively (Table 2).

Upon induction of FIP and subsequent saline treatment, a pronounced increase was observed in all biomarkers' levels. Specifically, the FIP-induced rats treated with saline displayed significantly elevated levels of AC (2.6±0.2, $p<0.001$), H (1.5±0.1, $p<0.01$), AL (2.1±0.2, $p<0.001$), PE (2.9±0.1, $p<0.001$), and TA (2.8±0.3, $p<0.001$), compared to the respective normal control values (Table 2).

However, the administration of 5 mg/kg FA to the FIP-induced rats led to significant mitigation of these elevated biomarker levels. The levels of AC (1.2±0.3, ##$p<0.001$##), H (0.9±0.1, ##$p<0.001$##), AL (1.1±0.2, #$p<0.05$#), PE (1.7±0.3, #$p<0.05$#), and TA (1.5±0.2, #$p<0.05$#) were notably reduced in comparison to the FIP and saline group (Table 2).

Table 1. The results of the biochemical analysis in the three study groups: Normal control, FIP and saline group, and FIP and 5 mg/kg Folic Acid group

	Normal control	FIP and saline	FIP and 5 mg/kg Folic Acid
Plasma MDA (nM/mg protein) level	14.3±1.02	48.3±1.6**	33.5±0.8#
Plasma soluble ST2 level	0.85±0.1	2.59±0.2*	1.24±0.1#
Plasma TNF alfa (pg/ml) level	15.2±1.8	374.3± 8.2**	228.1±5.5##

Results were presented as mean±SEM. Statistical analyses were performed by one- way ANOVA. *$p<0.05$, **$p<0.001$ different from normal groups; #$p<0.01$, ##$p<0.001$ different from FIP and saline group

Table 2. The results of the histopathological examination of the lung in the three study groups: Normal control, FIP and saline group, and FIP and 5 mg/kg Folic Acid group

	Normal control	FIP and saline	FIP and 5 mg/kg Folic Acid
AC	0.3±0.2	2.6±0.2**	1.2±0.3##
H	0.2±0.1	1.5±0.1*	0.9±0.1##
AL	0.3±0.2	2.1±0.2**	1.1±0.2#
PE	0.5±0.1	2.9±0.1**	1.7±0.3#
TA	0.2±0.2	2.8±0.3**	1.5±0.2#

Results were presented as mean±SEM. Statistical analyses were performed by one- way ANOVA. *$p<0.01$, **$p<0.001$ different from normal groups; #$p<0.05$, ##$p<0.001$ different from FIP and saline group

The respiratory gas exchange parameters, including arterial oxygen tension (PaO2) and arterial carbon dioxide tension (PaCO2), exhibited significant variations across the experimental groups. In the normal control group, the PaO2 level was recorded at 99.5±4.4 mmHg, reflecting normal oxygenation levels (Table 3).

In contrast, the FIP-induced rats treated with saline displayed a markedly reduced PaO2 level of 54.6±3.8 mmHg ($p<0.001$), indicating severe impairment in oxygen exchange. Remarkably, the administration of 5 mg/kg FA to FIP-induced rats resulted in a significant improvement in PaO2 levels, measuring 85.1±5.7 mmHg ($p<0.05$), compared to the FIP and saline group (Table 3).

Analysis of arterial carbon dioxide tension (PaCO2) revealed noteworthy differences among the experimental groups. The normal control group exhibited a PaCO2 level of 40.6±2.9 mmHg, which falls within the normal range. In the FIP-induced group treated with saline, the PaCO2 level was reduced to 31.6±1.9 mmHg ($p<0.05$). Similarly, the FIP-induced rats administered with 5 mg/kg FA displayed a PaCO2 level of 30.5±1.3 mmHg, comparable to the FIP and saline group (Table 3).

Table 3. The results of the blood gas analysis in the three study groups: Normal control, FIP and saline group, and FIP and 5 mg/kg Folic Acid group

	Normal control	FIP and saline	FIP and 5 mg/kg Folic Acid
PaO2 (mmHg)	99.5±4.4	54.6±3.8**	85.1±5.7#
PaCO2 (mmHg)	40.6±2.9	31.6±1.9*	30.5±1.3

Results were presented as mean±SEM. Statistical analyses were performed by one- way ANOVA and post- hoc Bonferroni test. *$p<0.05$, **$p<0.001$ different from normal groups; #$p<0.05$ different from FIP and saline group

The histopathological analysis of lung tissues was performed using hematoxylin and eosin (H&E) staining to assess the structural changes and inflammatory responses. Representative micrographs captured at 40x magnification are presented below (Figure 1).

A. Normal Control Group Lung: Figure 1A shows lung tissue from the normal control group. Alveolar structures appear intact and well-maintained.

B. FIP Group with Severe Histopathologic Alterations: Figure 1B displays lung tissue from the FIP group, demonstrating severe histopathological alterations characterized by increased alveolar inflammation (*) and thickened septal structures (arrow).

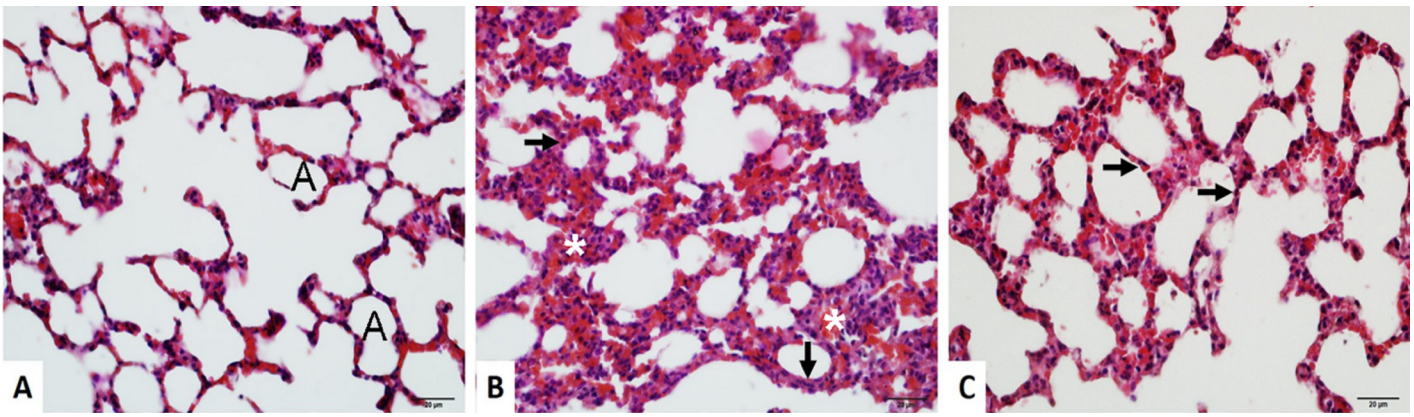

Figure 1. Lung histolopathology x40 magnification H&E staining. A: Normal control group lung, (A) Alvelol, B: FIP groups showed severe histopathologic alteration related to increased alveolar inflammation (*) and septal septal thickness (arrow), C: FIP and 1 ml/kg tap water (plasebo) groups showed severe histopathologic alteration related to increased alveolar inflammation (*) and septal septal thickness (arrow), D: FIP and 5 mg/kg Folic Acid groups showed decreased inflammation and septal septal thickening (arrow). Scale bar=20µm

C. FIP and Placebo Group with Severe Histopathologic Alterations: Figure 1C depicts lung tissue from the FIP group treated with 1 ml/kg tap water (placebo). Like the FIP group, this group exhibits marked alveolar inflammation (*) and septal thickening (arrow).

D. FIP and 5 mg/kg FA Group with Reduced Inflammation: Figure 1D illustrates lung tissue from the FIP group treated with 5 mg/kg FA. Notably, this group reduces inflammation and septal thickening (arrow), suggesting a potential protective effect of FA treatment.

The scale bar in all micrographs corresponds to 20 µm, indicating the relative size of the captured tissue area.

DISCUSSION

Sepsis-induced lung injury remains a critical clinical challenge, often leading to ARDS and compromised respiratory function (13,14). In this study, we aimed to investigate the potential therapeutic effects of FA in mitigating the pathological alterations associated with sepsis-induced lung injury and to explore the potential interplay between FA and the sST2 (sST2) protein, a known inflammation biomarker.

Our results provide compelling evidence for the beneficial effects of FA in the context of sepsis-induced lung injury. FA is a cofactor in one-carbon metabolism that promotes the restoration of methionine from homocysteine-mediated preservation of neuronal integrity and has been shown to have antioxidant activity (15). New data have been added to

the literature to strengthen the idea that FA is an essential micronutrient that plays a novel role in combating ROS. Therefore, it acts as a redox regulator through the proper regulation of GSH biosynthesis, GSH transport system, and mitochondrial GSH recycling through the reorganization of the precipitating proteins of ROS and proper regulation of redox homeostasis and prevention of mitochondrial GSH depletion (16). The profound increase in oxidative stress, as indicated by elevated MDA levels in the FIP and saline group, underscores the magnitude of the oxidative damage inflicted upon lung tissues. However, FA administration was associated with a significant reduction in MDA levels. FA's anti-inflammatory and antioxidant properties likely contribute to these effects, as it regulates GSH biosynthesis and reduces the production of pro-inflammatory mediators (17).

Similarly, Shalby et al. show FA's antioxidant effect in acute lung injury in rats (18). This finding aligns with FA's known antioxidant properties, which could counteract the generation of reactive oxygen species and prevent oxidative stress-induced cellular damage. Similarly to MDA in TNF-α, FA reduces TNF-α levels in the FIP group.

A study conducted by Hoogerwerf et al. 2010 observed that sST2 concentration could predict the severity of sepsis (19). Moreover, Hur et al. 2015 similarly describe that sST2 has a prognostic role in sepsis. In this study, we observed a noteworthy decrease in sST2 levels upon FA treatment. sST2, a decoy receptor for interleukin-33 (IL-33) (20), is associated with inflammation and immune responses. The substantial elevation of sST2 levels in the FIP and saline group likely reflects the exaggerated inflammatory response of sepsis-induced lung injury. FA's ability to attenuate sST2 levels might suggest a regulatory effect on the immune response, potentially via modulation of IL-33 signaling. Although the precise mechanisms underlying this interaction warrant further investigation, our findings suggest that FA might exert its anti-inflammatory effects through modulation of the IL-33/ST2 pathway.

As known, methotrexate is the antagonist of FA and causes lung injury-like side effects (21). Contrary histopathological analysis shows the protective effects of FA. The reduced alveolar inflammation and septal thickening observed in the FIP and 5 mg/kg FA group suggest potential mitigation of lung injury by FA administration.

The intricate relationship between FA and the IL-33/ST2 pathway warrants special attention. IL-33, a cytokine involved in immune responses and tissue repair, binds to its receptor ST2L on immune cells to initiate signaling. The soluble form of ST2 acts as a decoy receptor, competing with ST2L for IL-33 binding. Upon FA treatment, the observed reduction in sST2 levels might reflect potential crosstalk between FA and the IL-33/ST2 axis. Given FA's ability to attenuate the inflammatory response, it is plausible that FA may modulate IL-33 signaling by altering sST2 levels (22).

Limitations

The study utilized a rat model of sepsis-induced lung injury, which may need to fully capture human sepsis's complexity. The study employed a specific dosage of Folic Acid (5mg/kg) for treatment. The optimal dosage and timing of Folic Acid administration for sepsis-induced lung injury in humans might vary and need to be explored. While the study hinted at potential mechanisms underlying the observed effects, mechanistic insights into how Folic Acid interacts with the IL-33/ST2 pathway and modulates inflammatory responses remain speculative. The study focused on histopathological and biomarker changes in a controlled experimental setting. Clinical translation of these findings to actual patient outcomes requires rigorous clinical trials considering factors such as patient heterogeneity, comorbidities, and variations in treatment responses. The study evaluated the effects of Folic Acid alone. The study duration might have yet to capture the long-term effects of Folic Acid treatment or the potential for disease progression beyond the observed timeframe. Longer-term studies provide a more comprehensive understanding of Folic Acid's sustained effects.

CONCLUSION

This study provides valuable insights into the potential therapeutic benefits of FA in sepsis-induced lung injury. FA demonstrated its capacity to alleviate oxidative stress, inflammation, and histopathological alterations, collectively indicating its protective effects on lung tissues. Additionally, the modulation of sST2 levels and its potential interaction with the IL-33/ST2 pathway suggest a complex network of immune regulation that merits further investigation.

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