Effects of melatonin in an experimental model of ventilator-induced lung injury

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Pedreira PR, García-Prieto E, Parra D, Astudillo A, Díaz E, Taboada F, Albaiceta GM. Effects of melatonin in an experimental model of ventilator-induced lung injury. Am J Physiol Lung Cell Mol Physiol 295: L820–L827, 2008. First published September 19, 2008; doi:10.1152/ajplung.90211.2008.—Melatonin is a free radical scavenger and a broad-spectrum antioxidant and has well-documented immunomodulatory effects. We studied the effects of this hormone on lung damage, oxidative stress, and inflammation in a model of ventilator-induced lung injury (VILI), using 8- to 12-wk-old Swiss mice (n = 48). Animals were randomized into three experimental groups: control (not ventilated); low-pressure ventilation (peak inspiratory pressure 15 cmH2O, positive end-expiratory pressure (PEEP) 2 cmH2O), and high-pressure ventilation (peak inspiratory pressure 25 cmH2O, PEEP 0 cmH2O). Each group was divided into two subgroups: eight animals were treated with melatonin (10 mg/kg ip, 30 min before the onset of ventilation) and the remaining eight with vehicle. After 2 h of ventilation, lung injury was evaluated by gas exchange, wet-to-dry weight ratio, and histological analysis. Levels of malondialdehyde, glutathione peroxidase, interleukins IL-1β, IL-6, TNF-α, and IL-10, and matrix metalloproteinases 2 and 9 in lung tissue were measured as indicators of oxidation status, pro-/anti-inflammatory cytokines, and matrix turnover, respectively. Ventilation with high pressures induced severe lung damage and release of TNF-α, IL-6, and matrix metalloproteinase-9. Treatment with melatonin improved oxygenation and decreased histological lung injury but significantly increased oxidative stress quantified by malondialdehyde levels. There were no differences in TNF-α, IL-1β, IL-6, or matrix metalloproteinases caused by melatonin treatment, but IL-10 levels were significantly higher in treated animals. These results suggest that melatonin decreases VILI by increasing the anti-inflammatory response despite an unexpected increase in oxidative stress.

mechanical ventilation; oxidative stress

MECHANICAL VENTILATION is often a necessary treatment for respiratory failure and a supportive measure in critically ill patients. However, it is well-known that ventilation with high volume or pressure may be harmful, causing damage on previously healthy lungs or worsening it in already injured ones (46). Among ventilated patients, those with acute lung injury (ALI, a syndrome characterized by acute respiratory failure, hypoxemia with an arterial Po2 (PaO2)/fraction of inspired oxygen (FiO2) ratio below 300, and bilateral lung infiltrates and edema) or acute respiratory distress syndrome (ARDS, a form of ALI with more severe hypoxemia defined by a PaO2/FiO2 ratio below 200) are at special risk for ventilator-induced lung injury (VILI). The mechanisms responsible for this VILI are complex (31). Among others, there is a state of acute inflammation, initially local, which may evolve into a systemic inflammatory response syndrome (49). Lung inflammatory response is characterized by neutrophil recruitment and the release of a great variety of inflammatory mediators (5). It is not clear whether such damage results from proinflammatory cytokines overproduction, a decrease in the production of anti-inflammatory cytokines, or both. Many experimental and clinical studies on models of ALI/ARDS have demonstrated increases in proinflammatory cytokines such as IL-1β or TNF-α correlating positively with pulmonary neutrophilia. At the same time, greater increases occurred in receptors and/or antagonists (soluble TNF-α receptors, IL-1β receptor antagonist, soluble IL-1 receptor II, and soluble IL-6 receptor) and anti-inflammatory cytokines like IL-10, providing a key mechanism for limiting the net inflammatory response in the lungs (3, 39, 51). Neutrophils (key cells in this pathology), apart from releasing many other factors, release free radicals, which contribute to maintain inflammation and induce an oxidative stress state that exceeds the antioxidant defense mechanisms (9). This oxidative stress can also activate the extracellular matrix remodeling processes (26), which play a relevant role in VILI (17).

Ventilation with low tidal volume lung protective strategies has been shown to diminish the damage induced by mechanical ventilation in experimental models of ALI/ARDS and decreased mortality in patients with ALI/ARDS compared with the use of higher tidal volumes (1). However, there are patients at risk of VILI despite low-volume ventilation (48). Up to now, there has been no pharmacological treatment that could act synergistically with protective ventilation strategies in minimizing/preventing VILI.

Melatonin is a hormone that is the main secretory product of the pineal gland, from where it is released to the blood. Its concentration exhibits a circadian rhythm since its secretion occurs during darkness (41). It is also produced in other organs, including the alveolar epithelium, gastrointestinal tract, skin, or bone marrow (28). Circadian fluctuations of melatonin are triggered by changes of the photoenvironment and appear to be additionally controlled by nutritional factors and stress (24). More research is needed to decipher under which circumstances extrapineal melatonin is released. Melatonin is a sleep promoter and a chemical signal of light and darkness. Moreover, this hormone is a free radical scavenger and broad-

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spectrum antioxidant and has well-documented immunomodulatory effects (8) in part by modifying gene expression in inflammatory cells (22). There are some studies reporting the protective effects of this hormone in sepsis in both humans and animals, decreasing the levels of inflammatory cytokines and oxidative stress (20, 21). As oxidative stress and inflammation play a key role in the pathogenesis of VILI (38), we hypothesized that melatonin could be useful as a pharmacological treatment to attenuate VILI. In this experimental study, we analyze the magnitude of lung damage, oxidative stress, and inflammation in a model of VILI and the effects of melatonin treatment, comparing the results with protective strategies of mechanical ventilation and spontaneously breathing animals.

METHODS

Animals. All experiments were performed with 8- to 12-wk-old male Swiss mice (mean weight 35 ± 0.4 g). All mice were kept under specific pathogen-free conditions with free access to food and water and exposed to 12-h light-dark cycles. The experiments were approved by the Committee on Animal Experimentation of the Universidad de Oviedo, Oviedo, Spain.

Melatonin preparation. Pharmaceutical grade melatonin was purchased from Sigma (St. Louis, MO) and dissolved in absolute ethanol (0.02 ml). Before injection, melatonin was diluted further with sterile saline to a final concentration of 1 mg/ml. The dose of melatonin chosen (10 mg/kg) was selected based on prior studies demonstrating a protective effect in a model of septic shock (7).

Experimental protocol. Mice were anesthetized with ketamine (100 mg/kg) and xylazine (10 mg/kg) administered intraperitoneally. Level of anesthesia was assessed throughout experiments, and additional anesthetic was given as needed. Mice (n = 48) were randomly divided into 3 ventilation groups, each with 16 mice: control (awake animals breathing spontaneously in an environment with 0.5 FIO2), low-pressure ventilation [peak inspiratory pressure (PIP) 15 cmH2O (PIP15), positive end-expiratory pressure (PEEP) 2 cmH2O, rate 100 breaths/min], and high-pressure ventilation (PIP 25 cmH2O, PEEP 0, rate 50 breaths/min). Preliminary experiments demonstrated that these settings resulted in tidal volumes of ~10 ml/kg and 20 ml/kg in the low- and high-pressure ventilation groups, respectively. Respiratory rates for each group were selected to achieve normocapnia [35–45 mmHg arterial PCO2 (PaCO2)] based on preliminary experiments.

In ventilated animals, a tracheotomy was performed under anesthesia, and the trachea was cannulated with a 20-gauge angiocatheter, which was secured in place with suture to prevent air leak. The left lung was fixed with intratracheal formaldehyde at a pressure of 20 cmH2O and immersed in the same fixative for 24 h. After fixation, it was included in paraffin and processed for standard hematoxylin-eosin staining. One pathologist (A. Astudillo), blinded to the experimental conditions, evaluated three slices of the left lung. A quantitative scale scoring congestion and edema, hemorrhage, inflammatory cells, and septal thickening (scored from 0 to 4 each) was used (5).

Malondialdehyde measurement. Measurement of malondialdehyde (MDA) has been used as an indicator of lipid peroxidation, as polyunsaturated fatty acid peroxides generate MDA on decomposition. Frozen tissue samples were homogenized in 200 μl of phosphate buffer containing 4 μl of butylated hydroxytoluene. The crude homogenate was centrifuged at 3,000 rpm for 10 min at 4°C. Protein concentration in the supernatant was measured using a bicinchoninic acid (BCA) assay (Pierce). MDA was measured in the supernatant using a commercial kit (LPO-586; Oxis Research) and normalized to the protein concentration.

Glutathione peroxidase. Glutathione peroxidase (GPx) is an antioxidant enzyme that catalyzes the oxidation of glutathione, therefore decreasing oxidative stress within the cell. Melatonin can induce the expression of this enzyme (14). The activity of this enzyme was measured using the GPx-340 assay (Oxis Research) according to manufacturer’s instructions.

Cytokines. Tissue cytokine measurement was obtained as a measure of pro- and anti-inflammatory activity in the lungs. Lung tissue was homogenized in a lysis buffer containing 20 mM Tris, 300 mM sucrose, 1% Triton X-100, and a protease inhibitor cocktail without EDTA (Complete; Roche) and centrifuged, and supernatants were collected. The protein content of the lysate was quantified. Levels of IL-1β, IL-6, TNF-α, and IL-10 were measured in lung homogenates using standard ELISA kits purchased from Bender MedSystems and eBioscience. Results are expressed as picograms per milligram protein.

Gelatin zymography. Matrix metalloproteinases 2 (MMP-2) and 9 (MMP-9) were measured as markers of extracellular matrix remodeling using standard gelatin zymography. The volume of lung homogenate corresponding to 95 μg of protein was loaded in an 8% SDS-polyacrylamide gel containing 0.2% gelatin. An electrophoresis was performed, and the gel was washed three times in 2.5% Triton X-100 and incubated overnight at 37°C in a buffer containing 20 mM Tris-HCl, 5 mM CaCl2, pH 7.4. Afterward, it was stained using Coomassie blue and destained with a mixture of acetic acid and methanol. Gels were scanned, and the intensity of the bands was quantified (in arbitrary density units) using ImageJ software (National Institutes of Health). All gels contained one sample of each experimental group to overcome differences between gels.

Statistical analysis. All data are expressed as means ± SE. Variables were compared using a two-way ANOVA, with melatonin treatment and ventilatory strategy as factors. Post hoc tests were done when appropriate using the Bonferroni correction. PaCO2 and pH values were compared using t-tests for the difference between melatonin and vehicle-treated mice with the same ventilatory strategy. A P value lower than 0.05 was considered significant.

RESULTS

Forty-eight animals were included in the study: 16 assigned to each ventilatory strategy or control. All animals survived the experiment.

Gas exchange. Hypoxia and a reduced PaO2-to-FIO2 ratio is a defining feature of ALI/ARDS. We assessed lung function by analysis of arterial blood gases at the end of the experiment (Table 1). High-pressure ventilation (PIP25) induced a significant hypoxia compared with vehicle-treated controls (with a 66% decrease in PaO2-to-FIO2 ratio; P = 0.016) and low-pressure ventilated animals (with a 64% decrease in PaO2-to-FIO2 ratio; P = 0.049). Melatonin treatment prevented hypoxia in the high-pressure ventilated group (P = 0.04), maintaining
oxygen at baseline levels. Melatonin had no significant effect on oxygenation in control and low-pressure ventilated animals. Although ventilatory settings were set to maintain normocapnia (35–45 mmHg PaCO2) in all ventilation groups, pH analysis revealed a trend toward decreasing pH with high-pressure ventilation. Melatonin treatment was associated with a lower PaCO2 and higher pH in the high pressure group compared with vehicle treatment (P < 0.05; Table 1).

Lung injury. Structural lung injury was assessed by measuring lung edema and histological injury score. High-pressure ventilation induced a significant increase in lung edema with a 69% increase in wet-to dry weight ratio (Table 1; P < 0.01 for the difference between ventilatory strategies in the ANOVA), with significant differences compared with low-pressure ventilation and controls (P < 0.001 in the post hoc tests). There was no significant difference in lung edema in low-pressure-treated animals vs. controls. There were no significant differences in lung edema with melatonin treatment, although there was a trend toward decreased edema with melatonin treatment in the PIP25 group (P = 0.14).

The degree of tissue injury was quantified in histological preparations. There was a sixfold increase in the injury score after high-pressure ventilation in vehicle-treated mice (Fig. 1A). These animals developed alveolar wall thickening, inflammatory infiltrates, and important interstitial hemorrhage compared with control and low-pressure vented animals. Treatment with melatonin significantly attenuated lung injury in PIP25 animals. Further analysis revealed that melatonin treatment significantly decreased hemorrhage (Fig. 1C) and inflammatory infiltrate (Fig. 1D) with a trend toward decreased wall thickening compared with vehicle-treated PIP25 while having minimal effect on congestion. Melatonin treatment had no significant effect on lung injury score in control and low-pressure ventilated animals. Figure 2 shows representative histological preparations from each experimental group.

Oxidative stress. Oxidative stress was quantified through the levels of MDA and GPx in lung tissue homogenates as an indicator of lipid peroxidation and the activity of antioxidant enzymes, respectively. These results are presented in Fig. 3. Injurious ventilation increased MDA levels in lung tissue (Fig. 3A; P < 0.001 for the effect of mechanical ventilation in ANOVA; P = 0.08 in the post hoc test for PIP25 vs. control group). The combination of melatonin plus ventilation with a PIP of 25 cmH2O doubled tissue MDA levels over the control group (P < 0.001 in post hoc test). We did not find significant

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†P < 0.05 compared with control group with the same treatment (vehicle/melatonin). ‡P < 0.05 compared with peak inspiratory pressure 15 cmH2O (PIP15) group with the same treatment (vehicle/melatonin). *P < 0.05 compared with vehicle-treated mice within the same ventilatory group. #P < 0.05 in the t-test compared with the high-pressure ventilation vehicle-treated group. PaO2, arterial PO2; FIO2, fraction of inspired oxygen; PaCO2, arterial PCO2.

Fig. 1. Histological scores of lung injury in vehicle- and melatonin-treated animals (white and black bars, respectively). A: composite score. B–E: scores in each category evaluated (congestion, alveolar and interstitial hemorrhage, inflammatory infiltrate, and septal thickening). #P < 0.05 compared with control group with the same treatment (vehicle/melatonin). †P < 0.05 compared with peak inspiratory pressure of 15 cmH2O (PIP15) group with the same treatment (vehicle/melatonin). *P < 0.05 compared with peak inspiratory pressure of 15 cmH2O (PIP15) group with the same treatment.
changes in GPx activity with ventilation or melatonin treatment (Fig. 3B).

**Inflammatory response.** We quantified the levels of IL-1β, TNF-α, and IL-6 as representative of proinflammatory cytokines. Injurious ventilation significantly increased TNF-α and IL-6 compared with controls and low-pressure ventilated animals (Fig. 4, A–C; P < 0.05). We also observed a nonsignificant (P = 0.08) trend toward higher IL-1β levels in high-pressure ventilated mice. Melatonin treatment had no significant effect on TNF-α, IL-6, or IL-1β compared with vehicle treatment in any group.

IL-10 was measured as a representative anti-inflammatory cytokine. Melatonin doubled IL-10 levels in all groups (Fig. 4D; P = 0.001 for the effect of melatonin treatment in the ANOVA). In the post hoc tests, values of IL-10 were significantly higher in the animals treated with melatonin in both groups of mechanical ventilation but not in the control group (P = 0.07). The TNF-α-to-IL-10 and IL-6-to-IL-10 ratios were calculated to assess the proinflammatory to anti-inflammatory balance. The graphs in Fig. 4, E and F, show a clear proinflammatory shift caused by high-pressure ventilation that is dampened by melatonin treatment.

**Gelatinase activity.** Standard gelatin zymographies were done to evaluate the activity of matrix metalloproteinases 2 and 9. There were no significant changes in MMP-2 activity, irrespective of the ventilatory strategy and treatment with melatonin (Fig. 4G). Mechanical ventilation induced an increase in the levels of MMP-9 both in high and low PIP groups compared with controls (Fig. 4H). No differences were found in each group between animals treated with melatonin or just with vehicle.

**DISCUSSION**

Our results show that treatment with melatonin is protective against VILI. Ventilation with high PIP and 0 PEEP resulted in significant lung injury in mice with impaired oxygenation, increased lung edema, and severe histological damage characterized by acute inflammation and alveolar hemorrhage. Melatonin pretreatment improved oxygenation, preserving PaO₂-to-
Fig. 4. Inflammation and matrix remodeling in each experimental group. Proinflammatory (IL-1β, TNF-α, and IL-6) and anti-inflammatory (IL-10) cytokines and matrix metalloproteinases (MMP) 2 and 9 were measured in lung tissue homogenates (A–D and G and H, respectively). The TNF-α-to-IL-10 and IL-6-to-IL-10 ratios were calculated as indicators of the pro-/anti-inflammatory balance (E and F). White bars: vehicle-treated animals. Black bars: melatonin-treated animals. *P < 0.05 compared with control group with the same treatment (vehicle/melatonin). †P < 0.05 compared with PIP15 group with the same treatment (vehicle/melatonin). ‡P < 0.05 compared with vehicle-treated mice within the same ventilatory group.

FIO₂, ratio above 300, and ameliorated histological lung injury. This protective effect was associated with an increase in the anti-inflammatory hormone, IL-10. Unexpectedly, melatonin increased tissue oxidation, as measured by MDA.

**Melatonin signaling and biological effects.** Melatonin has important antioxidant properties due to direct and indirect effects. It directly scavenges reactive oxygen species, prevents lipid peroxidation, reduces mitochondrial hydroperoxide levels, and restores glutathione homeostasis. Moreover, it has indirect antioxidant effects, since it stimulates the activities of the two enzymes involved in the GSH cycling, namely glutathione reductase and GPs (13).

Other effects of melatonin are mediated by its interaction with two specific membrane receptors (MT1 and MT2) and intracellular proteins (50). Both receptors are coupled to G proteins, and their activation results in changes in intracellular cyclic nucleotides (cAMP and cGMP), modifying various downstream signaling pathways. Melatonin has been shown to
inhibit JNK, c-Jun, and NF-κB cascades (23, 30), all major regulators of the immune response and apoptosis, which are key processes during VILI.

It has been proposed that the immune effects of melatonin are mediated by the MT2 receptor (13). Interestingly, expression of this receptor appears to be restricted to the brain and the lungs, in opposite to a wide distribution of MT1 receptors (35). These findings and our results suggest a major role of melatonin in the regulation of the lung immune response.

**Oxidative stress.** During mechanical ventilation, there are many potentially oxidant-producing sources, including leukocytes, parenchymal cells, prooxidant enzymes, and the high oxygen concentration in the gases inhaled during mechanical ventilation. Neutrophils release free radicals, which contribute to maintaining the inflammation and inducing a prooxidant state that exceeds antioxidative defense mechanisms (40). The role of oxidative stress in the pathogenesis of ALI is widely documented (9, 16, 42) and is implied in the mechanisms of lung injury induced by mechanical ventilation (38). In our study, ventilation with high pressure caused a small increase in oxidative stress, quantified through the MDA levels. It may be possible that the short ventilation period is not enough to develop a more significant level of oxidative stress. There were no changes in GPx activity among the six groups, perhaps for the same reason.

Surprisingly, melatonin treatment increased MDA levels after high-pressure ventilation even more than the animals of the same group treated with vehicle. Although melatonin has widely documented antioxidative effects, as with many hormones, it can also exert prooxidant effects in unfavorable chemical environments (high FIO2) and concentrations. Medina-Navarro et al. (32) highlighted the prooxidant properties of melatonin in vitro after interaction with oxygen, an effect that may be especially important in VILI where patients are invariably ventilated with high levels of oxygen. In addition, some studies have shown a prooxidant effect in different cell types, including red blood cells, hepatocytes, and cancer cells (4, 37, 52). Thus melatonin may exert both pro- and antioxidative effects depending on the redox state within the tissue. In our study, we have used pharmacological doses (10 mg/kg body wt) based on prior studies demonstrating protection in a model of lethal septic shock (7). The importance of melatonin dosage is a controversial issue, especially as these doses are higher than known physiological levels of melatonin. As with other pharmacological treatments, such as corticosteroids and ascorbate, melatonin may exhibit both prooxidant and antioxidative effects in a dose-dependent manner. Further studies will be required to identify a dose that maximizes the anti-inflammatory and antioxidative properties of melatonin while minimizing its proinflammatory properties. Additionally, hypotension and shock can significantly influence oxidation. We did not monitor hemodynamics in our experiments so we cannot directly comment on the presence of hypotension in our mice; however, none of the animals suffered from metabolic acidosis, allowing us to infer a situation of preserved tissue perfusion.

Oxidative stress may start the activation of extracellular matrix remodeling processes (43, 54), which play a relevant role in VILI (2, 17, 27). Melatonin decreases the activities of MMP-2 and MMP-9 in other disease models (47). However, in our study, no differences were observed in MMP-2 and MMP-9 levels among the animals treated with melatonin. It is possible that the mechanisms responsible for the activation of these enzymes depend more on the activation of proinflammatory cascades such as those mediated by the NF-κB (54). In addition, the 2-h duration of our studies may have been too short to find significant changes in matrix remodeling.

**Inflammatory response.** Damage induced by high-pressure ventilation originates on the mechanical stimulus to the alveoli, starting a series of biochemical signals inside the cell and finally inducing an inflammatory response (19). This inflammation is initially local, but it may later spread into a systemic inflammatory response syndrome (46). The anti-inflammatory properties of melatonin could attenuate this response to mechanical ventilation. Gitto et al. reported a beneficial effect of treatment with melatonin in newborns with sepsis (20) and bronchopulmonary dysplasia (21), showing in both cases an improvement of the clinical outcome with a decrease in the levels of proinflammatory cytokines. Similarly to our results, Carrillo-Vico et al. (7) found in a murine model of septic shock that melatonin increased the production of the anti-inflammatory cytokine IL-10, improving the survival of the animals. This cytokine has also a relevant prognostic value in patients with ARDS, in which lower levels are associated to a poor outcome (12).

Therefore, the beneficial effect of melatonin in our model is probably explained by its role as an immunomodulator. Our results demonstrated a marked decrease in inflammatory infiltrate in high-pressure ventilated animals treated with melatonin. Although melatonin did not significantly decrease the proinflammatory cytokines measured (IL-1β, IL-6, and TNF-α) at this short time point, it did significantly increase IL-10 levels, thus altering the pro-to-anti-inflammatory cytokine balance. IL-10 is known to inhibit the release of other proinflammatory cytokines (30), and longer duration studies would be needed to further explore the effects of melatonin on proinflammatory cytokine expression. In addition, IL-10 can have direct effects on immune cells. Couper et al. (10) showed that during infection this cytokine inhibits the activity of T helper type 1 (Th1) cells, natural killer (NK) cells, and macrophages, cell types known to be involved in the pathogenesis of VILI (17). Moreover, IL-10 is also known to regulate apoptosis and chemokine release (27), which are also important in lung injury.

**Clinical implications.** Critically ill patients present alterations in the normal melatonin secretion pattern due to different factors including lack of light-dark cycles, underlying illness, and medications (6). Studies performed in critically ill patients with sepsis (34) showed higher levels of this hormone than normal. Olofsson et al. (36) found lower levels of melatonin and the lack of circadian rhythm in sedated and artificially ventilated intensive care patients. The substitutive treatment with this hormone was found to be useful increasing sleep time and quality in critically ill patients due to its regulatory role in sleep disturbances (45).

Because of its anti-inflammatory effects, high-dose melatonin may be a viable therapy for treatment of acute inflammatory disorders including the systemic inflammatory response syndrome, sepsis, and ALI/ARDS. Melatonin inhibits the inflammatory response (53) and NO synthesis and prevents mitochondrial dysfunction (15) in sepsis models. In septic newborns (20), melatonin improved outcome by reducing ox-
idative stress and decreasing the inflammatory response and clinical trials evaluating the effect of melatonin in adult septic patients have been proposed (13).

Regarding its effects in acute respiratory failure, melatonin has protective effects in radiation (44-) and carrageenan (11)-induced lung injury. In both of these studies, similar to our findings, the lung inflammatory infiltrate was reduced in melatonin-treated animals. In a clinical trial, Gitto et al. (21) studied the effects of melatonin in ventilated newborns with bronchopulmonary dysplasia with encouraging results: their study confirmed a decrease in the inflammatory response after melatonin treatment, with decreased proinflammatory cytokines (IL-6, IL-8, and TNF-α). This was related to an improved clinical outcome. Although these studies also found a decrease in oxidative stress markers with melatonin treatment, the rise in MDA levels seen in our study after injurious ventilation advises for caution and imposes the need to widen the studies to evaluate the dose-response effects before using it as treatment in the clinical practice. The experimental design precludes any direct translation to the clinical practice of this result, which is statistically significant but small in absolute values and below other published data (25).

Despite these limitations, our results show that a single dose of melatonin was able to prevent the severe hypoxemia, maintaining a PaO₂/FiO₂ ratio above 300, and acidemia in high-pressure ventilated mice and reduced histological lung injury by more than 50%. Our model looked specifically at the effects of mechanical ventilation in inducing lung injury. However, in the clinical setting, mechanical ventilation is only one of the many conditions that cause or contribute to ALI/ARDS. Indeed, mechanical ventilation often serves as a “second hit” to lung injured by sepsis, pneumonia, pancreatitis, and other acute inflammatory states. In these settings, melatonin may have an even greater role in protecting against lung injury. However, further studies will be needed to put the effects of melatonin in ALI/ARDS into its appropriate biological context. Although no animal model will fully recapitulate the clinical syndrome of VILI, our results suggest that melatonin warrants further exploration as a promising new therapeutic for ALI/ARDS.

Conclusions. In conclusion, melatonin reduces VILI, improving oxygenation and decreasing tissue injury. These results may be attributable to an anti-inflammatory effect due to an increase in IL-10 expression or due to other direct effects of melatonin. However, the increase in oxidative stress with melatonin in high-pressure ventilated animals raises concerns about the safety of this treatment and requires further study.

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MELATONIN IN VILI


