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Roxadustat Protects Against Hypoxia-Induced Organ Damage in Acute High-Altitude Models: A Pharmacodynamic Study

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ABSTRACT

This study aimed to evaluate the protective effects of roxadustat against hypoxia-induced injury during rapid ascent to high altitude. BALB/C mice were randomly assigned to receive roxadustat at doses of 7.8, 15.6, or 31.2 mg/kg, or to control groups. The anti-hypoxic efficacy of roxadustat at the recommended dose was assessed using a controlled atmospheric pressure hypoxia model. Additionally, Wistar rats were randomly allocated to groups exposed to normal oxygen, hypoxia, acetazolamide, or roxadustat to assess protection against hypoxic injury. Blood samples were collected for arterial blood gas analysis, inflammatory markers, and oxidative stress measurements, while tissue samples were subjected to histopathological examination. Roxadustat treatment significantly prolonged survival time in mice compared with the normal oxygen group, with the medium dose producing the greatest increase (19.05%). In rats, roxadustat improved blood oxygen saturation (SatO2) and arterial oxygen partial pressure (PaO2), and significantly elevated erythrocyte count, hemoglobin, and hematocrit levels. Plasma concentrations of IL-6, TNF-α, and IFN-γ were markedly reduced. Roxadustat also attenuated oxidative stress in hypoxic tissues. Histological analysis revealed that roxadustat substantially mitigated hypoxia-induced damage in the heart, brain, lungs, liver, and kidneys. Roxadustat effectively alleviates hypoxia-induced inflammation, oxidative stress, and organ damage, demonstrating its potential to enhance physiological adaptation to high-altitude exposure.

Keywords: Roxadustat, High altitude, Hypoxia, Pharmacodynamics, Erythrocyte

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Introduction

Hypoxia can inflict damage on erythrocytes, vascular endothelial cells, and vital organs such as the lungs, brain, and heart. Severe cases may lead to high-altitude cerebral edema (HACE) or high-altitude pulmonary edema (HAPE), both potentially fatal. These conditions are largely driven by the accumulation of reactive oxygen species (ROS), the release of inflammatory mediators, and erythrocyte injury [1].

Roxadustat, a hypoxia-inducible factor–proline hydroxylase inhibitor (HIF-PHI), has been approved in China for the treatment of renal anemia following the completion of Phase III clinical trials on December 18, 2018 [2]. Proline hydroxylase (PHD) is the key enzyme regulating the degradation of hypoxia-inducible factor (HIF), which in turn controls erythropoietin (EPO) expression. EPO is a primary driver of erythropoiesis [3]. Roxadustat stabilizes HIF, thereby promoting EPO expression by reducing HIF degradation by PHD [4, 5]. Enhanced erythropoiesis increases hemoglobin and erythrocyte levels, improving oxygen transport and alleviating hypoxemia [6].

Previous studies have investigated the pharmacodynamics of roxadustat using both atmospheric pressure hypoxia models and acute high-altitude exposure. Building upon these findings, the current study employed a randomized controlled experimental design in animal models to assess the anti-hypoxic effects of roxadustat.

Materials and Methods

Ethical statement

This study was approved by the Scientific Research Management Ethics Committee of the 940th Hospital of the Joint Logistic Support Force of the People's Liberation Army (Approval No. 2022KYLL155). All procedures adhered to the 3R principles (Replacement, Reduction, and Refinement) to ensure ethical treatment of animals, optimize experimental design, and maintain reliability and accuracy of data.

Chemicals and reagents

Roxadustat capsules (20 mg × 3; AstraZeneca), normal saline (Shijiazhuang Siyao Pharmaceutical Co., Ltd.), heparin (Shanghai First Biochemical Pharmaceutical Co., Ltd.), acetazolamide (purity >98%, Shanghai Yuanye Biotechnology Co., Ltd., CAS#59-66-5), ELISA kits for TNF-α and IL-6, MDA, SOD, and GSH assay kits (Nanjing Jiancheng Institute of Biological Engineering), and 4% paraformaldehyde (Wuhan Xaver Biotechnology Co., Ltd.) were used.

Animals and experimental design

Thirty-two male BALB/c mice (18–22 g) were randomly allocated into four groups (n=8 each): control, low-dose roxadustat (7.8 mg/kg), medium-dose (15.6 mg/kg), and high-dose (31.2 mg/kg). Additionally, 24 healthy male Wistar rats (18–22 g) were randomly assigned to four groups (n=6): normal oxygen, hypoxia, acetazolamide (22.5 mg/kg), and roxadustat (10.8 mg/kg).

Atmospheric pressure closed hypoxia experiment

Mice received intragastric administration of roxadustat or vehicle for one week. Doses were calculated based on body surface area conversion from human clinical dosing (7.8, 15.6, and 31.2 mg/kg). One hour after the fourth administration, mice were placed individually in 250 mL airtight jars containing sodium lime and filter paper, with the lid sealed using Vaseline to create a hypoxic environment. Survival time was recorded from the start of hypoxia until cessation of limb movement.

Acute high-altitude hypoxia experiment

Rats were pretreated with gavage for three days and transported from Lanzhou to a high-altitude field laboratory in Yushu Tibetan Autonomous Prefecture (altitude 4010 m; 33.1°N, 96.7°E; 10°C; 80% humidity). Animals were exposed to acute hypoxia for three days. On the fourth day, arterial and venous blood samples were collected under anesthesia, and myocardial, liver, brain, lung, and kidney tissues were harvested for biochemical and histological analyses.

Determination of hematological parameters

One hour post-administration, 0.5 mL of blood was collected from the orbital venous plexus into heparinized tubes. Samples were immediately analyzed using an automated hematology analyzer to assess routine blood parameters.

Assessment of inflammatory markers and erythropoietin

At the same time point, 0.5 mL of orbital blood was collected into heparinized tubes, centrifuged at 3500 rpm for 10 minutes at room temperature, and the supernatant was stored in liquid nitrogen. IL-6, IFN-γ, TNF-α, and EPO levels were later quantified using ELISA kits in strict accordance with manufacturer instructions.

Blood gas analysis

Following anesthesia, 0.5 mL of abdominal aortic blood was collected and immediately analyzed using a blood gas analyzer to determine oxygenation parameters.

Oxidative stress evaluation

After blood collection, myocardial, hepatic, cerebral, pulmonary, and renal tissues were excised on ice, washed in pre-cooled saline, blotted dry, and stored in liquid nitrogen. For analysis, tissues were weighed, homogenized in pre-cooled saline at a 1:9 ratio (w/v), centrifuged at 4000 rpm for 10 minutes at 4°C, and the supernatant was used to prepare a 10% tissue homogenate. Levels of SOD, MDA, and GSH were measured according to kit instructions.

Histopathological Examination (HE Staining)

Tissues from two rats per group were collected, washed with pre-cooled saline, and immediately fixed in 4% paraformaldehyde. Samples were then dehydrated, embedded, sectioned, and stained with hematoxylin and eosin for morphological assessment.

Statistical analysis

Data were analyzed using SPSS 21.0 software. One-way ANOVA followed by independent-sample t-tests was used to compare groups. Results are expressed as mean ± standard deviation (SD), and $P < 0.05$ was considered statistically significant.

Results and Discussion

Roxadustat enhances survival in mice under atmospheric hypoxia

Roxadustat treatment significantly prolonged survival time in mice exposed to atmospheric hypoxia **(Table 1).** The low-, medium-, and high-dose groups showed survival increases of 13.73% (32.72 ± 5.24 min vs. 28.77 ± 1.91 min, $P < 0.05$), 19.05% (34.25 ± 3.64 min vs. 28.77 ± 1.91 min, $P < 0.01$), and 14.15% (32.84 ± 3.40 min vs. 28.77 ± 1.91 min, $P < 0.05$), respectively. Among the tested doses, the medium dose produced the greatest protective effect against hypoxia.

Table 1. Effects of different doses of roxadustat on the survival time of mice. error bars indicate SD (n=8/per Group $\bar{x} \pm s$)

Group	Dose (mg/kg)	Survival Time (Min)	Increase Rate
Control group	–	28.77±1.91	
Low dose roxadustat group	7.8	32.72±5.24*	13.73%
Mediumdose roxadustat group	15.6	34.25±3.64**	19.05%
High dose roxadustat group	31.2	32.84±3.40*	14.15%

Notes: Compared with control group, *P<0.05; **P<0.01.

Effects of roxadustat on blood gas parameters in high-altitude hypoxic rats

Following exposure to high-altitude hypoxia, normal rats exhibit compensatory physiological adjustments, including increases in hemoglobin concentration and hematocrit, along with reductions in blood oxygen saturation (SaO_2) and arterial oxygen partial pressure (PaO_2). As presented in **Table 2**, compared with the normoxic control group, the hypoxic group showed significant decreases in SaO_2 and PaO_2 ($P < 0.01$), and significant elevations in hematocrit (Hct), blood pH, and hemoglobin (HGB) levels ($P < 0.01$).

Rats treated with roxadustat exhibited notable improvements in oxygenation: SaO_2 increased by 3.21% (94.00 ± 0.72 vs. 91.08 ± 0.46, $P < 0.01$) and PaO_2 increased by 11.56% (65.93 ± 2.84 vs. 59.10 ± 1.64, $P < 0.01$) relative to the hypoxic group. Meanwhile, Hct, pH, and HGB values were reduced by 12.46% (36.33 ± 0.52 vs. 41.50 ± 0.55, $P < 0.01$), 0.27% (7.42 ± 0.03 vs. 7.44 ± 0.01, $P < 0.01$), and 11.85% (121.50 ± 0.84 vs. 137.83 ± 2.14, $P < 0.01$), respectively.

These findings indicate that roxadustat can mitigate excessive compensatory changes in blood parameters and facilitate physiological adaptation to hypoxic conditions at high altitude.

Table 2. comparison of blood gas indexes in each group. error bars indicate SD (n=6/per Group $\bar{x} \pm s$)

Group	SaO_2 (%)	PaO_2	Hct (%)	pH (mmHg)	HGB (g/L)
Normal oxygen group	96.7±0.58	90.22±3.47	35.17±1.33	7.39±0.02	118.50±2.74
Hypoxic group	91.08±0.46##	59.10±1.64##	41.50±0.55##	7.44±0.01##	137.83±2.14##
Acetazolamide group	91.47±1.00	64.00±2.08**	36.50±0.84**	7.38±0.01**	123.33±2.50**
Roxadustat group	94.00±0.72**	65.93±2.84**	36.33±0.52**	7.42±0.03**	121.50±0.84**

Notes: Compared with normal oxygen group, ##P<0.01; Compared with hypoxic group, **P<0.01.

Abbreviations: SaO_2, oxygen saturation; PaO_2, oxygen partial pressure; Hct, hematocrit; HGB, hemoglobin.

Effects of roxadustat on hematological parameters in high-altitude hypoxic rats

High-altitude hypoxia can significantly impact physiological parameters, and routine blood analysis serves as a key measure to evaluate such changes. As shown in **Table 3**, compared with the normoxic control group, the hypoxic group exhibited significant reductions in red blood cell count (RBC) and hemoglobin (HGB) levels ($P < 0.01$), while mean corpuscular volume (MCV) was significantly elevated ($P < 0.01$).

Treatment with roxadustat significantly improved these hematological indices: RBC increased by 7.99% (8.65 ± 0.19 vs. 8.01 ± 0.14, P < 0.01), HGB by 7.62% (10.87 ± 0.15 vs. 10.10 ± 0.24, P < 0.01), and hematocrit (HCT) by 5.09% (50.13 ± 0.78 vs. 47.70 ± 0.81, P < 0.01) compared to the hypoxic group.

Abnormalities in RBC, HGB, and HCT are key indicators for the development of chronic mountain sickness under prolonged hypoxic conditions. These results suggest that roxadustat can effectively restore hematological parameters in rats exposed to acute high-altitude hypoxia. Although HGB was measured in both arterial blood (blood gas analysis) and venous blood (routine hematology), the overall trends were consistent, supporting the drug's positive effect on oxygen-carrying capacity.

Table 3. Comparison of blood routine indexes in each group. error bars indicate SD (n=6/per Group $\bar{x} \pm s$)

Group	RBC (10^6/uL)	HGB (mmol/L)	HCT (%)	MCV (fl)
Normal oxygen group	8.97±0.24	16.15±0.68	47.75±2.01	51.38±1.19
Hypoxic group	8.01±0.14##	10.10±0.24##	47.70±0.81	59.16±0.99##
Acetazolamide group	8.17±0.26	10.25±0.21	49.17±0.85	60.28±1.52
Roxadustat group	8.65±0.19**	10.87±0.15**	50.13±0.78**	60.60±1.51

Notes: Compared with normal oxygen blank group, ##P<0.01; Compared with hypoxic blank group, **P<0.01.
Abbreviations: RBC, red blood cell (counts); HGB, hemoglobin; HCT, hematocrit; MCV, mean erythrocyte volume.

Effects of roxadustat on plasma inflammatory markers and erythropoietin in high-altitude hypoxic rats

Hypoxia is a major trigger of inflammation, which can lead to tissue injury when excessive. After three days of high-altitude exposure, plasma analysis revealed that the levels of IFN-γ, IL-6, and TNF-α in the hypoxic model group were significantly elevated compared with the normoxic control group. Treatment with roxadustat markedly reduced these inflammatory markers: IFN-γ decreased by 26.66% (1038.97 ± 38.44 vs. 1416.62 ± 101.79, P < 0.01), IL-6 by 51.44% (50.28 ± 4.13 vs. 103.54 ± 10.63, P < 0.01), and TNF-α by 42.06% (135.18 ± 11.81 vs. 233.30 ± 6.67, P < 0.01) **(Figures 1a–1c).**

Erythropoietin (EPO), produced by renal tubular interstitial cells, plays a critical role in stimulating erythrocyte production under hypoxic conditions. Compared with the normoxic group, EPO levels were significantly reduced in hypoxic rats (P < 0.01). Roxadustat administration significantly increased EPO levels by 64.40% (207.54 ± 27.09 vs. 126.24 ± 13.79, P < 0.01) relative to the hypoxic group **(Figure 1d).**

These findings indicate that roxadustat effectively mitigates hypoxia-induced inflammation while enhancing EPO production, thereby promoting erythropoiesis and improving oxygen-carrying capacity under high-altitude hypoxia.

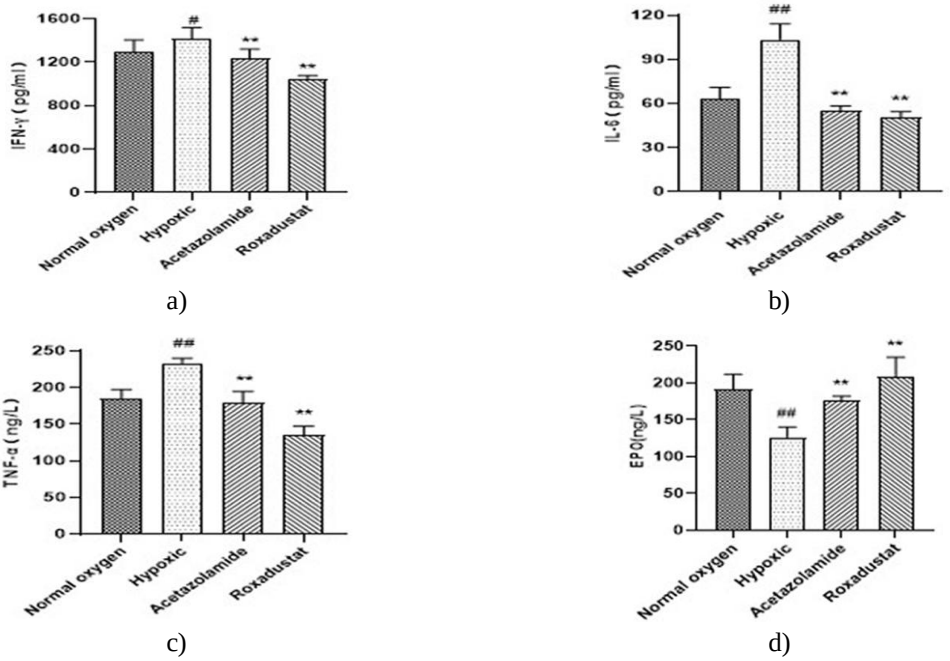


Figure 1. Effects of roxadustat on inflammatory factor and EPO in rats plasma. The content of IFN-γ (a), IL-6 (b), TNF-α (c) and EPO (d). Error bars indicate SD (n=6/per group).

Notes: #P<0.05, ##P<0.01 versus normal oxygen group; **P<0.01 versus hypoxic group.

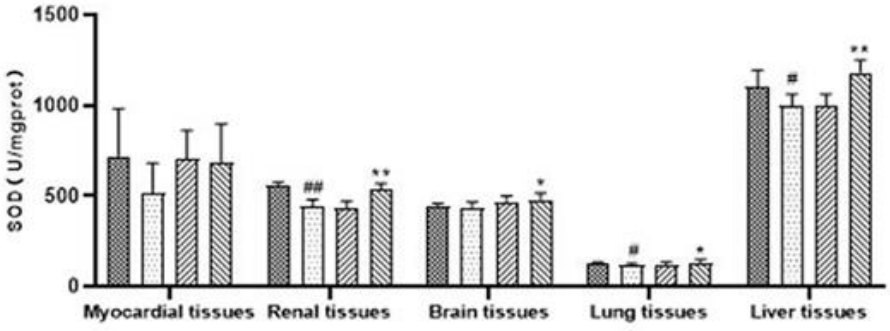
Abbreviations: IFN-γ, interferon-γ; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; EPO, erythropoietin.

Effects of roxadustat on oxidative stress in high-altitude hypoxic rats

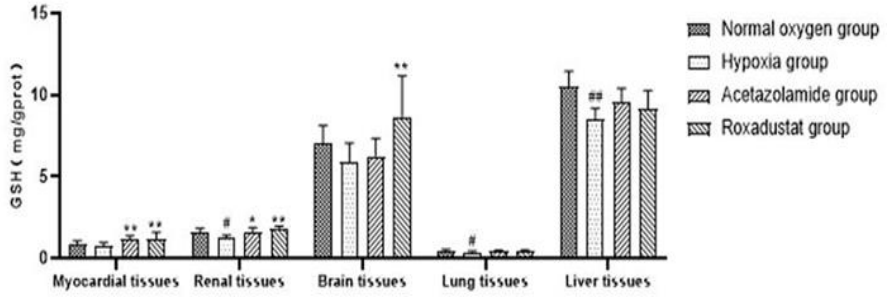
To evaluate the protective effects of roxadustat on tissue oxidative damage under hypoxia, we assessed superoxide dismutase (SOD) activity, glutathione (GSH) content, and malondialdehyde (MDA) levels in multiple rat tissues. After three days of high-altitude hypoxia, SOD activity in myocardial, renal, lung, and liver tissues was significantly reduced in the hypoxic group compared with the normoxic controls **(Figure 2a).** Concurrently, MDA levels in myocardial, renal, brain, and lung tissues were significantly elevated **(Figure 2b)**, while GSH content in myocardial, renal, brain, lung, and liver tissues was markedly decreased **(Figure 2c).**

Roxadustat treatment significantly mitigated these changes. SOD activity in brain, lung, liver, and renal tissues increased by 9.64% (480.16 ± 37.19 vs. 437.96 ± 29.84, $P < 0.05$), 21.61% (134.15 ± 17.06 vs. 110.31 ± 9.12, $P < 0.05$), 18.68% (1182.57 ± 69.81 vs. 996.40 ± 66.30, $P < 0.01$), and 34.98% (535.28 ± 34.27 vs. 396.55 ± 60.13, $P < 0.01$), respectively **(Figure 2a)**. GSH levels in myocardial, brain, and renal tissues were significantly elevated by 53.85% (1.20 ± 0.41 vs. 0.78 ± 0.20, $P < 0.01$), 47.03% (8.66 ± 2.25 vs. 5.89 ± 1.05, $P < 0.01$), and 48.80% (1.86 ± 0.13 vs. 1.25 ± 0.16, $P < 0.01$) **(Figure 2b)**. MDA levels were significantly reduced in myocardial, brain, and lung tissues by 27.70% (2.61 ± 0.60 vs. 3.61 ± 0.51, $P < 0.01$), 40.32% (0.74 ± 0.30 vs. 1.24 ± 0.37, $P < 0.01$), and 36.11% (0.23 ± 0.03 vs. 0.36 ± 0.05, $P < 0.01$) **(Figure 2c).**

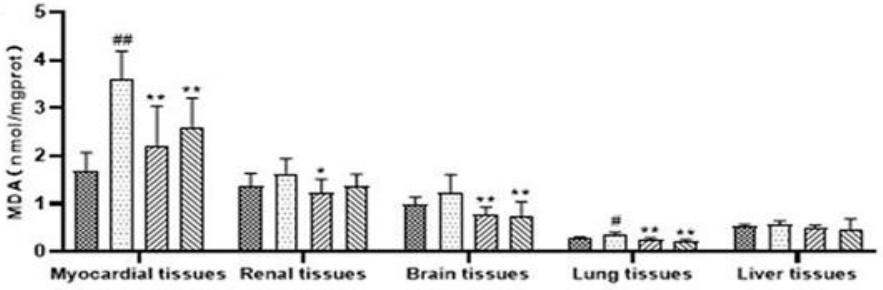
These findings indicate that roxadustat effectively attenuates oxidative stress induced by acute high-altitude hypoxia, suggesting a protective role against tissue damage in hypoxic conditions.



a)



b)



c)

Figure 2. Effects of roxadustat on SOD activity (a), GSH (b) and MDA (c) content in myocardial, renal, brain, lung and liver of hypoxic rats. Error bars indicate SD (n=6/per group).

Abbreviations: SOD, superoxide dismutase; GSH, glutathione; MDA, malondialdehyde.

Notes: $^{\#}P<0.05$, $^{\#\#}P<0.01$ versus normal oxygen group; *P<0.05, **P<0.01 versus hypoxic group.

Effects of roxadustat on histopathology in high-altitude hypoxic rats

Histological analysis of myocardial tissue revealed that in the normoxic control group, cardiac fibers were regularly arranged with intact nuclei **(Figure 3a).** In contrast, myocardial fibers in the hypoxic group appeared disordered, with wavy breaks, fiber disruption (indicated by arrows), and evident inflammatory cell infiltration. Treatment with roxadustat markedly improved myocardial architecture, restoring orderly fiber alignment, reducing inflammation, and maintaining uniform cytoplasmic staining.

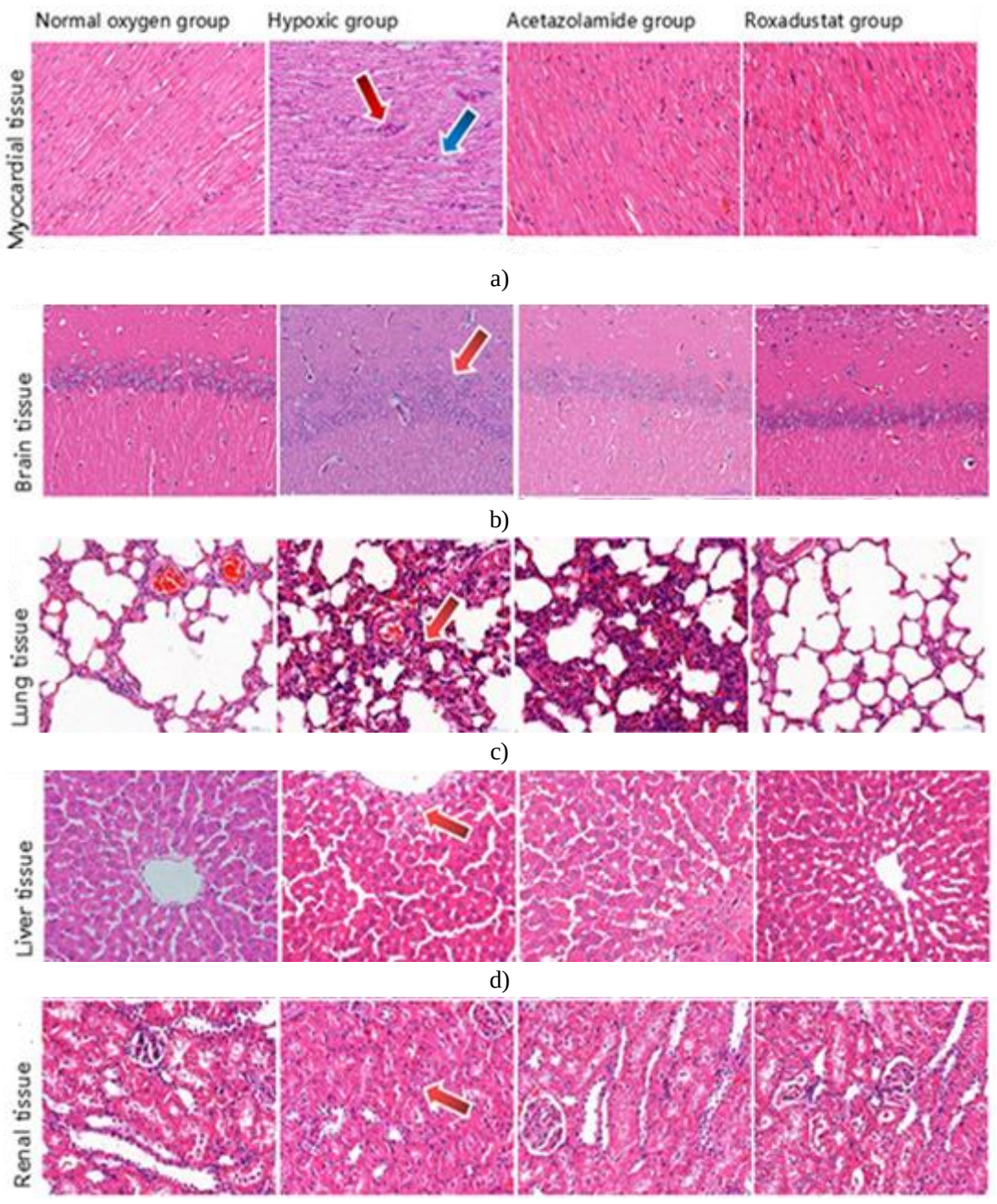


Figure 3. Pathological results of myocardial (a), brain (b), lung (c), liver (d), and renal (e) tissues in rats (HE, 400.0×).

Notes: Red arrows in figure (a) inflammatory cell infiltration; Blue arrows in (a) myocardial fiber disruption; Red arrows in (b) disturbed arrangement of pyramidal cells in the hippocampus; Red arrows in (c) alveolar wall thickening with inflammatory cell infiltration; Red arrows in figure (d) hepatocyte vacuolation; Red arrows in (e) renal tubular epithelial cell edema.

Effects of roxadustat on histopathology in high-altitude hypoxic rats

In cerebral tissue, hippocampal pyramidal cells in the normoxic control group were densely and orderly arranged, with normal cellular morphology **(Figure 3b).** Hypoxia disrupted this arrangement, producing loose and disorganized pyramidal cells (arrow). In contrast, roxadustat treatment preserved the normal structure and density of hippocampal cells.

Lung tissue of normoxic rats displayed thin-walled alveoli and clearly defined nuclei **(Figure 3c).** In the hypoxic group, alveolar walls were thickened and incompletely formed, with inflammatory cell infiltration and fibrous hyperplasia (arrow). Roxadustat treatment restored alveolar wall thickness, normalized architecture, and reduced inflammatory cell infiltration.

Liver tissue in the control group showed cells arranged in cord-like patterns around central veins **(Figure 3d).** Hypoxic liver exhibited nuclear vacuolation and spotty necrosis (arrow), whereas roxadustat preserved normal hepatic structure, with no vacuolation or necrosis.

Renal tissue in the control group was normal **(Figure 3e).** Hypoxia induced epithelial cell edema, narrowed and convoluted tubule lumens, dilated interstitial capillaries, and glomerular erythrocyte exudation. Roxadustat reduced tubular edema and glomerular red blood cell exudation, restoring renal architecture.

The volume of oxygen available to the alveoli was fixed because both control and treated mice were placed in an identical confined chamber during the atmospheric-pressure confinement hypoxia experiment. The findings indicated that high, medium, and low doses of roxadustat significantly extended the survival time of hypoxia-sensitive mice, with the medium dose producing the best survival outcome, corresponding to the human-equivalent dose. Arterial blood was assessed through blood-gas analysis, while venous blood was examined using routine hematological tests. Blood-gas measurements are widely used to evaluate acid–base balance and the severity of hypoxia, whereas abnormalities in RBC, HGB, and HCT in routine blood tests are key markers for diagnosing chronic plateau disorders. The results suggested that roxadustat improved systemic oxygenation and thereby reduced the likelihood of chronic high-altitude disease. Since high-altitude hypoxia can induce inflammatory mediators—and inflammation itself can generate hypoxic microenvironments—inflammatory factors serve as indicators of tissue injury in mice. MDA reflects the degree of lipid peroxidation driven by oxygen radicals and thus represents cellular damage, while SOD and GSH counter oxidative-stress-induced cell death by neutralizing excess ROS and reactive nitrogen species and stabilizing intracellular DNA and proteins. The findings demonstrated that roxadustat reduced inflammatory factor release and oxidative-stress injury caused by hypoxia, consistent with the histopathological observations. Overall, roxadustat mitigates hypoxia-induced tissue damage in rats and exerts an anti-hypoxic protective effect.

Roxadustat inhibits prolyl hydroxylase (PH) activity by acting as a substrate mimic, helping to maintain a balance between HIF synthesis and degradation, and it is already used clinically to treat anemia in chronic kidney disease (CKD) patients undergoing dialysis. In diabetic nephropathy, where inflammatory cytokines and reactive oxygen species are elevated [7], and proteinuria may worsen in obesity and insulin-resistant states [8], it remains unclear whether roxadustat could serve as an effective anti-inflammatory and antioxidant therapy. Roxadustat may also hold therapeutic potential in preventing retinopathy of prematurity, promoting bone and tendon repair [9], and treating bronchopulmonary dysplasia in premature infants [10]. In a 7% oxygen rat model, Yasuoka *et al.* found that roxadustat stimulated hypoxia-induced EPO production in several tissues, particularly the kidney [11]. Hypoxia initiates various adaptive responses mediated by HIF transcriptional complexes, which directly enhance the transcription of genes related to erythropoiesis, angiogenesis, vascular regulation, metabolism, and cell survival. Current evidence suggests several possible mechanisms through which roxadustat counteracts high-altitude hypoxia.

Hypoxia-inducible factor-1 (HIF-1) consists of HIF-1α and HIF-1β subunits. HIF-1α plays a central role in maintaining oxygen homeostasis, and its oxygen-regulated α-chain binds to the aryl hydrocarbon receptor nuclear transporter. Prolyl hydroxylase domain enzymes (PHDs) are essential oxygen sensors that regulate HIF-1α activity. Under normoxic conditions, iron- and 2-oxoglutarate-dependent hydroxylation of proline residues enables binding to the von Hippel–Lindau E3 ubiquitin ligase complex, resulting in HIF-1α polyubiquitination and proteasomal degradation [12]. Hypoxia inhibits PHD activity, thereby stabilizing HIF-1α. As a HIF-PHI, roxadustat stabilizes HIF, prevents its degradation, reverses hypoxia-induced suppression of gene transcription, restores normoxic physiological responses, and reduces hypoxia-mediated injury. Roxadustat can also increase

cellular IKKβ and NF-κB activity by inhibiting PHD, and NF-κB directly regulates HIF-1α, amplifying cellular responses to cytokines [13].

During inflammation or hypoxia, HIFs enhance extracellular adenosine levels, and adenosine signaling plays a critical role in minimizing tissue injury under hypoxic and inflammatory conditions [14]. Both hypoxic and inflammatory stimuli increase the release of extracellular ATP and ADP, and HIF-1α regulates adenosine-generating pathways. CD39 (which converts ATP to AMP) and CD73 (which converts AMP to adenosine) metabolize these nucleotides [15], producing adenosine that activates endothelial adenosine receptors [16]. Extracellular adenosine receptor (AR) signaling provides cardioprotection and reduces myocardial reperfusion injury across species [17–20]. Myocardial ischemia is linked to oxygen deprivation, and SP-1–mediated induction of CD39, along with HIF-1α–mediated induction of CD73 and adenosine receptors, helps cardiac tissue adapt to ischemia and improves outcomes in ischemia–reperfusion injury [21]. Intestinal epithelial cells also express adenosine receptors, and increasing HIF-1α with PHD inhibitors or augmenting adenosine signaling via AR agonists may benefit patients with inflammatory bowel disease, intestinal ischemia/reperfusion injury, and colon cancer [22]. Adenosine signaling similarly protects lung tissue by activating alveolar epithelial ARs during acute lung injury [23]. Therefore, administering adenosine or targeting oxygen-sensor enzymes such as PHDs to prevent HIF-1α hydroxylation and increase HIF stabilization represents a promising therapeutic strategy. Whether HIF-mediated regulation of extracellular adenosine contributes to the anti-hypoxic actions of roxadustat warrants further investigation.

Conclusion

Two conceptual pathways can regulate HIF stabilization: (1) pharmacological stabilization of HIF—primarily via prolyl hydroxylase inhibition, as seen with HIF-PHIs such as roxadustat; and (2) direct activation of HIF target genes, including adenosine receptors. Our findings indicate that roxadustat elevates RBC and Hb levels, alleviates hypoxemia, suppresses inflammatory factor expression, reduces oxidative-stress injury, and protects against high-altitude hypoxia. HIF-PHIs increase total iron-binding capacity and reduce inflammatory oxidative stress in the treatment of renal anemia, with relatively few adverse effects [24]. Taken together, both theoretical and experimental evidence demonstrate that roxadustat has significant anti-hypoxic properties. This study provides a foundation for its potential clinical expansion.

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Conflict of Interest: None

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Ethics Statement: None

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