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NARRATIVE REVIEW

Xenon as a Potential Enhancer of Hypoxic Adaptation Rather Than Its Substitute

a narrative review

HIGHLIGHTS

- Xenon transiently increases erythropoietin (EPO) via HIF-1α activation but lacks sustained hematological adaptation.
- Xenon-induced HIF activation is partial and context-independent, unlike the systemic response to physiological hypoxia.
- No evidence that xenon improves hemoglobin mass, VO_2max, or aerobic performance in

isolation.

- Xenon should be viewed as a potential modulator of hypoxic signaling, not a substitute for hypoxic exposure.
- Future research must integrate xenon with hypoxia and exercise to evaluate synergistic adaptive effects.

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ABSTRACT

BACKGROUND: Xenon has been proposed as a potential agent influencing erythropoiesis through activation of hypoxia-inducible pathways. However, its role in high-altitude physiology and hypoxic adaptation remains unclear and controversial.

AIM: This study aimed to evaluate whether xenon may act as a modulator of hypoxic adaptation rather than a substitute for hypoxic exposure.

MATERIALS AND METHODS: This study is a narrative literature review based on scientific publications indexed in the PubMed database between 1998 and 2025. The literature search included keywords such as xenon, hypoxia, HIF-1α, erythropoietin, hypoxic adaptation, and acclimatization.

RESULTS: Available evidence indicates that xenon transiently increases erythropoietin levels via activation of the HIF pathway; however, these effects do not translate into sustained physiological adaptations such as increased hemoglobin mass or improved aerobic performance. Notably, most studies have evaluated xenon in isolation, without integration into complex adaptive conditions such as combined hypoxia and physical training.

CONCLUSIONS: Xenon does not appear to substitute for hypoxic adaptation. Its potential role as a modulator of hypoxia-induced physiological responses remains insufficiently explored and requires further investigation within integrated experimental models.

KEYWORDS xenon; hypoxia; HIF-1α; erythropoietin; acclimatization

GRAPHICAL ABSTRACT

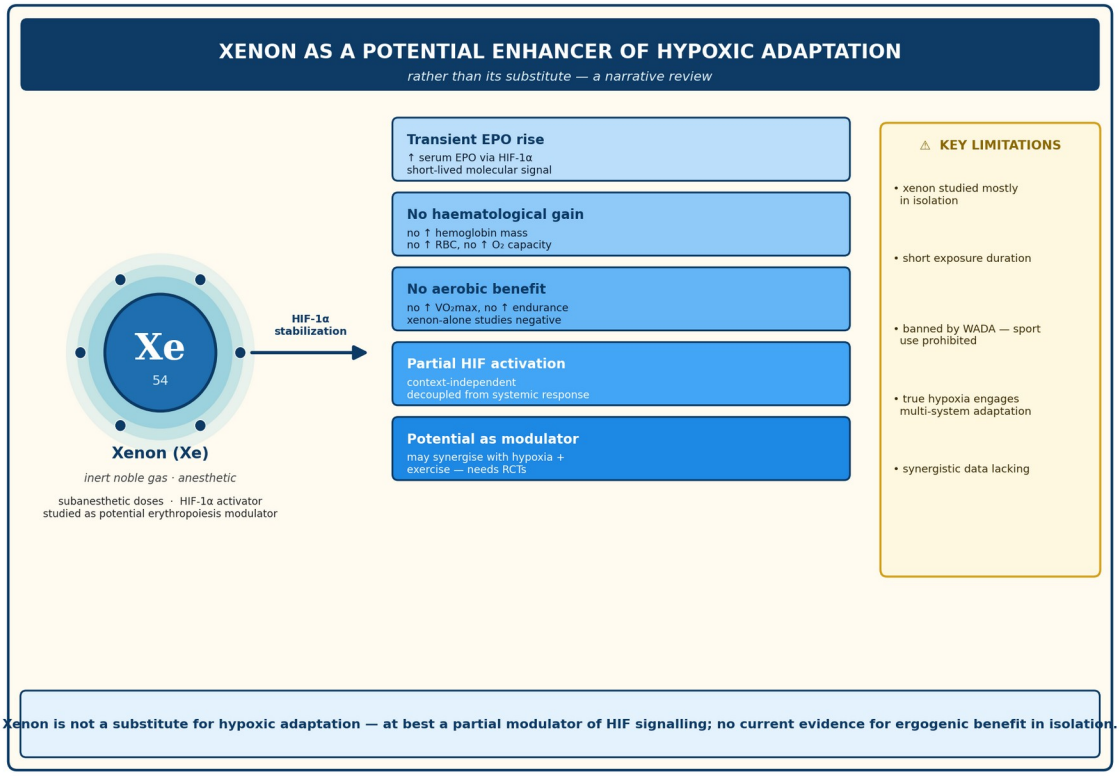

Figure 1. *Graphical overview of xenon effects on hypoxic pathways — from transient HIF-1α activation and EPO increase to the lack of systemic adaptation (hemoglobin, VO_2max) compared to physiological hypoxia.*

PLAIN LANGUAGE SUMMARY

Xenon is an inert gas used in anesthesia that has been suggested to mimic some effects of low oxygen (hypoxia) by activating specific molecular pathways (HIF-1α) that increase erythropoietin (EPO). However, this review shows that while xenon might briefly raise EPO levels, it does not lead to the real physical adaptations seen when people train at high altitude, such as increased hemoglobin or better endurance. Unlike true hypoxia, which triggers a whole-body response involving breathing, heart, and blood changes,

xenon's effect is limited and short-lived. Therefore, xenon cannot replace altitude training or hypoxic exposure. It might potentially enhance adaptation if used together with hypoxia and exercise, but this has not yet been proven. Currently, there is no evidence that xenon alone improves athletic performance or oxygen transport capacity.

TABLE OF CONTENTS

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1. INTRODUCTION

Adaptation to hypoxia is a complex physiological process that enables the maintenance of adequate oxygen delivery under conditions of reduced oxygen availability [1,2,5]. This process is particularly relevant in high-altitude environments, where decreased atmospheric pressure leads to hypobaric hypoxia and imposes significant stress on multiple organ systems [3,4,7]. Effective acclimatization involves coordinated responses of the respiratory, cardiovascular, hematological, and cellular systems [3,5]. In recent years, increasing attention has been directed toward strategies aimed at enhancing hypoxic adaptation, including both traditional approaches such as altitude training and experimental interventions targeting specific molecular pathways [7,11]. Among these, xenon has emerged as a potential agent of interest [10,11]. As an inert noble gas used in anesthesia [9], xenon has been shown to activate hypoxia-inducible factors (HIF), particularly HIF-1α, which play a central role in regulating erythropoietin (EPO) production and erythropoiesis [6,11]. Despite evidence that xenon may transiently increase EPO levels, current studies do not demonstrate sustained physiological adaptations, such as increased hemoglobin mass or improved aerobic performance [5,17,18,21]. This discrepancy suggests a dissociation between molecular signaling and systemic adaptation. Importantly, most studies have evaluated xenon in isolation, without considering the integrative nature of hypoxic adaptation, which depends on repeated exposure, multi-system responses, and interaction with physical activity [3,5]. Therefore, xenon may not act as a substitute for hypoxic exposure but rather as a potential modulator of hypoxic signaling. Such a role would imply that xenon could enhance adaptive responses when combined with appropriate physiological stimuli, such as hypoxia and exercise. Accordingly, the aim of this study was to evaluate whether xenon may function as an enhancer of hypoxic adaptation rather than its substitute.

2. RESEARCH MATERIALS AND METHODS

This study is a narrative literature review. The analysis was conducted based on scientific publications available in the PubMed database published between 1998 and 2025. The literature search was performed in January 2026. The literature search was conducted using English keywords: xenon, hypoxia, hypoxic adaptation, HIF-1α, erythropoietin, and acclimatization. Original research articles, review papers, and experimental studies investigating the physiological, molecular, and clinical effects of xenon in the context of hypoxia were included in the analysis. Particular attention was given to studies examining the effects of xenon on erythropoiesis and erythropoietin (EPO) levels, activation of hypoxia-inducible factors (HIF pathways), and physiological adaptations to hypoxia. Studies analyzing xenon exclusively in non-physiological or unrelated contexts were excluded. Publications not directly related to hypoxic adaptation or integrative physiological responses were also excluded from the analysis. A total of 21 publications were considered relevant and included in the final analysis.

3. RESULTS

3.1. Effects of Xenon on Erythropoiesis

Available studies indicate that xenon administration may lead to a transient increase in erythropoietin (EPO) levels, likely mediated through activation of hypoxia-inducible factor (HIF-1α) [15,17,18]. This effect has been observed in both experimental and clinical settings. However, despite this molecular response, the increase in EPO does not appear to translate into sustained hematological adaptations. No consistent changes have been reported in hemoglobin mass, red blood cell count, or oxygen-carrying capacity following xenon exposure [5,14].

3.2. Xenon and the HIF Pathway

Xenon has been shown to influence the HIF signaling pathway, particularly through stabilization or activation of HIF-1α [11]. This pathway plays a central role in cellular responses to hypoxia, regulating genes involved in erythropoiesis, angiogenesis, and metabolic adaptation. However, the mechanism of HIF activation induced by xenon differs from that triggered by physiological hypoxia. Under hypoxic conditions, HIF activation results directly from reduced oxygen availability and is tightly integrated with systemic physiological responses. In contrast, xenon-induced HIF activation appears to be partial and context-independent, lacking integration with broader systemic responses.

Table 1. *Comparison of HIF pathway activation under hypoxic conditions vs xenon exposure.*

Aspect	Physiological Hypoxia	Xenon Exposure
Trigger	Oxygen reduction	Pharmacological
Duration	Sustained	Transient
Downstream gene activation	Broad	Partial
Angiogenesis	Induced	Minimal
Metabolic adaptation	Yes	No
Systemic integration	Multi-system	Isolated
Functional outcome	Acclimatization	No measurable

3.3. Xenon in Context of Systemic Hypoxic Adaptation

Physiological adaptation to hypoxia is a complex, multi-system process involving coordinated changes in respiratory function, cardiovascular regulation, microcirculation, and mitochondrial efficiency [3,5]. Current evidence indicates that xenon does not replicate these integrative adaptations. Most studies have evaluated xenon in isolation, without concurrent exposure to hypoxia or physical training stimuli [8].

Table 2. *Comparison of temporal dynamics of hypoxic adaptation and xenon exposure.*

Process	Physiological Hypoxia	Xenon Exposure
EPO	Sustained ↑	Transient ↑
RBC mass	↑	No change
Hemoglobin mass	↑	No change
Aerobic performance	Improved	Unchanged

Duration of stimulus	Days–weeks	Minutes–hours
Integration of responses	Yes	No

4. DISCUSSION

The present review highlights a fundamental inconsistency between the molecular effects of xenon and its lack of measurable impact on systemic physiological adaptation. Although xenon has been shown to transiently increase erythropoietin (EPO) levels and activate components of the HIF pathway [15,17,18], these effects do not translate into meaningful improvements in oxygen transport capacity or aerobic performance [5,6,16]. This discrepancy suggests that activation of isolated molecular pathways is insufficient to induce complex adaptive processes. The differences identified in this review are further illustrated by the comparative analyses presented in Table 1 and Table 2. While xenon influences selected elements of the HIF signaling pathway, its effects remain partial and lack the broad downstream activation observed under physiological hypoxia. Moreover, hypoxic adaptation is characterized by sustained and cumulative responses, whereas xenon induces only transient molecular changes without long-term functional consequences. These findings indicate that effective adaptation depends not only on specific molecular signals, but also on their duration, repetition, and integration within a multi-system physiological context.

The HIF-1α pathway is a master regulator of cellular oxygen homeostasis, orchestrating the transcription of hundreds of target genes involved in erythropoiesis, angiogenesis, glucose metabolism, and mitochondrial function [6,11]. Under physiological hypoxia, the sustained stabilization of HIF-1α drives a comprehensive adaptive response that involves multiple organ systems acting in concert. Xenon, by contrast, appears to engage this pathway through a distinct and possibly incomplete mechanism, yielding a transient and functionally limited response [8,15]. The pharmacokinetic profile of xenon — characterized by rapid washout due to its low blood-gas partition coefficient — likely contributes to the brevity of its molecular effects [9]. From a doping perspective, the potential use of xenon in sport has been a subject of concern, particularly given early evidence of transient EPO elevation following xenon inhalation [17,18]. The UIAA Medical Commission has issued a position statement highlighting that current evidence does not support meaningful performance enhancement through xenon use, while noting potential safety concerns [8]. Studies specifically designed to assess athletic performance following xenon inhalation have found no significant improvements in VO_2max or other indices of endurance capacity [15,16]. These findings are consistent with the absence of sustained hematological adaptations and further reinforce the view that transient molecular signaling alone is insufficient to produce physiologically meaningful outcomes.

The concept of xenon as a potential enhancer of hypoxic adaptation — rather than its substitute — remains an open and largely unexplored research question. If xenon were to be applied in conjunction with physiological hypoxia and structured physical training, it is plausible that its molecular effects could contribute to a broader adaptive response. Synergistic interactions between pharmacological HIF activation and exercise-induced signaling have not been systematically investigated. Furthermore, the timing, dose, and mode of xenon administration relative to hypoxic and exercise stimuli remain undefined. These represent important gaps in the current evidence base that future research should address.

5. CONCLUSIONS

Xenon cannot be considered a substitute for hypoxic adaptation, as its effects are limited to transient molecular responses without corresponding systemic physiological changes. However, the evidence presented in this review suggests that xenon may have the potential to act as a modulator of hypoxia-induced adaptive processes, rather than an independent stimulus. Future research should focus on integrative experimental models combining xenon exposure with hypoxia and structured physical training, to determine whether xenon can meaningfully influence adaptive outcomes under physiologically relevant conditions.

6. DISCLOSURE

6.1. Author Contributions

Conceptualization: Michał Tryba, Anna Paluch, Anna Ignatowicz, Katarzyna Gunia. Methodology: Michał Tryba, Anna Paluch, Andrzej Palak, Aleksandra Adamczyk, Agata Żak. Software: Andrzej Palak, Marcin Rebizant, Mateusz Banasik, Michał Tryba. Validation (Check): Agata Żak, Anna Ignatowicz, Katarzyna Gunia. Formal analysis: Gabriela Grylowska, Andrzej Palak, Agata Żak, Katarzyna Gunia, Anna Ignatowicz. Investigation: Anna Paluch, Agata Żak, Gabriela Grylowska, Katarzyna Gunia, Anna Ignatowicz. Resources: Michał Tryba, Mateusz Banasik, Andrzej Palak, Aleksandra Adamczyk. Data curation: Gabriela Grylowska, Mateusz Banasik, Anna Ignatowicz, Marcin Rebizant, Michał Tryba. Writing – original draft: Michał Tryba, Aleksandra Adamczyk, Katarzyna Gunia, Marcin Rebizant. Writing – review and editing: Anna Paluch, Andrzej Palak, Aleksandra Adamczyk, Mateusz Banasik. Visualization: Anna Paluch, Gabriela Grylowska, Agata Żak, Katarzyna Gunia, Anna Ignatowicz. Supervision: Mateusz Banasik, Gabriela Grylowska, Marcin Rebizant. Project administration: Michał Tryba, Agata Żak, Aleksandra Adamczyk, Marcin Rebizant.

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6.3. Institutional Review Board Statement

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6.4. Informed Consent Statement

Not applicable.

6.5. Conflict of Interest

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6.6. Data Availability Statement

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6.7. Acknowledgements

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6.8. CRediT Author Contributions (taxonomy)

Mapped to the CRediT (Contributor Roles Taxonomy, NISO Z39.104-2022). Author initials: MT=Michał Tryba; APa=Anna Paluch; GG=Gabriela Grylowska; KG=Katarzyna Gunia; AA=Aleksandra Adamczyk; MB=Mateusz Banasik; MR=Marcin Rebizant; AŻ=Agata Żak; AP=Andrzej Palak; AI=Anna Ignatowicz.

- Conceptualization: MT, APa, AI, KG
- Methodology: MT, APa, AP, AA, AŻ
- Software: AP, MR, MB, MT
- Validation (Check): AŻ, AI, KG
- Formal analysis: GG, AP, AŻ, KG, AI
- Investigation: APa, AŻ, GG, KG, AI
- Resources: MT, MB, AP, AA
- Data curation: GG, MB, AI, MR, MT
- Writing – original draft: MT, AA, KG, MR
- Writing – review & editing: APa, AP, AA, MB
- Visualization: APa, GG, AŻ, KG, AI
- Supervision: MB, GG, MR
- Project administration: MT, AŻ, AA, MR
- Funding acquisition: Not applicable

Declaration of the use of generative AI and AI-assisted technologies in the writing process

In preparing this work, the authors used ChatGPT for the purpose of language editing, translation into English and improving readability. After using this tool, the authors have reviewed and edited the content as needed and accept full responsibility for the substantive content of the publication.

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