https://doi.org/10.15360/1813-9779-2025-3-2563

The Effects of Xenon on GSK-3β, NF-κB, and Nrf2 Levels in the Rat Brain: An Experimental Study

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For citation: *Evgeniy E. Beda, Mikhail V. Gabitov, Ivan V. Redkin, Ivan A. Kryukov, Oleg A. Grebenchikov.* The Effects of Xenon on GSK-3β, NF-κB, and Nrf2 Levels in the Rat Brain: An Experimental Study. *Obshchaya Reanimatologiya = General Reanimatology.* 2025; 21 (3). https://doi.org/10.15360/1813-9779-2025-3-2563 [In Russ. and Engl.]

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Summary

Aim. To evaluate the impact of subanesthetic concentrations of xenon on the brain levels of GSK-3β, NF-κB, and Nrf2 in intact rats.

Materials and Methods. Male laboratory rats were randomly assigned to three groups (*N*=5 per group): the control group received inhalation of a nitrogen-oxygen gas mixture; the Xe-70 group received 70% xenon; and the Xe-35 group received 35% xenon. Following euthanasia, brain tissue samples were analyzed using Western blotting and densitometric quantification to assess levels of phosphorylated GSK-3β, NF-κB, and Nrf2.

Results. Inhalation of xenon-oxygen mixtures led to a statistically significant increase in phosphorylated GSK-3β levels in both the Xe-70 group (95% CI: 593,723–1,018,826; *P*=0.0001; *R*=0.72) and the Xe-35 group (95% CI: 458,413–872,807; *P*=0.0001; *R*=0.80), compared with controls. Xenon exposure also resulted in a significant reduction in NF-κB levels in the Xe-70 (95% CI: 205,138–601,617; *P*=0.0005; *R*=0.95) and Xe-35 (95% CI: 217,700–608,462; *P*=0.0003; *R*=0.95) groups. Furthermore, Nrf2 protein expression was significantly elevated in the Xe-35 group compared to controls (95% CI: 260,926–692,532; *P*=0.0002; *R*=0.91).

Conclusion. Subanesthetic xenon concentrations exert a significant modulatory effect on GSK-3β, NF-κB, and Nrf2 expression in the brain tissue of intact rats.

Keywords: xenon; GSK-3β; NF-κB; Nrf2; brain; rats

Conflict of interest. The authors declare no conflict of interest.

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Introduction

A complex network of biochemical reactions enables cells to perceive, transmit, and interpret signals, thereby coordinating vital physiological processes such as growth, differentiation, metabolism, and apoptosis. These signaling pathways are usually organized into cascades, in which the number of signaling molecules increases at each successive level as the signal propagates from the initial stimulus. The core components of these cascades include receptors that bind signaling molecules, such as hormones, cytokines, and neurotransmitters, along with intracellular kinases and adaptor proteins that relay the signal and effector molecules that elicit the final cellular response, such as gene activation or metabolic reprogramming. The most extensively studied signaling pathways include PI3K/AKT/mTOR, MAPK/ERK, Wnt, JAK-STAT, Hedgehog, and Fas [1–5].

Glycogen synthase kinase 3 (GSK-3) is a key mediator in several of these signaling cascades. GSK-3 exists in two isoforms, GSK-3α and GSK-3β, which share approximately 85% amino acid sequence homology and display high identity within their kinase domains. Unlike most kinases, GSK-3 is constitutively active and is inactivated by phosphorylation at specific serine residues (Ser21 in GSK-3α and Ser9 in GSK-3β). GSK-3β plays a pivotal role in regulating cellular metabolism, proliferation, apoptosis, and synaptic plasticity [6].

Nuclear factor erythroid 2-related factor 2 (Nrf2) is a transcription factor that serves as a master regulator of the cellular antioxidant response. Consisting of 605 amino acids, Nrf2 includes seven functional domains, designated Neh1–Neh7. Nrf2 governs the expression of genes that encode antioxidant and cytoprotective proteins, such as glutathione S-transferase and heme oxygenase-1, which enable cells to counteract oxidative stress and inflammation [7, 8].

NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) is a ubiquitous transcription factor that regulates the cellular inflammatory response. The NF-κB complex comprises several proteins, including NFKB1, NFKB2, REL, RELA, and RELB. This complex controls the expression of proinflammatory cytokines (e. g., TNF-α, IL-6, and IL-1β) and chemokines, playing a central role in orchestrating innate and adaptive immune functions [9].

In recent years, the use of xenon-based general anesthesia in surgical practice has become sporadic. Despite its declining use as an anesthetic, there is growing interest in exploring the therapeutic potential of xenon [10–15]. This trend is driven by the realization that subanesthetic concentrations of xenon–those insufficient to induce anesthesia–can minimize the risk of adverse events such as impaired consciousness or respiratory depression while reducing the consumption of this expensive gas without compromising its pharmacological activity. Notably, the minimum alveolar concentration (MAC) of xenon in humans ranges from 63.1% to 71% [16, 17]. Interestingly, xenon's MAC differs substantially in laboratory animals, reaching 95% in mice and up to 161% in rats [18].

Numerous studies have demonstrated that subanesthetic concentrations of xenon have organ-protecting effects. Several of xenon's molecular targets are of particular pharmacodynamic interest. Xenon inhibits NMDA receptors and activates ATP-sensitive and two-pore domain potassium channels, including TREK-1 and TASK-3. This produces neuroprotective effects. Xenon activates signaling pathways, including MAPK and PI3K/Akt, which contribute to cardioprotection. It also enhances the expression of protein kinase B (Akt) and hypoxia-inducible factor 1-alpha (HIF-1α), underlying its renoprotective action [19–26].

GSK-3β, Nrf2, and NF-κB are key regulators of cellular homeostasis in the central nervous system. They play critical roles in stress resistance, inflammation regulation, and the maintenance of neural integrity. The dynamic interplay and balance among these signaling molecules are essential for normal cerebral function, and their dysregulation has been implicated in the pathogenesis of neurodegenerative and other disorders.

This study aimed to investigate the effect of subanesthetic concentrations of xenon on the levels of GSK-3β, NF-κB, and Nrf2 in intact rat brain tissue.

Materials and Methods

The study was conducted on fifteen male Wistar rats, each weighing between 250 and 350 grams. All experimental procedures were performed in strict compliance with national and international guidelines, including Recommendation No. 33 of the Eurasian Economic Commission, dated November 14, 2023; Directive 2010/63/EU of the European Parliament and Council, regarding the protection of animals used for scientific purposes; national standards for the housing and care of laboratory animals; and facility equipment and procedural regulations (GOST 33215-2014). The animals were housed in ventilated cages under controlled environmental conditions (temperature: 18–22°C; humidity: 30–70%) with a 12-hour light/dark cycle (lights on from 9:00 a.m. to 9:00 p.m.). All rats were provided with standard chow pellets and had ad libitum access to purified drinking water via bottle feeders. On the day before the experiment, food was withheld, but water remained freely available.

The study protocol was approved by the Local Ethics Committee of the Federal Research and Clinical Center of Intensive Care Medicine and Rehabilitology (Approval No. 3/23/2, October 11, 2023).

The animals were randomly assigned to three experimental groups:

- Group 1 (*N*=5): control group that received inhalation of a nitrogen–oxygen gas mixture (70% nitrogen and 30% oxygen) for 60 minutes;
- Group 2 (*N*=5): experimental group that received inhalation of a xenon–oxygen gas mixture (70% xenon and 30% oxygen) for 60 minutes (Xe-70 group);
- Group 3 (*N*=5): experimental group that received inhalation of a xenon–oxygen–nitrogen gas mixture (35% xenon, 30% oxygen, and 35% nitrogen) for 60 minutes (Xe-35 group).

Twenty-four hours after completing the experimental procedures, the animals were euthanized with an overdose of anesthetic. According to the protocol described by Grebenchikov et al. [27], protein concentrations in brain tissue and Western blot analyses were performed. Densitometric quantification was carried out using publicly available ImageJ software (National Institutes of Health, USA). The protein levels of GSK-3β, NF-κB, and Nrf2 were expressed in arbitrary units of chemiluminescence (a.u.c.).

Statistical analyses were conducted using GraphPad Prism (version 10.4.2; GraphPad Software, USA). The Shapiro–Wilk test was used to evaluate the normality of the data distribution. Results are presented as the median [*Q1; Q3*], where *Q1* and *Q3* represent the first and third quartiles, respectively. Nonparametric methods were employed for variables exhibiting non-normal distribution in at least one group. The Mann–Whitney *U* test with Bonferroni correction was used for pairwise comparisons, and the Kruskal–Wallis test was used to assess differences among all three groups. Post hoc pairwise analyses were performed using Dunn's test with Bonferroni adjustment. Effect sizes were estimated as the ratio of medians, and 95% confidence intervals were calculated using a nonparametric bootstrap method.

A two-tailed *P* value of less than 0.05 was considered statistically significant for all analyses.

Results

Inhaling the xenon-oxygen mixture resulted in a statistically significant increase in the phosphorylated form of GSK-3β in the Xe-70 (95% CI: 593,723–1,018,826; *P*=0.0001; *R*=0.72) and Xe-35 (95% CI: 458,413–872,807; *P*=0.0001; *R*=0.80) groups, as compared to the control group (see Table, Fig. *a* and *b*). According to the effect size (r) classification, values between 0.5 and 0.7 indicate a large effect, and values greater than 0.7 indicate a very large effect.

No statistically significant differences were observed between groups receiving xenon-oxygen mixtures at different concentrations (70% and 35% Xe). Although phospho-GSK-3β levels were higher in the Xe-70 group than in the Xe-35 group, the difference was not significant (Xe-70: 1,485,347 [1,283,380–1,711,439] vs. Xe-35: 1,406,472 [1,165,272–1,573,930]; P = 0.075). Similarly, NF-κB levels did not differ significantly between the Xe-70 (731,687 [555,120–912,777]) and Xe-35 (745,535 [531,662–880,721]) groups (*P*=0.069). Analysis of Nrf2 levels across the groups also revealed no statistically significant differences (*P*=0.089).

However, densitometric analysis of the Western blots showed that inhaling the xenon–oxygen mixture led to a significant reduction in NF-κB levels in both the Xe-70 (95% CI: 205,138–601,617; *P*=0.0005; *R*=0.95) and Xe-35 (95% CI: 217,700–608,462; *P*=0.0003; *R*=0.95) groups compared to the control group (see Table, Fig. *c* and *d*).

Inhaling the xenon-oxygen mixture resulted in a non-significant increase in Nrf2 levels in the Xe-70 group, while the Xe-35 group exhibited a significant increase compared to the control group (95% CI: 692,532–260,926; *P*=0.0002; *R*=0.91) (see Table, Fig. *e* and *f*).

Discussion

Determining the modulation of key signaling pathways is a promising strategy for studying agents with potential anti-inflammatory, anti-apoptotic, and cytoprotective properties. It is well-established that the active form of GSK-3β promotes opening of the mitochondrial permeability transition pore (mPTP), which leads to disruption of the membrane potential, activation of caspases, neuronal damage, and apoptosis. Conversely, GSK-3β inactivation via phosphorylation is associated with protective mechanisms, including reduced cell death, enhanced survival, and attenuated inflammation. Various upstream regulators modulate GSK-3β activity in response to signals such as Wnt, phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT), extracellular signal-regulated kinase (ERK), and p38 mitogen-activated protein kinase (MAPK). Therefore, pharmacological inhibition of GSK-3β is a promising therapeutic approach for treating acute brain disorders and chronic neurodegenerative diseases [28].

Using xenon at subanesthetic concentrations (35% and 70%) was associated with a significant increase in the phosphorylated form of GSK-3β in intact rat brains. This indicates xenon's ability to inactivate the enzyme, suggesting potential cytoprotective modulation. Similar findings were reported recently by Ershov et al., who demonstrated that administering a xenon–oxygen mixture at subanesthetic concentrations increased phospho-GSK-3β levels in an ischemia model [29].

Recent studies have shown that GSK-3β phosphorylation enhances Nrf2 expression [30, 31]. In our study, Western blot analysis revealed that inhaling 35% xenon significantly increased Nrf2 levels in laboratory animal brain tissue. These results suggest that subanesthetic concentrations of xenon can modulate the GSK-3β/Nrf2 signaling pathway, promoting cellular protection against oxidative stress.

The NF-κB signaling cascade plays a central role in regulating the expression of pro-inflammatory genes. The canonical NF-κB pathway is activated by IL-1 receptors, TNF receptors, and Toll-like receptors. In contrast, the non-canonical pathway is triggered by specific members of the TNF superfamily, such as CD40 ligand, B-cell activating factor (TNFSF13B), and lymphotoxin. Inhibiting NF-κB activity reduces inflammation and apoptosis, which is particularly relevant in the context of autoimmune diseases [32]. Yang et al. demonstrated that a xenon–

Table. Levels of the investigated markers in rat brain tissue during xenon–oxygen mixture inhalation.

Markers	Values in the groups, a. u. c.		
	Control	Xe-70	Xe-35
Phospho-GSK-3β	739898 [517983–868427]	1485347 [1283380–1711439]	1406472 [1165272–1573930]
P value*		0,0001	0,0001
NF-κB	1157280 [871386–1294758]	731687 [555120–912777]	745535 [531662–880721]
P value*		0,0005	0,0003
Nrf2	1111432 [867718–1241235]	1306910 [220388–1800363]	1550695 [1289715–1785378]
P value*		0,087	0,0002

Note. Data are presented as densitometric analysis results of Western blots; a. u. c. — arbitrary units of chemiluminescence; * — compared to the control group.

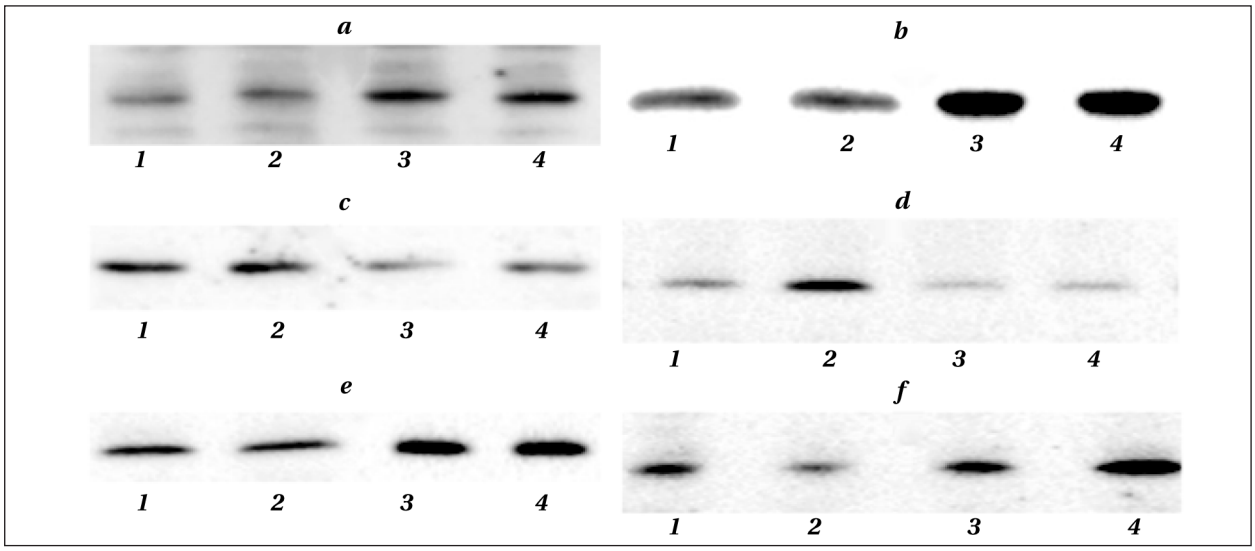

Fig. Western blot analysis of phospho-GSK-3β, NF-κB, and Nrf2 levels in the study groups.
Note. *a, b* — phospho-GSK-3**β**; *c, d* — NF-*κ*B; *e, f* — Nrf2; *1, 2* — control group samples; *3, 4* — experimental group samples

oxygen mixture (70% xenon and 30% oxygen) suppresses NF-*κ*B/NLRP3 inflammasome activation in a murine model of acute lupus nephritis [33].

In vitro studies have demonstrated that xenon modulates the PI3K/AKT/mTOR signaling pathway. This modulation promotes HIF-1*α* activation and suppresses NF-*κ*B-dependent pro-inflammatory and pro-apoptotic signaling. This modulation reduces apoptosis via increased Bcl-2 expression and HMGB-1 inhibition and attenuates inflammation by downregulating NF-*κ*B-mediated pathways [34]. In our study, inhaling xenon–oxygen mixtures at 35% and 70% concentrations significantly reduced NF-*κ*B levels in laboratory animal brain tissue. These results imply that subanesthetic concentrations of xenon have anti-inflammatory and anti-apoptotic effects *in vivo*.

It should be noted, however, that no statistically significant differences were observed between the Xe-35 and Xe-70 groups in terms of GSK-3β, NF-*κ*B, or Nrf2 levels. This may indicate an insufficient sample size or a nonlinear dose-response relationship of the investigated molecular markers within the tested concentration range and exposure time frame.

Conclusion

This study demonstrated that administering xenon at subanesthetic concentrations significantly alters the expression levels of GSK-3β, NF-*κ*B, and Nrf2 in intact rat brain tissue.

Activation of Nrf2 and suppression of the GSK-3β/NF-*κ*B signaling axis under xenon's influence may improve outcomes in cerebral conditions by reducing inflammation and neuronal loss.

These results underscore xenon's cytoprotective potential and highlight the need for further research to elucidate its therapeutic efficacy and underlying mechanisms.

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Received 14.03.2025
Accepted 06.06.2025