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Metabolomic analysis of rat arterial serum under hypobaric hypoxia: Adaptive regulation of physiological systems by metabolic reprogramming

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ABSTRACT

Objective: To investigate the associations between metabolic changes and functions, including energy metabolism, immune response, and redox balance, under short-term hypobaric hypoxia exposure. Non-targeted metabolomics and bioinformatics analysis were applied to explore the adaptive mechanisms of organisms in hypobaric hypoxia.

Methods: Healthy adult male Sprague—Dawley rats were placed in environments simulating altitudes of 6500 m (HC group) and 1588 m (Control group). After 14 days, arterial serum samples were analyzed using Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS). Significant metabolites ($P < 0.05$, VIP >1) were identified, and KEGG enrichment analysis was conducted. Differential metabolites were globally analyzed with MetaboAnalyst 5.0.

Results: A total of 117 significantly altered metabolites were identified. In the HC group, 84 metabolites significantly increased, while 33 metabolites significantly decreased compared to the Control group. KEGG enrichment analysis revealed significant metabolic pathways, including the PPAR signaling pathway, bile secretion, arginine biosynthesis, alcoholism, and cholesterol metabolism ($P < 0.05$). Global analysis indicated that these differential metabolites were involved in various pathways, such as energy metabolism, amino acid metabolism, nucleotide metabolism, lipid metabolism, vitamin and cofactor metabolism, steroid metabolism, neurotransmitter metabolism, and heme metabolism, all of which play crucial roles in multiple biological processes.

Conclusion: Short-term hypobaric hypoxia exposure significantly altered the metabolite profiles in the arterial serum samples of rats, revealing adaptive metabolic reprogramming in energy metabolism, redox balance, immune function, endocrine regulation, and neurological systems.

1. Introduction

The plateau environment, characterized by hypobaric hypoxia presents a unique extreme condition [1,2]. Approximately 140 million people, or 2 % of the global population reside in high-altitude areas [2]. With the rise in tourism, emergency rescue operations, transportation development, and military activities, the number of individuals entering high-altitude environments is steadily increasing, raising high-altitude-related illnesses to a global public health concern [3]. Hypobaric hypoxia poses significant health challenges, severely impairing aerobic metabolism and triggering a variety of health complications [4]. In response, the body initiates a series of metabolic adaptations to maintain energy balance and mitigate oxidative stress, typically taking about 14 days [5,6]. Adaptation to hypoxia involves physiological adjustments and may activate complex molecular and cellular mechanisms that could pose long-term health risks [7,8]. While extensive research has validated physiological responses to acute hypoxia and systemic pathological changes during short-term adaptation, the underlying molecular mechanisms remain incompletely understood.

Untargeted metabolomics is a powerful tool for revealing global

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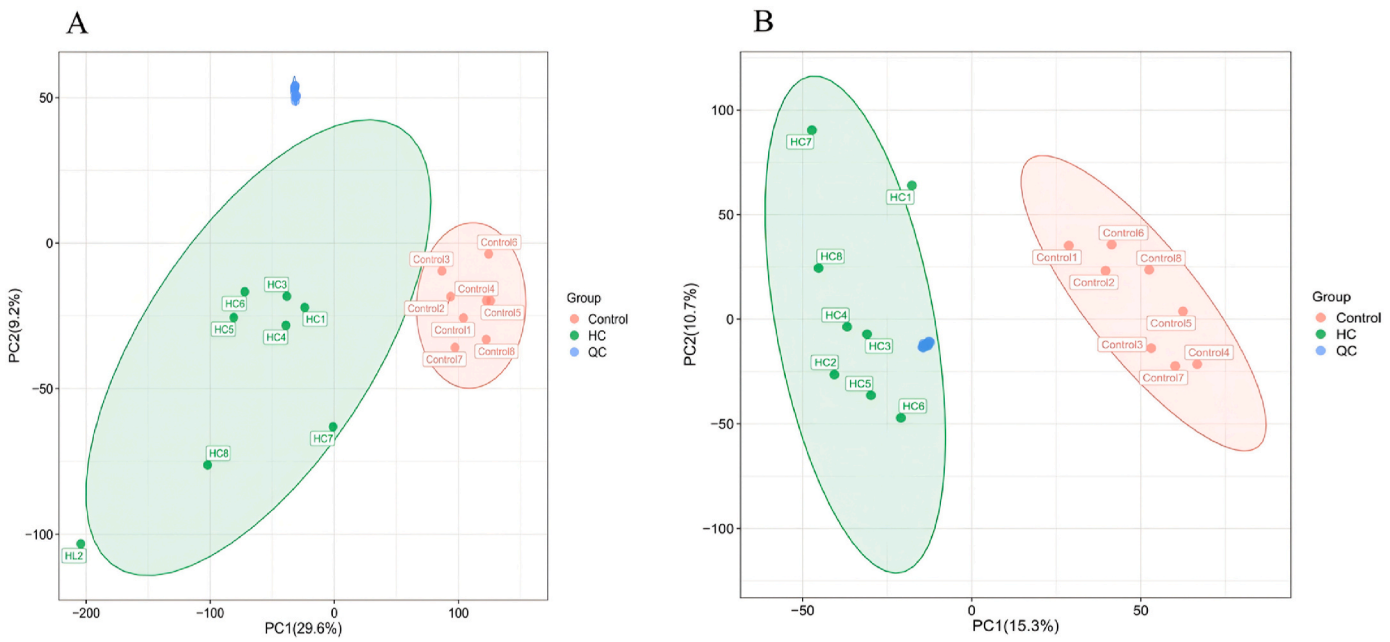


Fig. 1. PCA showing significant differences in arterial serum metabolites between Control and HC groups (Panel A: PCA plot under a positive ion mode. Panel B: PCA plot under a negative ion mode). The data from the QC samples were centralized and consistent to ensure the stability and reproducibility of the experiments.

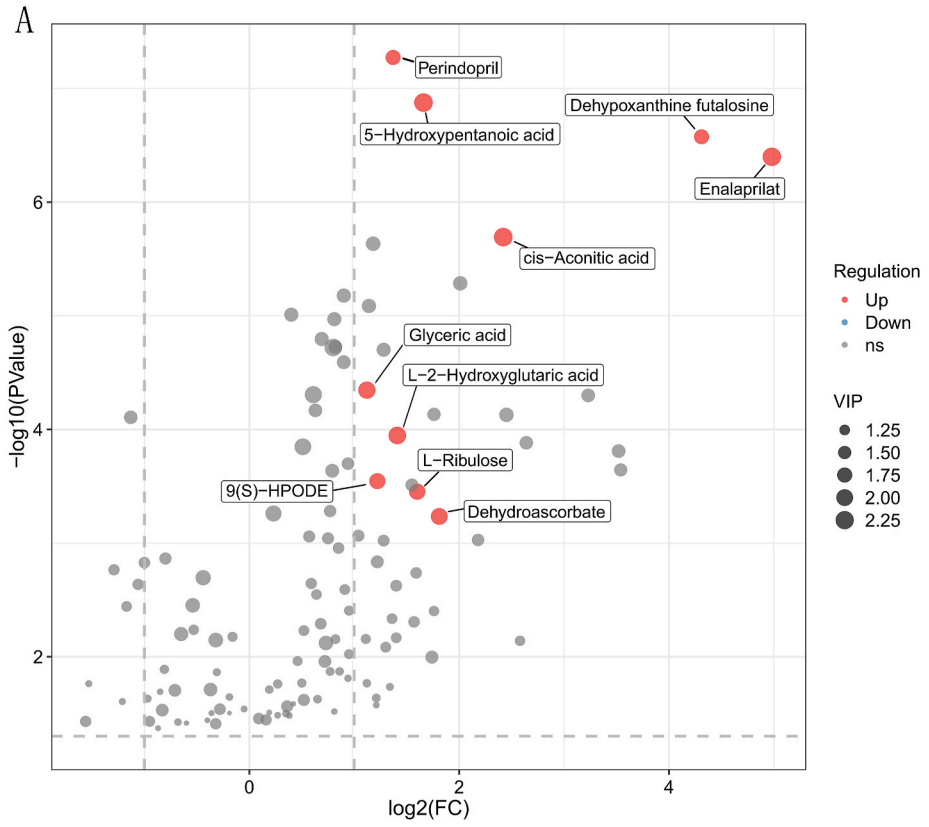


Fig. 2. (A) Changes in arterial serum metabolites following short-term hypobaric hypoxic exposure. The metabolites were screened based on the criteria of a fold change (FC) > 2 and VIP >1.7. The top ten most significant differential metabolites are highlighted. (B) Clustering heatmap of 117 significantly different metabolites, demonstrating metabolite differences between the control and HC groups. Data screening criteria were $P < 0.05$ and VIP >1. Cluster analysis was performed using Euclidean distance and the mean linkage method.

Fig. 2. (*continued*).

metabolic changes in hypobaric hypoxia and identifying metabolites and signaling molecules involved in the adaptation process at the molecular level [3,9]. Studies have shown that hypobaric hypoxia impacts various metabolic pathways, including lipid metabolic homeostasis, energy metabolism regulation, and hormone synthesis and secretion [10,11]. Furthermore, varying exposure durations to hypobaric hypoxia lead to distinct changes in metabolic pathways [10,12].

Emerging research indicates that hypobaric hypoxia exerts a comprehensive and significant impact on the body [10]. Due to hypoxia's effects on pulmonary circulation, some studies have found that

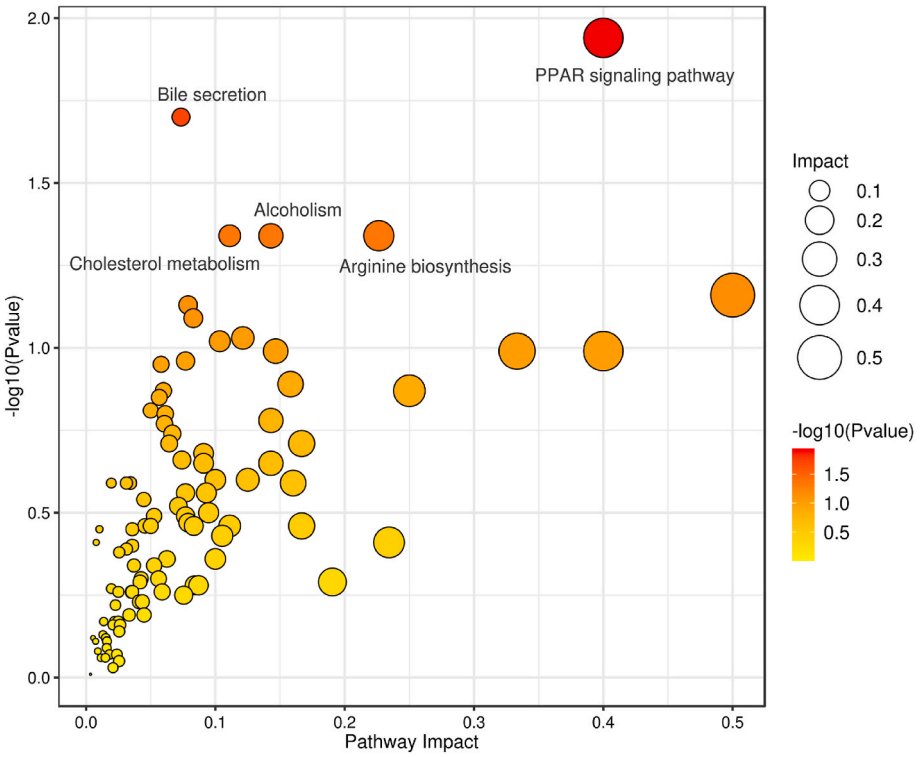


Fig. 3. KEGG enrichment analysis results of differential metabolites. The significance threshold is set at $P < 0.05$, indicating significantly enriched metabolic pathways.

metabolites in arterial blood are more abundant than those in venous blood [13]. Based on these findings, we further investigated the impact of short-term hypobaric hypoxia exposure on arterial serum metabolites and their relationship with physical performance with the aim to uncover the underlying physiological adaptation mechanisms and to enhance our understanding of the effects of extreme environments on health.

2. Materials and methods

2.1. Models and grouping

Eight-week-old male Sprague-Dawley rats (Beijing Huafukang Biotechnology Co., Ltd.; Animal License Number: SCXK (Beijing) 2024–0003; n = 16) were used in this study. The rats were housed under a 12-h light/dark cycle (07:00–19:00) at a temperature of 22 ± 2 °C and relative humidity of 45%–55 %, with free access to standard feed and water. The rats were randomly assigned to two groups: a Control group (n = 8) and a hypobaric hypoxic chamber group (HC group, n = 8). The HC group was placed in a hypobaric hypoxic chamber simulating an altitude of 6500 m (pressure: 43.12 kPa) for 14 days, while the Control group was housed at an altitude of 1588 m (pressure: 83.56 kPa) in Lanzhou, China. The hypobaric hypoxic simulation chamber was provided by Guizhou Fenglei Aviation Machinery Manufacturing Company (Guizhou, China). Hypoxic exposure for 14 days was followed by the administration of phenobarbital (50 mg/kg) to anesthetize the rats before collecting blood from the abdominal aorta, after which the rats were euthanized. This statement adheres to the ARRIVE guidelines. Our animal experimental protocol was approved by the Animal Protection and Use Institution Committee of the 940th Hospital of Joint Logistics Support Force of Chinese People's Liberation Army (NO. 2022KYLL168), China, and all animal care followed the institutional guidelines.

2.2. Metabolomics analysis method

2.2.1. Metabolite extraction method

Before blood collection, all rats underwent overnight fasting. Blood samples were drawn from the abdominal aorta using vacuum sterile blood collection tubes and allowed to rest at room temperature for 1.5 h, followed by collection of the serum. A 100 μL aliquot of serum was mixed with 400 μL of methanol solution and vortexed for 1 min at 4 °C. The mixture was then centrifuged at 12,000 rpm for 10 min, and the supernatant was collected and dried. The dried samples were reconstituted in 150 μL of 80 % methanol in water, with 2-chloro-L-phenylalanine (4 ppm) added as an internal standard. After filtration, the samples were analyzed using Liquid chromatography-mass spectrometry (LC-MS) using a Thermo Vanquish ultra-high-performance liquid chromatography system (Thermo Fisher Scientific, USA) equipped with an ACQUITY UPLC® HSS T3 column (2.1 × 100 mm, 1.8 μm) (Waters, Milford, MA, USA).

2.2.2. Metabolite analysis method

Raw mass spectrometry data were converted to mzXML format using Proteowizard software (v3.0.8789). Peak detection, alignment, and filtering were conducted using the R package XCMS (v3.12.0). Systematic error correction for quality control (QC) samples was performed by using the Support Vector Regression methodology, and metabolites with a relative standard deviation > 30 % were excluded. The final metabolites were identified through matching against public databases for qualitative analysis.

2.2.3. Metabolomics data analysis

Metabolomics data analysis was performed using the R software package Ropls for Principal Component Analysis (PCA). The explanatory power of the model was represented by R^2X and R^2Y. P-values and Variable Importance in Projection (VIP) scores (VIP >1) were calculated through statistical tests to evaluate the contribution of variables to the model. Inter-group differences in metabolites were assessed using Fold

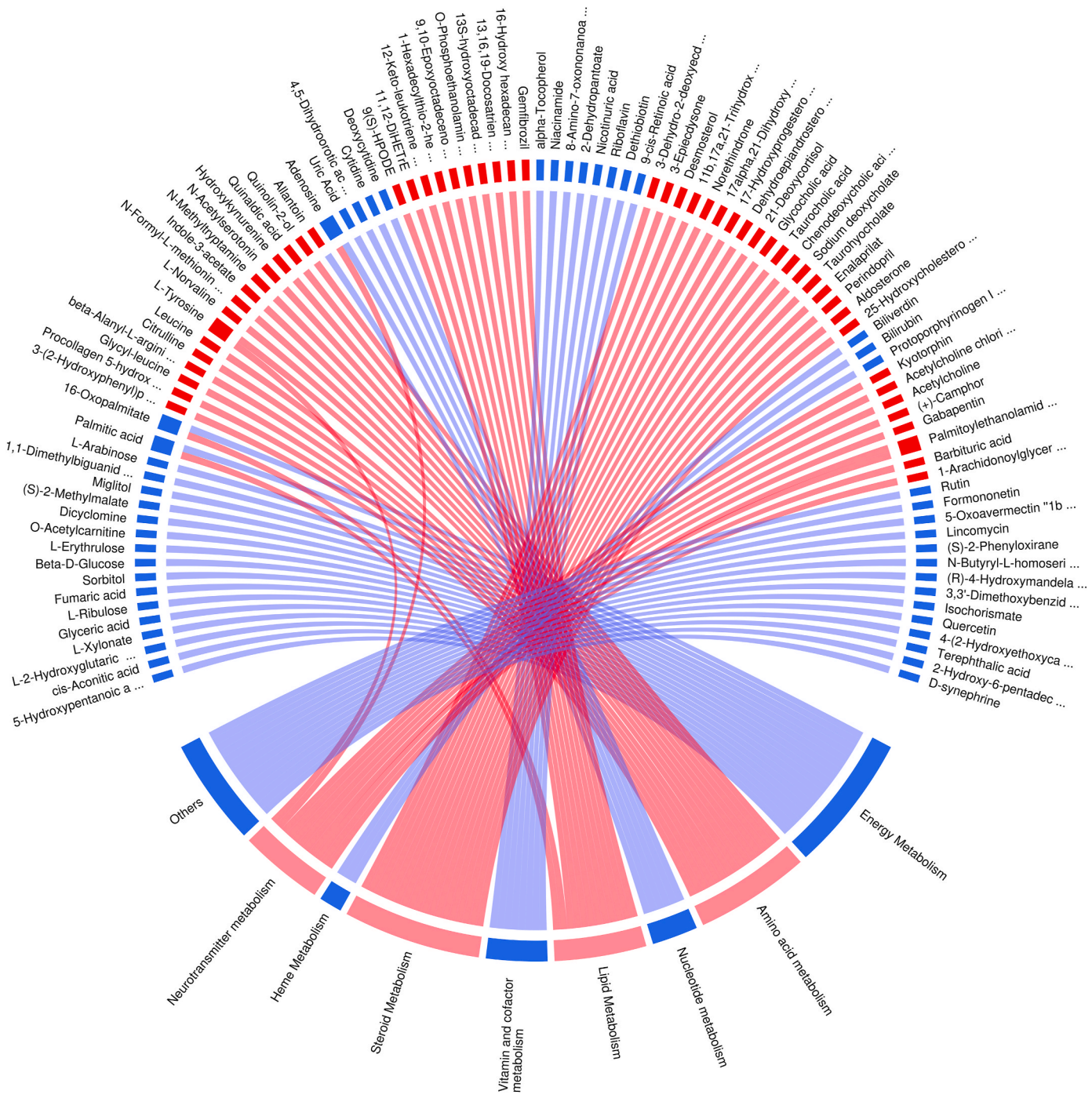


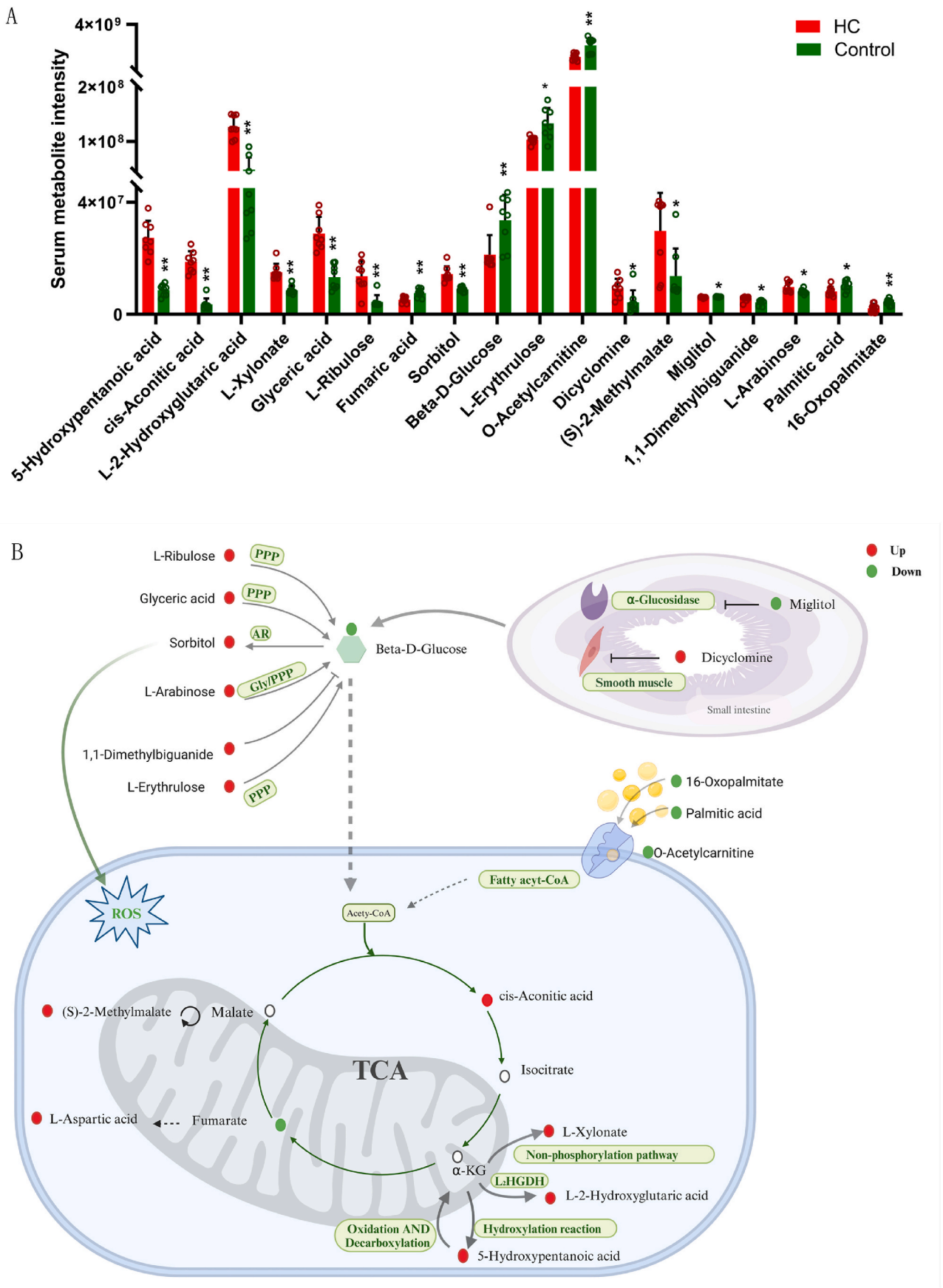
Fig. 4. Chord diagram illustrating the associations between differentially expressed metabolites and their corresponding metabolic pathways under hypobaric hypoxia. Major metabolic pathways (e.g., energy metabolism, amino acid metabolism, and nucleotide metabolism) are labeled at the bottom, while metabolites with significant changes are at the top. Each chord represents a connection from the involved metabolic pathway to the differentially expressed metabolite, with the width of the chord indicating the number of associations. Adjacent metabolites and metabolic pathways have been visually grouped by color to enhance the clarity and readability of the diagram.

Change (FC), with significant differences defined at $P < 0.05$. Graphical representations were generated using GraphPad Prism 10 software.

3. Results

3.1. Metabolomics results

This study employed non-targeted metabolomics technology to analyze the serum metabolites of the Control and HC groups. To ensure data accuracy and stability, QC samples were utilized. In positive ion mode, the R^2X value of the PCA plot was 0.511, while in negative ion mode, the R^2X value was 0.504, indicating the stability and reliability of the data (Fig. 1). PCA analysis further demonstrated a significant separation between the two groups, suggesting that hypobaric hypoxic exposure significantly influenced the serum metabolite profile of the rats.



(caption on next page)

Fig. 5. (A) The significance analysis of differential metabolites in the energy metabolism pathway, with asterisks indicating statistical significance (*P < 0.05, **P < 0.01). HC group) and 1588 m (Control group). (B) The location and interaction relationships of differential metabolites within the energy metabolism network. After exposure to hypobaric hypoxia, metabolites associated with glucose acquisition, glycolysis, and gluconeogenesis, which are related to reduced fasting blood glucose, levels, depict significant changes. Metabolites related to fatty acid β-oxidation,which are crucial for energy production, are significantly reduced. In addition metabolites and by-products in the TCA cycle exhibit significant alterations. ⊣ indicates inhibitory effects and → denotes promoting effects. The red color indicates an increase after exposure to hypobaric hypoxia, while the green color indicates a decrease. PPP, Pentose Phosphate Pathway; AR, Aldose Reductase; α-KG, Alpha-Ketoglutarate; L2HGDH, L-2-Hydroxyglutarate Dehydrogenase; Gly, Glycolysis.

3.2. Metabolite screening and differential analysis

Statistical analysis with thresholds of $P < 0.05$ and VIP >1 identified a total of 117 differential metabolites. Of these, 84 metabolites were significantly increased in the hypobaric hypoxic group, while 33 showed significant reductions (Fig. 2B). The top ten significantly differential metabolites included 5-hydroxy pentanoic acid, *cis*-aconitic acid, enalaprilat, perindopril, dehypoxanthine futalosine, L-2-hydroxyglutaric acid, glyceric acid, 9(S)-HPODE, L-ribulose, and dehydroascorbate (Fig. 2A). Notably, these metabolites are closely linked to mitochondrial function, energy metabolism, redox balance, and cardiovascular function.

3.3. Metabolic pathway analysis

To further elucidate the biological significance of these differential metabolites, the Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis was performed. The analysis revealed significant enrichment in several key pathways, including the PPAR signaling pathway, bile secretion, arginine biosynthesis, alcoholism, and cholesterol metabolism (Fig. 3). These pathways are strongly linked to energy metabolism, lipid metabolism, bile acid metabolism, cardiovascular regulation, and immune modulation.

3.4. Global analysis of metabolites

MetaboAnalyst 5.0 was utilized for a systematic analysis of the differential metabolites in arterial serum. These metabolites included carbohydrates, amino acids, lipids, steroids, nucleotides, xenobiotics, and other unidentified compounds. As illustrated in Fig. 4, these metabolites participate in critical metabolic pathways, such as energy metabolism, amino acid metabolism, nucleotide metabolism, lipid metabolism, vitamin and cofactor metabolism, steroid metabolism, neurotransmitter metabolism, and heme metabolism.

Specifically, exposure to hypobaric hypoxia significantly altered metabolites associated with glucose metabolism, fatty acid oxidation, and the tricarboxylic acid (TCA) cycle (Fig. 5). Notable increases were observed in glyceric acid, *cis*-aconitic acid, 5-hydroxy pentanoic acid, and L-2-hydroxyglutaric acid, while β-D-glucose, fumaric acid, and palmitic acid significantly decreased.

Changes in amino acids and their derivatives were also prominent (Fig. 6). Dimethylglycine, kyotorphin, glutathione, and leucine exhibited marked increases, whereas glycyl-leucine, citrulline, and procollagen 5-hydroxy-L-lysine significantly decreased (Table S1). In the tryptophan metabolic pathway, significant decreases were noted in hydroxykynurenine, quinaldic acid, and quinolin-2-ol from the kynurenine pathway. Conversely, N-acetylserotonin from the serotonin pathway significantly increased, while N-methyltryptamine showed a decrease. Additionally, indole-3-acetate significantly increased under hypoxic conditions.

As shown in Fig. 7, nucleotide-related metabolites, including allantoin, uric acid, and adenosine, exhibited significant increases, whereas cytidine notably decreased (Table S2).

Lipid-related metabolites also demonstrated significant changes (Fig. 8). Phospholipid-related metabolites such as O-Phosphoethanolamine (OPEA) and 1-hexadecylthio-2-hexadecanoylamino-1,2-dideoxy-*sn*-glycero-3-phosphocholine (HEX-2-HAD-PC) significantly increased. Unsaturated fatty acid-related metabolites, including 9(S)-HPODE, 11,12-dihydroxy-9Z,15Z-octadecadienoic acid (11,12-DiHETrE), and 12-keto-leukotriene B4 (12-Keto-LTB4), also showed significant increases. In contrast, 13,16,19-docosatrienoic acid and 9,10-epoxyoctadecenoic acid (9,10-EpOME) significantly decreased.

In the realm of sterol metabolites, as illustrated in Fig. 9, desmosterol and 11β,17α, 21-trihydroxy pregnenolone significantly increased. Steroid hormones, including 11β,17α and 21-trihydroxy pregnenolone, also exhibited significant increases, while dehydroepiandrosterone (DHEA) significantly decreased. Furthermore, bile salt metabolites such as glycocholic acid, taurocholic acid, and sodium deoxycholate significantly increased, whereas chenodeoxycholic acid notably decreased.

As depicted in Fig. 10, among the metabolites related to vitamins and cofactors, dehydroascorbate, α-tocopherol, and 9-cis-retinoic acid significantly increased, while niacinamide and 4-pyridoxic acid notably decreased.

Fig. 11 shows that neurorelated metabolites, such as kyotorphin, barbituric acid, and (+)-camphor, exhibited significant increases, whereas acetylcholine chloride, acetylcholine, and palmitoylethanolamide significantly decreased.

As illustrated in Fig. 12, metabolites associated with heme metabolism revealed that protoporphyrinogen IX, linked to heme synthesis, increased, while bilirubin and biliverdin, associated with red blood cell degradation, also rose significantly. Detailed changes in other metabolites are presented in Table S3.

4. Discussion

An increasing number of studies explored metabolic changes under hypobaric hypoxic conditions, identifying issues such as impaired energy metabolism, altered drug metabolism pathways, and iron metabolism imbalances [14–17]. Modern scientific developmental trends suggest that the applications of systems biology approaches provide valuable insights into these complex phenomena, thereby facilitating a comprehensive analysis of biological response mechanisms under hypobaric hypoxic stress [18,19]. Therefore, this study analyzed the effects of short-term continuous hypobaric hypoxic exposure on arterial serum metabolites in rats, revealing metabolic reprogramming across multiple pathways. These metabolic changes reflect the body's adaptive mechanisms to hypobaric hypoxic environments and involve extensive adjustments in energy metabolism, redox balance, immune regulation, and neural function. Notably, alterations in energy metabolism represent one of the most significant characteristics under hypoxic conditions. Our findings demonstrated that hypobaric hypoxic exposure significantly reduced fasting blood glucose levels, with significant changes observed in metabolites related to glucose uptake, glycolysis, gluconeogenesis, and fatty acid β-oxidation— [15,20–23]. These changes indicate metabolic adaptations by organisms toward optimizing their energy utilization and ensuring survival under extreme conditions. The elevated levels of sorbitol, for instance, suggest the activation of the polyol pathway, which is considered a compensatory mechanism under mitochondrial damage to alleviate disturbances in glucose metabolism. This pathway activates in response to cellular stress and is crucial for maintaining energy homeostasis [24,25]. Additionally, alterations in mitochondrial metabolic products, such as decreased fumaric acid and increased L-2-hydroxyglutaric acid in the TCA cycle, indicate impaired mitochondrial function, leading to reduced energy efficiency. These impairments activate alternative signaling pathways to sustain energy production [26–29]. While these compensatory mechanisms may

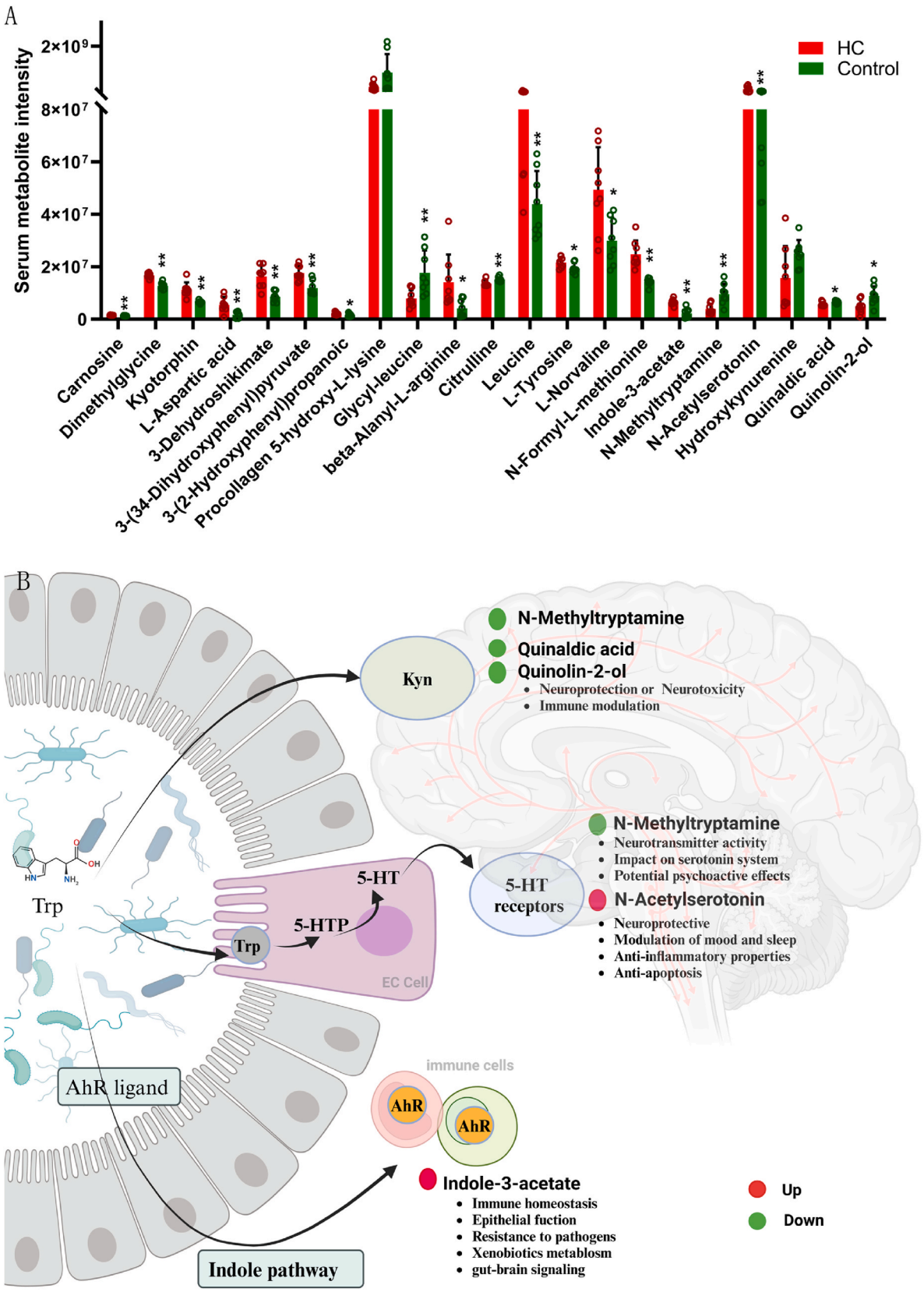


Fig. 6. (A) Significance analysis of amino acid-related metabolites. (B) Positions and functions of differential metabolites in the tryptophan metabolism pathway. After exposure to hypobaric hypoxia, tryptophan undergoes intestinal metabolism, which induces significant changes in the serum concentrations of kynurenine, 5-hydroxytryptamine (5-HT), and other indole pathway metabolites. The red color indicates an increase after exposure to hypobaric hypoxia, while the green color indicates a decrease. AhR, Aryl Hydrocarbon Receptor; Trp, Tryptophan; 5-HT, Serotonin; 5-HTP, 5-Hydroxytryptophan; Kyn, Kynurenine; EC cell, Enterochromaffin Cells.

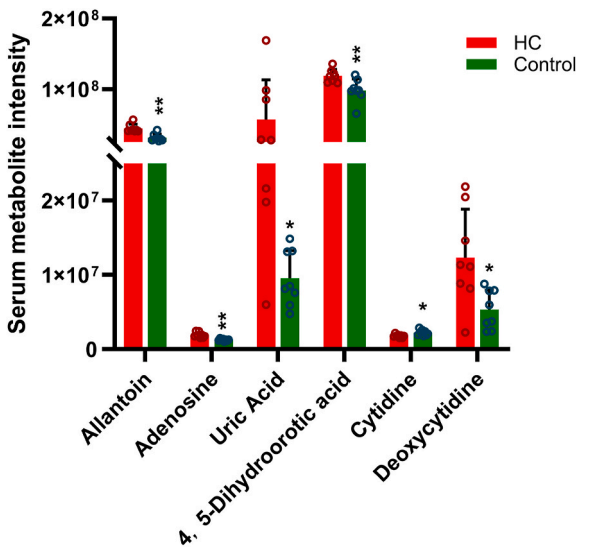


Fig. 7. Significance analysis of differential metabolites in the nucleotide metabolism pathway.

temporarily alleviate metabolic stress, they could result in long-term cellular damage, dysfunction, and accelerated aging, ultimately contributing to tissue injury. This metabolic reprogramming highlights the challenges cells face in maintaining essential functions under low-pressure, hypoxic conditions.

The maintenance of redox balance is crucial for adaptation to hypobaric hypoxia. In this study, significant elevations were observed in antioxidant metabolites such as glutathione, dehydroascorbate, and α-tocopherol, reflecting an enhanced antioxidant defense mechanism in the organism [30–35]. Additionally, the increase in 9-cis-retinoic acid not only enhances antioxidant defense but also regulates gene expression by activating retinoic acid receptors, thereby promoting cellular differentiation and tissue repair [36–38]. Despite the positive effects of metabolic reprogramming on antioxidant defense and energy metabolism regulation, adverse effects are evident. For example, the reduction in procollagen 5-hydroxy-L-lysine could impact tissue repair and structural integrity, potentially accelerating the aging process [39,40]. In hypobaric hypoxia, immune system regulation is characterized by significant changes in the levels of unsaturated fatty acid oxidation products, such as 9(S)-HPODE, 11,12-DiHETrE, and 2-keto-LTB4. These metabolites are involved in inflammatory responses, pulmonary hypertension, cognitive impairment, and cell proliferation and apoptosis, by regulating the release of inflammatory factors and the activation of immune cells [41–46]. Additionally, sterol metabolites such as desmosterol and 25-hydroxycholesterol exhibited significant increases in their levels. These metabolites can regulate cell membrane fluidity, thereby influencing the functional activity of macrophages and contributing to the maintenance of immune homeostasis [47–49]. Notably, hypobaric hypoxic conditions significantly alter the concentrations of metabolites involved in tryptophan metabolism, including those in the kynurenine, serotonin (5-hydroxytryptamine), and indole pathways. These metabolites play important roles in regulating inflammation, immune responses, and maintaining neurological functions, particularly through the gut-brain axis, achieving multi-level regulation of immune functions and the nervous system [50].

Nucleotide metabolism undergoes significant changes under hypobaric hypoxia [51]. This study demonstrates that the increase in allantoin and uric acid suggests an enhancement of the purine metabolism pathway, which may serve as a protective mechanism against hypoxic stress [52,53]. The elevation of adenosine levels contributes to the maintenance of cardiovascular and neurological functions [54]. However, the reduction in cytidine and the increase in 4,5-dihydroorotic acid reflect the cell's demand for regulating RNA synthesis and repair processes. The increase in deoxycytidine indicates an enhancement in DNA repair capacity [51], which is crucial for resisting genomic instability caused by hypoxia. These metabolic changes are closely linked to pathological processes such as cardiovascular disease, aging, and neurodegenerative disorders.

Regarding endocrine hormone regulation, hypoxic conditions lead to a decrease in serum levels of DHEA in adult male rats, while norethindrone levels increase, indicating a negative impact of hypoxia on the reproductive endocrine system [55,56]. Significant increases in key metabolites within the glucocorticoid synthesis pathway underscore their essential role in responding to environmental stress under hypoxic conditions [57–60]. The increase in aldosterone contributes to the maintenance of blood pressure and electrolyte balance in response to the physiological stress induced by hypobaric hypoxia [61]. Furthermore, the samples in this study were obtained from the abdominal aorta, providing an effective reflection of the metabolic status in the pulmonary artery and cardiac circulation. The findings revealed significant elevations in the levels of perindopril and enalaprilat, indicating that the body employs hormonal and pharmacological pathways to regulate blood pressure in response to hypertension and cardiovascular stress elicited by hypoxia [62,63]. These metabolic changes reveal the complex regulatory strategies of the endocrine system in adapting to hypobaric hypoxia.

Neuroregulation is a critical aspect of the adaptive process to hypobaric hypoxia. The current study revealed increases in the levels of (+)-Camphor and Kyotorphin, along with a decrease in Gabapentin levels, suggesting that the organism may alleviate hypoxia-induced neuroinflammation by enhancing analgesic and anti-inflammatory actions [64–67]. Although barbituric acid itself does not directly act on the nervous system, its related metabolites exert sedative and antiepileptic effects by interacting with GABA receptors [68]. Additionally, the increase in L-tyrosine levels may improve mood and cognitive function by modulating dopamine synthesis [69,70]. Collectively, these changes exert a protective effect on the nervous system. However, the significant reduction in acetylcholine and its chloride may impair cognitive and motor functions [71,72], reflecting the negative impact of hypobaric hypoxia on neurological health.

In terms of heme synthesis, hypobaric hypoxic conditions lead to a significant increase in protoporphyrinogen IX, bilirubin, and biliverdin, indicating an increased burden on heme synthesis. These changes suggest that the body enhances heme synthesis to adapt to the hypoxic environment, a core characteristic of hypoxic adaptation mechanisms [73–75].

Finally, enrichment analysis of differential metabolites reveals significant alterations in metabolic pathways related to the PPAR signaling pathway, bile secretion, arginine biosynthesis, alcoholism, and cholesterol metabolism under hypobaric hypoxic conditions. These changes resonate with the physiological adjustments in energy metabolism, immune regulation, and cardiovascular function, further highlighting the central role of metabolic reprogramming in maintaining homeostasis and adapting to hypobaric hypoxic environments [76–80].

This study systematically explored the relationship between differentially expressed metabolites and physiological metabolic pathways under hypobaric hypoxia through metabolomics analysis. The results revealed that short-term hypobaric hypoxia exposure triggers metabolic reprogramming and plays a critical role in maintaining homeostasis, indicating significant adaptive changes in various aspects including energy metabolism, redox balance, immune response, endocrine function, and nervous system regulation. These findings together provide new insights into understanding the metabolic adaptation mechanisms of the body under hypobaric hypoxia, particularly in the context of physiological and health impacts under extreme environments. However, the study has certain limitations; primarily, the lack of direct functional validation of these metabolic changes. Therefore, future research should integrate multi-omics data and experimental

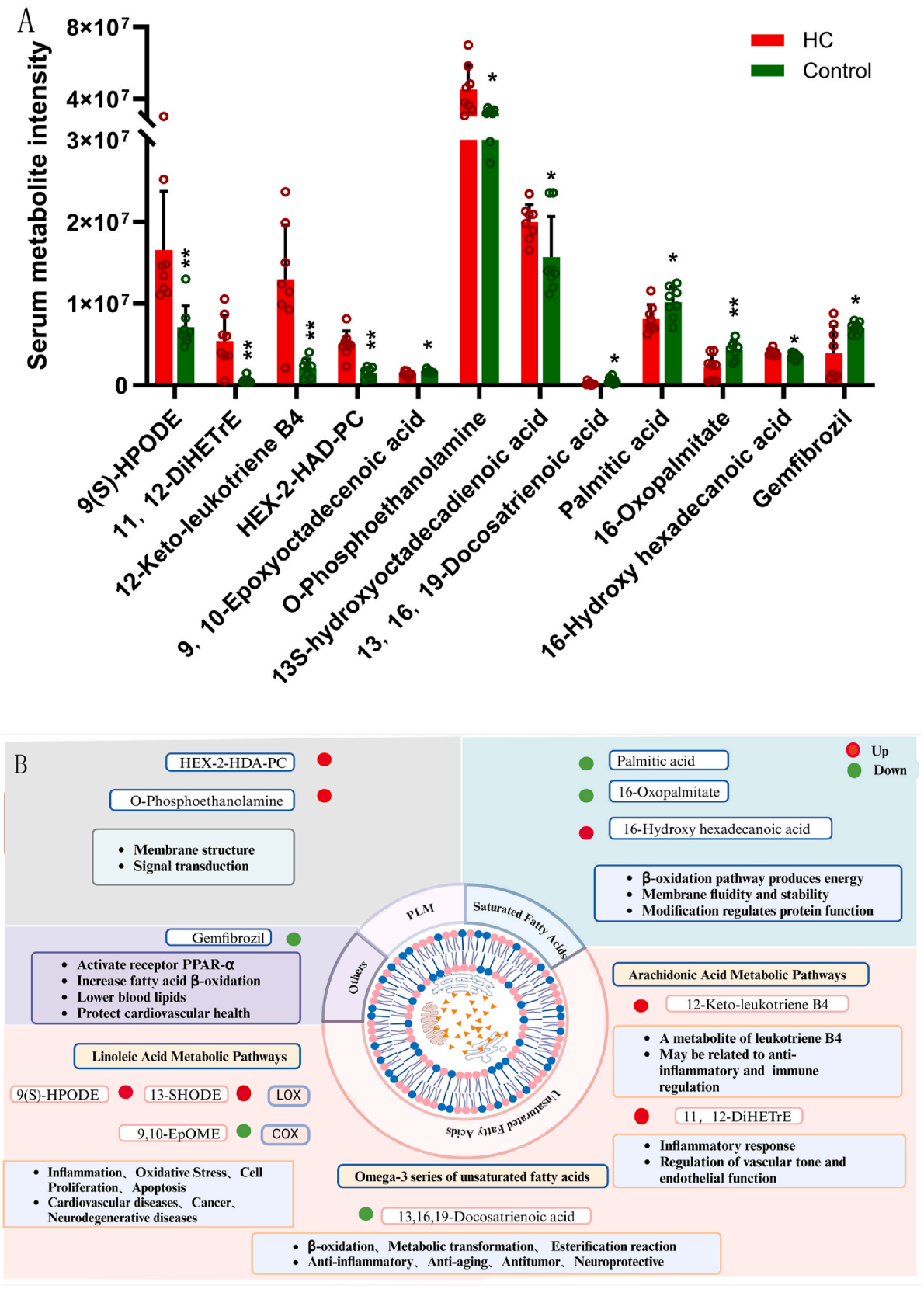


Fig. 8. (A) Significance analysis of differential metabolites in the lipid metabolism pathway. (B) Biological functions involving differential metabolites. The differential metabolites identified primarily include phospholipids, saturated fatty acids, and unsaturated fatty acids. Specifically, the unsaturated fatty acids include linoleic acid, arachidonic acid, and omega-3 polyunsaturated fatty acids. These metabolites are involved in key biological processes such as cell signaling, inflammation, oxidative stress, and energy metabolism.9,10-EpOME, 9,10-Epoxyoctadecenoic acid; 11,12-DiHETrE, 11,12-Dihydroxy-9Z,15Z-octadecadienoic acid; 9(S)-HPODE, 9(S)-Hydroperoxyoctadecadienoic acid; 1-hexadecylthio-2-hexadecanoylamino-1,2-dideoxy-*sn*-glycero-3-phosphocholine,HEX-2-HAD-PC; PLM, Phospholipid metabolism; COX, Cyclooxygenase pathway; LOX, Lipoxygenase pathway.

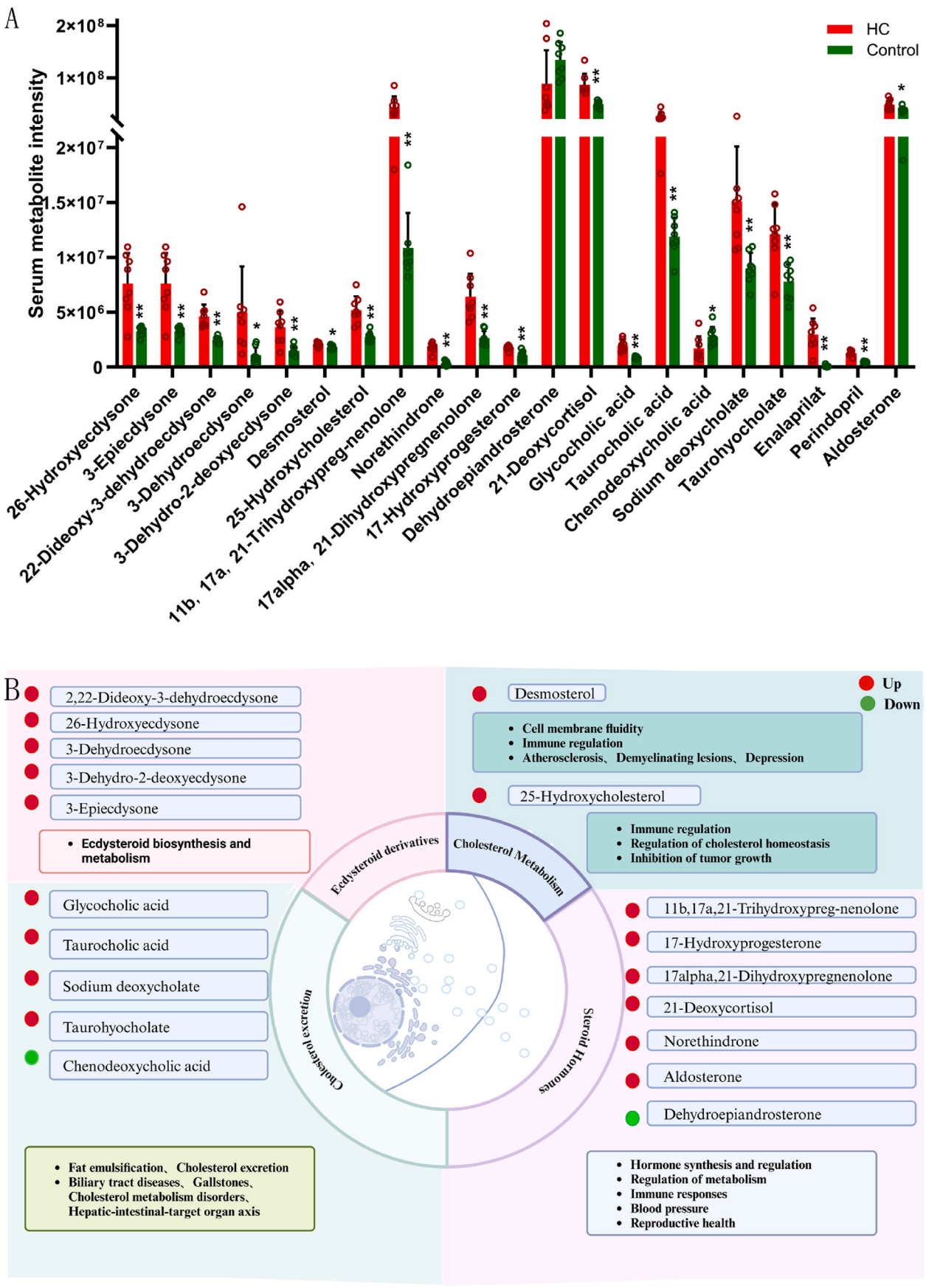


Fig. 9. (A) Significance analysis of differential metabolites in the steroid metabolism pathway. (B) Biological functions involving differential metabolites. The figure illustrates changes in sterol metabolites, including cholesterol metabolism, steroid hormones, cholesterol excretion, and ecdysteroid derivatives. Notably, steroid hormones, which are closely related to stress and blood pressure regulation, indicated significant modifications in response to hypobaric hypoxia.

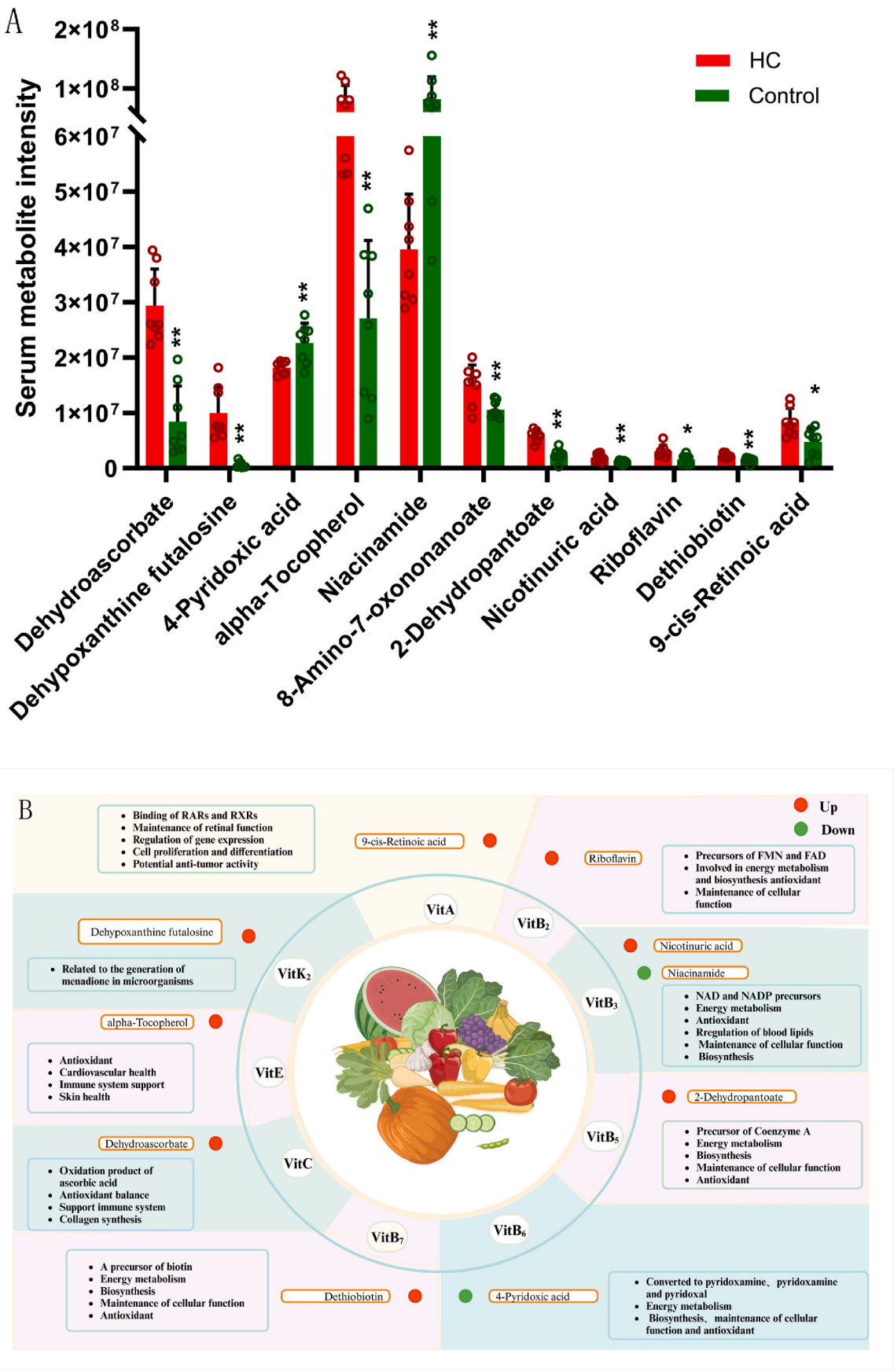


Fig. 10. (A) Significance analysis of differential metabolites in the vitamin and cofactor metabolism pathway. (B) Biological functions involving differential metabolites. As shown in the figure, these metabolites participated in diverse metabolic pathways within the body, including those involving vitamins and cofactors, which were critical for processes such as redox balance and energy metabolism. RAR,Retinoic Acid Receptor; RXR,Retinoid X Receptor.

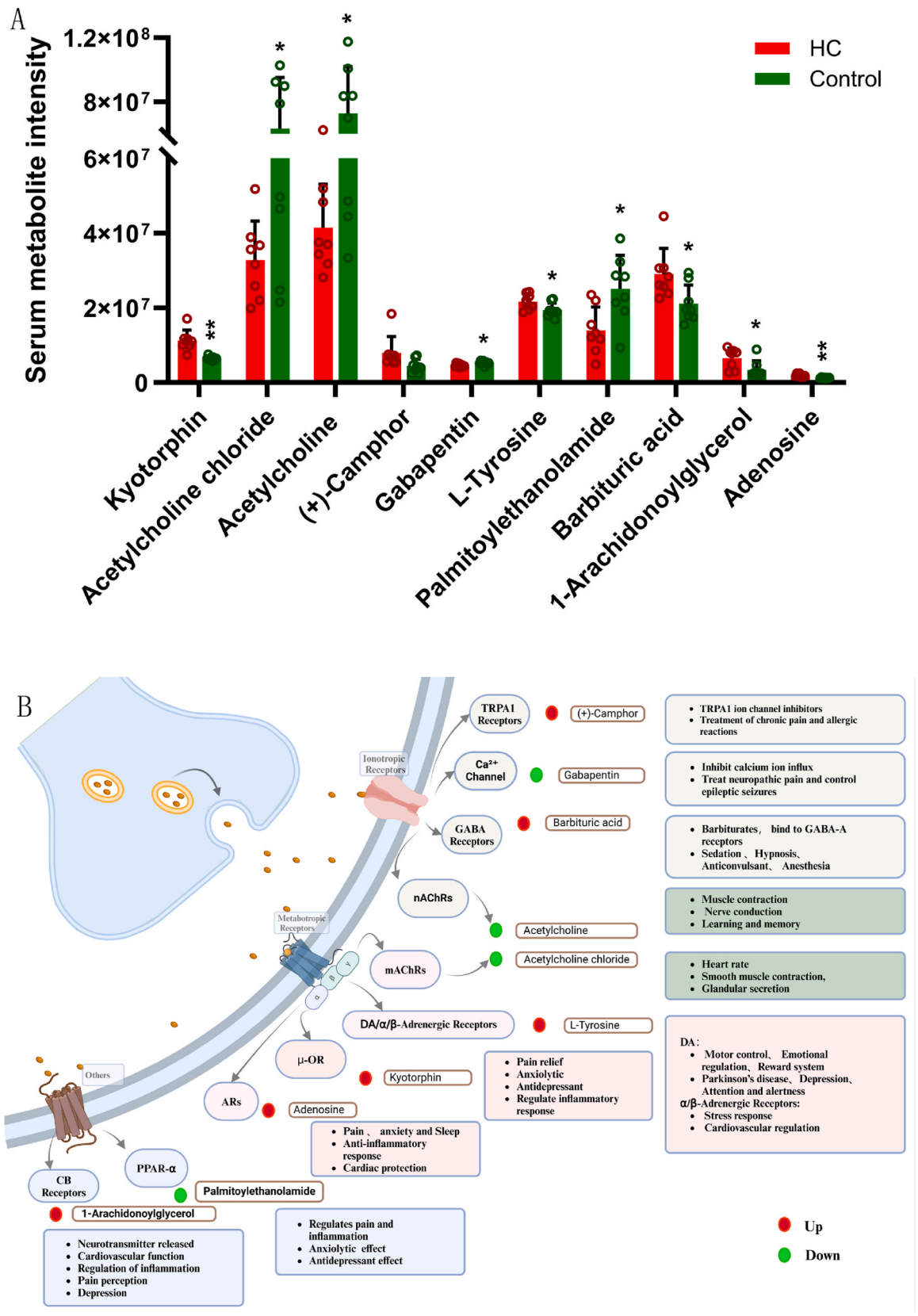


Fig. 11. (A) Significance analysis of differential metabolites in the neurotransmitter metabolism pathway. (B) Biological functions involving differential metabolites. Hypobaric hypoxia exposure altered ionotropic receptors, metabotropic receptors, and other receptors. These changes influenced the key physiological processes, including analgesia, sedation, cognition, mental state, and cardiovascular regulation. TRPV1, Transient Receptor Potential Vanilloid 1; CB Receptor, Cannabinoid Receptor; Ars, Adrenergic Receptors; μ-OR, μ-Opioid Receptor; mAChRs/nAChRs, muscarinic Acetylcholine Receptors/nicotinic Acetylcholine Receptors; TRPA1, Transient Receptor Potential Ankyrin 1.

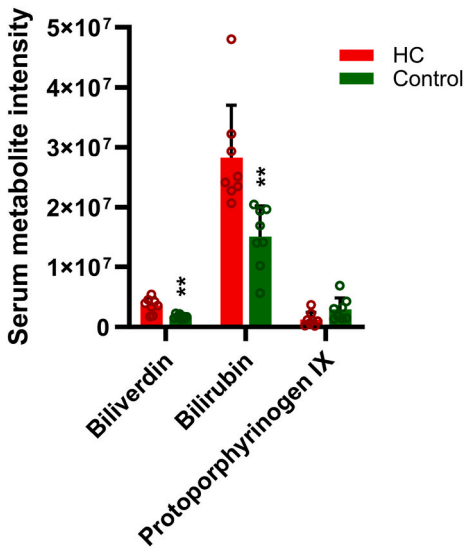


Fig. 12. Significance analysis of differential metabolites in the heme metabolism pathway.

verification to elucidate the mechanisms behind these metabolic alterations. In addition, increasing the sample size is expected to enhance the generalizability and clinical applicability of the results, thereby providing new perspectives and strategies for health management in extreme environments. Through further research, we can comprehensively understand the physiological adaptation mechanisms influenced by hypobaric hypoxia and provide solid scientific evidence for related research and clinical applications.

CRediT authorship contribution statement

Dengqin Ma: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Investigation. **Bing Li:** Software, Visualization. **Bang Xin:** Software, Methodology. **Bingfang Xie:** Methodology. **Enpen Zhu:** Software. **Zihao Zhang:** Writing – review & editing. **Xiaoqin Ha:** Writing – review & editing, Project administration.

Declaration of competing interest

The authors declare that there are no conflicts of interest regarding the publication of this article. All authors have no financial and personal relationships with other people or organizations that could inappropriately influence their work. Specifically, no author has received any funding, gifts, or other benefits from any commercial entities related to the content of this study. Additionally, there are no patents, products in development, or marketed products related to this work that could pose a conflict of interest. We confirm that the manuscript has been read and approved by all authors and that we have adhered to the ethical standards as set forth in the relevant guidelines and regulations of the institution where the work was carried out.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbrep.2025.101943.

Data availability

Data will be made available on request.

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