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高海拔低压低氧环境对认知功能影响的研究进展

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摘　要

高海拔地区有着低压低氧、日照时间长的特点。长期生活在高海拔地区，随着慢性低氧血症的出现，部分人群可能会出现反应迟钝、记忆力减退等认知功能减退的症状。低压低氧环境下，易诱发睡眠障碍、抑郁症等疾病，除此之外它还可导致神经递质异常、神经元凋亡和氧化应激，这些都可能与认知功能的改变有关。本文综述了高海拔低压低氧环境对人们认知功能的影响及相关机制，以期为高海拔环境下认知障碍的预防与治疗研究提供新思路。

关键词

高海拔，认知功能，低压低氧，机制，预防

Research Progress on the Effect of High-Altitude Hypobaric Hypoxic Environments on Cognitive Function

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Abstract

High altitude areas are characterized by low pressure, low oxygen and long hours of sunlight. Living

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at high altitude for a long time, with the emergence of chronic hypoxemia, some people may experience symptoms of cognitive impairment such as slow response and memory loss. Hypobaric hypoxia environment is prone to induce sleep disorders, depression and other diseases, in addition to which it can lead to abnormal neurotransmitters, neuronal apoptosis and oxidative stress, all of which may be associated with the changes of cognitive function. This paper reviews the effects of high-altitude hypobaric hypoxia environment on people's cognitive function and the related mechanisms, in order to provide new ideas for the prevention and treatment of cognitive impairment in high altitude environment.

Keywords

High-Altitude, Cognitive Function, Hypobaric Hypoxic, Mechanism, Prevention

1. 引言

认知障碍(Cognitive Impairment, CI)是指因各种原因所导致的一个或多个认知域功能不同程度的损害[1]。影响认知功能的因素众多，其中环境因素就占有重要地位，有研究发现，与低海拔组相比，长期居住生活在高海拔地区的老年人似乎更有可能出现不同程度的认知障碍，且很容易发展为痴呆[2]。这是由于随着海拔的升高，大气压呈指数下降，导致环境中的氧分压逐渐降低，称为低压缺氧(Hypobaric Hypoxic, HH) [3]。氧气对于神经元功能和大脑的生长至关重要，脑组织对于缺血缺氧也最为敏感，轻度缺氧时，会出现烦躁、头痛、疲惫、呼吸困难等现象。随着缺氧时间的增加，症状也会进一步加重，表现为判断力下降、注意力不集中、记忆力减退等，严重时会对脑细胞产生不可逆的损伤。根据世界卫生组织标准，高海拔地区通常是指海拔在 2500 m 以上的地区。近年来，前往高海拔地区工作、生活和旅游的人群比例逐年升高，人们逐渐开始研究它对于认知功能的影响。

2. 高海拔低压低氧环境对大脑结构的影响

长期处于一个低压低氧环境中，不仅对认知、心理产生影响，还可能导致大脑结构的改变，这种变化可能是认知功能变化的结构基础[4]。例如海马体是学习和记忆的整合中枢，非常容易受到缺血缺氧的影响，低压低氧会严重损害初级神经元的结构完整性和海马体的线粒体形态[5] [6]。有研究表明海马结构受损在认知障碍中发挥着重要作用[7] [8]。大脑结构的损伤，如海马缺血、颞叶损伤、基底节或小脑损伤，以及脑萎缩或功能连接中断，都可能导致认知功能障碍[9]-[12]。一项在高海拔地区开展的队列研究发现，生活在高海拔地区的居民，扣带回前部、舌回、额下回和岛叶的脑血流量发生了变化[13]。灰质密度降低是大脑萎缩的一个定量指标，表明神经元丢失和大脑皮层变薄。长期暴露在高海拔环境下的人群，其左侧颞叶上极、双侧颞中极和右侧中回的灰质密度会显著降低[14]。Zhang 等[15]也发现岛叶皮质是高海拔移民和当地人一致受到影响的大脑区域。静息状态下大脑功能网络的改变可能是执行控制受损的功能基础。一项研究表明，在拉萨大学学习 2 年后，当地学生在静息状态下左/右额顶神经网络、感觉运动网络和听觉网络内的神经元共同激活减少[16]。另一项研究也表明在高海拔地区暴露 2 年后，一些重要区域功能网络的拓扑性质发生变化 [17]。这些研究表明，长期暴露在低压低氧环境会导致大脑结构的改变，这种

变化可能是认知功能变化的结构基础。

3. 高海拔低压低氧环境下认知障碍的相关机制

虽然大量研究表明高海拔低压低氧会对认知功能产生影响，但是关于它如何影响认知功能的研究及数据很少，现有研究认为高海拔低压低氧导致认知功能障碍的主要机制有氧化应激、神经递质释放、神经细胞损伤及血脑屏障通透性的改变等[18] [19]。

3.1. 氧化应激

长期暴露于低压低氧环境时，细胞线粒体会产生活性氮、活性氧和其他自由基，导致氧化应激反应，而体内自由基的积累促使氧自由基形成和抗氧化防御系统失衡，形成脑损伤从而造成认知功能的下降[20]。另外，高海拔暴露还会导致大脑线粒体功能障碍，增强氧化应激。在低氧环境下，炎症活动和氧化应激增加，影响神经退行性变和神经保护，从而影响认知功能[21]。当机体暴露于低氧环境时，白介素-1 (IL-1)、肿瘤坏死因子-α (*TNF-α*)等炎性因子分泌增多，在损害淋巴细胞和中性粒细胞的同时，会加重氧化应激反应，从而导致蛋白质结构变化和炎症，最终影响神经系统功能[22]。

3.2. 神经递质释放

乙酰胆碱及谷氨酸都已被证明在注意力、执行功能、工作记忆等认知领域发挥重要作用[23] [24]。谷氨酸是神经系统中的兴奋性氨基酸，在高海拔地区，由于氧气的匮乏，导致兴奋性氨基酸再摄取功能紊乱，从而影响兴奋性氨基酸的活动。同时低氧会使突出膜发生去极化，导致大量的谷氨酸递质进入突触间隙，诱导神经元的过度激活并死亡。异常的谷氨酸能和 GABA 能的神经传递也是认知障碍的驱动因素[25]。在缺氧环境中，GABA 的释放随着谷氨酸脱羧酶的限速酶的合成增加而增加，从而影响认知功能。在缺氧环境中，血液中氧气水平的降低会改变 5-羟色胺和多巴胺的合成，而 5-羟色胺和多巴胺水平的变化也会导致嗅皮层、小脑和脑干的改变，从而加剧大脑功能的恶化[26]。

3.3. 神经细胞损伤

长期暴露于高原低氧环境会导致红细胞异常增多而引起高原红细胞增多症(High altitude polycythemia, HAPC)。促红细胞生成素是一种糖蛋白激素，可以促进骨髓中红细胞的生成，从而增加血液的携氧能力。有学者发现，低压低氧环境也会影响促红细胞生成素和炎症因子及红细胞生成，进而导致 HAPC 影响认知功能[27]。红细胞增多最明显的影响是血液粘稠度增加和微循环障碍，导致大脑结构和功能的累积性改变，进一步加重相关脑区和神经核缺氧，从而导致认知功能减退[28]。此外，上述环境还可诱导低氧诱导因子(HIF)生成，它会通过促进神经元自噬激活而导致脑损伤[29]。脑源性神经营养因子(brain-derived neurotrophic factor, BDNF)是调节从胚胎到成年阶段的神经发生和突触发生的关键生长因子。低氧可以降低脑源性神经营养因子的血清水平，这也是认知能力下降的原因之一[30] [31]。

3.4. 血脑屏障损害

血脑屏障(Blood-Brain Barrier, BBB)是一种位于血液和脑组织之间的动态内皮细胞屏障，由主要排列在脑微血管系统内的脑内皮细胞组成，其次是周细胞、基底膜和星形胶质细胞[32] [33]。该屏障在脑微环境的动态平衡调节中发挥重要作用，这是神经元稳定和协调活动所必需的。低氧条件下，血脑屏障会由多种因素导致一定程度的破坏，可能与血管内的一些细胞因子的增加有关[34]。而血脑屏障的损害被认为是认知障碍的重要发病机制之一[35]。

4. 高海拔低压低氧环境与认知功能

4.1. 睡眠障碍与认知功能

睡眠障碍(Sleep Disorder, SD)是指睡眠–觉醒过程中表现出来的各种功能障碍。研究发现 SD 与空间记忆、数字符号显著相关。高海拔的低压低氧环境会导致体内呼吸异常，进而导致睡眠时频繁觉醒和对空气的感知不足，就会使睡眠结构发生改变，如夜间觉醒增加、慢波睡眠减少，从而导致 SD。SD 一方面可以影响睡眠期间的呼吸模式和神经元生化过程，导致神经退行性变化和所涉及的神经递质稳态紊乱记忆力和敏捷性受损，另一方面通过改变中枢系统中树突棘的密度和形态，影响大脑功能以及信息处理和储备[28] [31]。Morrison 等[36]发现到高海拔地区旅行的人觉醒频繁，慢波睡眠时间较短，睡眠质量差是造成高海拔地区负面情绪和认知受损的可能因素。高原红细胞增多症也会导致入睡困难和夜间易醒，这反过来会导致记忆力、注意力和精神灵活性等认知功能的下降[27]。

4.2. 抑郁症与认知功能

抑郁症(Major Depressive Disorder, MDD)是一种情绪障碍，其特征是持续的悲伤和/或无法体验快乐，并伴随着日常功能缺陷的疾病。研究发现，随着海拔的升高，消极情绪逐渐增加，而积极情绪呈下降趋势，藏族居民比居住在平原地区的居民更容易患上抑郁症，且抑郁发生率与海拔高度呈显著正相关[37]。5-羟色胺和多巴胺是一种与情绪相关的关键神经递质，在低氧低压环境中，血液中氧气水平的降低会改变 5-羟色胺和多巴胺的合成，从而导致高海拔地区患抑郁症的风险增加[38]。高原气候寒冷干燥，缺氧条件，大风和强烈的紫外线辐射，使人们更容易产生负面情绪，并产生与精神健康障碍(如抑郁症状)的出现有关的神经元变化[39] [40]。MDD 与老年人群认知障碍风险的增加有关，MDD 的认知损害主要集中在记忆力、注意力、执行功能以及信息加工速度等方面[41] [42]。认知功能障碍也是重度抑郁障碍的一个核心病理特征。

5. 高原环境下认知功能的防治

5.1. 高压氧治疗

高压氧治疗(Hyperbaric Oxygen, HBO)是通过头罩、面罩或高压舱内的气管导管吸入 100%的氧气的治疗方法。HBO 被认为可以减少神经炎症反应、血脑屏障通透性和细胞凋亡，同时积极影响神经发生、神经元和轴突完整性以及突触形成，进而潜在地影响患者的认知功能[43]。一例病例报告指出，HBO 3 周后的总体认知功能以及包括记忆、注意力、信息处理速度和执行功能在内的所有认知功能领域都有改善[44]。HBO 不仅能治疗颅脑损伤与卒中后相关的认知障碍，也能改善认知老化和神经退行性疾病引起的认知功能减退[45]。

5.2. 谷氨酰胺与脑肠轴

谷氨酰胺可以直接改变大脑中的神经递质活动、提高脑细胞的代谢水平，改善认知功能和记忆力。大脑和肠道通过多种生理途径相连，包括神经、内分泌、免疫和代谢途径。肠–脑轴可以促进中枢神经系统的变化。特定的饮食和饮食习惯可以对平衡的微生物群组成产生积极影响，从而有助于增强认知功能[46] [47]。因此，我们认为补充谷氨酰胺可以减轻高原低氧引起的炎症所致的认知恶化。谷氨酰胺是谷胱甘肽合成的前体物质。通过补充谷氨酰胺来增加谷胱甘肽合成，抑制核转录因子 κB 途径活性，降低白介素-8 (IL-8)和 TNF-α 的水平，减轻炎性反应，从而改善认知功能。高原的低压缺氧环境似乎可以影响肠道屏障机制，增加肠道通透性[48]。谷氨酰胺可以通过改善肠道环境，减少肠道渗漏引起的炎症，从而改

善认知和情绪[49]。

5.3. 高原习服

高原习服又称为高海拔适应，是指居住在相对低海拔的个体进入相对较高海拔的地区后，机体的各种组织器官发生一系列的形态结构和功能变化来适应高原低氧环境。通过高原习服，人们能快速适应高原低氧低压环境。目前主要通过低氧预适应、适应性锻炼和阶梯习服等方式进行高海拔适应[50]。

6. 小结与展望

高海拔地区的低压低氧环境会造成脑组织缺氧，进而通过心理生理变化、氧化应激、神经递质的改变、大脑结构的改变引起认知功能的改变。随着经济及高原旅游业的发展，越来越多的人在高海拔地区工作、生活和旅游，高原环境带来的身心健康挑战日益突出。但就目前而言，仍需更多的基础及临床研究证实低压低氧环境对认知功能的影响。后期通过控制相关因素，尽可能早预防、早干预低压低氧环境对人体认知功能的影响，降低低压低氧环境下认知障碍发病率，延缓认知障碍的发展进程，减轻疾病负担并提高低压低氧环境下居民的生活水平。

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参考文献

[1] Ni, X., Wu, F., Song, J., An, L., Jiang, Q., Bai, T., *et al*. (2022) Chinese Expert Consensus on Assessment of Cognitive Impairment in the Elderly. *Aging Medicine*, **5**, 154-166. https://doi.org/10.1002/agm2.12222

[2] Liu, S., Wang, F., Zhang, C., Zhang, Q., Dang, Z., Ng, C.H., *et al*. (2022) Cognitive Impairment and Its Associated Factors in Older Adults Living in High and Low Altitude Areas: A Comparative Study. *Frontiers in Psychiatry*, **13**, Article ID: 871414. https://doi.org/10.3389/fpsyt.2022.871414

[3] Zhu, D., Zhang, M., He, B., Wan, Y., Wang, L. and Gao, F. (2022) The Role of Sex and Ovarian Hormones in Hippocampal Damage and Cognitive Deficits Induced by Chronic Exposure to Hypobaric Hypoxia. *Frontiers in Neuroscience*, **16**, Article ID: 953417. https://doi.org/10.3389/fnins.2022.953417

[4] Terraneo, L. and Samaja, M. (2017) Comparative Response of Brain to Chronic Hypoxia and Hyperoxia. *International Journal of Molecular Sciences*, **18**, Article No. 1914. https://doi.org/10.3390/ijms18091914

[5] Zhang, Z., Sun, Y., Yuan, Z., Wang, L., Dong, Q., Zhou, Y., *et al*. (2022) Insight into the Effects of High-Altitude Hypoxic Exposure on Learning and Memory. *Oxidative Medicine and Cellular Longevity*, **2022**, Article ID: 4163188. https://doi.org/10.1155/2022/4163188

[6] Fogwe, L.A., Reddy, V. and Mesfin, F.B. (2024) Neuroanatomy, Hippocampus. StatPearls Publishing LLC, Treasure Island.

[7] Calabresi, P., Castrioto, A., Di Filippo, M. and Picconi, B. (2013) New Experimental and Clinical Links between the Hippocampus and the Dopaminergic System in Parkinson's Disease. *The Lancet Neurology*, **12**, 811-821. https://doi.org/10.1016/s1474-4422(13)70118-2

[8] Churchyard, A. and Lees, A.J. (1997) The Relationship between Dementia and Direct Involvement of the Hippocampus and Amygdala in Parkinson's Disease. *Neurology*, **49**, 1570-1576. https://doi.org/10.1212/wnl.49.6.1570

[9] Lisman, J., Buzsáki, G., Eichenbaum, H., Nadel, L., Ranganath, C. and Redish, A.D. (2017) Viewpoints: How the Hippocampus Contributes to Memory, Navigation and Cognition. *Nature Neuroscience*, **20**, 1434-1447. https://doi.org/10.1038/nn.4661

[10] Moriguchi, T., Harii, N., Goto, J., Harada, D., Sugawara, H., Takamino, J., *et al*. (2020) A First Case of Meningitis/Encephalitis Associated with SARS-Coronavirus-2. *International Journal of Infectious Diseases*, **94**, 55-58. https://doi.org/10.1016/j.ijid.2020.03.062

[11] Zhang, Y.Q., Zhang, W.J., Liu, J.H. and Ji, W.Z. (2022) Effects of Chronic Hypoxic Environment on Cognitive Function and Neuroimaging Measures in a High-Altitude Population. *Frontiers in Aging Neuroscience*, **14**, Article ID: 788322. https://doi.org/10.3389/fnagi.2022.788322

[12] Quattrocchi, C.C., Longo, D., Delfino, L.N., Errante, Y., Aiello, C., Fariello, G., *et al*. (2012) MR Differential Diagnosis of Acute Deep Grey Matter Pathology in Paediatric Patients. *Pediatric Radiology*, **43**, 743-761. https://doi.org/10.1007/s00247-012-2491-2

[13] Wang, X., Wei, W., Yuan, F., Li, S., Lin, J. and Zhang, J. (2018) Regional Cerebral Blood Flow in Natives at High Altitude: An Arterial Spin Labeled MRI Study. *Journal of Magnetic Resonance Imaging*, **48**, 708-717. https://doi.org/10.1002/jmri.25996

[14] Braunsdorf, M., Blazquez Freches, G., Roumazeilles, L., Eichert, N., Schurz, M., Uithol, S., *et al*. (2021) Does the Temporal Cortex Make Us Human? A Review of Structural and Functional Diversity of the Primate Temporal Lobe. *Neuroscience & Biobehavioral Reviews*, **131**, 400-410. https://doi.org/10.1016/j.neubiorev.2021.08.032

[15] Zhang, X. and Zhang, J. (2022) The Human Brain in a High Altitude Natural Environment: A Review. *Frontiers in Human Neuroscience*, **16**, Article ID: 915995. https://doi.org/10.3389/fnhum.2022.915995

[16] Chen, X., Liu, J., Wang, J., Xin, Z., Zhang, Q., Zhang, W., *et al*. (2020) Altered Resting-State Networks May Explain the Executive Impairment in Young Health Immigrants into High-Altitude Area. *Brain Imaging and Behavior*, **15**, 147-156. https://doi.org/10.1007/s11682-019-00241-1

[17] Xin, Z., Chen, X., Zhang, Q., Wang, J., Xi, Y., Liu, J., *et al*. (2020) Alteration in Topological Properties of Brain Functional Network after 2-year High Altitude Exposure: A Panel Study. *Brain and Behavior*, **10**, e01656. https://doi.org/10.1002/brb3.1656

[18] Hota, S.K., Barhwal, K., Baitharu, I., Prasad, D., Singh, S.B. and Ilavazhagan, G. (2009) *Bacopa monniera* Leaf Extract Ameliorates Hypobaric Hypoxia Induced Spatial Memory Impairment. *Neurobiology of Disease*, **34**, 23-39. https://doi.org/10.1016/j.nbd.2008.12.006

[19] Jain, K., Prasad, D., Singh, S.B. and Kohli, E. (2015) Hypobaric Hypoxia Imbalances Mitochondrial Dynamics in Rat Brain Hippocampus. *Neurology Research International*, **2015**, Article ID: 742059. https://doi.org/10.1155/2015/742059

[20] Bailey, D.M., Brugniaux, J.V., Filipponi, T., Marley, C.J., Stacey, B., Soria, R., *et al*. (2018) Exaggerated Systemic Oxidative-Inflammatory-Nitrosative Stress in Chronic Mountain Sickness Is Associated with Cognitive Decline and Depression. *The Journal of Physiology*, **597**, 611-629. https://doi.org/10.1113/jp276898

[21] Bhatt, S., Nagappa, A.N. and Patil, C.R. (2020) Role of Oxidative Stress in Depression. *Drug Discovery Today*, **25**, 1270-1276. https://doi.org/10.1016/j.drudis.2020.05.001

[22] Snyder, B., Shell, B., Cunningham, J.T. and Cunningham, R.L. (2017) Chronic Intermittent Hypoxia Induces Oxidative Stress and Inflammation in Brain Regions Associated with Early-Stage Neurodegeneration. *Physiological Reports*, **5**, e13258. https://doi.org/10.14814/phy2.13258

[23] Cools, R. and Arnsten, A.F.T. (2021) Neuromodulation of Prefrontal Cortex Cognitive Function in Primates: The Powerful Roles of Monoamines and Acetylcholine. *Neuropsychopharmacology*, **47**, 309-328. https://doi.org/10.1038/s41386-021-01100-8

[24] Gil, S.M. and Metherate, R. (2018) Enhanced Sensory-Cognitive Processing by Activation of Nicotinic Acetylcholine Receptors. *Nicotine & Tobacco Research*, **21**, 377-382. https://doi.org/10.1093/ntr/nty134

[25] Cunha-Rodrigues, M.C., Balduci, C.T.D.N., Tenório, F. and Barradas, P.C. (2018) GABA Function May Be Related to the Impairment of Learning and Memory Caused by Systemic Prenatal Hypoxia-Ischemia. *Neurobiology of Learning and Memory*, **149**, 20-27. https://doi.org/10.1016/j.nlm.2018.01.004

[26] Sharma, R., Cramer, N.P., Perry, B., Adahman, Z., Murphy, E.K., Xu, X., *et al*. (2019) Chronic Exposure to High Altitude: Synaptic, Astroglial and Memory Changes. *Scientific Reports*, **9**, Article No. 16406. https://doi.org/10.1038/s41598-019-52563-1

[27] Li, Y. and Wang, Y. (2022) Effects of Long-Term Exposure to High Altitude Hypoxia on Cognitive Function and Its Mechanism: A Narrative Review. *Brain Sciences*, **12**, Article No. 808. https://doi.org/10.3390/brainsci12060808

[28] Shanjun, Z., Shenwei, X., Bin, X., Huaijun, T., Simin, Z. and Peng, L. (2020) Individual Chronic Mountain Sickness Symptom Is an Early Warning Sign of Cognitive Impairment. *Physiology & Behavior*, **214**, Article ID: 112748. https://doi.org/10.1016/j.physbeh.2019.112748

[29] Niu, G., Zhu, D., Zhang, X., Wang, J., Zhao, Y. and Wang, X. (2018) Role of Hypoxia-Inducible Factors 1α (HIF1α) in SH-SY5Y Cell Autophagy Induced by Oxygen-Glucose Deprivation. *Medical Science Monitor*, **24**, 2758-2766. https://doi.org/10.12659/msm.905140

[30] McMorris, T., Hale, B.J., Barwood, M., Costello, J. and Corbett, J. (2017) Effect of Acute Hypoxia on Cognition: A Systematic Review and Meta-Regression Analysis. *Neuroscience & Biobehavioral Reviews*, **74**, 225-232. https://doi.org/10.1016/j.neubiorev.2017.01.019

[31] Raven, F., Van der Zee, E.A., Meerlo, P. and Havekes, R. (2018) The Role of Sleep in Regulating Structural Plasticity and Synaptic Strength: Implications for Memory and Cognitive Function. *Sleep Medicine Reviews*, **39**, 3-11. https://doi.org/10.1016/j.smrv.2017.05.002

[32] Zarekiani, P., Breur, M., Wolf, N.I., de Vries, H.E., van der Knaap, M.S. and Bugiani, M. (2021) Pathology of the Neurovascular Unit in Leukodystrophies. *Acta Neuropathologica Communications*, **9**, Article No. 103. https://doi.org/10.1186/s40478-021-01206-6

[33] Serlin, Y., Shelef, I., Knyazer, B. and Friedman, A. (2015) Anatomy and Physiology of the Blood-Brain Barrier. *Seminars in Cell & Developmental Biology*, **38**, 2-6. https://doi.org/10.1016/j.semcdb.2015.01.002

[34] V. Lafuente, J., Bermudez, G., Camargo-Arce, L. and Bulnes, S. (2016) Blood-Brain Barrier Changes in High Altitude. *CNS & Neurological Disorders—Drug Targets*, **15**, 1188-1197. https://doi.org/10.2174/1871527315666160920123911

[35] Li, R., Wang, T., Lyu, P., Liu, Y., Chen, W., Fan, M., *et al*. (2018) Effects of Plasma Lipids and Statins on Cognitive Function. *Chinese Medical Journal*, **131**, 471-476. https://doi.org/10.4103/0366-6999.225062

[36] Morrison, S.A., Mirnik, D., Korsic, S., Eiken, O., Mekjavic, I.B. and Dolenc-Groselj, L. (2017) Bed Rest and Hypoxic Exposure Affect Sleep Architecture and Breathing Stability. *Frontiers in Physiology*, **8**, Article No. 410. https://doi.org/10.3389/fphys.2017.00410

[37] Hernández-Vásquez, A., Vargas-Fernández, R., Rojas-Roque, C. and Gamboa-Unsihuay, J.E. (2022) Association between Altitude and Depression in Peru: An 8-Year Pooled Analysis of Population-Based Surveys. *Journal of Affective Disorders*, **299**, 536-544. https://doi.org/10.1016/j.jad.2021.12.059

[38] Kious, B.M., Kondo, D.G. and Renshaw, P.F. (2018) Living High and Feeling Low: Altitude, Suicide, and Depression. *Harvard Review of Psychiatry*, **26**, 43-56. https://doi.org/10.1097/hrp.0000000000000158

[39] Pun, M., Guadagni, V., Bettauer, K.M., Drogos, L.L., Aitken, J., Hartmann, S.E., *et al*. (2018) Effects on Cognitive Functioning of Acute, Subacute and Repeated Exposures to High Altitude. *Frontiers in Physiology*, **9**, Article No. 1131. https://doi.org/10.3389/fphys.2018.01131

[40] Hüfner, K., Sperner-Unterweger, B. and Brugger, H. (2019) Going to Altitude with a Preexisting Psychiatric Condition. *High Altitude Medicine & Biology*, **20**, 207-214. https://doi.org/10.1089/ham.2019.0020

[41] Aajami, Z., kazazi, L., Troski, M., Bahrami, M. and Borhaninejad, V. (2020) Relationship between Depression and Cognitive Impairment among Elderly: A Cross-Sectional Study. *Journal of Caring Sciences*, **9**, 148-153. https://doi.org/10.34172/jcs.2020.022

[42] 中华医学会精神医学分会抑郁障碍研究协作组. 抑郁症认知症状评估与干预专家共识[J]. 中华精神科杂志, 2020, 53(5): 369-376.

[43] Daly, S., Thorpe, M., Rockswold, S., Hubbard, M., Bergman, T., Samadani, U., *et al*. (2018) Hyperbaric Oxygen Therapy in the Treatment of Acute Severe Traumatic Brain Injury: A Systematic Review. *Journal of Neurotrauma*, **35**, 623-629. https://doi.org/10.1089/neu.2017.5225

[44] Maroon, J.C. (2022) The Effect of Hyperbaric Oxygen Therapy on Cognition, Performance, Proteomics, and Telomere Length—The Difference between Zero and One: A Case Report. *Frontiers in Neurology*, **13**, Article ID: 949536. https://doi.org/10.3389/fneur.2022.949536

[45] Marcinkowska, A.B., Mankowska, N.D., Kot, J. and Winklewski, P.J. (2021) Impact of Hyperbaric Oxygen Therapy on Cognitive Functions: A Systematic Review. *Neuropsychology Review*, **32**, 99-126. https://doi.org/10.1007/s11065-021-09500-9

[46] Huang, T., Lai, J., Du, Y., Xu, Y., Ruan, L. and Hu, S. (2019) Current Understanding of Gut Microbiota in Mood Disorders: An Update of Human Studies. *Frontiers in Genetics*, **10**, Article No. 98. https://doi.org/10.3389/fgene.2019.00098

[47] Novotný, M., Klimova, B. and Valis, M. (2019) Microbiome and Cognitive Impairment: Can Any Diets Influence Learning Processes in a Positive Way? *Frontiers in Aging Neuroscience*, **11**, Article No. 170. https://doi.org/10.3389/fnagi.2019.00170

[48] Brown, E. and Taylor, C.T. (2017) Hypoxia-Sensitive Pathways in Intestinal Inflammation. *The Journal of Physiology*, **596**, 2985-2989. https://doi.org/10.1113/jp274350

[49] L'Huillier, C., Jarbeau, M., Achamrah, N., Belmonte, L., Amamou, A., Nobis, S., *et al*. (2019) Glutamine, but Not Branched-Chain Amino Acids, Restores Intestinal Barrier Function during Activity-Based Anorexia. *Nutrients*, **11**, Article No. 1348. https://doi.org/10.3390/nu11061348

[50] Jung, M., Zou, L., Yu, J.J., Ryu, S., Kong, Z., Yang, L., *et al*. (2020) Does Exercise Have a Protective Effect on Cognitive Function under Hypoxia? A Systematic Review with Meta-Analysis. *Journal of Sport and Health Science*, **9**, 562-577. https://doi.org/10.1016/j.jshs.2020.04.004