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不同海拔高原低压缺氧环境下大鼠肠道病理损伤特点*

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摘要 目的:探讨不同海拔高度的高原低压缺氧环境下大鼠肠道病理损伤的特点。**方法:**将 30 只 SD 雄性大鼠随机分 5 组:平原对照组、5000 米海拔高度 10 天组、5000 米海拔高度 21 天组、6500 米海拔高度 10 天组、6500 米海拔高度 21 天组,每组 6 只。大鼠在平原环境或模拟高原环境中常规饲养,在相应时间点,深度麻醉受试大鼠致死,取材,固定、HE 染色后镜检并进行病理学损伤评分。**结果:**各高原组空、回肠病理损伤评分均显著高于平原对照组($P<0.01$),5000 m 暴露 21d 组空肠、回肠、结肠病理损伤评分显著高于 5000 m 暴露 10 d 组,明显低于 6500 m 暴露 21d 组,6500 m 暴露 10d 组空肠、回肠、结肠病理损伤评分显著高于 5000 m 暴露 10 d 组($P<0.01$ 或 $P<0.05$)。5000 m 暴露 10 d 组结肠损伤病理评分与平原对照组比较差异无统计学意义,其余高原组结肠病理损伤评分均显著高于平原对照组($P<0.01$ 或 $P<0.05$)。5000 m 暴露 21 d 组空肠与结肠病理损伤评分存在显著性差异($P<0.05$); 6500 m 暴露 21 d 组空肠和回肠均与结肠病理损伤评分存在显著性差异($P<0.05$, $P<0.01$)。**结论:**肠道粘膜随着海拔高度和缺氧时间的延长而损伤加重。在相同的情况下,小肠的损伤较结肠严重,但空肠和回肠的损伤无明显差异,结肠损伤的发生较晚且与高原环境停留时间具有明显关系,提示在进入高原早期应将小肠病理损伤的防治作为重点。

关键词:高原;低压缺氧;肠道;病理损伤

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Characteristics of Pathological Injury of Intestinal Tract in Rats under Hypobaric Hypoxia Environment at Different High Altitude*

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ABSTRACT Objective: To study the characteristics of intestinal tract pathological injury of rats in hypobaric hypoxia at different high altitude. **Methods:** 30 male SD rats were randomly divided into 5 groups: Plain group ($n=6$), High-altitude (HA) 5000 m for 10 day group ($n=6$), HA 5000 m for 21day group ($n=6$), HA 6500 m for 10day group ($n=6$), HA 6500 m for 21day group ($n=6$). Rats were raised normally either in plain or simulated high altitude environment, at the corresponding time point, rats were euthanized, small intestines were harvested, fixed tissues were processed routinely into paraffin and sections were stained routinely with hematoxylin and eosin. Morphologic parameters were measured by optical microscope and then the pathological injury score were evaluated. **Results:** The pathological injury scores of jejunum and ileum in the high altitude group were significantly higher than that of the plain group ($P<0.01$), the pathological injury scores of jejunum, ileum and colon were significantly higher in the HA 5000 m for 21 day group than that of the HA 5000 m for 10 day group, but significant lower than that of the HA 6500 m for 21 day group, the pathological injury scores of jejunum, ileum and colon were significantly higher in the HA 6500 m for 10 day group than that of the HA 5000 m for 10 day group ($P<0.01$, $P<0.05$). The pathological injury scores of colon were significantly higher in the groups of the high altitude than the plain group except for the HA 5000 m for 10 day group ($P<0.01$, $P<0.05$). The pathological injury scores of jejunum had significant different with that of the colon in the HA 5000 m for 21 day group ($P<0.05$); the pathological injury scores of both jejunum and ileum had significant different with that of the colon in the HA 6500 m for 21 day group ($P<0.05$, $P<0.01$). **Conclusions:** The injuries of the intestinal mucosa became serious with the with rising altitude and the stayed time, the intestinal injuries were more serious than that of colon at same situation, however there were no significant different between jejunum and ileum, the injuries of colon happened later than intestine, and they correlated with the stay time in the high altitude, which indicated that intestinal injury should be pay more attention in the early time of entering the hypobaric hypoxia environment of the high altitude.

Key words: High altitude; Hypobaric hypoxia; Intestinal tract; Pathological injury

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前言

与低海拔地区相比,高原环境的主要特点是低气压、缺氧、低温、强紫外线和气候多变等,此环境对人类的生存是一种挑战^[1,2]。高原环境对人体的影响是多方面的,但是更多的研究都更集中于心、肺脑等较大脏器、血液循环以及认知功能方面,对于消化系统方面的研究较少^[3]。有研究表明暴露于高原低氧环境可严重损伤肠粘膜结构,不仅引起肠粘膜绒毛卷曲、倒伏、凝结,也使肠粘膜微血管损伤、通透性增高,导致纤维蛋白及血细胞大量漏出,使粘膜屏障功能严重破坏^[4]。同时,机体对缺氧环境产生应激,交感神经兴奋性增加,使肠粘膜下静脉开放,流经肠粘膜血流减少,加剧胃肠粘膜缺血缺氧,使肠粘膜受损^[5,6]。但不同海拔的高原环境下停留不同时间时,空肠、回肠和结肠粘膜的病理损伤特点目前尚未见到明确报道。因此,本研究在我院西北特殊环境人工实验舱内模拟不同海拔高度,探讨在不同海拔高度的高原低压缺氧环境下停留不同时间对大鼠空肠、回肠、结肠的病理损伤特点,以期高原条件下营养支持和肠粘膜损伤保护的研究提供理论依据。

1 材料与方法

1.1 实验动物及分组

30 只雄性 SD 大鼠,250-280 g,购自新疆实验动物研究中心,生产许可证号:SCXK(新)2011-0001,使用许可证号:SYXK(军)2012-0027。预饲一周后,实验分 5 组:平原对照组(6 只)、5000 米海拔高度 10 天组(6 只)、5000 米海拔高度 21 天组(6 只)、6500 米海拔高度 10 天组(6 只)、6500 米海拔高度 21 天组(6 只)。高原环境在我院研制的“西北特殊环境人工实验舱”中进行,分别设置 5000 米、6500 米海拔高度,温度均控制在 25℃。实验组分批放置在 5000 米或 6500 米海拔高度环境,放置时间分别为 10 天和 21 天,对照组 6 只放置在平原环境下,高原实验组在进入高原模拟环境中给予正常饮食。

1.2 方法

1.2.1 取材和固定 在相应时间点,3%戊巴比妥钠 30 mg/kg 体重腹腔注射深度麻醉动物致死,对处死的大鼠迅速取出大鼠消化道各段组织,生理盐水冲洗肠道内容物,将肠道横切面剖开平摊于包埋盒内,注明标本号、高原高度及标本名称后,立即投入 10%中性甲醛固定液中充分固定。固定 24 小时后,进行修剪、取材,石蜡包埋。

1.2.2 检测指标及病理学评分 进行病理切片、HE 染色、光镜下观察组织病理学变化,BI2000 图像分析系统采图。参考 Chiu's^[7]评分法进行肠道病理学损伤评分,具体为:正常的肠黏膜 0 分;肠黏膜顶端上皮轻度水肿、毛细血管扩张充血 1 分;肠黏膜上皮细胞与固有层间隙增大 2 分;肠黏膜部分固有层顶端裸露、上皮细胞脱落 3 分;黏膜固有层裸露或腺上皮结构消失、毛细血管扩张充血,可能伴随固有层炎细胞浸润 4 分;肠黏膜出血、溃疡,固有层崩解 5 分,由 2 名副主任医师职称的病理专家进行读片并评分。

1.3 统计学分析

统计学软件采用 SPSS 23.0,计量资料均以均数±标准差表示,多组间比较采用单因素方差分析,两组间比较采用 LSD 法,以 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 各组大鼠空肠损伤病理学评分比较

各组大鼠在不同海拔的高原模拟舱内暴露不同时间后,空肠镜下可见:(1)5000 m 暴露 10 d 后,空肠黏膜皱襞表面变性,有炎细胞浸润,部分固有层毛细血管扩张充血(见图 1-A),平均病理学损伤评分为 1.68 ± 0.46 ;(2)5000 m 暴露 21 d 后,空肠固有层血管扩张充血,有多个炎细胞浸润,部分黏膜下层血管扩张充血(见图 1-D),平均病理学损伤评分为 2.37 ± 0.50 ;(3)6500 m 暴露 10 d 后,可见空肠固有层血管扩张充血,大量炎细胞浸润,部分黏膜下层血管扩张充血(见图 1-G),平均病理学损伤评分为 2.74 ± 0.43 ;(4)6500 m 暴露 21 d 后,空肠部分绒毛表面上皮变性脱落(见图 1-J),平均病理学损伤评分为 4.01 ± 0.68 。空肠平原对照组病理损伤评分为 0.75 ± 0.21 ,各高原组空肠病理损伤评分均显著高于平原对照组($P<0.01$),5000 m 暴露 21 d 组空肠病理损伤评分显著高于 5000 m 暴露 10 d 组,明显低于 6500 m 暴露 21 d 组,6500 m 暴露 10 d 组空肠病理损伤评分显著高于 5000 m 暴露 10 d 组($P<0.01$ 或 $P<0.05$)。

2.2 各组大鼠回肠损伤病理学评分比较

各组大鼠在不同海拔的高原模拟舱内暴露不同时间后回肠镜下可见:(1)5000 m 暴露 10 d 后,回肠固有层毛细血管扩张充血,间质细胞水肿,偶见部分腺上皮细胞核浓缩(见图 1-B),平均病理学损伤评分为 1.79 ± 0.52 ;(2)5000 m 暴露 21 d 后,回肠固有层毛细血管扩张充血,腺体结构基本正常(见图 1-E),平均病理学损伤评分为 2.43 ± 0.57 ;(3)6500 m 暴露 10 d 后,回肠部分固有层毛细血管扩张充血,周围有较多炎细胞浸润,黏膜下肌层未见异常,固有层有较多炎细胞浸润(见图 1-H),平均病理学损伤评分为 2.98 ± 0.55 ;(4)6500 m 暴露 21 d 后,回肠部分黏膜皱襞变性坏死,有大量炎细胞浸润,部分黏膜肌下层、固有层血管扩张充血,肌层未见明显病变(见图 1-K),平均病理学损伤评分为 4.32 ± 0.51 。回肠平原对照组病理损伤评分为 0.81 ± 0.22 ,各高原组回肠病理损伤评分均显著高于平原对照组($P<0.01$),5000 m 暴露 21 d 组回肠病理损伤评分显著高于 5000 m 暴露 10 d 组,明显低于 6500 m 暴露 21 d 组,6500 m 暴露 10 d 组回肠病理损伤评分显著高于 5000 m 暴露 10 d 组($P<0.01$ 或 $P<0.05$)。

2.3 各组大鼠结肠损伤病理学评分

各组大鼠在不同海拔的高原模拟舱内暴露不同时间后回肠镜下可见:(1)5000 m 暴露 10 d 后,结肠粘膜顶端上皮轻度水肿、毛细血管扩张充血(见图 1-C),平均病理学损伤评分为 1.25 ± 0.41 ;(2)5000 m 暴露 21 d 后,结肠固有层与黏膜下层部分血管扩张充血(见图 1-F),平均病理学损伤评分为 1.95 ± 0.73 ;(3)6500 m 暴露 10 d 后,黏膜下血管扩张充血,有大量杯

状细胞(见图 1-I),平均病理学损伤评分为 2.39 ± 0.50 ; (4)6500 m 暴露 21 d 后,结肠肠黏膜部分固有层顶端裸露、上皮细胞脱落(见图 1-L),平均病理学损伤评分为 3.22 ± 0.61 。结肠平原对照组病理损伤评分为 0.82 ± 0.26 ,除了 5000 m 暴露 10 d 组结肠损伤病理评分与平原对照组比较差异无统计学意义外,其余

高原组结肠病理损伤评分均显著高于平原对照组 ($P < 0.01$ 或 $P < 0.05$)。5000 m 暴露 21 d 组结肠病理损伤评分显著高于 5000 m 暴露 10 d 组,明显低于 6500 m 暴露 21 d 组,6500 m 暴露 10 d 组结肠病理损伤评分显著高于 5000 m 暴露 10 d 组 ($P < 0.01$ 或 $P < 0.05$)。

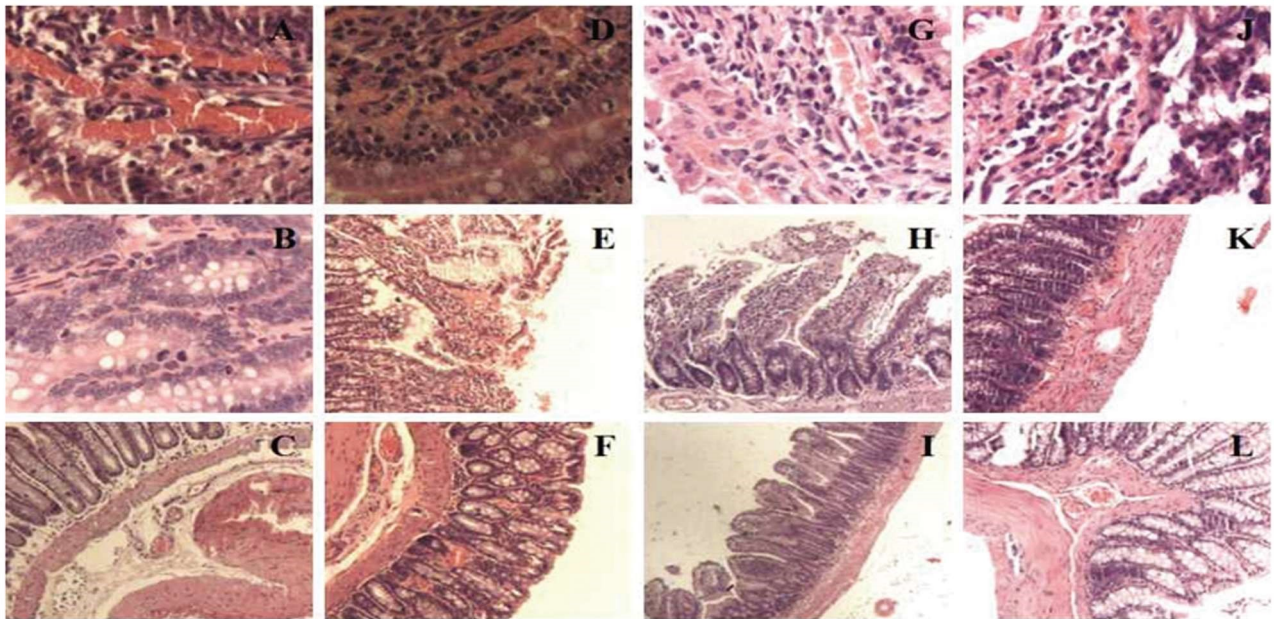


图 1 空肠、回肠、结肠在不同海拔高度和时间点的 HE 染色结果($\times 200$)

Fig.1 Pathological observation of jejunum, ileum and colon at different altitude for different time detected by HE staining($\times 200$)

注:5000 m, 10 d 组(A 空肠, B 回肠, C 结肠); 5000 m, 21 d 组(D 空肠, E 回肠, F 结肠);

6500 m, 10 d 组(G 空肠, H 回肠, I 结肠); 6500 m, 21 d 组(J 空肠, K 回肠, L 结肠);

Note: 5000 m, 10 d group(A jejunum, B ileum, C colon); 5000 m, 21 d group(D jejunum, E ileum, F colon);

6500 m, 10 d group(G jejunum, H ileum, I colon); 6500 m, 21 d group(J jejunum, K ileum, L colon); ($\times 200$)

2.4 同一海拔高度及放置时间空肠、回肠及结肠间病理损伤评分比较

虽然各组中空肠、回肠的病理损伤评分均高于结肠,但平原组、5000 m 暴露 10 d 组和 6500 m 暴露 10 d 组的空肠、回肠和结肠病理损伤评分比较差异均无统计学意义 ($P > 0.05$); 5000 m 暴

露 21 d 组空肠与结肠病理损伤评分存在显著性差异 ($P < 0.05$); 6500 m 暴露 21 d 组空肠和回结肠均与结肠病理损伤评分存在显著性差异 ($P < 0.05$, $P < 0.01$); 虽然高原实验组回肠的病理损伤评分均略高于空肠,但差异均无统计学意义 ($P > 0.05$)。见表 1。

表 1 各组肠病理损伤评分比较($\bar{x} \pm s$)

Table 1 Comparison of the pathological injury score of Jejunum, Ileum and Colon between different groups($\bar{x} \pm s$)

Group	0 d		10 day		21 day
	Plain	5000 m	6500 m	5000 m	6500 m
Jejunum	0.75 ± 0.21	1.68 ± 0.46	2.37 ± 0.50	2.74 ± 0.43	$4.01 \pm 0.68^{\#}$
Ileum	0.81 ± 0.22	1.79 ± 0.52	2.43 ± 0.57	$2.98 \pm 0.55^{\#}$	$4.32 \pm 0.51^*$
Colon	0.82 ± 0.26	1.25 ± 0.41	1.95 ± 0.73	2.39 ± 0.50	3.22 ± 0.61

Note: compared with the colon group, $^{\#}P < 0.05$, $^*P < 0.01$.

3 讨论

高原缺氧可引起机体产生复杂的病理生理改变。急进高原后,除有头昏、头痛、胸闷、心慌、气短等急性高原反应外,高原胃肠应激反应的发生率较高,甚至可出现胃肠道出血和消化性溃疡等。高原胃肠应激综合症的发生与肠道黏膜屏障的损伤有关。在高原低氧条件下,机体交感神经兴奋,肠血管收缩,肠道

缺血缺氧加重,肠粘膜中氧自由基生成过多导致粘膜损伤^[8,9]。Xu C 等^[10]将大鼠放置在模拟高原 7000 m 的气候舱内 5 天,发现高原缺氧可引起引起小肠绒毛的破坏。

本研究结果显示空肠、回肠、结肠的病理学评分随着海拔高度和缺氧时间的延长而增加。高原对肠道损害与高原海拔高度和高原暴露时间均存在一定关系,其损伤的可能机制如下: (1)小肠运输功能障碍: Wojtal KA 等^[11]研究认为缺氧是影响小

肠功能的重要因素,氧供的减少影响着十二指肠的溶质载体的表达模式,同时影响着血清炎症因子水平和生物活性物质的变化,提示人类暴露在缺氧环境下,小肠的运输功能受到明显影响,进而影响肠道功能。(2)炎症因子表达及信号通路异常:Zhang FX 等将大鼠分别放在平原(500 m),高原海拔 3842 m 和 4767 m 两个海拔高度 3 天后,发现低压氧缺氧可提高缺氧诱导因子-1 α (HIF-1 α)和诱导型一氧化氮合酶(iNOS)的表达,并随着粘膜的损害加重而表达增加,提示 HIF-1 α 引导的 iNOS 表达在肠粘膜损害过程中可能发挥了一定的作用。HIF-1 α 是形成促红细胞生成素的调节因子,促红细胞生成素可提高组织氧供以对抗缺氧造成的损害。在缺氧条件下,HIF-1 α 氧气依赖的羟基化减少,HIF-1 α 活性增加。多个研究表明缺氧通过 PI3-kinase/AKT/mTOR 通路诱导 HIF-1 α 的表达^[12-15]。Luo H 等^[16]研究认为 Toll 样受体-4(TLR4)和核转录因子- κ B(NF- κ B)随着大鼠在高原环境的急性缺氧在肠组织中表达增加,应用 NF- κ B 抑制剂 PDTC 可逆转 TLR4 和 NF- κ B 的表达从而减轻肠道的损害和细菌移位,因此,TLR4/NF- κ B 信号通路可能是缺氧诱导肠粘膜屏障破坏和细菌移位的重要机制。(3)细菌移位、内毒素及细胞凋亡:Zhou QQ 等^[17]将 SD 大鼠放置在 7000 海拔高度 72 小时,发现小肠伴随着粘膜固有层水肿和红细胞渗出,出现上皮细胞凋亡、绒毛脱落、炎症细胞增加,提示小肠损害的示踪剂硝酸镧出现在细胞间隙,细菌明显移位到肠系膜淋巴结和脾脏,血清内毒素、二氨基氧化酶(DAO)、丙二醛(MDA)水平明显升高,然而肠内超氧化物歧化酶(SOD)、DAO、谷氨酰胺(Gln)水平明显减低。(4)肠道微生物特性改变:Adak A 等^[18]研究表明在高原低压缺氧环境下,胃肠道功能紊乱是一个常见现象。高原缺氧能够改变胃肠道微生物特性,随之出现上皮细胞屏障功能异常,因而认为肠道微生物的改变可能与小肠粘膜损伤有关。(5)自噬的影响:Zhang FX 等^[19]将大鼠放置模拟 4767 m 的高原减压舱内,与平原组相比,急性暴露高原环境可引起小肠上皮的时间依赖性损伤,在急性暴露 6 h 后,伴随着小肠损害可见自噬小体出现,自噬在小肠功能衰竭时明显增多,在急性暴露高原环境 6 h、12 h、24 h 及 48 h 后可见调控自噬的关键蛋白 Beclin1 和 LC3B 表达明显高于平原组。

本研究结果提示结肠损伤可能与高原暴露时间有关,结肠损伤在进入高原早期不明显,在高原环境缺氧暴露时间越长,损伤越明显,我们推测其可能原因与结肠肠道菌群的变化有关。Adak A 等^[20]研究发现低压缺氧是急性高原病包括一些非特异性胃肠道并发症的关键始动因素,将大白鼠连续放在 55 kPa 大气压(4872.9 m 海拔高度)30 天,每天 8 小时,大肠菌群数与抗氧化指标过氧化氢酶(CAT)、SOD 和 MDA 增高及大肠上皮细胞还原型谷胱甘肽(GSH)和氧化型谷胱甘肽(GSSG)的减少有关。经过 30 天的缺氧刺激,需氧菌密度明显减少 104 倍,而厌氧菌增加 209 倍,大肠杆菌增加 125 倍。其他绝对厌氧菌如双歧杆菌类(3 倍)、拟杆菌类(134 倍)、乳酸杆菌类(7 倍),其他专性厌氧菌如产气荚膜梭菌(40 倍)等均与对照组相比明显升高。因而推测由高原缺氧所控制着的大肠需氧菌和厌氧菌的比例,在大肠上皮粘膜屏障破坏而造成大肠病理学损伤方面起重要作用。

总之,肠道黏膜随着海拔高度和缺氧时间的延长而损伤加重,在相同的情况下,小肠的损伤较结肠严重,但空肠和回肠的损伤无明显差异,结肠损伤的发生较晚且与高原环境停留时间具有明显关系,提示在进入高原早期应将小肠病理损伤的防治作为重点。

参考文献(References)

- [1] Netzer N, Strohl K, Faulhaber M, et al. Hypoxia-related altitude illnesses[J]. J Travel Med, 2013, 20: 247-255
- [2] Shin T. High Altitude Illnesses in Hawaii [J]. Hawaii J Med Public Health, 2014, 73(11Suppl 2): 4-6
- [3] Adak A, Maity C, Ghosh K, et al. Dynamics of predominant microbiota in the human gastrointestinal tract and change in luminal enzymes and immunoglobulin profile during high-altitude adaptation [J]. Folia Microbiol (Praha), 2013, 58: 523-528
- [4] 周波, 杨定周, 周其全. 模拟高原低氧环境暴露下家兔小肠黏膜扫描电镜观察[J]. 胃肠病学和肝病学杂志, 2009, 18(8): 751-753
Zhou Bo, Yang Ding-zhou, Zhou Qi-quan. The SEM observation of small intestinal mucosa in the rabbits under simulated high-altitude hypoxia [J]. Chinese Journal of Gastroenterology and Hepatology, 2009, 18(8): 751-753
- [5] Rodway GW, Hoffman LA, Sanders MH. High-altitude-related disorders-Part I: Pathophysiology, differential diagnosis, and treatment[J]. Heart Lung, 2003, 32(6): 353-359
- [6] Palmer BF, Clegg DJ. Oxygen sensing and metabolic homeostasis[J]. Mol Cell Endocrinol, 2014, 397: 51-58
- [7] Chiu CJ, McArdle AH, Brown R, et al. Intestinal Mucosal Lesion in Low-Flow States[J]. Arch Surg, 1970, 101(4): 478-483
- [8] 金其贯, 余奇, 金爱娜, 等. 模拟高原训练对大鼠小肠粘膜屏障的影响及其小麦肽的干预作用 [J]. 西安体育学院学报, 2014, 31(2): 225-230
Jin Qi-guan, She Qi, Jin Ai-na, et al. The effects of simulated altitude training on intestinal mucosa barrier in rats and the intervention of wheat peptide [J]. Journal of Xi'an Physical Education University, 2014, 31(2): 225-230
- [9] Yang Y, Qiu Y, Wang W, et al. Adenosine A2B receptor modulates intestinal barrier function under hypoxic and ischemia/reperfusion conditions[J]. Int J Clin Exp Pathol, 2014, 7: 2006-2018
- [10] Xu C, Sun R, Qiao X, et al. Effect of vitamin e supplementation on intestinal barrier function in rats exposed to high altitude hypoxia environment[J]. Korean J Physiol Pharmacol, 2014, 18(4): 313-20
- [11] Wojtal KA, Cee A, Lang S, et al. Downregulation of duodenal SLC transporters and activation of proinflammatory signaling constitute the early response to high altitude in humans [J]. Am J Physiol Gastrointest Liver Physiol, 2014, 307(7): G673-88
- [12] Zhang F, Wu W, Deng Z, et al. High altitude increases the expression of hypoxia-inducible factor 1 α and inducible nitric oxide synthase with intestinal mucosal barrier failure in rats [J]. Int J Clin Exp Pathol, 2015, 8(5): 5189-5195
- [13] Uusijarvi J, Eriksson K, Larsson AC, et al. Effects of hyperbaric oxygen on nitric oxide generation in humans [J]. Nitric Oxide, 2015, 44: 88-97

- Public Health, 2009, 26(5): 469-470
- [10] Junior OT, Roderjan CN, Neto EDC, et al. Haff disease associated with the ingestion of the freshwater fish *Mylossoma duriventre* (pacu-mantega) [J]. *Revista Brasileira de Terapia Intensiva*, 2013, 25 (4): 348-351
- [11] Yuen Y, Chen QT. Clinical analysis of 6 cases of Haff disease caused by crayfish[J]. *Natl Med J China*, 2001, 81(2): 1530-1531
- [12] Xie P, Hu J, Huang JM, et al. Crayfish-related Haff disease rhabdomyolysis; diagnosis supported by bone scintigraphy[J]. *Hell J Nucl Med*, 2013, 16(1): 60-61
- [13] Yi F, Yuan X G, Wang Y, et al. Clinical treatment of Food-borne rhabdomyolysis diagnosis [J]. *Intern Intensive Med*, 2012, 18 (6): 301-302
- [14] Feng G, Luo Q, Zhuang P, et al. Haff disease complicated by multiple organ failure after crayfish consumption: A case study [J]. *Rev Bras Ter Intensiva*, 2014, 26(4): 407-409
- [15] Gan L, Li Q, Gong NK, et al. Two cases of rhabdomyolysis diagnosis caused by eating crayfish [J]. *Liaoning Med Univ*, 2015, 36 (10): 111-112
- [16] Shenzhen Daily. Four Hospitalized after Eating Too Much Crawfish [R]. Available online: http://www.szdaily.com/content/2016-08/09/content_13700987.htm (accessed on 30 September 2016)
- [17] Zhang Bo, Yang Guang, Yu Xiang-bao, et al. Haff Disease after Eating Crayfish in East China[J]. *Intern Med*, 2012, 51(5): 487-489
- [18] Huang X, Li Y, Huang Q, et al. A past Haff disease outbreak associated with eating freshwater pomfret in South China [J]. *BMC Public Health*, 2013, 13(1): 447-454
- [19] Chen X.F, Huang P.P, Kang J, et al. Unexplained rhabdomyolysis: Clinical analysis of twenty three cases[J]. *Chin Emerg Med*, 2010, 19 (4): 1062-1065
- [20] Wu J.Z. A report on the diagnosis of rhabdomyolysis caused by crayfish in China [C]. In *Proceedings of the Second National Symposium on Acute and Severe Poisoning and Taishan Poisoning and Occupational Disease Summit Forum*, Jinan, China, 2011, 5(1): 25-30
- [21] Han L, Zhang J. Analysis of 11 cases of rhabdomyolysis syndrome caused by crayfish[J]. *Intern. Intensive Med*, 2011, 17(4): 314-316
- [22] Tong W, Yin GL. Treatment of two cases of rhabdomyolysis caused by eating crayfish[J]. *Nurs Pract Res*, 2011, 8(12): 157-158
- [23] Zhu L. Investigation of two crayfish cases related to rhabdomyolysis syndromes[J]. *Prev Med Trib*, 2015, 21: 700-703
- [24] Chen Y, Yuan B, Xie G, et al. Outbreak of Haff disease caused by consumption of crayfish (*Procambarus clarkii*), Nanjing, Jiangsu Province[J]. *Food Control*, 2016, 59(1): 690-694
- [25] Han LL, Xu RJ. Investigation and analysis of "crayfish incident" in Nanjing[J]. *Chin Health Insp*, 2012, 19(1): 75-78
- [26] Yuan BJ, Wu CL, Guo BF. Analysis of 2 cases of new rhabdomyolysis syndrome in Nanjing[J]. *Jiangsu Prev Med*, 2013, 24(1): 43-44
- [27] Zong WQ, Zhen SQ, Yuan BJ, et al. Epidemiological analysis of rhabdomyolysis syndrome caused by crayfish in Jiangsu Province during 2012 to 2014[J]. *Ood Saf Qual*, 2015, 6(2): 4258-4261
- [28] Chan TY. The Emergence and Epidemiology of Haff Disease in China [J]. *Toxins(Basel)*, 2016, 8(12): 351-359
- [29] Zong WQ, Zheng SQ, Liu JF. One severe case report of crayfish induced rhabdomyolysis diagnosis[J]. *Jiangsu J Prev Med*, 2016, 27(2): 227-228
- [30] Hou PS, Liu DS. We don't need to be worried about crawfish[R]. *Health Manag*, 2011, 2(1): 54

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- [14] Marhold M, Tomasich E, El-Gazzar A, et al. HIF-1alpha Regulates mTOR Signaling and Viability of Prostate Cancer Stem Cells[J]. *Mol Cancer Res*, 2015, 13: 556-564
- [15] Lee SH, Jee JG, Bae JS, et al. A Group of Novel HIF-1alpha Inhibitors, Glyceollins, Blocks HIF-1alpha Synthesis and Decreases Its Stability via Inhibition of the PI3K/AKT/mTOR Pathway and Hsp90 Binding[J]. *J Cell Physiol*, 2015, 230: 853-862
- [16] Luo H, Guo P, Zhou Q. Role of TLR4/NF- κ B in damage to intestinal mucosa barrier function and bacterial translocation in rats exposed to hypoxia[J]. *PloS One*, 2012, 7(10): e46291
- [17] Zhou QQ, Yang DZ, Luo YJ, et al. Over-starvation aggravates intestinal injury and promotes bacterial and endotoxin translocation under high-altitude hypoxic environment [J]. *World J Gastroenterol*, 2011, 17(12): 1584-1593
- [18] Adak A, Ghosh, Mondal KC. Modulation of small intestinal homeostasis along with its microflora during acclimatization at simulated hypobaric hypoxia[J]. *Indian J Exp Biol*, 2014, 52(11): 1098-1105
- [19] Zhang F, Deng Z, Li W, et al. Activation of autophagy in rats with plateau stress-induced intestinal failure [J]. *Int J Exp Pathol*, 2015, 8 (2): 1816-1821
- [20] Adak A, Maity C, Ghosh K, et al. Alteration of predominant gastrointestinal flora and oxidative damage of large intestine under simulated hypobaric hypoxia[J]. *Z Gastroenterol*, 2014, 52(2): 180-186