低压低氧暴露对大鼠空间记忆及海马谷氨酸受体表达的影响*

付中伟 徐 玫 杜可军 戴 鹏 陈迎雷 黄冠鹏 蔡同建 骆文静 陈景元△

(第四军医大学军事预防医学院劳动与环境卫生教研室 陕西 西安 710032)

摘要 目的：观察低压低氧暴露对成年大鼠空间记忆及谷氨酸递质系统受体(AMPA,NMDA)的影响。方法：SD大鼠随机分成两组，对照组和低氧组(n=10)，经过5天的Morris水迷宫训练，分别接受常压和低压低氧暴露7天，再通过Morris水迷宫观察暴露后的空间记忆，western blot检测GluR1，NMDA受体表达情况。结果：水迷宫结果显示低压低氧暴露后，平均逃脱潜伏期增长，平台搜索能力下降。Western blot结果显示磷酸化的GLUR1受体和NMDA受体水平升高。结论：低压低氧暴露可诱导大鼠的空间记忆损伤，其机制可能与谷氨酸递质系统紊乱造成的兴奋性中毒有关。

关键词：低压低氧；谷氨酸；空间记忆；GluR1；NMDA；兴奋性中毒

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Effect of Hypobaric Hypoxia to The Spatial Memory and Glutamate Receptor*

FU Zhong-wei, XU Mei, DU Ke-jun, DAI Peng, CHEN Ying-lei,

HUANG Guan-peng, CAI Tong-jian, LUO Wen-jing, CHEN Jing-yuan△

(Department of Occupational and Environmental Health, Faculty of Military Preventive Medicine, the Fourth Military Medial University, Shaanxi, Xi'an 710032, China)

ABSTRACT Objective: To investigate the effects of explosure to hypobaric hypoxia environment on spatial memory in adult rats and AMPA, NMDA receptors. Methods: Adult male SD rats were allocated randomized to the control and hypoxia groups. After five days of Morris Water Maze test training, two groups respectively exposed to normal atmospheric pressure or hypobaric hypoxia for 7days. The spatial memory was observed by morris water maze test. Western blot was used to detect the expression of GluR1 and NMDA. Result: In the Morris Water Maze test, the average escape latency increased and the ability to searching platform decreased significantly in the hypoxia group. Western blot results showed that the levels of p- GluR1 and NMDA rose. Conclusion: Exposing to hypobaric hypoxia leads to spatial memory damage in adult rats which may be related to the excitotoxicity resulted by glu transmitter system disorder.

Key words: Hypobaric hypoxia; Spatial memory; Glutamate; GluR1; NMDA; Excitotoxicity

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前言

高海拔低气压环境可对人体产生生理和心理上的影响，尤其是初到高原者，可能会产生剧烈的急性高原反应如头痛，恶心，失眠，眩晕，严重者发生急性高原病中高原脑水肿，高原肺水肿，其致死率很高[1]。另外处于不同的海拔及不同的低压持续时间会对认知功能产生影响[1,2]。人群研究和动物实验发现围产期低氧暴露会使智力发育滞后和发育不足[3,4]。低压低氧暴露同样对成年大鼠的学习记忆功能产生不利影响[5]。

在学习记忆产生的机制中，谷氨酸系统被认为有重要的意义。谷氨酸是神经系统内重要的神经递质。脑内的谷氨酸主要由谷氨酰胺被谷氨酰胺酶水解成Glu，发挥神经递质作用。离子型谷氨酸受体NMDA和代谢性谷氨酸受体AMPA是参与形成长时程增强(LTP)的主要受体[6,7]，LTP被认为与学习记忆有重要的联系[8,9]。另外谷氨酸系统过度开放会引起神经兴奋性中毒，对脑功能产生不利影响[10]。高原低压环境会对脑内神经递质系统产生影响[11,12]，本研究将探讨谷氨酸递质系统在低氧对学习记忆影响中的作用，研究这一问题将有助于了解低压低氧对脑影响的机制。

1 材料方法

1.1 实验动物和分组

选用20只SD雄性大鼠，体重200± 25g，随机分为两组，对照组和低氧组(n=10)。动物饲养与室温，12小时照明~12小时无照明的动物房内，无限制食物与水饲养。

1.2 Morris水迷宫训练

水迷宫直径2 m，深度0.5 m，实验时装水约0.3 m深，水温21~24℃，用白色素(二氧化钛)将水池染混。水迷宫空间人为分

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作者简介：付中伟(1984)，男，硕士，研究方向为特种环境神经毒理，电话：029-84774866，E-mail: 24007481@qq.com

△通讯作者：陈景元，Tel：029-84774401，E-mail: jy_chen@fmmu.edu.cn.

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为 4 个象限 (Q1-Q4,见图 1.1) ,潜伏平台直径 10 cm,置于 Q1 水面下约 1.5 cm(如图 1.1) 。将大鼠置于潜伏平台 (Q1) 30 s 后,按随机象限顺序置入水中 60 s 或大鼠找到潜伏平台为止,按此法每个象限训练 2 次。训练 5 天。

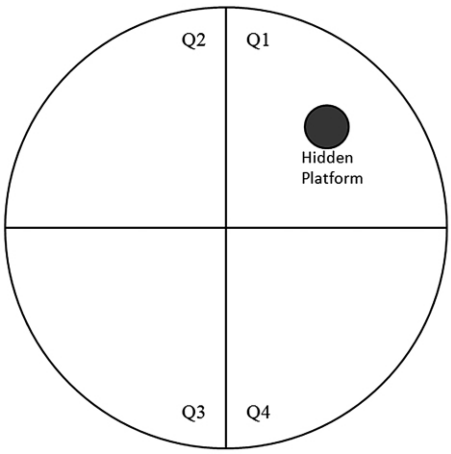

图 1.1: Morris 水迷宫示意图

Fig 1.1:Sketch of Morris Water Maze

1.3 低压低氧暴露

将低氧组大鼠置入低氧舱内,期间自由进食水,将气压控制在 50 kPa 水平 (模拟 5000~6000 m 海拔) ,持续 12 小时后,移至动物房内 (约 100 kPa) 。同时间对照组置于动物房 (100 kPa) 内,自由饮水。按此法暴露 7 天。

1.4 暴露后水迷宫检测

1.4.1 定位巡航测试 水迷宫内设定潜伏平台 (Q1) ,按随机象限将大鼠置入水中 60 s 或大鼠找到潜伏平台为止,每个象限测试 1 次。观察暴露后 2 天 (day13,day14) 的水平。

1.4.2 平台搜索测试 暴露后第 3 天 (day15) ,将大鼠从 Q3 置入无潜伏平台的水迷宫中,观察 60 s 内大鼠经过原平台次数及 Q1 搜索分布时间。

1.5 Western Blot

暴露后第 4 天 (day16) 将动物用 1 %戊巴比妥纳麻醉后,断头处死,取脑组织分离海马,用碧云天公司提供的组织裂解液 (含 1 % PMSF,SIGMA) 按每 1 mg 加入 10 μl 裂解组织,充分裂解后 4 ℃离心 15 min (12000 r/min) 后,取上清后将每组上清分别混合,进行蛋白定量,然后用裂解液配平浓度。最后加入 2 × SDS 上样缓冲液后煮沸 5 min、利用变性聚丙烯酰胺凝胶进行电泳分离,湿法将蛋白转移至 PVDF 膜,用 5 % TBST- 脱脂牛奶进行室温封闭 1 h。一抗 4℃孵育过夜,用 TBST 洗涤 3 次,加入二抗,室温孵育 2 h。TBST 洗涤 3 次,利用 FluorChem FC2 成像系统进行化学发光。

1.6 数据处理

用 SPSS19.0 软件进行统计分析,计量资料用均值± 标准差 ($\bar{x}\pm s$) 表示。两组间进行 t 检验比较,取 P<0.05 作为检验水准。

2 结果

2.1 低氧暴露前两组大鼠的水迷宫训练结果

如图 2.1 中 day1~day5 所示,通过 5 天训练,两组大鼠的逃脱潜伏期明显下降 (P<0.05) ,但对照组与低氧组两组间无统计学差异。

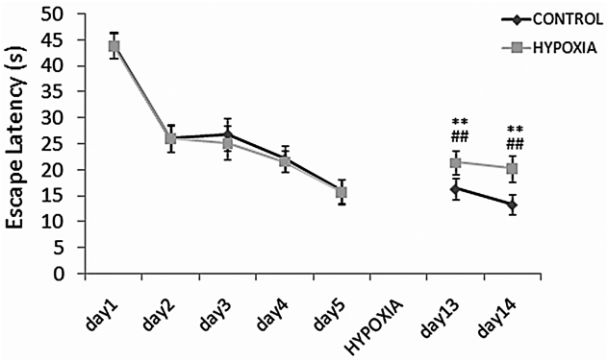

图 2.1.大鼠低氧暴露前后水迷宫平均逃脱潜伏期 (*P<0.05 vs 同日对照组数据,#P<0.05 vs 同组 day5 数据)

Fig. 2.1 Average escape Latency before/after exposure to hypoxia in MWM.(*P<0.05 vs the control group on the same day, #P<0.05 vs the same group on the day5)

表 2.1 大鼠低氧暴露前后水迷宫平均逃脱潜伏期

Tabel 2.1 Average escape Latency before/after exposure to hypoxia in MWM

	Control	Hypoxia
Day1	44.05± 2.60	43.93± 2.47
Day2	26.01± 2.47	26.15± 2.72
Day3	26.84± 3.2	25.22± 3.25
Day4	22.12± 2.50	21.64± 2.07
Day5	16.02± 2.30	15.74± 2.42
Day13	16.36± 1.98	21.42± 2.19**
Day14	13.34± 1.88	20.27± 2.57**

Note:*P<0.05 vscontrol.

2.2 暴露后水迷宫测试

通过 7 天低氧暴露,在暴露后 1、2 天 (day13,14) 的定位巡航实验中,低氧组大鼠的逃脱潜伏期较对照组有明显的升高 (P<0.05) (图 2.1),同时低氧组暴露后较暴露前 Day5 逃脱潜伏期明显升高 (P<0.05) (图 2.1)。在暴露后第 3 天的平台搜索实验中,低氧组大鼠在经过平台次数 (图 2.2A) 、Q1 搜索时间分布较

对照组明显减少 (P<0.05) (图 2.2B),而对照组则无明显差异。两组间游泳速度无差别(图 2.2C)。这部分结果提示低氧暴露对大鼠的空间记忆形成了损伤。

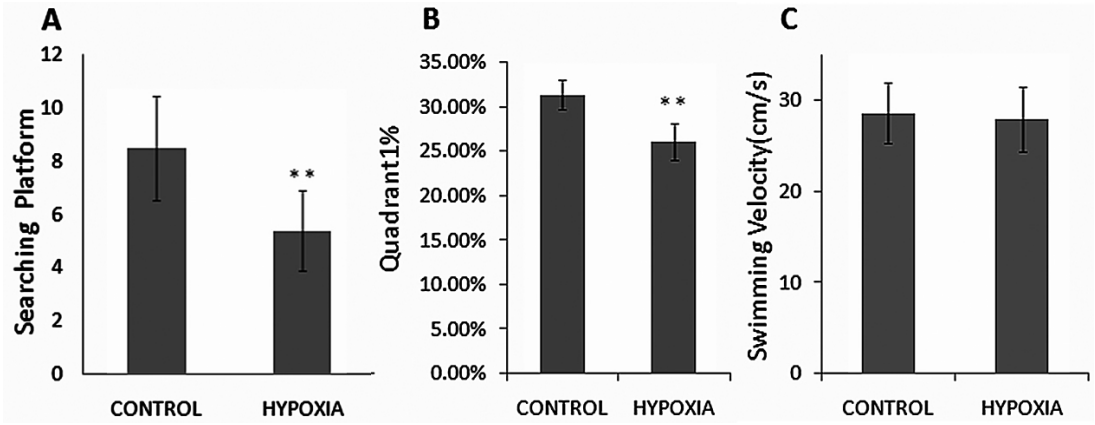

图 2.2 大鼠平台搜索实验各数据对比。A 经过平台区域次数。B :Q1 分布百分比例。C :平均游泳速度对比。(* P<0.05 vs 对照组。)

Fig.2.2 Data in rats searching platform experiments. A: The Frequency of passing through the platform. B: The percentage of serching in the quadrant 1. C: The swimming velocity.(* P<0.05 vs the control group)

表 2.2 大鼠平台搜索实验各数据

Table 2.2 Data in rats searching platform experiments

	Control	Hypoxia
Frequency	8.5± 1.96	5.4± 1.51 **
Quadrant 1%	31.41± 1.72	26.09± 2.03 **
Swimming velocity (cm/s)	28.6± 3.37	27.9± 3.55

Note:* P<0.05 vscontrol group.

2.3 低氧暴露后大鼠海马组织内的 GluR1 磷酸化升高,NMDA 表达增高

通过 7 天的低氧暴露,检测发现大鼠海马组织内 AMPA 受体中 GluR1 受体的 831,845 位点磷酸化均升高 (P<0.05),NMDA (NR1,NR2) 表达量升高。

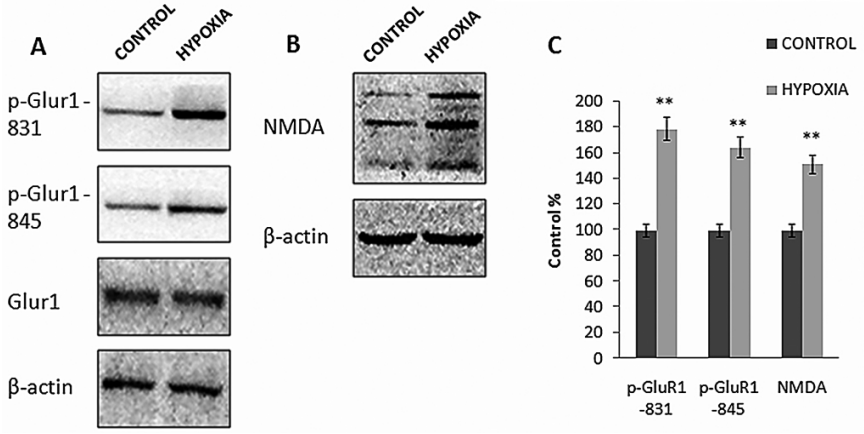

图 2.3 各组 Glur1 及 NMDA 受体表达情况。A :Glur1 831 和 845 位点磷酸化水平及总 Glur1 表达。B :NMDA 受体的表达情况。C :灰度分析。(* P<0.05 vs 对照组。)

Fig. 2.3 GluR1 and NMDA expression. A p-GluR1(831,845)/GluR1 expression. B: NMDA expersion. C: Quantification. (* P<0.05 vs the control group)

3 讨论

高原低压低氧对于认知功能有影响[13],低压低氧暴露的气压值和暴露时间与学习能力的降低呈高度依赖性[13]。谷氨酸受体 AMPA 和 NMDA 在学习记忆形成的机制中十分重要[6,7],了解谷氨酸受体在低压环境中的变化有助于研究低压低氧对脑的影响。

低压低氧暴露会引起脑内众多部位的神经元死亡,如海马 CA1、CA3、齿状回、丘脑、皮质、纹状体[14,15,16,17]。在行为学研究中,19 天 7000 m 暴露水平会使新生大鼠的空间记忆产生严重的损伤[18],在成年大鼠中,2-6 小时的低压暴露就会使大鼠 Morris 水迷宫行为出现显著改变[13],但其中的机制还不明确。

低氧暴露会引起 NMDA 受体的开放呈先升高后降低的趋势[19],长期暴露引起 NMDA 受体开放降低,从而影响 LTP 的形成,造成学习记忆的受损。然而在高原的初期,脑内处于低灌注水平,易造成兴奋性中毒[20]。低氧造成神经细胞外液的 Glu 水平增高,抑制谷氨酸 - 胱氨酸转运系统,阻止其摄取胱氨酸用于合成谷胱甘肽[21],过度刺激谷氨酸受体。Glu 与 NMDA 持续结合,使得钙离子通道持续开放,导致钙离子内流,作用可持续 7 天左右,造成细胞死亡[22]。另外兴奋性中毒造成的线粒体功能不全,大量产生氧自由基,可以使钙离子通道通透性进一步增加[23]。线粒体形成的氧自由基又可以激活 NMDA 受体[24],GluR 的过度活化同时可以诱导细胞凋亡[25],钙离子可以激活核酸内切酶,蛋白激酶 C 等,诱导凋亡基因表达,这可能是其造成学习记忆损伤的一个原因。兴奋性毒性也可以诱导 Caspase-3 的表达[26],同时激活凋亡相关蛋白 p53[27]。

本研究中观察到低压低氧暴露后空间记忆的损伤,另外 GluR1 和 NMDA 受体较对照组显著增高,说明突触谷氨酸受体持续开放,提示神经元细胞兴奋性中毒。综上所述,在低氧暴露早期或急性期,由于谷氨酸递质系统紊乱,引起神经系统兴奋性中毒,造成神经元死亡,可能是低氧暴露诱导空间记忆损伤的机制。我们的结果有助于预防和保护高原低压低氧环境对于健康的影响。

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