研究论文

雌性棕色田鼠和昆明小鼠在慢性间歇性低氧条件下血象变化的比较

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摘 要：本文旨在对雌性棕色田鼠(*Lasiopodomys mandarinus*)和昆明小鼠(*Mus musculus*)在慢性间歇性低氧条件下血象的变化进行比较，从而为地下生活鼠种血液系统对慢性间歇性低氧的应答对策的研究提供基础数据。采用实验氧舱对棕色田鼠和昆明小鼠进行每天 4 h、持续 28 d 的慢性间歇性低氧(氧浓度 10.0%)处理，然后对其血象进行了比较分析。结果显示：(1)常氧下棕色田鼠的红细胞计数(red blood cell count, RBC)显著高于昆明小鼠，而红细胞平均体积(mean corpuscular volume, MCV)则显著小于昆明小鼠，慢性间歇性低氧处理后昆明小鼠的 MCV 和红细胞压积(hematocrit, HCT)显著增加，而棕色田鼠 MCV 和 HCT 无明显影响；(2)常氧条件下棕色田鼠的平均血红蛋白含量(mean corpuscular hemoglobin, MCH)显著低于昆明小鼠，而平均血红蛋白浓度(mean corpuscular hemoglobin concentration, MCHC)则显著高于昆明小鼠，慢性低氧处理后昆明小鼠血红蛋白(hemoglobin, HGB)含量和 MCH 均显著增加，而在棕色田鼠仅出现 MCH 的明显增加；(3)常氧条件下棕色田鼠的白细胞计数(white blood cell count, WBC)和血小板(platelet, PLT)都显著低于昆明小鼠，慢性低氧处理后棕色田鼠和昆明小鼠的 WBC 和 PLT 均未发生显著变化。以上结果表明，棕色田鼠作为地下生活鼠种，对低氧环境具有较好的耐受性，其血液系统对低氧胁迫的应答机制与地面生活鼠种昆明小鼠不同。

关键词：慢性间歇性低氧；棕色田鼠；昆明小鼠；血象
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Comparison of hemogram changes under chronic intermittent hypoxia in *Lasiopodomys mandarinus* and Kunming *Mus musculus*

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Abstract: Mandarin vole (*Lasiopodomys mandarinus*) spends almost all of its life underground and must have evolved remarkable adaptations to cope with the subterranean hypoxic stress. The aim of present study is to explore the adaptation mechanism through the comparison of hemogram changes under chronic intermittent hypoxia in Mandarin vole and Kunming (KM) mouse (*Mus musculus*). Mandarin vole and KM mouse were treated with chronic intermittent hypoxia (10.0% oxygen), which was maintained by an oxygen cabin, for 4 h per day during four weeks. Then blood samples from the animals with and without hypoxia treatment were analyzed by a hematology analyzer. The results showed that under normoxic condition mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), white blood cell count (WBC) and platelet (PLT) in Mandarin vole were significantly lower than those in KM mouse. On the contrast, red blood cell count (RBC) and mean corpuscular hemoglobin concentration (MCHC) in Mandarin vole were higher than that in KM mouse. After four-week chronic intermittent hypoxia treatment, the hemogram changes were as following. MCV and HCT were elevated in Mandarin vole, not affected in KM mouse. Both hemoglobin (HGB) content and MCH in KM mouse increased, while only MCH increased in Mandarin vole. No obvious changes of WBC and PLT were found in two species. These results suggest that the adaptive mechanism of blood system in Mandarin vole responding to hypoxic conditions is different from that of KM

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mouse. As a subterranean vole, the Mandarin vole has a better tolerance to hypoxia.

Key words: chronic intermittent hypoxia; Mandarin vole; Kunming mouse; hemogram

氧是影响生物生存的关键资源，是机体代谢的基础。低氧作为一种特殊的环境因子，可使机体及细胞产生生理性改变并引发诸多生理响应[1]。地下生活鼠种主要营地下穴居生活，而地下洞道内氧气浓度较低。研究表明，在降雨期黏土洞道内的氧气浓度仅为正常值的7% [2,3]。长期的地下洞道生活使地下生活鼠种对低氧具有很好的耐受性[4,5]，其呼吸系统及血液系统对低氧环境产生了良好的应答机制，如肺泡气体扩散能力较强、血氧含量高[6,7]、红细胞较多、血红蛋白含量较高、血液携氧能力强[3,8-10]、骨骼肌毛细血管密度大[11,12]、红细胞体积小[13-15]等，这些适应性特征提高了氧在血管中的运输及组织间的扩散能力。另一方面，地下生活鼠种在应对低氧胁迫的同时，还要防止出现肺动脉高压及红细胞增多症[16-19]。目前，地下生活鼠种已被作为低氧适应和低氧生理学研究的模型动物[20,21]。

棕色田鼠(*Lasiopodomys mandarinus*)是主要分布在华北平原农作区、以地下洞道生活为主的小型啮齿动物[22]。目前对棕色田鼠的研究报道较多，主要涉及婚配制度[23]、生活史特征[24]、种群生态学[25,26]、社会行为学和遗传学[27,28]等方面，但对棕色田鼠地下环境适应机制等方面的研究尚较少[29]。本实验通过比较棕色田鼠和昆明小鼠(*Mus musculus*)在慢性间歇性低氧条件下的血象变化，旨在为揭示地下生活鼠种血液系统对慢性间歇性低氧的应答策略提供基础数据。

1 材料与方法

1.1 实验动物 棕色田鼠活捕于河南省新郑地区(34°52' N，113°85' E)农田，用聚乙烯标准饲养箱(37 cm×26 cm×17 cm)单只喂养于室内，建立室内种群。以兔饲料和鼠饲料(河南省实验动物中心生产)为主要食物，辅以少量新鲜胡萝卜，提供充足饮水。以锯末为垫料，脱脂棉为巢材。饲养室温度控制在20~24 ℃，明暗周期为12 h:12 h (光照时间8:00~20:00)。

从室内种群中选择健康成年雌性棕色田鼠20只(体重30~45 g)用于实验；实验所用雌性昆明小鼠购自河南省实验动物中心(合格证号：0003433)，3月龄，共20只(体重 25~40 g)。动物饲养与实验均遵照郑州大学有关动物实验的规定进行。

1.2 实验方法 实验设置鼠种和氧气浓度两种因素。鼠种有棕色田鼠和昆明小鼠两个水平，氧气浓度因素为常氧状态和慢性间歇性低氧(氧浓度10.0%)的比较。实验过程如下：将10只雌性棕色田鼠和10只雌性昆明小鼠置于实验动物氧舱(DS-II动物实验加压舱，潍坊华信锅炉氧舱制造有限公司)中进行低氧处理，通过控制氧气和氮气流量模拟10.0%氧浓度的常压低氧环境。低氧处理时间为每天4 h (8:00~12:00)，持续28 d[30]; 另选10只雌性棕色田鼠和10只雌性昆明小鼠作为对照组，不进行低氧处理。

1.2.1 取血方法 低氧处理结束后，将实验动物移出氧舱，立即注射20%氨基甲酸乙酯溶液使动物麻醉(注射量为0.05 mL/g，腹腔注射)，迅速摘取眼球取血，用EDTA钾盐作抗凝处理。对照组同样处理。

1.2.2 血象测定 采用Sysmex Xs-800i全自动血液分析仪(希森美康公司，日本)测定血象指标，测定指标包括红细胞计数(red blood cell count, RBC)、红细胞压积(hematocrit, HCT)和红细胞平均体积(mean corpuscular volume, MCV); 血红蛋白(hemoglobin, HGB)含量、平均血红蛋白含量(mean corpuscular hemoglobin, MCH)和平均血红蛋白浓度(mean corpuscular hemoglobin concentration, MCHC); 白细胞计数(white blood cell count, WBC)和血小板(platelet, PLT)。

1.3 数据分析 所有数据均采用mean±SEM表示。采用SPSS 13.0对数据进行统计分析。采用One-Sample Kolmogorov-Smirnov检验所有数据的分布类型；采用奇异值(outlier)分析剔除异常值；用双因素方差分析(two-way ANOVA)方法分析鼠种和氧气浓度两个因素对实验动物血象指标的影响；用 *t* 检验对组间差异进行检验。以 α=0.05为显著性临界值，所有检验均为双尾(two-tailed)。

2 结果

2.1 慢性间歇性低氧对红细胞参数的影响

常氧条件下(对照组)，棕色田鼠的RBC显著多

于昆明小鼠(t=3.085, P=0.007)，且慢性间歇低氧未导致其显著增加；而棕色田鼠的HCT (t=-4.107, P=0.001)和MCV (t=-5.556, P<0.001)则明显小于昆明小鼠，低氧处理使昆明小鼠的HCT (t=-3.498, P=0.003)和MCV (t=-2.976, P=0.008)显著增加，但不影响棕色田鼠HCT和MCV(表1)。双因素方差分析结果显示：棕色田鼠的RBC显著高于昆明小鼠($F_{(1,30)}$=8.787, P=0.006)，而HCT ($F_{(1, 30)}$=37.076, P<0.001)和MCV ($F_{(1, 30)}$=82.162, P<0.001)则显著地低于昆明小鼠；低氧处理对两种鼠的RBC作用不显著，但能使HCT ($F_{(1, 30)}$=9.348, P=0.005)和MCV ($F_{(1, 30)}$=12.024, P=0.002)显著增加；低氧处理与鼠种间交互作用不显著(表1)。

表1. 棕色田鼠和昆明小鼠红细胞计数(RBC)、红细胞压积(HCT)和红细胞平均体积(MCV)的变化

Table 1. Changes of red blood cell count (RBC), hematocrit (HCT) and mean corpuscular volume (MCV) in Mandarin vole and KM mouse

	Mandarin vole		KM mouse		Two-way ANOVA results		
	Normoxia	Hypoxia	Normoxia	Hypoxia	Species	Hypoxia	Species×Hypoxia
RBC (10^{12}/L)	11.25±0.29**	11.18±0.36	10.20±0.19	10.49±0.20	++	NS	NS
HCT (%)	42.16±1.67**	46.84±1.66	50.27±1.06	55.28±0.89**	++	++	NS
MCV (fL)	39.40±1.60**	42.49±0.29	49.15±0.74	53.64±1.36**	++	++	NS

Mean±SEM, n=10. **P<0.01 vs KM mouse in normoxia. Two-way ANOVA is used to analyze the effects of species and hypoxia on the indices, as well as their interaction effect. ++, P<0.01; NS, no significance.

2.2 慢性间歇性低氧对HGB参数的影响

常氧条件下(对照组)，两种鼠的HGB含量差异不显著，棕色田鼠的MCH (t=-2.971, P=0.008)相对昆明小鼠较低，而MCHC (t=5.434, P<0.001)则较高。低氧处理使棕色田鼠(t=-2.779, P=0.012)和昆明小鼠(t=-4.089, P=0.001) MCH均显著增加，但仅使昆明小鼠HGB显著增加(t=-4.464, P<0.001); 两种鼠的MCHC在低氧适应前后均没有显著性变化(表2)。双因素方差分析结果显示：两种鼠的HGB含量差异不显著，但红细胞MCH ($F_{(1, 30)}$=17.122, P<0.001)和MCHC ($F_{(1,30)}$=93.656, P<0.001)均存在显著性差异；低氧处理可显著提高两种鼠的HGB含量($F_{(1,30)}$=4.387, P=0.045)和MCH ($F_{(1, 30)}$=19.788, P<0.001)；低氧处理和鼠种间的交互作用不显著(表2)。

表2. 棕色田鼠和昆明小鼠血红蛋白(HGB)含量、平均血红蛋白量(MCH)和平均血红蛋白浓度(MCHC)的变化

Table 2. Changes of hemoglobin (HGB) content, mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC) in Mandarin vole and KM mouse

	Mandarin vole		KM mouse		Two-way ANOVA results		
	Normoxia	Hypoxia	Normoxia	Hypoxia	Species	Hypoxia	Species×Hypoxia
HGB (g/L)	160.11±4.15	168.30±5.92	153.60±1.82	164.38±1.44**	NS	+	NS
MCH (pg)	14.31±0.23**	15.12±0.18#	15.07±0.11	15.89±0.17**	++	++	NS
MCHC (g/L)	366.30±10.04**	356.78±2.37	307.20±4.17	297.33±5.35	++	NS	NS

Mean±SEM, n=10. #P<0.05 vs mandarin vole in normoxia. **P<0.01 vs KM mouse under normoxia. Two-way ANOVA is used to analyze the effects of species and hypoxia on the indices, as well as their interaction effect. +, P<0.05; ++, P<0.01; NS, no significance.

2.3 慢性间歇性低氧对WBC和PLT的影响

常氧条件下(对照组)，棕色田鼠的WBC (t=-2.233, P=0.039)和PLT数量(t=-6.846, P<0.001)均显著低于昆明小鼠。低氧处理未显著改变棕色田鼠和昆明小鼠的WBC和PLT数量(表3)。双因素方差分析表明，棕色田鼠的WBC ($F_{(1,30)}$=29.906, P<0.001)和PLT数量($F_{(1,30)}$=80.120, P<0.001)均显著低于昆明小鼠；低氧处理后两种鼠的WBC和PLT数量都没有发生显著变化；低氧处理和鼠种间的交互作用不显著(表3)。

表3. 棕色田鼠和昆明小鼠白细胞计数(WBC)和血小板(PLT)的变化

Table 3. Changes of white blood cell count (WBC) and platelet (PLT) in Mandarin vole and KM mouse

	Mandarin vole		KM mouse		Two-way ANOVA results		
	Normoxia	Hypoxia	Normoxia	Hypoxia	Species	Hypoxia	Species×Hypoxia
WBC (10^9/L)	4.47±0.69*	3.45±0.09	6.25±0.41	7.14±0.49	++	NS	NS
PLT (10^9/L)	270.50±34.57**	313.60±35.73	877.60±81.67	768.67±41.58	++	NS	NS

Mean±SEM, *n*=10. $^*P<0.05$, $^{**}P<0.01$ *vs* KM mouse in normoxia. Two-way ANOVA is used to analyze the effects of species and hypoxia on the indices, as well as their interaction effect. ++, $P<0.01$; NS, no significance.

3 讨论

低氧环境可对动物机体的生理状况、生理指标产生较大影响，导致机体的心、脑、肾脏、肺脏、血管等器官发生明显的组织学改变[31,32]，使RBC增加、右心室肥大、肺动脉压升高、体重减轻[33,34]、血糖及血液中胆固醇的水平降低[35]等。慢性间歇性低氧对心血管具有保护作用[36-38]，对神经元有保护作用[39]。但是，慢性间歇性低氧使机体出现肺动脉高压、红细胞增多[34]等症状，增加了血液黏稠度和血液循环阻力，使心脏负荷加大，引发红细胞增多症[16-19]。已有研究显示，地下生活鼠种可通过减小红细胞体积[13-15]、降低血液黏稠度[3,9,40]和调整2,3-磷酸甘油酸和HGB的比率[13-15]等血液生理学适应以规避上述风险。

本实验结果表明，营地下生活的棕色田鼠对慢性间歇性低氧环境具有很好的适应能力和较强的耐受性，而地上生活起源的昆明小鼠则对慢性间歇性低氧反应剧烈。棕色田鼠最低能承受的氧浓度在2%~3%，而昆明小鼠在氧浓度为4%时即表现出明显的不适症状甚至死亡(未发表数据)。棕色田鼠主要通过增加红细胞MCH来提高血液的携氧能力、而不是依赖增加RBC来应对慢性间歇性低氧。但是，红细胞MCH的增加，导致MCV变大，进而使HCT也随之变大。棕色田鼠的HCT、MCV和MCH都显著小于昆明小鼠，而红细胞MCHC显著大于后者，表明棕色田鼠血液的携氧能力强，血液黏稠度小，运输能力强，提示棕色田鼠对低氧具有较好的耐受能力。由于雌性棕色田鼠的RBC和HGB量较雄性偏高[29]，其低氧耐受能力更高一些，所以本研究选择了雌性棕色田鼠作为研究对象。为便于比较，选取雌性昆明小鼠作为对照。

棕色田鼠WBC数量显著少于昆明小鼠，慢性低氧处理对其无显著影响，可能与其地下相对稳定而单一的洞道环境有关。棕色田鼠的PLT显著少于昆明小鼠，且低氧处理后未发生显著变化。PLT较少可降低血液黏稠度，减小血液循环的阻力，有利于氧气的运输，这也是长期对低氧生活适应的结果。昆明小鼠经低氧处理后PLT数量减少，也是慢性低氧适应的结果。

综上所述，营地下生活的棕色田鼠对低氧具有较强的耐受性。长期的地下低氧生活使棕色田鼠的血液系统形成了有效的低氧应对策略，同时也表明不同进化途径(地下生活鼠种和地面生活鼠种)的鼠类对低氧环境具有不同的应答机制。有关雄性棕色田鼠血象对低氧的应答特征以及雌雄之间对低氧应答的差异等尚待进一步探讨。

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