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七氟烷全身麻醉对失血性休克复苏小鼠血流动力学及记忆功能的影响机制*

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摘要 目的:探讨七氟烷全身麻醉对失血性休克复苏小鼠血流动力学及记忆功能的影响机制。**方法**:将建立成功的42只失血性休克复苏小鼠按照随机数字表法平分为3组-模型组、氧气组、七氟烷组,对照组吸入空气4 h,氧气组吸入100.0 %氧气4 h,七氟烷组吸入100.0 %氧气和2.5 %七氟烷4 h,监测与记录小鼠血流动力学及记忆功能变化情况。**结果**:氧气组、七氟烷组麻醉后第3 d与第7 d的Morris水迷宫逃避潜伏期少于模型组,穿越原平台次数多于模型组(P<0.05),氧气组与七氟烷组对比差异有统计学意义(P<0.05)。氧气组、七氟烷组麻醉后第3 d与第7 d的去甲肾上腺素(Norepinephrine,NE)pD_2与Emax值高于模型组(P<0.05),七氟烷组高于氧气组(P<0.05)。氧气组、七氟烷组麻醉后第3 d与第7 d的脑组织凋亡指数低于模型组(P<0.05),七氟烷组低于氧气组(P<0.05)。氧气组、七氟烷组麻醉后第3 d与第7 d的海马组织Akt、Caspase-3蛋白相对表达水平低于模型组(P<0.05),七氟烷组低于氧气组(P<0.05)。**结论**:七氟烷全身麻醉在失血性休克复苏小鼠的应用能抑制Akt、Caspase-3蛋白的表达,可抑制脑组织神经细胞凋亡,可改善血流动力学状况,促进小鼠记忆能力的恢复。

关键词:七氟烷;全身麻醉;失血性休克;复苏;小鼠;记忆功能;血流动力学

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Effects of Sevoflurane General Anesthesia on Hemodynamics and Memory Function in Hemorrhagic Shock Resuscitation Mice*

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ABSTRACT Objective: To investigate the effect of sevoflurane general anesthesia on hemodynamics and memory function in mice resuscitated from hemorrhagic shock. **Methods:** The 42 successfully established hemorrhagic shock resuscitation mice were divided into 3 groups according to the random number table method: model group, oxygen group and sevoflurane group. The control group were inhaled air for 4 hours, and the oxygen group inhaled 100.0 % oxygen for 4 h, the sevoflurane group inhaled 100.0 % oxygen and 2.5 % sevoflurane for 4 h. The changes of hemodynamics and memory function of mice were monitored and recorded. **Results:** The escape latency of Morris water maze in oxygen group and sevoflurane group were less than that in model group (P<0.05), and the number of crossing the original platform were more than that in model group (P<0.05). There were significant difference compared between oxygen group and sevoflurane group (P<0.05). The PD_2 and Emax values of norepinephrine (NE) in oxygen group and sevoflurane group were higher than those in model group (P<0.05), and those in sevoflurane group were higher than those in oxygen group (P<0.05). The apoptosis index of brain tissue in oxygen group and sevoflurane group were lower than that in model group (P<0.05), and that in sevoflurane group were lower than that in oxygen group (P<0.05). The relative expression levels of Akt and caspase-3 protein in hippocampus of oxygen group and sevoflurane group were lower than those of model group (P<0.05), and sevoflurane group were lower than that of oxygen group (P<0.05). **Conclusion:** Sevoflurane general anesthesia in hemorrhagic shock resuscitation mice can inhibit the expression of Akt and caspase-3 protein, inhibit neuronal apoptosis in brain tissue, improve hemodynamics and promote the recovery of memory ability in mice.

Key words: Sevoflurane; General anesthesia; Hemorrhagic shock; Recovery; Mice; Memory function; Hemodynamics

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前言

失血性休克是比较常见的危重症,伴有比较严重的炎症反应和免疫应激反应,会导致严重的免疫功能紊乱与器官功能衰

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竭[1]。随着医学技术尤其是复苏技术的发展,当前失血性休克患者的死亡率明显下降,但是在复苏过程中可诱发相关级联瀑布式反应,导致多脏器功能障碍、脓毒症等疾病的发生与发展[2,3]。有研究显示,失血性休克复苏患者血流动力学异常可加重细胞缺氧和损伤,是休克患者血压难以回升和导致死亡的主要原因之一[4,5]。失血性休克在复苏过程中多需要进行全身麻醉,但是常规麻醉药物可能会影响机体的血流动力学状况,也可能对机体的认知功能有一定的负面影响[6,7]。七氟烷是一种临床比较常见的挥发性麻醉药,具有对循环系统引起的波动小、作用时间短、起效迅速等特点[8,9]。有研究显示七氟烷可以诱导β 淀粉样蛋白形成,继而激活半胱氨酸蛋白酶 -3(caspase-3),并可影响突触后蛋白与前蛋白的表达,导致机体出现认知功能缺陷[10,11]。还有研究显示七氟烷处理在小鼠脑缺血中具有神经保护作用,有助于清除兴奋性毒性物质及氧自由基、调控水及离子动态平衡[12,13],但是具体的作用机制还不明确。本文探讨与分析了七氟烷全身麻醉对失血性休克复苏小鼠血流动力学及记忆功能的影响机制。现报道如下。

1 材料与方法

1.1 主要研究材料

55 只清洁级健康雄性 C57BL/6 小鼠购自上海杰思捷实验动物有限公司(体重 25-30 g,10-12 周龄,许可证号:35821444)。小鼠饲养于本实验室,饲养于 12 h 明暗交替、相对湿度 40.0~70.0%、温度 20.0~25.0℃的环境。所有小鼠在饲养及实验过程中给予伦理待遇,自由饮食、饮水,经适应 1 周时间后进行实验。

显微手术器械保存于本实验室,七氟烷购自江苏恒瑞医药股份有限公司,批号为国药准字 H20213735,兔抗 Akt 抗体、兔抗 Caspase-3 抗体购自大连 TAKARA 公司,二抗购自美国 Jackson ImmunoResearch 公司。

1.2 失血性休克复苏小鼠模型的建立

小鼠给予腹腔注射 0.2 mL/10 g 体重的 1.25 %三溴乙醇,于腹股沟处行约 0.5 cm 斜行切口,在镜下行左侧股浅动脉穿刺置管术。注入 25 IU/mL 的 0.02 mL 肝素液后将针头经三通连接生物血压传感器,以 0.03 mL/min 速度放血,并实时监测血压,使平均动脉压下降至 30.0 mmHg 左右,并将维持血容量休克水平 90 min 左右。休克结束 30 min 回输贮血或生理盐水复苏,然后结扎股浅动脉,拔除动脉置管,缝合腹股沟切口。

1.3 小鼠分组与麻醉

剔除死亡小鼠 6 只,建模失败 7 只,将建模成功的 42 只小鼠随机平分为 3 组 - 模型组、氧气组、七氟烷组。将小鼠置于特制的麻醉箱内,保持麻醉箱温度为(37.0±0.5)℃,气流流量为 4 L/min。小鼠保持自主呼吸,用 Datex-Ohmeda 麻醉机进行吸入麻醉和吸氧,对照组吸入空气 4 h,氧气组吸入 100.0%体积分数的氧气 4 h,七氟烷组吸入 100.0%体积分数的氧气和 2.5 %体积分数的七氟烷 4 h。

1.4 观察指标

1.4.1 Morris 水迷宫行为学测试 每组在麻醉后第 3 d 与第 7 d 各处死 7 只小鼠,在处死前进行 Morris 水迷宫行为学测试,房间内光照恒定,水温保持 21.0~23.0℃,将小鼠分别从 4 个不同起始点面向池壁放入水中,记录小鼠的逃避潜伏期与穿越原平台次数。

1.4.2 血流动力学状况 无菌条件下取肠系膜上动脉主干及分支,清除周围结缔组织,取一级分支制成血管环(长度 2.5 mm,直径 10~100 μm)。在 K-H 液中按累积浓度法测定血管环对去甲肾上腺素(Norepinephrine,NE)的反应性,生理记录仪记录血管环张力,以收缩力 / 血管环重量(g/mg)为量化标准,用 NE 的 pD2(-log[NE])、Emax(最大收缩反应)评价血流动力学状况。

1.4.3 凋亡指数检测 取处死小鼠的脑组织,采用 TUNEL 法检测脑组织细胞凋亡指数,严格按照 TUNEL 试剂盒说明书(上海生工公司)进行操作。

1.4.4 Akt、Caspase-3 蛋白相对表达检测 取大鼠的大脑海马组织,组织匀浆离心后取上清液,采用 SDSG 电泳分离蛋白,转膜,封闭 1 h,加入兔抗 Akt 抗体、兔抗 Caspase-3 抗体(1:1000)4 ℃孵育过夜,TBST 洗涤 3 次后(每次 5min),加入二抗(1:2000,羊抗兔 HRP 标记的抗体)室温孵育 1 h,TBST 洗涤 3 次后(每次 5 min),采用增强化学发光法进行显色,在化学发光计算设备进行曝光。

1.5 统计方法

本次研究统计软件为 SPSS24.00,计量数据以均数±标准差表示,计数数据采用百分比表示,对比为单因素方差分析,检验水准:α=0.05。

2 结果

2.1 行为学结果对比

氧气组、七氟烷组麻醉后第 3 d 与第 7 d 的 Morris 水迷宫逃避潜伏期少于模型组(P<0.05),穿越原平台次数多于模型组,氧气组与七氟烷组对比差异有统计学意义(P<0.05)。见表 1。

表 1 三组行为学结果对比

Table 1 Comparison of the behavioral results for the three groups

Groups	n	Anesthesia 3 d		Anesthesia 7 d	
		Escape from latency(s)	Crossing of original platform(n)	Escape from latency(s)	Crossing of original platform(n)
The sevoflurane group	7	41.48±3.34[ab]	3.45±0.25[ab]	35.68±2.54[ab]	3.87±0.33[ab]
Oxygen group	7	51.49±4.19[a]	2.84±0.33[a]	46.88±3.16[a]	2.42±0.17[a]
Model group	7	69.36±2.58	1.20±0.32	69.83±3.16	1.21±0.15
F		18.023	11.013	24.202	13.863
P		＜0.001	＜0.001	＜0.001	＜0.001

Note: Compared with the model group, [a]P<0.05; compared with the oxygen group, [b]P<0.05. The same below.

2.2 血流动力学状况对比

氧气组、七氟烷组麻醉后第 3 d 与第 7 d 的 NE pD_2 与 Emax 值高于模型组(P<0.05),七氟烷组高于氧气组(P<0.05)。见表 2。

表 2 三组麻醉不同时间点的血流动力学状况对比

Table 2 Hemodynamic status comparison of the three groups at different time points of anesthesia

Groups	n	Anesthesia 3 d		Anesthesia 7 d	
		pD_2	Emax(g/mg)	pD_2	Emax(g/mg)
The sevoflurane group	7	7.13±0.04[ab]	1.09±0.05[ab]	7.45±0.09[ab]	1.34±0.10[ab]
Oxygen group	7	6.33±0.13[a]	0.69±0.02[a]	6.89±0.10[a]	0.92±0.08[a]
Model group	7	5.87±0.22	0.37±0.11	5.82±0.18	0.38±0.09
F		8.982	18.832	9.445	20.172
P		＜0.001	＜0.001	＜0.001	＜0.001

2.3 凋亡指数对比

氧气组、七氟烷组麻醉后第 3 d 与第 7 d 的脑组织凋亡指数低于模型组(P<0.05),七氟烷组低于氧气组(P<0.05)。见表 3。

表 3 三组麻醉不同时间点的凋亡指数对比(%)

Table 3 Comparison of apoptosis index in the three groups at different time points of anesthesia with (%)

Groups	n	Anesthesia 3 d	Anesthesia 7 d
The sevoflurane group	7	7.82±0.18[ab]	5.38±0.27[ab]
Oxygen group	7	16.03±2.17[a]	12.09±1.76[a]
Model group	7	31.42±3.28	31.32±1.11
F		38.952	43.928
P		＜0.001	＜0.001

2.4 Akt、Caspase-3 蛋白相对表达水平对比

氧气组、七氟烷组麻醉后第 3 d 与第 7 d 的海马组织 Akt、Caspase-3 蛋白相对表达水平低于模型组，七氟烷组低于氧气组(P<0.05)。见表 4。

表 4 海马组织蛋白相对表达比较

Table 4 Comparison of relative expression of hippocampal tissue protein

Groups	n	Anesthesia 3 d		Anesthesia 7 d	
		Akt	Caspase-3	Akt	Caspase-3
The sevoflurane group	7	0.98±0.02[ab]	0.78±0.03[ab]	0.79±0.03[ab]	0.69±0.08[ab]
Oxygen group	7	1.78±0.32[a]	1.67±0.13[a]	1.54±0.18[a]	1.36±0.18[a]
Model group	7	3.38±0.13	2.89±0.28	2.89±0.11	2.18±0.98
F		26.044	24.143	19.882	20.115
P		＜0.001	＜0.001	＜0.001	＜0.001

3 讨论

失血性休克是机体在短时间内大量失血,致使全身循环血量急剧下降，最终导致重要脏器的代谢紊乱及功能障碍的疾病[14]。复苏是该疾病的主要治疗方法,能提高患者的生存率。但是失血性休克复苏患者常出现血管高反应性,主要表现为全身血管对缩血管物质和舒血管物质的反应增加,可导致患者预后变差[15,16]。压力控制失血性休克模型当前建立失血性休克复苏小鼠的主要模型之一，可以控制休克的严重度并监测生理指标,且具有可重复性、标准化等优点。

吸入氧气为失血性休克复苏机体的常见治疗手段,但是可以激活特定的酶继而引起 tau 蛋白的磷酸化产生认知功能障碍[17,18]。七氟烷为一种一种挥发性麻醉药,可降低脑的氧代谢率与增加脑血流量。而且与异氟烷相比,七氟烷有较小的毒性,不会影响成年鼠和老年鼠的获得性学习记忆力[19]。并且七氟烷能稳定膜电位,使细胞膜超极化,降低谷氨酸的转运,调节细胞的兴奋性,减少钙离子内流[20,21]。本研究显示氧气组、七氟烷组麻醉后第 3 d 与第 7 d 的 Morris 水迷宫逃避潜伏期少于模型组(P<0.05),穿越原平台次数多于模型组(P<0.05),氧气组与七氟烷组对比差异有统计学意义(P<0.05),表明七氟烷全身麻醉在失血性休克复苏小鼠的应用能改善小鼠的记忆功能,与上述研究结果一致[19,20]。

在失血性休克的情况下，早期可通过一系列应激反应尽可能地维持重要器官的血流动力学状况[22,23]。失血性休克复苏小鼠血流动力学异常的发生主要有受体失敏和血管平滑肌细胞膜超极化两种机制，特别是休克后血管平滑肌细胞肌肉收缩蛋白对钙的敏感性降低，也表现为肌肉收缩效率降低，可导致肠系膜上动脉血管对 NE 的反应性和钙敏感性却呈双相变化[24,25]。本研究显示氧气组、七氟烷组麻醉后第 3 d 与第 7 d 的 NE pD_2 与 Emax 值高于模型组，七氟烷组高于氧气组(P<0.05)，表明七氟烷全身麻醉在失血性休克复苏小鼠的应用能改善血流动力学状况，结合 Xu D[26]等研究分析：七氟烷可减少核因子 KB 入核，抑制炎症因子的表达，抑制神经元的钙离子和兴奋性氨基酸浓度的升高，从而发挥神经保护作用。另外，Wang F[27]和 Li Y[28]的研究显示：七氟烷吸入能增加小鼠海马神经元 β，γ 分泌酶的活性，从而发挥一种神经保护机制，保持小鼠的血流动力学在稳定状态，也有利于维持细胞膜静息电位的形成和膜电位的复极化，与本研究结果一致。

研究发现 Akt 的激活可通过内皮一氧化氮合酶产生一氧化氮，在脂多糖诱导内毒素休克的人脐静脉内皮细胞，通过磷酸化活化 Akt，可调节内毒素休克的血管反应性[29]。Akt 也是钙调蛋白依赖通路的重要信号分子之一，对于理解失血性休克模型血流动力学异常的发生具有重要意义[30]。细胞凋亡是一系列高度调控的 Caspase-3 级联反应事件的结果，Caspase-3 被证实处于该级联反应的下游，可通过降解细胞内相应底物使细胞死亡，也可能是凋亡事件的重要执行者[31]。本研究显示 氧气组、七氟烷组麻醉后第 3 d 与第 7 d 的海马组织 Akt、Caspase-3 蛋白相对表达水平低于模型组(P<0.05)，七氟烷组低于氧气组(P<0.05)，表明七氟烷全身麻醉在失血性休克复苏小鼠的应用能抑制 Akt、Caspase-3 蛋白的表达。有研究显示 [32,33]：七氟烷可使 Caspase-3 蛋白表达降低，抑制老年鼠神经元细胞凋亡，可发挥改善神经退行性变和认知功能的作用，与本研究结果一致。本研究由于经费限制，没有设置空白对照组，也没有对七氟烷的浓度进行对比分析，将在后续研究中探讨。

总之，七氟烷全身麻醉在失血性休克复苏小鼠的应用能抑制 Akt、Caspase-3 蛋白的表达，可抑制脑组织神经细胞凋亡，可改善血流动力学状况，促进小鼠记忆能力的恢复。

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