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瑞芬太尼痛觉过敏小鼠中脑导水管周围灰质 Mu 阿片受体和神经元限制性沉默因子表达水平的变化

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[摘要] 目的：观察瑞芬太尼痛觉过敏小鼠中脑导水管周围灰质(periaquductal gray，PAG)中Mu阿片受体(Mu-opioid receptor，Mor)和神经元限制性沉默因子(neuron-restrictive silencer factor，NRSF)表达水平的变化。**方法：**32只小鼠采用随机数字表法随机分入4组(n=8)：对照组(C组)、切口痛组(I组)、瑞芬太尼组(R组)和切口痛+瑞芬太尼组(IR组)。采用Von Frey细丝和BME-410A型热痛刺激仪测量小鼠术前24 h和术后2，6，24，48 h的机械缩足反射阈值(paw withdrawal mechanical thresholds，PWMT)和热缩足反射潜伏期((paw withdrawal thermal latency，PWTL)。Western印迹检测术后48 h小鼠PAG中Mor和NRSF的表达水平。**结果：**与C组和术前基础值比较，I组、R组和IR组术后2~48 h PWMT和PWTL均显著降低(P<0.01)；术后2，6 h时R组较I组PWMT和PWTL略高(P<0.01)，术后24，48 h时两组间差异无统计学意义(P>0.05)；与I组比较，IR组术后PWMT和PWTL显著降低，并持续到术后48 h(P<0.01)。与C组和I组比较，R组和IR组Mor表达均显著降低(P<0.01)，NRSF表达显著升高(P<0.01)，C组和I组之间Mor和NRSF表达差异无统计学意义(P>0.05)。**结论：**术中短时程输注瑞芬太尼可诱导小鼠术后痛觉过敏，同时瑞芬太尼还诱导PAG中Mor水平降低及NRSF水平增加，该变化可能参与瑞芬太尼诱导的痛觉过敏的形成。

[关键词] 瑞芬太尼；痛觉过敏；Mu阿片受体；神经元限制性沉默因子

Changes of Mu-opioid receptor and neuron-restrictive silencer factor in periaquductal gray in mouse models of remifentanil-induced postoperative hyperalgesia

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ABSTRACT **Objective:** To determine the changes of Mu-opioid receptor (Mor) and neuron-restrictive silencer factor (NRSF) in periaquductal gray (PAG) in mouse models of remifentanil-induced postoperative

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hyperalgesia.

Methods: Thirty-two Kun-Ming mice were randomly divided into 4 groups (8 mice in each group): Group C (mice underwent a sham procedure and saline was infused subcutaneously over a period of 30 min), Group I (mice underwent a surgerical incision and the same volume of saline), Group R (mice underwent a sham procedure and remifentanil was infused subcutaneously at the moment of surgeical incision over a period of 30 min), and group IR (mice underwent a surgerical incision and remifentanil). Paw withdrawal mechanical threshold (PWMT) and paw withdrawal thermal latency (PWTL) tests were performed 24 h before the operation and 2, 6, 24, and 48 h after the operation. The specimens were collected after behavioral testings at 48 h. The expressions of Mor and NRSF in mice's PAG neurons were determined by Western blot.

Results: Mechanical allodynia and thermal hyperalgesia developed in Group I, R and IR (P<0.01). Intraoperative infusion of remifentanil enhanced mechanical allodynia and thermal hyperalgesia in mice with planta incision (P<0.01). In Group R and Group IR, the expression of Mor was significantly lower (P<0.01) and NRSF was significantly higher (P<0.01) when compared with Group C and Group I.

Conclusion: Intraoperative infusion of remifentanil induces postoperative hyperalgesia in mouse models, accompanied with decreased expressions of Mor and increased of NRSF level in PAG neurons, which may be involved in remifentanil induced hyperalgesia.

KEY WORDS remifentanil; hyperalgesia; Mu-opioid receptor; neuron-restrictive silencer factor

瑞芬太尼是一种人工合成的超短效Mu阿片受体(Mu-opioid receptor，Mor)激动剂，起效迅速，半衰期短，不依赖肝肾功能迅速代谢，广泛用于临床麻醉[1]。然而近年动物实验[2]和临床研究[3]均显示，术中短时程输注瑞芬太尼可诱发撤药后痛觉过敏即阿片诱导的痛觉过敏(opioid induced hyperalgesia，OIH)，使其在临床麻醉的广泛应用受到挑战。OIH的发生机制目前尚不完全清楚。

Mor是临床阿片类药物发挥镇痛效应的主要靶位[4]，Mor活化也是阿片类药物产生促伤害效应所必需[5]。Mor激动剂可诱导与急、慢性疼痛相似的神经元可塑性改变[6-8]，这些可塑性改变与痛觉过敏的形成有关[9-10]。研究[11-13]显示在神经病理痛、癌性痛及阿片耐受模型中，Mor水平发生可塑性下调。Cabanero等[14]报道大鼠背根神经节阿片受体下调可能参与了阿片诱导的痛觉过敏的发生。中脑导水管周围灰质(periaquductal gray，PAG)是机体重要的下行抑制系统的组成部分，与疼痛调控密切相关，是Mor激动剂发挥镇痛作用的重要部位。术中短时程输注瑞芬太尼是否影响PAG中Mor水平，并参与瑞芬太尼诱导的痛觉过敏的发生尚未见报道。神经元限制性沉默因子(neuron-restrictive silencer factor NRSF)为一段长为21~23 bp的保守DNA序列，是一种重要的基因启动子的抑制子，抑制多种与神经功能密切相关基因的表达。在全脑缺血模型[15]和外周神经损伤所致的神经病理性疼痛模型[16]中NRSF继发性沉默MOR基因参与了神经元Mor表达水平的下调。

本研究拟观察瑞芬太尼痛觉过敏小鼠PAG中Mor和NRSF表达水平的变化，以探讨NRSF继发性沉默MOR是否参与瑞芬太尼诱发痛觉过敏的形成。

1 材料与方法

1.1 材料

清洁级雄性昆明小白鼠，体质量20~25 g，由北京维通利华实验动物技术有限公司提供。Von Frey细丝购自美国Stoelting公司。BME-410A 型热痛刺激仪购自中国医学科学院生物医学研究所。七氟醚为上海恒瑞医药有限公司产品。盐酸瑞芬太尼粉剂为宜昌人福药业有限公司产品。Mu兔抗(ab 10275)，NRSF兔抗(ab 21635)，β-actin(ab 8227)，HRP标记的山羊抗兔IgG(ab1 36817)均购自美国Abcam公司。

1.2 方法

1.2.1 动物分组

32只小鼠采用随机数字表法随机分入4组

(n=8)：对照组(C组)，皮下泵注生理盐水0.4 mL；切口痛组(I组)，切皮同时，皮下泵注生理盐水0.4 mL；瑞芬太尼组(R组)，皮下泵注瑞芬太尼0.8 μg/kg(0.4 mL，采用生理盐水溶解)；切口痛+瑞芬太尼组(IR组)，切皮同时，皮下泵注瑞芬太尼0.8 μg/kg(0.4 mL)。所有操作均在鼻罩吸入七氟醚下进行(麻醉诱导3%，麻醉维持1%)，泵注时间均为30 min，泵注速度为0.8 mL/h。

1.2.2 *动物模型*

参照Celerier等[17]的方法建立切口痛模型。用10%碘伏消毒右后爪，用20号刀片从足底近端0.3 cm处开始向脚趾方向作一长约0.7 cm的切口，纵行切开皮肤和皮下筋膜，暴露趾部肌肉，用眼科镊挑起足底肌肉，纵行分离，保持肌肉起止及附着完整。轻压止血后，用6-0丝线缝合切口两针，手术切口以碘伏消毒并涂抹金霉素抗菌软膏，手术过程约5 min。

1.2.3 *行为学测试*

实验前7 d，每日将小鼠置于实验观察箱中适应30 min。术前24 h及术后2，6，24，48 h进行行为学测试。采用Von Frey细丝测定机械缩足反射阈值(paw withdrawal mechanical thresholds，PWMT)。小鼠单独放入底为0.5 cm×0.5 cm的金属筛网的透明有机玻璃箱(9 cm×9 cm×9 cm)内适应30 min，用Von Frey细丝垂直作用于小鼠切口附近皮肤，小鼠出现抬足或添足行为视为阳性反应，刺激力度从0.4 g开始，根据“up and down”法增加或降低纤毛力度，力度0.008~2 g，每个强度反复刺激5次，间隔5 s，每次刺激持续1 s，以“up and down”法计算小鼠的PWMT。2 g无阳性反应时记为2 g。采用BME-410A型热痛刺激仪测量热缩足反射潜伏期(paw withdrawal thermal latency，PWTL)。小鼠单独放入底部为3 cm厚玻璃的透明有机玻璃箱(9 cm×9 cm×9 cm)内适应30 min，热辐射源置于玻璃板底部，照射右侧伤口附近的脚底表面。调节光束强度，使小鼠基础阈值为11~14 s，截断时间为20 s。从热辐射开始至小鼠出现热缩足逃避反射时间为热缩足发射潜伏期，重复3次，每次间隔10 min。

1.2.4 Western 印迹

深麻醉下，参照Garzon等[18]描述的方法，取出脑组织，沿上、下丘平面做2 mm厚的冠状切片，将含PAG的脑片平铺在玻璃片上，用内径为2 mm的玻璃管提取区域脑组织，储存在液氮中。组织样本在预冷的提取全蛋白的蛋白裂解液中匀浆，充分裂解。蛋白裂解液在4 ℃下14 000 r/min离心10 min，提取上清液。采用Bradford方法测定蛋白浓度。50 μg蛋白样本采用8% SDS-PAGE分离，分离后将蛋白质转移至PVDF膜上。5%脱脂奶粉室温下封闭30 min，加入一抗(NRSF 1∶500，Mu 1∶2 000)4 ℃孵育过夜。TBST洗涤后加入二抗(1∶5 000)室温孵育2 h，TBST洗涤，将ECL显影溶液加于膜上，然后用X光胶片曝光1~10 min。结果采用Quantity One analysis software (Bio-Rad，Hercules，CA)，进行分析，以目标蛋白除以β-actin内参条带的IOD值作为最终结果进行统计分析。

1.3 统计学处理

用SPSS13.0统计软件进行统计分析。计量资料以均数±标准差($\bar{x}\pm s$)表示。组内、组间比较采用差异重复测量的方差分析。Post hoc检验采用LDS法。检验水准为双侧α=0.05，P<0.05为差异有统计学意义。

2 结　果

2.1 各组小鼠术后 PWMT 和 PWTL 的变化

术前24 h测得的PWMT和PWTL作为基础阈值。各组间基础阈值比较差异无统计学意义(P>0.05)，总体PWMT和PWTL分别是(1.8±0.13) g和(12.68±0.50) s。C组各时间点PWMT和PWTL均无明显差异(P>0.05)。与C组和术前基础值比较，I组、R组和IR组术后2~48 h的PWMT和PWTL均显著降低(P<0.01)；术后2，6 h的R组PWMT和PWTL高于I组(P<0.01)，术后24，48 h两组间差异无统计学意义(P>0.05)；IR组术后PWMT和PWTL均显著降低于I组，并持续到术后48 h(P<0.01，表1~2)。

表 1　各组小鼠术后机械缩足反射阈值的变化 (n=8，$\bar{x}\pm s$，g)

Table 1　Changes of PWMT during the postoperative period in each group (n=8, $\bar{x}\pm s$, g)

组别	Baseline	术后			
		2 h	6 h	24 h	48 h
对照组	1.83 ± 0.13	1.79 ± 0.16	1.78 ± 0.23	1.82 ± 0.17	1.80 ± 0.21
切口痛组	1.83 ± 0.18	0.63 ± 0.12**††	0.70 ± 0.08**††	0.80 ± 0.08**††	0.94 ± 0.13**††
瑞芬太尼组	1.83 ± 0.12	1.15 ± 0.13**††‡‡	0.95 ± 0.09**††‡‡	0.88 ± 0.12**††‡‡	0.93 ± 0.09**††‡‡
切口痛+瑞芬太尼组	1.82 ± 0.12	0.35 ± 0.13**††‡‡	0.37 ± 0.11**††‡‡	0.32 ± 0.09**††‡‡	0.38 ± 0.14**††‡‡

与Baseline(术前24 h测量值)比较，**P<0.01；与对照组比较，††P<0.01；与切口痛组比较，‡‡P<0.01

表 2 各组小鼠术后热缩足反射潜伏期的变化 (n=8，$\bar{x} \pm s$，s)

Table 2 Changes of remifentanil on PWTL during the postoperative period in each group (n=8, $\bar{x} \pm s$, s)

组别	Baseline	术后			
		2 h	6 h	24 h	48 h
对照组	12.72 ± 0.41	12.74 ± 0.60	12.6 ± 0.50	12.74 ± 0.60	12.71 ± 0.68
切口痛组	12.68 ± 0.42	6.62 ± 1.26**††	6.38 ± 1.51**††	6.88 ± 1.22**††	7.57 ± 1.26**††
瑞芬太尼组	12.71 ± 0.59	10 ± 0.68**††‡‡	8.87 ± 0.6**††‡‡	7.76 ± 1.07**††	8.21 ± 1.34**††
切口痛+瑞芬太尼组	12.61 ± 0.62	4.68 ± 1.23**††‡‡	3.92 ± 0.85**††‡‡	3.55 ± 0.37**††‡‡	3.98 ± 0.79**††‡‡

与Baseline(术前24 h测量值)比较，**P<0.01；与对照组比较，††P<0.01；与切口痛组比较，‡‡P<0.01

2.2 Mor 及 NRSF 在各组 PAG 中的表达

与C组和I组比较，R组和IR组Mor表达显著降低(P<0.01)，NRSF表达显著升高(P<0.01)；C组和I组之间Mor和NRSF表达差异无统计学意义(P>0.05，图1)。

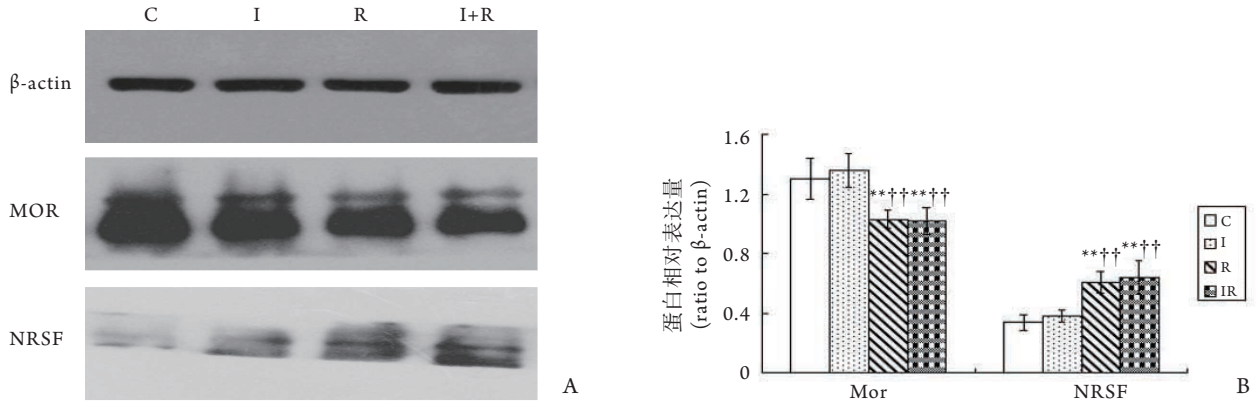

图1 Western印迹分析Mor和NRSF在各组小鼠PAG中的表达

Figure 1 Expression level of Mor and NRSF in PAG of mice in each group by Western blot

A: Electrophoretogram of Western blot; B: Histograms showing the relative expression levels of Mor and NRSF. C: Control; I: Incisional pain; R: Remifentanil; I+R: Incisional pain+Remifentanil. **P<0.01 vs Group C; ††P<0.01 vs Group I

3 讨 论

瑞芬太尼是一种人工合成的短效Mor激动剂，镇痛效能与芬太尼相当，因其独特的药理学特点，广泛应用于临床麻醉。大量的研究[2-3]显示瑞芬太尼短时程输注可诱导OIH，与长效阿片类药物比较，瑞芬太尼更易诱导痛觉过敏[19]。其发机制尚不清楚，临床缺乏确切有效的治疗措施，使其在临床麻醉的广泛应用受到挑战。

脊髓N-甲基-D-天冬氨酸(N-methyl-D-aspartic acid，NMDA)受体系统是中枢促伤害感受系统的重要组成部分，在中枢敏化的形成和维持中均发挥重要作用。大量的动物实验支持脊髓NMDA受体系统活化参与OIH发生[20-21]。但临床研究中矛盾的结果提示OIH的发生可能还有其他机制的参与[22]。Simonnet等[23]认为疼痛敏化是中枢神经系统促伤害感受系统活性和抗伤害感受系统活性失衡的结果。作为机体抗伤害感受系统重要组成部分的阿片系活化后可抑制伤害信息上传和活化下行疼痛调制，发挥镇痛作用[24-26]，阿片系统本身是否发生可塑性变化并参与阿片诱导的痛觉过敏的发生，目前鲜有报道。成年动物Mor水平可发生可塑性改变，癌痛[13]、神经病理痛[12]和炎性痛[27]模型中Mor也发生可塑性的上调或下调。提示Mor水平变化也是神经元发生可塑性改变的方式之一。Cabanero等[14]报道瑞芬太尼短时程输注能诱导大鼠背根神经节阿片受体下调，通过转基因技术增加背根神经节脑啡肽表达能完全抑制瑞芬太尼诱导的术后机械和热痛觉过敏的发生。另有研究[5]报道，Mor特异拮抗剂纳洛酮能阻断瑞芬太尼诱导的痛觉过敏。这些研究均提示Mor与瑞芬太尼诱发的促伤害感受密切相关。

Mor在中枢神经系统中广泛分布，主要集中在与疼痛密切相关的PAG、蓝斑核和脊髓背角浅层。

PAG被认为是阿片类药物中枢镇痛的主要作用部位，其神经纤维主要投射到延髓头端腹侧区域的中缝大核，蓝斑核及脑桥和延髓的其他核团。这些区域的神经元再发出投射纤维，直接或间接作用脊髓背角中间抑制性神经元，对脊髓后角投射神经元发挥抑制性调制，抑制伤害信息向脑内传递[28]，是中枢性疼痛调制的关键部位。转录因子介导长时程转录调控在神经元功能可塑性改变中发挥重要作用[29]。NRSF是多种神经元特异基因的转录抑制子，参与神经元功能必需的多种基因表达的调控如：如离子通道、神经递质受体和突触囊泡蛋白[30-32]。在全脑缺血模型[15]和外周神经损伤所致的神经病理性疼痛模型[16]中NRSF继发性沉默Mor基因参与了神经元Mor表达水平的下调。

本研究中瑞芬太尼短时程输注能诱发小鼠痛觉过敏和增加切口痛小鼠术后机械和热痛觉过敏。伴随痛敏的发生，瑞芬太尼还诱导了小鼠PAG中Mor表达水平的下调和NRSF表达水平的上调，提示PAG中Mor下调和NRSF上调可能在瑞芬太尼诱导的痛觉过敏的形成中发挥作用。但瑞芬太尼诱发的痛觉过敏小鼠PAG中Mor表达水平的下调是否确为NRSF在转录水平调控所致？阻断NRSF的抑制性调控能否改善瑞芬太尼诱发的痛觉过敏？这些问题都有待于我们进一步的研究。

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