

研究论文

CX3CR1介导切口术后的机械痛敏：针药复合麻醉的作用

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摘要: 术后痛是临床中最常见和最需要紧急处理的疼痛, 它阻碍患者康复, 且容易引起术后并发症。针药复合麻醉是传统针刺和现代麻醉技术相结合的新麻醉方法, 即药物全身麻醉的同时在穴位施加针刺, 可加强镇痛效果, 减少术后痛的发生, 但其作用机制尚不明确。趋化因子受体CX3CR1参与多种病理性疼痛的发生和发展, 本研究旨在探索CX3CR1是否参与针药复合麻醉的术后镇痛机制。建立C57BL/6J小鼠足趾切口痛模型, 用行为学测试检测小鼠痛阈, 用免疫组织化学法和Western blot检测脊髓CX3CR1的蛋白表达。结果显示, 小鼠足趾切口引起明显的机械触诱发痛和热痛觉过敏。针药复合麻醉明显抑制机械触诱发痛, 但对热痛觉过敏没有影响。CX3CR1主要表达于脊髓背角小胶质细胞中, 其蛋白水平在足趾切口术后3 d显著升高, 针药复合麻醉对CX3CR1蛋白表达水平未见显著影响。CX3CR1基因敲除小鼠足趾切口术后3 d机械痛阈较野生型C57BL/6J小鼠明显升高, 但针药复合麻醉的镇痛作用消失; 小鼠鞘内注射CX3CR1中和抗体同样可翻转针药复合麻醉的术后镇痛作用。以上结果提示, 脊髓小胶质细胞中的CX3CR1参与足趾切口痛和针药复合麻醉术后镇痛作用。

关键词: 手术切口痛; 针药复合麻醉; CX3CR1受体; 小胶质细胞; 脊髓

中图分类号: Q42; R338

Roles of CX3CR1 in mediation of post-incision induced mechanical pain hypersensitivity: Effects of acupuncture-combined anesthesia

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Abstract: Post-incision pain often occurs after surgery and is emergent to be treated in clinic. It hinders the rehabilitation of patients and easily leads to various types of postoperative complications. Acupuncture-combined anesthesia (ACA) is the combination of traditional acupuncture and modern anesthesia, which means acupuncture is applied at acupoints with general anesthesia. It was testified that ACA strengthened the analgesic effect and reduced the occurrence of postoperative pain, but its mechanism was not clear. Numerous reports have shown that chemokine receptor CX3CR1 is involved in the development and progression of many pathological pains. The present study was aimed to reveal whether ACA played the analgesic roles in the post-incision pain by affecting CX3CR1. A model of toe incision pain was established in C57BL/6J mice. The pain threshold was detected by behavioral test, and the expression of CX3CR1 protein was detected by immunohistochemical method and Western blot. The results showed that the significant mechanical allodynia and thermal hyperalgesia were induced by paw incision in the mice. Mechanical allodynia was significantly suppressed by ACA, but thermal hyperalgesia was not changed. CX3CR1 was mainly expressed in microglia in the spinal cord dorsal horn, and its protein level was significantly increased at 3 d after incision compared with that of naïve C57BL/6J mice. ACA did not affect CX3CR1 protein expression at 3 d after incision in the toe incision model mice. Paw withdrawal threshold was significantly increased at 3 d after incision in CX3CR1 knockout (KO) mice compared with that in the C57BL/6J mice. But the analgesic effect of ACA was disappeared in CX3CR1 KO mice. Accordingly, it was also blocked when neutralizing antibody of CX3CR1 was intrathecally injected

Received 2017-10-24 Accepted 2017-11-13

This work was supported by the National Basic Research Program of China (No. 2013CB531905), the National Natural Science Foundation of China (No. 81571064), and the National Basic Science Talent Cultivation Foundation of China (No. J1210041).

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(i.t.) 1 h before ACA in the C57BL/6J mice. These results suggest that CX3CR1 in microglia is involved in post-incision pain and analgesia of ACA.

Key words: post-incision pain; acupuncture-combined anesthesia; CX3CR1 receptor; microglia; spinal cord

术后痛是临床中最常见和最需要紧急处理的疼痛,属于急性痛,其机制有别于炎症痛,也不同于神经损伤引起的神经病理性痛。术后痛不仅给患者带来身体上的痛苦和心理上的负担,且限制患者尽早活动,不利于患者排便和排痰,从而减慢身体恢复,还易使胃肠道、心肺功能、内分泌代谢等出现异常,引起各类术后并发症。1958年我国医生依据针刺穴位可以镇痛创造了针刺代替麻醉药进行外科手术,谓之“针刺麻醉”,虽然在多种手术中成功地应用了针刺麻醉,但是术中存在镇痛不全、肌肉紧张和内脏牵拉反应等问题^[1,2]。为了克服这些缺点,近年来临床采用“针药复合麻醉”,即将现代麻醉技术和针刺麻醉结合起来,针刺增强药物麻醉效应、减少麻醉药物毒副反应,这种新型麻醉方法既保留了针刺镇痛的优势又解决了针刺麻醉镇痛不全的难题,有利于患者生命体征、内环境的稳定,参与重要的器官保护^[3]。

本研究应用大鼠足掌切口痛模型^[4]和转基因技术,研究术后痛脊髓水平的分子机制。CX3CL1是一种趋化因子,在炎症情况下趋化白细胞从血液循环到组织损伤部位。在脊髓水平,CX3CL1主要存在于神经元和星形胶质细胞中,以膜结合型和游离型两种功能形式存在,膜结合型的CX3CL1主要起细胞粘附作用,氮末端在细胞内,胞外的羧基端存在趋化因子区域。当伤害性信息传入,组织间的组织蛋白酶S、基质金属蛋白酶、A disintegrin and metalloproteinase 10 (ADAM 10)以及ADAM 17可以将趋化因子区域剪切下来,形成其活化形式——游离型CX3CL1。游离型的CX3CL1特异性地与表达在小胶质细胞膜上的CX3CR1受体结合,激活小胶质细胞的p38-MAPK、JNK、ERK1/2和ERK5等信号系统,从而介导神经元和胶质细胞间的信息传递^[5,6,7]。大量研究表明CX3CL1/CX3CR1信号通路参与介导神经病理性疼痛^[8,9]、炎症痛^[10,11]和骨痛^[12,13]。

我们的前期工作显示小胶质细胞参与电针对单关节炎的镇痛作用^[14,15],本研究在C57BL/6J和CX3CR1基因敲除(knockout, KO)小鼠上建立足跖

切口痛模型,并利用行为学、免疫组织化学和分子生物学等方法检测小鼠术后相关痛行为和趋化因子受体蛋白水平的变化,旨在揭示CX3CR1在手术切口痛和针药复合麻醉中的作用。

1 材料与方法

1.1 实验动物 本实验采用购自中国科学院上海实验动物中心的C57BL/6J小鼠,雄性,8~10周龄。CX3CR1 KO雄性小鼠购自Taconic (LCMI/NIAID/NIH Building 4, Room 111 Bethesda, MD 20892)。饲养环境为人工调节的12 h/12 h明暗间隔节律,自由饮食和饮水。所有动物行为的研究均严格遵照国际疼痛研究学会(International Association for the Study of Pain, IASP)的相关动物保护及使用规定,并获得复旦大学实验动物中心动物伦理委员会批准。将小鼠随机分组如下:Naïve组:未经任何处理的C57BL/6J小鼠;手术组:C57BL/6J小鼠或CX3CR1 KO小鼠,左后足跖切口;电针组:C57BL/6J小鼠或CX3CR1 KO小鼠给予针药复合麻醉,电针结束,即刻足跖切口。电针给药组:C57BL/6J小鼠电针前1 h鞘内注射CX3CR1中和抗体,余同电针组。每组8只小鼠。

1.2 主要实验仪器 TEC-3吸入式小动物麻醉机(上海瑞曼信息科技有限公司),von-Frey纤毛(Stoelting,美国),336型辐射热测试仪(IITC Life Science,美国),韩式电针仪(LH202HA,北京大学神经生物学研究所,华卫公司),无菌针灸针(云龙牌,中国),离心机(Eppendorf,芬兰),垂直电泳槽(Bio-Rad,美国),电转仪(Bio-Rad,美国),冰冻切片机(Leica,德国),激光共聚焦扫描显微镜(Olympus,日本)。

1.3 小鼠足跖切口痛模型的建立 将小鼠用2%异氟烷麻醉,对左后足进行消毒,用11号手术刀片距离足底近端3 mm处向足趾部做7 mm纵向切口,皮肤切开后,用弯头无齿眼科镊钝性剥离跟腱,并将跟腱及周围肌肉纵向切开,保持起始点完整,随后复原跟腱,按压止血,缝合皮肤。

1.4 针药复合麻醉 将小鼠用1%异氟烷浅麻醉,

保证小鼠在电针过程中不动即可。选取小鼠手术同侧阳陵泉和三阴交穴,阳陵泉穴位于腓骨小头前下凹陷中,三阴交穴位于内踝尖直上5 mm。将针灸针(0.16 mm × 7 mm)垂直于皮肤进针,进针深度分别为4 mm和2 mm。电针持续30 min,刺激强度为1、2、3 mA依次递增,每种强度持续10 min,刺激频率为2/100 Hz,电针时可见小鼠左足抖动幅度随刺激强度增加^[38]。电针结束后,增加异氟烷浓度(2%),即刻给予小鼠足跖切口。

1.5 行为学测试

1.5.1 von-Frey 测试 用 von Frey 法测定小鼠对机械刺激所引发的缩爪反应阈值(paw withdrawal threshold, PWT),将小鼠置于间距2 mm的金属网格上,用8 cm × 8 cm × 4 cm的有机玻璃盒罩住,室内温度控制在(22 ± 1) °C,并且保持环境安静。小鼠提前2~3日适应环境,每次至少2 h。测试时,提前1 h将小鼠放入有机玻璃盒内。依次使用0.16、0.4、0.6、1.0、1.4、2.0 g的 von Frey 纤毛刺激小鼠后足掌中心,受力标准以纤毛适度弯曲为度。每种强度的纤毛刺激5次,每次持续2 s,刺激间隔20 s以上,快速反射性缩爪视为有效反应。如果某种强度至少引起3次有效反应,则降低一个级别,降低的强度不能在5次中引起3次有效反应,就将上一个级别的纤毛强度定义为该动物的PWT^[16]。

1.5.2 Hargreaves 测试 用钨丝灯发出的辐射热刺激小鼠脚掌中心,引起小鼠缩爪反射,从热刺激开始到产生快速缩爪的时间视为缩爪反应潜伏期(paw withdrawal latency, PWL)。小鼠置于距离桌面30 cm的透明双层玻璃平台上,用8 cm × 8 cm × 4 cm有机玻璃盒罩住。室温控制在(22 ± 1) °C,保持环境安静。测试前3 d将小鼠放置于测试环境,每天适应至少2 h。测试时,小鼠提前适应1 h。为了防止温度过高引起实验动物灼伤,设定每次照射时间不超过20 s,刺激间隔不少于15 min,以测量3次的平均值作为该动物的PWL^[16]。

1.6 免疫组织化学检测 将小鼠用25%乌拉坦(1.5 g/kg, i.p.)麻醉,切开胸腔,暴露心脏,经升主动脉灌注37 °C生理盐水冲出血液,再灌注4 °C、4%多聚甲醛固定,取小鼠L4~L6脊髓。标本经过后固定和10%、20%、30%蔗糖溶液梯度脱水后冰冻切片(厚度为35 μm),10%正常驴血清室温封闭1 h,用兔抗CX3CR1抗体(1:200, Torrey Pines Biolabs)分别与羊抗Iba-1(1:500, Abcam)、鼠

抗GFAP(1:2 000, Sigma-Aldrich)、鼠抗NeuN抗体(1:500, Millipore)4 °C孵育过夜,漂洗后再用驴抗兔荧光二抗Alexa Flour 488(1:200)分别与驴抗羊荧光二抗Alexa Flour 546(1:200)或驴抗小鼠荧光二抗Alexa Flour 546(1:200)避光条件下室温孵育2 h,漂洗后封片,在激光共聚焦显微镜下观察和拍摄。

1.7 Western blot 检测 将小鼠麻醉(方法同免疫组织化学法)后,迅速剪去头部,置于冰上,将背部皮肤剪开,并且横向剪断其第12胸椎及第4腰椎,用冷的0.01 mol/L PBS溶液从尾端向头端吹出整段脊髓,取出L4~L6节段,在称量纸上分离出同侧背角,称重后立刻放入-80 °C的液氮中保存,使用RIPA(碧云天,中国)裂解液进行蛋白裂解,随后测定蛋白浓度。经SDS-PAGE凝胶电泳及转膜,将转好蛋白的PVDF膜放入含5%脱脂奶粉的TBST(封闭液)室温封闭2 h,再将膜移至加入兔抗CX-3CR1一抗(1:2 000, Torrey Pines Biolabs)和5%脱脂奶粉的TBST,4 °C孵育过夜,漂洗后放入TBST稀释的驴抗兔IgG-HRP(1:1 000, Santa Cruz)或抗GAPDH-HRP(1:20 000, KANC Chen)4 °C孵育2 h,避光条件下将转印膜置于显影液(Luminol Reagent),用全自动凝胶成像系统(Bio-Rad)检测信号强度。

1.8 统计学分析 数据用mean ± SEM表示,两种不同处理采用 t 检验(Student's t test),多时间点之间比较采用单因素方差分析(one-way ANOVA),多种处理、多时间点的行为学数据采用双因素方差分析(two-way ANOVA)。 $P < 0.05$ 时表示具有显著性差异。

2 结果

2.1 针药复合麻醉明显缓解术后机械痛敏

C57BL/6J雄性小鼠左后足跖切口,观察并记录术后6 h、1 d、3 d、7 d、10 d各时间点的热痛阈和机械痛阈。结果显示:术后6 h机械阈值下降,1和3 d达到最低值,7 d开始恢复,10 d接近基础值(two-way ANOVA, treatment: $F_{1,11} = 30.66$, $P < 0.001$; time: $F_{5,55} = 9.324$, $P < 0.001$; treatment × time: $F_{5,55} = 7.533$, $P < 0.001$)(图1A)。同样,热痛阈在术后6 h降至最低点,1 d后开始逐渐恢复,10 d与基础值无显著差异(two-way ANOVA, treatment: $F_{1,17} = 100.9$, $P < 0.001$; time: $F_{5,85} = 14.27$, $P < 0.001$; treatment × time: $F_{5,85} = 17.22$, $P < 0.001$)(图1B)。以上结果表

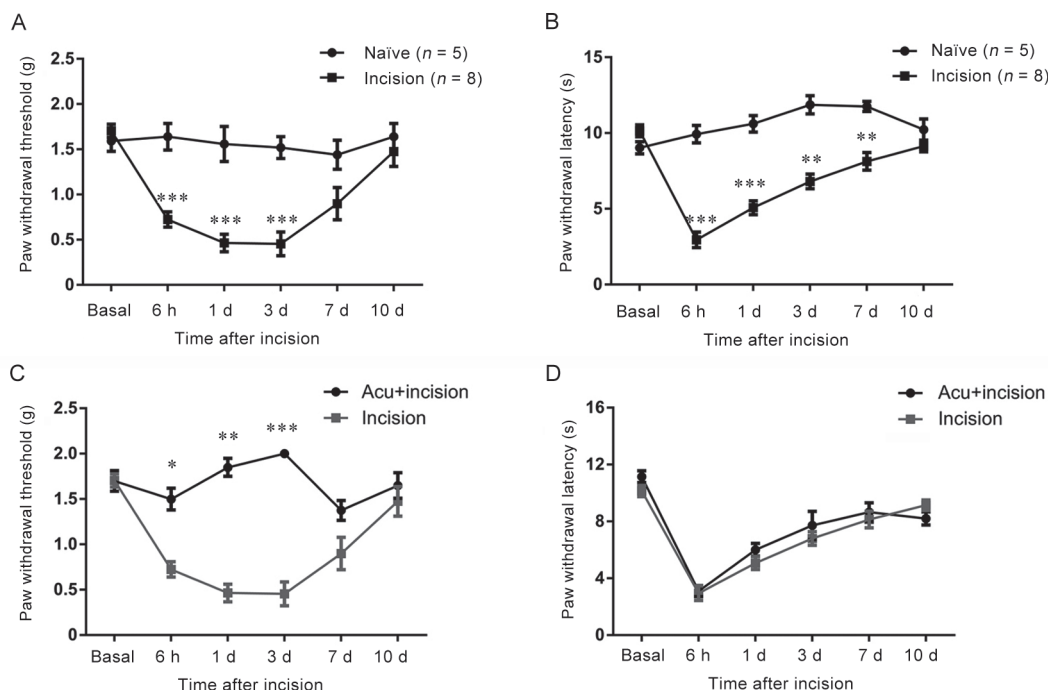


图 1. 足跖切口及针药复合麻醉对机械痛阈和热痛阈的影响

Fig. 1. The effects of incision on hind plantar or acupuncture-combined anesthesia (ACA) on mechanical and thermal threshold. A, B: Significant mechanical allodynia (A) and thermal hyperalgesia (B) were induced by paw incision. Mean $\pm$ SEM. ** $P < 0.01$, *** $P < 0.001$ vs naïve (two-way ANOVA). C, D: Mechanical allodynia (C) was significantly suppressed by ACA, but thermal hyperalgesia (D) was not changed. Mean $\pm$ SEM, $n = 8$. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ vs incision group (two-way ANOVA).

明小鼠足跖切口痛模型成功建立。

随后我们模拟了临床的针药复合麻醉，术后同样观察各时间点的机械痛阈和热痛阈，结果显示机械痛阈在术后 6 h、1 d、3 d 均未明显降低，与手术组小鼠相比差异显著 (two-way ANOVA, treatment: $F_{1,14} = 57.64$, $P < 0.001$; time: $F_{5,70} = 11.39$, $P < 0.001$; treatment $\times$ time: $F_{5,70} = 18.08$, $P < 0.001$) (图 1C)，但是热痛阈与手术组没有显著差异 (two-way ANOVA, treatment: $F_{1,14} = 2.757$, $P = 0.1191$; time: $F_{5,70} = 46.34$, $P < 0.001$; treatment $\times$ time: $F_{5,70} = 0.9023$, $P = 0.4846$) (图 1D)。以上结果显示，针药复合麻醉明显抑制机械触诱发痛，表明针药复合麻醉参与手术切口的镇痛作用。

2.2 CX3CL1/CX3CR1在脊髓背角的空间分布

本研究观察手术切口后 CX3CL1/CX3CR1 在小鼠脊髓中的表达，结果显示：在背角中，CX3CR1 主要与小胶质细胞特异性标记物 Iba-1 共标 (图 2)，高倍镜下，绿色的 CX3CR1 与红色 Iba-1 有良好的共染 (图 2A)，但是 CX3CR1 与星形胶质细胞标记物 GFAP (图 2B) 及神经元的特异性标记物 NeuN (图

2C) 不共标。CX3CL1 是 CX3CR1 的唯一配体，如图 3 所示，CX3CL1 主要与神经元的特异性标记物 NeuN 共标 (图 3A)，同时也与星形胶质细胞标记物 GFAP 有少量共标 (图 3B)，与小胶质细胞的特异性标记物 Iba-1 并不共染 (图 3C)。上述结果表明，CX3CR1 主要表达在小胶质细胞中，而其配体 CX3CL1 主要表达在神经元及星形胶质细胞中，与之前的文献报道结果一致。

2.3 CX3CR1参与手术切口痛

采用 Western blot 检测 C57BL/6J 小鼠术后 1 d、3 d、7 d CX3CR1 的蛋白表达，结果显示：术后 3 d，CX3CR1 的表达量上升，与正常 C57BL/6J 小鼠有显著性差异 (one-way ANOVA, treatment: $F_{3,36} = 3.598$, $P < 0.05$) (图 4A)。为了进一步验证 CX3CR1 对手术切口痛的作用，在 CX3CR1 KO 小鼠建立足跖切口痛，观察并记录其机械阈值。结果显示，术后 3 d CX3CR1 KO 小鼠机械阈值升高，与 C57BL/6J 小鼠有显著差异，术后 10 d 恢复至正常水平 (two-way ANOVA, treatment: $F_{1,14} = 8.830$, $P < 0.05$; time: $F_{5,70} = 53.82$, $P < 0.001$; treatment $\times$ time: $F_{5,70} = 6.293$, $P <$

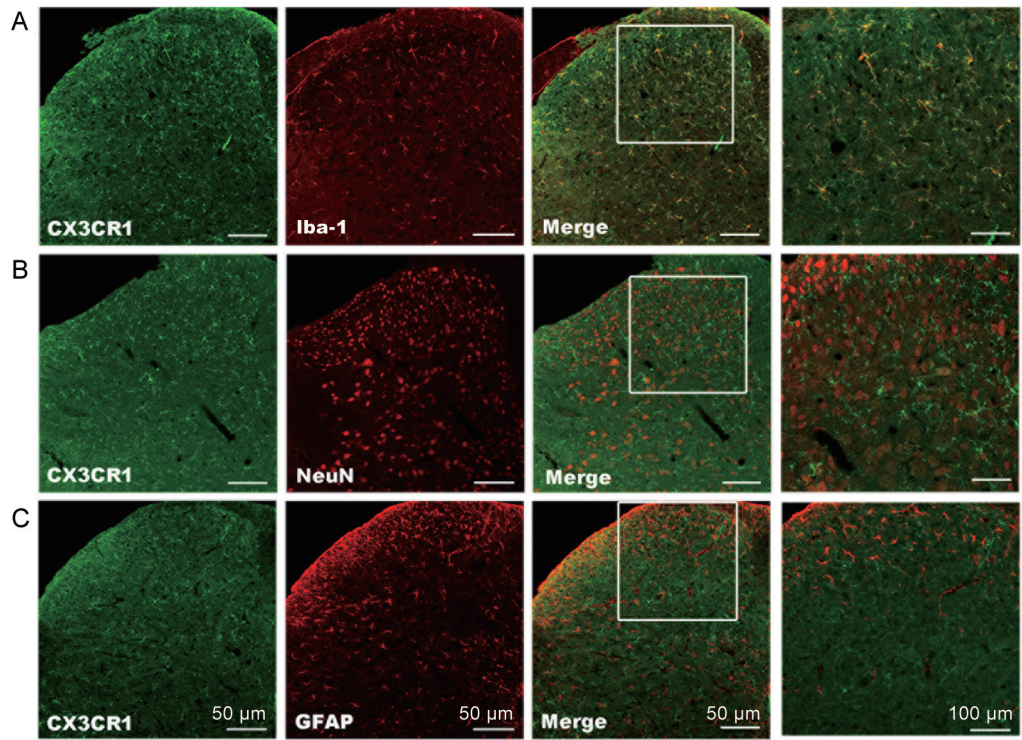


图 2. CX3CR1在脊髓背角中的表达
Fig. 2. The expression of CX3CR1 in the spinal dorsal horn detected by immunohistochemical method. CX3CR1 was mainly expressed in microglia (Iba-1 positive, *A*), but not expressed in neurons (NeuN positive, *B*) and astrocytes (GFAP positive, *C*) in post-incision mice. The pictures in the fourth column are enlargements of the framed areas.

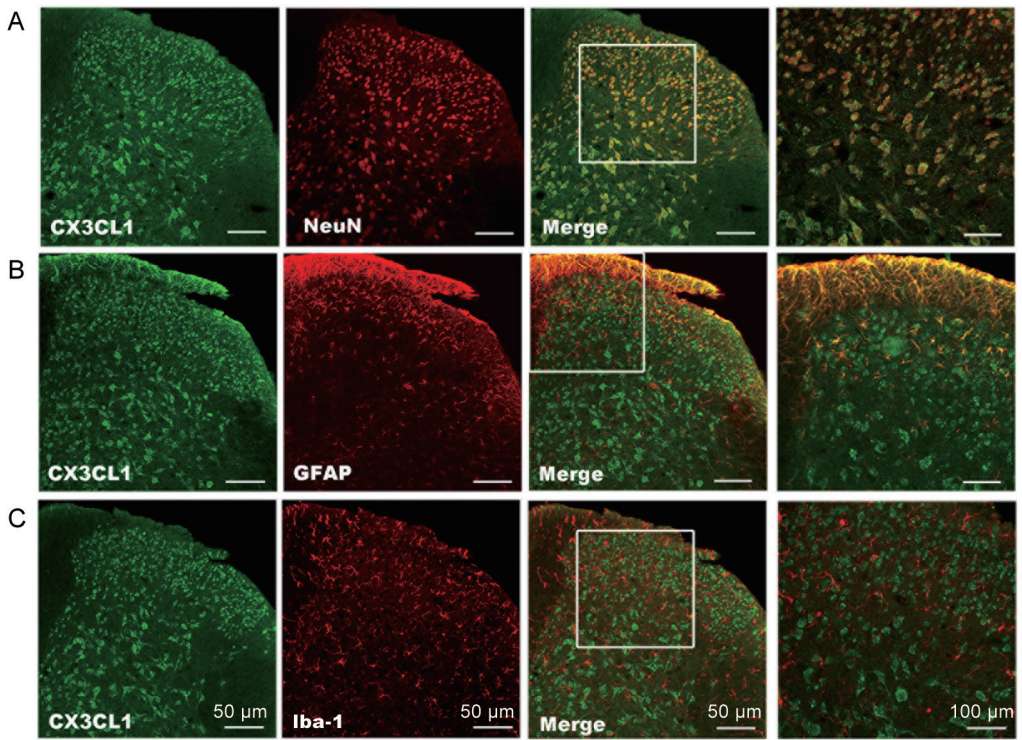


图 3. CX3CL1在脊髓背角中的表达
Fig. 3. The expression of CX3CL1 in the spinal dorsal horn detected by immunohistochemical method. CX3CL1 was mainly expressed in neuron (NeuN positive, *A*), partly in astrocyte (GFAP positive, *B*), and rarely in microglia (Iba-1 positive, *C*) in post-incision mice. The pictures in the fourth column are enlargements of the framed areas.

0.001)(图4B)。以上结果表明手术切口后 CX3CR1 蛋白表达量上升, 敲除 CX3CR1, 其痛阈较野生型 C57BL/6J 小鼠提前恢复, 提示 CX3CR1 参与手术切口痛。

2.4 基因敲除CX3CR1使针药复合麻醉的术后镇痛作用减弱

我们进一步观察了针药复合麻醉对 CX3CR1 KO 小鼠手术切口痛的影响, 行为学结果显示: 术

后 6 h、1 d、3 d, 机械阈值仍然显著下降, 与野生型 C57BL/6J 小鼠有显著差异。为了进一步确认该结果, C57BL/6J 小鼠针药复合麻醉前鞘内注射 CX3CR1 中和抗体 (5 μ g/5 μ L), 术后 6 h、1 d、3 d, 机械阈值也显著下降, 与 CX3CR1 KO 小鼠结果一致 (two-way ANOVA, treatment: $F_{2,21} = 15.34$, $P < 0.001$; time: $F_{5,105} = 19.77$, $P < 0.001$; treatment $\times$ time: $F_{10,105} = 8.760$, $P < 0.001$)(图5A)。

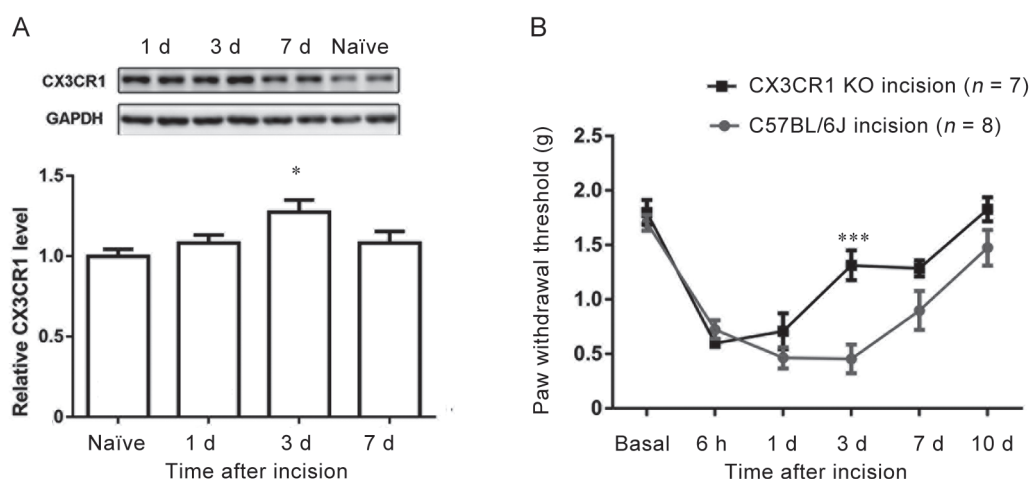


图 4. 足跖切口后CX3CR1表达增加及CX3CR1 KO机械触诱发痛减轻

Fig. 4. The protein expression of CX3CR1 was increased by hind plantar incision in naïve mice, while mechanical hyperalgesia was relieved in CX3CR1 knockout (KO) mice. A: The protein level of CX3CR1 was significantly increased at 3 d after paw incision in C57 BL/6J mice. Mean $\pm$ SEM, $n = 4$. * $P < 0.05$ vs naïve (one-way ANOVA). B: Paw withdrawal threshold was significantly increased at 3 d after incision in CX3CR1 KO mice compared with C57BL/6J mice. Mean $\pm$ SEM. *** $P < 0.001$ vs C57BL/6J incision group (two-way ANOVA).

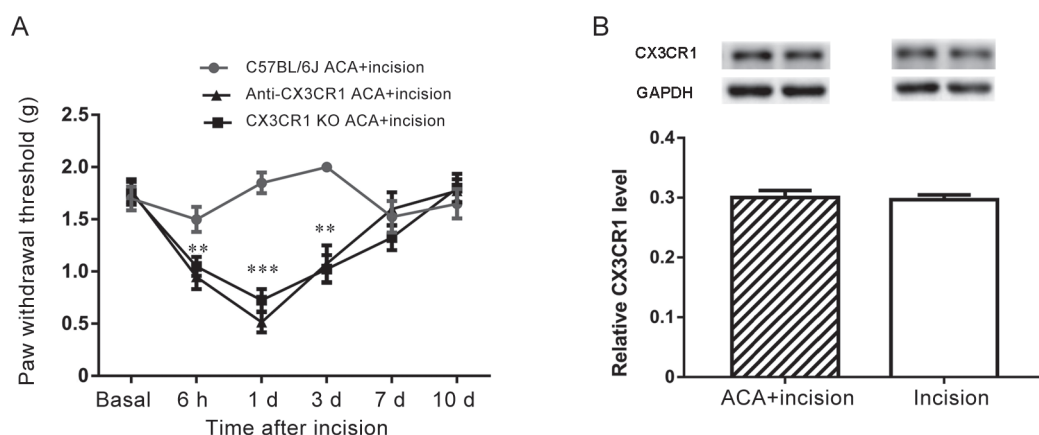


图 5. CX3CR1 KO小鼠不能实现针药复合麻醉的术后镇痛作用

Fig. 5. The analgesia of acupuncture-combined anesthesia (ACA) was abolished on CX3CR1 knockout (KO) mice. A: Anti-nociception of ACA was disappeared in CX3CR1 KO mice, and it was also blocked when neutralizing antibody of CX3CR1 was intrathecally injected (i.t.) 1 h before ACA in the C57BL/6J mice. Mean $\pm$ SEM, $n = 8$. ** $P < 0.01$, *** $P < 0.001$ vs C57BL/6J ACA+incision (two-way ANOVA). B: No significant difference of CX3CR1 protein at 3 d after incision was observed between incision and ACA+incision groups in C57BL/6J mice. Mean $\pm$ SEM, $n = 4$.

随后我们检测 C57BL/6J 小鼠给予针药复合麻醉术后 3 d 和给予普通麻醉手术切口术后 3 d 的 CX3CR1 的表达, 结果显示: 针药复合麻醉组相比于手术组小鼠没有显著性差异 (Student's *t*-test, $t = 0.5363$, $P = 0.5942$) (图 5B)。

以上结果提示, 敲除或中和 CX3CR1 受体, 针刺的镇痛作用都被削弱, 表明 CX3CR1 参与针药复合麻醉的术后镇痛作用。

3 讨论

术后痛是临床中最常见和最需要紧急处理的急性疼痛, 若处理不当, 则容易引起各类并发症, 甚至迁延成慢性疼痛, 严重影响患者的生存质量。根据本研究组以往的工作及相关文献报道, 存在于神经元和星形胶质细胞的 CX3CL1 与其在小胶质细胞上的唯一受体 CX3CR1 信号通路介导了神经元到小胶质细胞之间的信息传递, 并广泛参与慢性痛的发生和发展^[5-7]。本研究首次揭示了 CX3CR1 在术后疼痛和针药复合麻醉中的作用。切口痛发展过程中, CX3CR1 与 CX3CL1 在脊髓背角中均有表达, 并且 CX3CR1 的蛋白水平在术后 3 d 显著增高。在本研究中, 我们采用了两种方式阻断 CX3CL/CX3CR1 信号通路来验证本研究结果, CX3CR1 KO 小鼠的足趾切口痛恢复期提前, 而针药复合麻醉的电针镇痛效应完全被拮抗; 鞘内注射 CX3CR1 中和抗体以阻断 CX3CR1 的作用, 结果与 CX3CR1 KO 小鼠一致。这些结果提示, 针药复合麻醉可以预防术后痛, CX3CR1 不仅参与手术切口痛, 同时也参与了针药复合麻醉的术后镇痛。

本研究尚未对 CX3CR1 激活的上下游机制进行分析, 基于 CX3CR1 参与多种疼痛的机制研究, 我们推测 IL-1、IL-6 和 TNF- α 可能在 CX3CR1 介导针药复合麻醉中发挥重要作用。活化的胶质细胞可以通过调节突触周围的神经递质摄取, 影响神经元的活性^[17]。小胶质细胞是中枢固有的免疫细胞, 激活的小胶质细胞不仅可以释放经典的神经递质、调质等活性物质, 同时也与其他免疫细胞一样释放促炎性细胞因子, 如 IL-1、IL-6、TNF- α 等^[18-20], 激活下游信号通路。CX3CR1 主要表达在小胶质细胞中, 在大鼠单关节炎模型鞘内注射 CX3CR1 中和抗体不仅能减轻痛觉敏化, 也能抑制小胶质细胞的激活^[21, 22]; 在骨癌痛模型中鞘内注射白藜芦醇降低了 CX3CR1 的表达和胶质细胞的激活, 从而减轻了由

骨癌所引起的痛觉敏化^[23]; 在坐骨神经慢性结扎模型 (CCI) 中, 外源 IL-6 诱导 CX3CR1 的表达增加, 阻断 CX3CR1, 由 CCI 所引起的痛觉敏化也随之消失^[24]。综合上述结果, 不难设想, 切口术后痛导致类似的结果, 众多的细胞因子触发 CX3CR1 的激活, 参与针药复合麻醉的镇痛作用。

CX3CR1 既参与切口术后痛, 又在针药复合麻醉的镇痛中发挥作用, 这似乎是矛盾的。可能的解释是 CX3CL1/CX3CR1 信号通路具有双向调节作用。已经知道 CX3CL1/CX3CR1 在神经系统中发挥着重要的神经保护作用: 在色素性视网膜炎模型中, CX3CR1 的激活可以调节小胶质细胞的活化和迁移来保护神经元^[25]; 在帕金森病动物模型中, CX3CL1 可以降低多巴胺能运动神经元的损失, 减少运动协调的损失, 改善小胶质细胞的活化和促炎因子的释放^[13]。CX3CL1 作为一种双向调节因子, 在高浓度时, 可以增加脂多糖所引起的 IL-23 和 TNF- α 的表达; 低浓度时可以明显地减少 LPS 引起的巨噬细胞 TNF- α 的释放以及 ERK1/2 和 NF- κ B 的磷酸化^[26]。因此, CX3CR1 对切口痛和针药复合麻醉的双重作用, 可能与手术和针刺过程中释放的 CX3CL1 的量密切相关, 需要进一步追踪。

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