脊髓背角核因子κB表达与佐剂关节炎大鼠的痛觉过敏☆

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Correlation between hyperalgesia and nuclear factor-kappa B expression in spinal dorsal cord of rats with complete Freurd's adjuvant arthritis

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Abstract

BACKGROUND: Nuclear factor-kappa B (NF-κB), as a promoter of inflammatory reaction, stimulates injured parts or transcription of local inflammatory gene, promotes generation of inflammatory factors, and induces pain onset; however, the mechanism on chronic inflammatory pained spinal cord has been less reported.

OBJECTIVE: To explore the NF-κB expression in spinal dorsal horn and behavioral hyperalgesia by preparing rat models of complete Freurd's adjuvant arthritis.

METHODS: A total of 24 SD rats were randomly divides into sham-surgery group and complete Freund's adjuvant group, with 12 rats in each group. Adjuvant arthritis model was produced by injection of 50 μL complete Freund's adjuvant (CFA) to the right ankle joint after anesthesia. The same volume saline was injected to the rat right ankle joint in sham-surgery group. The mechanical pain threshold, paw withdrawal thermal latency (PWTL), the diameter of ankle, and NF-κB expression in spinal dorsal horn were investigated 2 days before and 4, 7, 14, 21, and 28 days after CFA injection.

RESULTS AND CONCLUSION: ① Three hours after CFA injection, the ankle joint appeared edema, but local inflamed and thermal symptoms were not obvious. The inflamed symptoms significantly appeared on right ankle joint and developed to food surface at 24 hours after CFA injection, while the symptoms lasted for 4 weeks. ② Diameter of right ankle was significantly increased at 4 days-4 weeks after CFA injection compared to intralateral ankle and before CFA injection ($P < 0.01$). ③ Compared to before injection and sham-surgery group, the mechanical pain threshold was significantly decreased at 4 days after CFA injection, and reached the lowest value at 21 days ($P < 0.01$). The PWTL was significantly decreased at 4 days after CFA injection and reached at the lowest level at 7 days, while the lowest level lasted for 4 weeks ($P < 0.01$). ④ The expression of NF-κB was significantly increased in I-VI in spinal dorsal horn in the complete Freund's adjuvant group, which was higher than sham-surgery group ($P < 0.01$). The results indicated that we could gain stable monoarthritis model by injecting CFA with oil-contained water into rat ankle joint space, and the model shown prolong and significant hyperalgesia to radial thermal and mechanical pressure; meanwhile, the NF-κB expression increased significantly in lamber I-VI in spinal dorsal horn after the ankle joint arthritis.

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摘要

背景：核因子κB作为炎症反应的启动因子，可刺激损伤部位或炎症局部基因的转录，促进炎性因子的产生，导致疼痛的发生，但其在参与慢性炎性疼痛脊髓机制中的作用目前研究甚少。

目的：制备稳定的油包水剂型完全弗式佐剂单关节炎大鼠模型，并对大鼠疼痛行为学痛觉过敏及脊髓背角核因子κB表达进行观察和探讨。

方法：24只大鼠被随机分为假手术对照组、完全弗氏佐剂组，每组12只。大鼠右踝关节腔内注射含灭活结核杆菌的黏稠油包水型完全弗式佐剂，假手术组注射50 μL生理盐水至大鼠右踝关节腔内，观察大鼠完全弗式佐剂注射前2 d，注射后4，7，14，21，28 d的机械压痛、辐射热痛、关节肿胀周径(内外踝下缘周长)及脊髓背角核因子κB表达的变化。

结果与结论：①注射3 h，大鼠右踝关节出现明显肿胀，但局部红、热不明显，注射24 h，右踝关节红肿显著且波及足跖面，并持续4周。②注射4 d~4周，大鼠右踝关节周径在较对侧及注射前显著增加($P < 0.01$)。③与注射前及假手术组相比，完全弗氏佐剂组机械压痛阈值在注射后4 d明显下降，注射后21 d降至最低值(P均 < 0.01)；注射4 d，与注射前相比，完全弗氏佐剂组大鼠患侧辐射热痛阈值明显下降，7 d降至最低点后逐渐稳定，并持续4周(P均 < 0.01)。④完全弗氏佐剂组大鼠患侧腰段脊髓背角Ⅰ~Ⅵ层核因子κB表达明显高于假手术组($P < 0.01$)。证实关节腔内注射油包水型完全弗式佐剂可获得稳定的单关节炎疼痛模型，大鼠关节致炎后出现明显的辐射热及压痛痛觉过敏，且持续时间长，痛敏阈值稳定，脊髓背角Ⅰ~Ⅵ层核因子κB表达明显升高。

关键词：佐剂性关节炎；痛觉异常；NF-κB；脊髓背角；大鼠
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0 引言

核因子κB是一种具有启动基因转录功能的蛋白质，作为多种基因表达调控的关键性转录因子，是启动多形核白细胞释放大量细胞因子触发炎症反应的关键[1-3]。因此，核因子κB在多种炎症性疾病及缺血再灌注损伤的发生中起重要作用，新近研究认为，核因子κB刺激基因的转录促进伤害性感受神经元超兴奋型的发展而参与疼痛的发生[4-8]。完全弗氏佐剂关节炎模型(complete Freund's adjuvant,CFA)是研究慢性炎性痛的常用模型[9-10]，能很好地模拟临床上常见的关节炎。故实验通过观察CFA致慢性炎性痛大鼠疼痛行为学及脊髓背角核因子κB表达的变化，初步探讨核因子κB与慢性炎性痛进展的关系。

1 材料和方法

设计：随机对照动物实验。

时间及地点：实验于2007-10/2008-05在广州医学院第二附属医院分子生物学实验室完成。实验室的生物安全的防护水平为BSL-3。

材料：雌性SD大鼠24只，体质量250~300 g，由广东省动物实验中心提供。实验过程中对动物处置符合2006年科学技术部发布的《关于善待实验动物的指导性意见》[11]。

主要试剂仪器与药品：

主要试剂仪器与药品	来源
完全弗氏佐剂	美国 Gibco 公司
核因子κB 抗体、二抗羊抗兔试剂盒	北京中杉生物技术公司
DAB 显色剂	武汉博士德生物技术公司
PL-200 热刺痛仪、压痛测试仪	成都泰盟科技有限公司

实验方法：

动物分组及模型制备：24只SD大鼠被随机分为假手术组(n=12)、完全弗氏佐剂关节炎组(n=12)。完全弗氏佐剂关节炎大鼠模型的制备，参见文献[10]。腹腔注射28 g/L戊巴比妥钠1 mL/kg，大鼠麻醉后将制备好的含灭活结核杆菌的黏稠油包水型完全弗式佐剂50 μL注射至大鼠右踝关节腔内，假手术组注射50 μL生理盐水至大鼠右踝关节腔内作为对照组。

致炎关节改变：观察大鼠注射完全弗氏佐剂后踝关节局部肿胀情况，记录注射前2 d，注射后4，7，14，28 d踝关节周径。

疼痛行为学观察：疼痛行为学的测试采用辐射热潜伏期及机械压痛阈值表示，于注射前2 d，注射后4，7，14，21，28 d进行测试，辐射热潜伏期的测试方法参见文献[12-14]。机械压痛测定方法如下：大鼠钻入机械压痛传感筒内将其双下肢露出并在大鼠背部妥善固定，逐渐增大压力作用至大鼠足背表面，直至大鼠出现缩爪反应，机械压痛仪则自动记录下大鼠缩爪的机械压力值。

脊髓背角核因子κB表达的检测：CFA致炎后4周，在戊巴比妥钠麻醉下，开胸经左心室升主动脉插管，先以生理盐水快速灌注冲洗，直至水变清亮后，再以40 g/L多聚甲醛磷酸盐缓冲液500 mL心内灌注固定，取$L_{4\sim5}$脊髓节段，多聚甲醛后固定及300 g/L蔗糖脱水后，做冰冻冠状切片(15 μm)，免疫组织化学法检测脊髓背角核因子κB的表达，切片中分别加入1∶400倍稀释的兔抗大鼠核因子κB抗体，4 ℃孵育过夜，次日采用HRP/DAB免疫组织化学法检测其表达。采用HSP-1100型细胞分析系统计算核因子κB的表达的阳性细胞数/视野。

主要观察指标：①致炎关节改变结果。②疼痛行为学观察。③脊髓背角核因子κB阳性细胞数的表达的检测。

设计、实施、评估者：均为第一作者，曾接受过科研设计实施的正规培训。

统计学分析：采用SPSS 10.0 软件进行分析，计量资料采用$\bar{x}\pm s$表示，组间比较采用重复测量的方差分析，组内比较采用配对t 检验，P < 0.01为差异有显著性意义。

2 结果

2.1 *实验动物数量分析* 实验选用大鼠24只，分为2组，无脱失，全部进入结果分析。

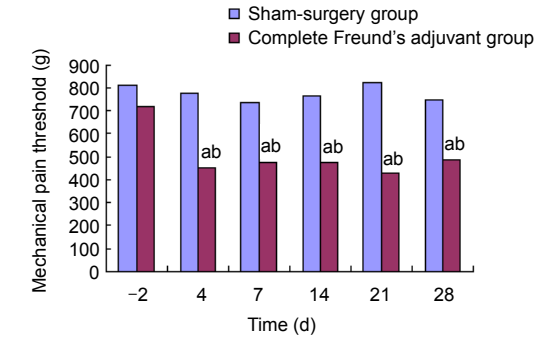
2.2 *致炎关节改变* 大鼠注射完全弗式佐剂3 h，右踝关节出现明显肿胀，但局部红、热不明显，注射后24 h右踝关节红肿显著且波及足跖面，少数大鼠甚至形成踝足跖部皮肤破损出血，1周时红肿渐局限于右踝关节局部，并持续至注射后4周。大鼠右踝关节周径在注射后4 d (3.10±0.02) cm至4周(3.05±0.01) cm，较对侧(2.37±0.01) cm及注射前(2.37±0.01) cm显著增加，差异具有显著性意义(P < 0.01)，而假手术组无异常。见表1。

表 1 两组大鼠致炎前后踝关节周径的比较
Table 1 Comparison of the ankle perimeter between two groups pre- or post-inflammation ($x\pm s$, cm)

Group	Ankle perimeter for pre- or post-inflammation (d)				
	−2	4	7	14	28
Sham-surgery					
Left	2.37±0.01	2.38±0.02	2.38±0.01	2.38±0.01	2.40±0.01
Right	2.36±0.01	2.37±0.02	2.37±0.02	2.37±0.02	2.38±0.03
CFA					
Left	2.36±0.01	2.37±0.01	2.37±0.02	2.38±0.01	2.41±0.02
Right	2.37±0.01	3.10±0.02[ab]	3.16±0.03[ab]	3.09±0.02[ab]	3.05±0.01[ab]

CFA: complete Freund's adjuvant; [a]P < 0.01, *vs.* pre-inflammation; [b]P < 0.01 *vs.* sham-surgery group

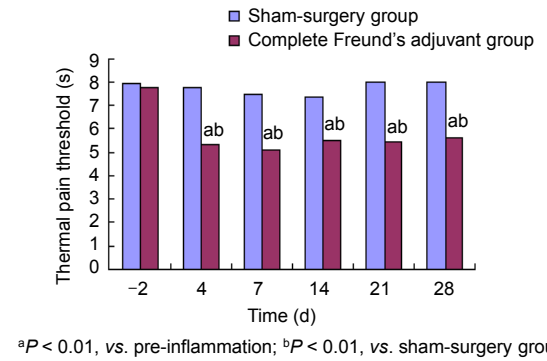
2.3 疼痛行为学观察 假手术组处理前后机械压痛阈值和辐射热潜伏期无明显改变，CFA组机械压痛阈值在注射后4 d明显下降，并于注射后21 d降至最低值，与注射前及假手术组相比，差异有显著性意义($P < 0.01$)；CFA组右踝关节注射完全弗式佐剂4 d后，大鼠患侧辐射热痛阈值明显下降，7 d降至最低点后逐渐稳定，并持续至观察期4周。与注射前及假手术组相比，差异有显著性意义($P < 0.01$)。见图1，2。



[a]$P < 0.01$, *vs.* pre-inflammation; [b]$P < 0.01$, *vs.* sham-surgery group

Figure 1 Comparison of mechanical pain threshold between two groups for pre- or post-inflammation ($\bar{x}\pm s$, g)

图 1 两组大鼠致炎前后机械压痛阈值的比较($\bar{x}\pm s$, g)

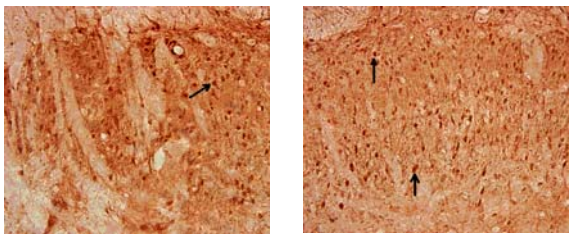


[a]$P < 0.01$, *vs.* pre-inflammation; [b]$P < 0.01$, *vs.* sham-surgery group

Figure 2 Comparison of the thermal pain threshold between two groups for pre- or post-inflammation($\bar{x}\pm s$, s)

图 2 两组大鼠致炎前后辐射热痛阈值的比较($\bar{x}\pm s$，s)

2.4 脊髓背角核因子κB阳性细胞数的表达的检测 见图3，4。

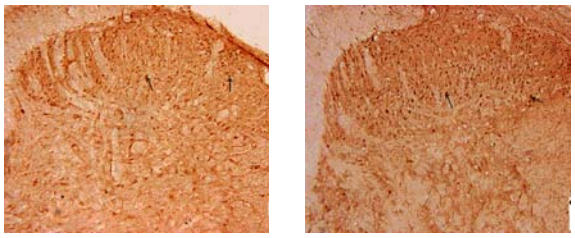


a: Sham-surgery group b: CFA group

CFA: complete Freund's adjuvant

Figure 3 NF-κB expression in spinal dorsal horn in the two groups (DAB staining, ×400)

图 3 假手术组与完全弗式佐剂关节炎组大鼠脊髓背角核因子κB 的表达(箭头示，DAB 染色，×400)



a: Sham-surgery group b: CFA group

CFA: complete Freund's adjuvant

Figure 4 NF-κB expression in spinal dorsal horn in the two groups (DAB staining, ×200)

图 4 假手术组与完全弗式佐剂关节炎组大鼠脊髓背角核因子κB 的表达(箭头示，DAB 染色，×200)

核因子κB表达呈胞核的棕褐色深染颗粒，主要位于脊髓背角的Ⅰ~Ⅵ层。假手术组脊髓背角核因子κB阳性细胞数为(96±27)个/视野，CFA组大鼠患侧腰段脊髓背角NF-κB表达明显增高，为(176±23)个/视野，与对照组相比，差异具有显著性意义($P < 0.01$)。

3 讨论

慢性炎性痛除具有炎症反应的红、肿、热症状外，尚具有对伤害性刺激敏感性增强和反应阈值降低的痛觉过敏和痛觉异常等特点[4,15-19]，该病程往往迁延反复，治疗效果不佳，也是目前慢性疼痛研究的热点。完全弗氏佐剂是灭活的结核杆菌与液体石蜡的混合物，是一种强大而有效的致炎剂，注射至啮齿类动物可引起局部明显持久的炎性反应，产生类似于人类风湿性关节炎的病理状态。因此，完全弗氏佐剂常被用于制作炎性痛模型进行研究。在临床上风湿性关节炎更多发生于女性患者，故实验中采用雌性大鼠作为研究对象。实验发现，大鼠后爪注射完全弗氏佐剂后，注射足踝关节周围出现红、肿、热表现持续时间长，同时出现对热痛和机械压痛的痛觉过敏，很好模拟了人类关节炎性痛的症状。

本实验中，完全弗氏佐剂诱导大鼠产生慢性炎性痛表现，在不同时间点对热痛阈和机械压痛的改变有所差异。大鼠后足注射CFA后，在注射后4 d观察即出现辐射热痛阈明显下降，于注射后7 d降至最低点，后逐渐稳定，并持续至注射后4周，在热痛敏的同时，大鼠也出现对机械压痛的敏感，机械压痛在注射后21 d降至最低。说明CFA诱导了长时间的机械痛敏和热痛敏现象，并具有较好的稳定性。Nagakura等[20]研究足底注射100 μL CFA致关节炎的疼痛变化规律，显示大鼠的触诱发痛在开始7 d内逐渐降低，以后渐趋稳定；热痛阈则在致痛后1 d则达最低值。实验结果与此结果有所差异，考虑为观察时间和周期更长所致。

慢性疼痛产生的机制极其复杂，研究表明p38、*c-fos*、*c-jun*基因，一氧化氮合酶、环氧合酶等等均参与

慢性神经痛或炎性疼痛的发生[21-25]。而核因子κB作为广泛存在于真核细胞的核转录因子，它在炎症过程和慢性疼痛发生发展中起着举足轻重的作用[1,4,26]。既往对核因子κB参与疼痛发生的研究多集中于关节局部炎症和慢性神经病理性疼痛。类风湿性关节炎患者关节滑膜抽提物NF-IkB活性明显高于骨关节患者[10]。而在佐剂性关节炎大鼠模型中，关节滑膜局部核因子κB活化也明显增加[15]。在部分坐骨神经损伤大鼠，损伤同侧脊髓激活的核因子κB免疫阳性神经元百分率明显增加。而使用核因子κB的抑制剂如S1627和核因子κB decoy，以及鞘内注射核因子κB反义寡核苷酸均能显著减轻坐骨神经慢性缩窄损伤大鼠的机械性痛觉异常的和热痛觉过敏反应[5-7,26]，上述研究说明核因子κB通路在关节炎发病和慢性神经病理性疼痛发病过程中起重要作用。在本实验中也观察了与慢性炎症反应密切相关的核因子κB的表达情况，研究发现，完全弗氏佐剂注射后大鼠踝关节周围出现红、肿、热表现，且出现对机械压痛和热痛的痛觉过敏，伴随上述行为学改变的是脊髓背角Ⅰ~Ⅵ层核因子κB表达明显增高，而假手术组的表达量相对较少。说明慢性关节炎性痛时，脊髓背角的核因子κB阳性神经细胞数量增加发生了激活。而核因子κB激活导致炎性疼痛的机制又如何呢?

已知核因子κB主要存在于中枢神经系统的神经元及胶质细胞。定位于突触部位突触前末端，突触后及核周胞质内。当机体受到损伤、炎症等伤害性刺激后，核因子κB能快速接受外界信息，由局部突触信号诱导其活化，活化的核因子κB可由轴突逆行运输进入胞核，将突触信号传至核内，并与靶基因结合，调控基因转录，并发挥其生物学效应[5, 25, 27]。IkB激酶(IKK)磷酸化IkB是核因子κB激活和核因子κB反应基因上调的第一步，使用IkB抑制剂S1627注射至炎性痛大鼠坐骨神经能减轻炎性和神经病理性疼痛，但对急性炎性疼痛无影响[6, 27]。说明核因子κB的激活参与了慢性炎性疼痛而非急性炎性痛进程。核因子κB调控参与炎性痛基因的表达，是导致痛觉易化的重要原因之一[28-29]，其具体机制尚需进一步深入研究。

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