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Calpain抑制剂ALLN对酵母多糖足底炎性疼痛模型大鼠的镇痛作用及其对脊髓背角

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Analgesic Effect of Calpain Inhibitor ALLN on the Zymosan-inducedPaw Inflammatory Pain and Its Effect on the Expressionof Cyclooxygenase-2 in the Spinal Dorsal Horn

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摘要 目的 评价calpain抑制剂ALLN对酵母多糖足底炎性疼痛模型大鼠的镇痛作用及其对脊髓背角环氧化酶-2（COX-2）表达水平的影响，探讨calpain在炎性疼痛中的作用机制。方法 SD大鼠48只，随机分为对照组、假手术组和酵母多糖组，按Meller方法制作酵母多糖足底炎性疼痛模型。分别于制模前和制模后0.5、1、2、4、8、24和48 h测定各组大鼠左侧后足机械刺激缩足阈值（MWT）和左侧后足最大厚度，并在指定时间点处死取制模侧腰段脊髓背角，采用Western印迹方法测定calpain的活性。另取SD大鼠64只，随机分为假手术组、二甲基亚砜（DMSO）溶剂对照组和ALLN治疗组。分别于制模前和制模后0.5、1、2、4、8、24和48 h测定各组大鼠左侧后足MWT和左侧后足最大厚度，并在指定时间点处死取制模侧腰段脊髓背角，采用Western印迹方法测定COX-2的含量变化。结果 与对照组和假手术组相比，酵母多糖组大鼠制模侧后足MWT显著降低（$P<0.05$），最大厚度显著增加（$P<0.01$），制模后4、24和48 h calpain活化水平明显增强（$P<0.01$）。与DMSO溶剂对照组大鼠比较，ALLN治疗组大鼠制模后相应时间点MWT显著增高（$P<0.05$），左足最大厚度显著减小（$P<0.05$），脊髓背角COX-2表达水平明显下降（$P<0.01$）。结论 酵母多糖足底炎性疼痛模型大鼠脊髓背角calpain活化增强。Calpain抑制剂ALLN可以显著缓解酵母多糖足底炎性疼痛模型大鼠的炎性疼痛和炎性水肿，并显著降低模型大鼠脊髓背角COX-2的表达水平，提示calpain活化后可能通过促进脊髓水平COX-2表达增加，参与炎性疼痛的形成。

关键词： 酵母多糖 炎性疼痛 环氧化酶-2 脊髓背角 钙离子依赖半胱氨酸蛋白酶 抑制剂

Abstract: Objective To examine the analgesic effect of calpain inhibitor ALLN on the zymosan-induced paw inflammatory pain and its effect on the expression of cyclooxygenase-2 (COX-2) in the spinal dorsal horn. Methods Forty-eight Sprague-Dawley rats were equally divided into three groups: control group, sham-operated group, and zymosan group. According to Meller's method, zymosan (1.25 mg) was injected intraplantarly to induce paw inflammation in zymosan group; an equal volume of PBS was administered in the sham-operated group. Mechanical withdrawal threshold (MWT) and maximum thickness of paw were tested or measured before and 0.5, 1, 2, 4, 8, and 24 hours after injection. All rats were killed at different occasions following surgery to examine calpain activity in the spinal dorsal horn with Western blot analysis. Another sixty-four Sprague-Dawley rats were divided into three groups: sham-operated group, zymosan-induced paw inflammation with intraperitoneal dimethyl sulphoxide (DMSO) treatment group, and zymosan-induced paw inflammation with intraperitoneal calpain inhibitor ALLN treatment group. MWT and maximum thickness of paw were tested or measured before and 0.5, 1, 2, 4, 8, and 24 hours after injection. All rats were killed at different occasions following surgery to examine the COX-2 expression in the spinal dorsal horn with Western blot analysis. Results MWT significantly decreased in the rats with zymosan-induced paw inflammation, while the maximum thickness of paw significantly increased, compared with control and sham-operated rats ($P<0.05$. Calpain in the ipsilateral spinal dorsal horn was dramatically activated after zymosan injection ($P<0.01$). Intraperitoneal ALLN injection significantly increased zymosan-induced MWT and decreased paw edema at the same time points after zymosan injection compared with DMSO treatment group ($P<0.05$). Meanwhile, calpain inhibitor ALLN treatment significantly decreased the COX-2 expression in the spinal dorsal horn compared with DMSO treatment ($P<0.01$).Conclusion Administration of calpain inhibitor ALLN is effective to attenuate zymosan-induced paw inflammatory pain. Calpain activation may be one aspect of the signaling cascade that increases the COX-2 expression in the spinal cord and contributes to mechanical hyperalgesia after peripheral inflammatory injury.

Keywords: zymosan inflammatory pain cyclooxygenase-2 dorsal horn calpain inhibitor

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