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慢性压迫损伤性神经病理性疼痛大鼠模型中脊髓背角 ERK、CREB、BDNF 表达的变化

徐良　裘涛　张丽娟　张伟骏

【 摘要 】 目的　通过建立慢性神经结扎性损伤(CCI)大鼠模型,揭示在神经病理性疼痛发生、发展过程中细胞外调节蛋白激酶(ERK)、环磷腺苷效应元件结合蛋白(CREB)、脑源性神经营养因子(BDNF)表达的变化。 方法　将 21 只大鼠随机双盲分为模型组、假手术组、U0126 组,每组各 7 只,模型组及 U0126 组建立 CCI 模型,假手术组暴露坐骨神经不做结扎,3 组均进行鞘内置管,U0126 组鞘内注射阻断剂 U0126 10μg/次,连续 3d;模型组造模成功后、假手术组术后予 0.9% 氯化钠溶液 0.12m l/kg 灌胃至术后 14d。对各组大鼠分别于术前、术后 1、7、14d 进行热痛觉过敏行为测试和机械刺激测试，采用 Western blot 法检测模型大鼠脊髓背角 ERK、CREB、BDNF 的表达水平。 结果　与假手术组相比,模型组大鼠术后热板及机械缩足反射阈值明显降低,差异均有统计学意义(均 $P<0.05$)。CCI 导致大鼠脊髓背角内胞浆与胞核内 ERK、CREB、BDNF 水平均增加,差异均有统计学意义(均 $P<0.01$)。ERK 阻滞剂 U0126 组能明显升高大鼠术后热板及机械痛敏阈值($P<0.05$),U0126 组导致大鼠脊髓背角内胞质与胞核内 CREB、BDNF 水平均明显降低,差异均有统计学意义(均 $P<0.05$)。 结论　CCI 模型导致痛觉过敏,U0126 可以减轻 CCI 大鼠的疼痛。ERK-CREB 磷酸化的通路参与 BDNF 对于背根神经节的神经元的保护和修复过程。

【 关键词 】 脑源性神经营养因子　神经病理性疼痛　细胞外调节蛋白激酶　环磷腺苷效应元件结合蛋白　慢性神经结扎性损伤

Expression of ERK, CREB and BDNF in spinal cord dorsal horn of rat model with chronic constriction injury-induced neuropathic pain

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【 Abstract 】 Objective　To investigate the expression of extracellular signal-regulated kinase (ERK), cAMP response element binding protein (CREB) and brain-derived neurotrophic factor (BDNF) in spinal cord dorsal horn of rat model with chronic constriction injury (CCI)-induced neuropathic pain. Methods　CCI model was induced by chronic nerve ligation in rats. Twenty one rats were randomly divided into model group, sham operation group and U0126 group with 7 in each group. The thermal hyperalgesia and mechanical stimulation were tested; the expressions of ERK, CREB and BDNF protein in rat spinal cord dorsal horn were detected by Western blot. Results　Compared with sham group, model group after the thresholds of thermal hyperalgesia and mechanical stimulation tests were significantly lower ($P<0.05$), and the expressions of ERK, CREB, and BDNF protein were significantly increased ($P<0.01$). ERK inhibitor U0126 significantly increased the thresholds of thermal hyperalgesia and mechanical stimulation tests ($P<0.05$), and also decreased the expressions of ERK, CREB and BDNF protein in spinal cord dorsal horn ($P<0.05$). Conclusion　CCI leads to hyperalgesia in rats, U0126 can reduce the pain in CCI rats, which indicates that ERK-CREB phosphorylation pathway may be involved in the protection and repair of dorsal root ganglion neurons by BDNF.

【 Key words 】 Brain-derivedneurotrophic factor　Neuropathic pain　Extracellular signal-regulated kinase　cAMP response element binding protein　Chronic nerve ligation injury

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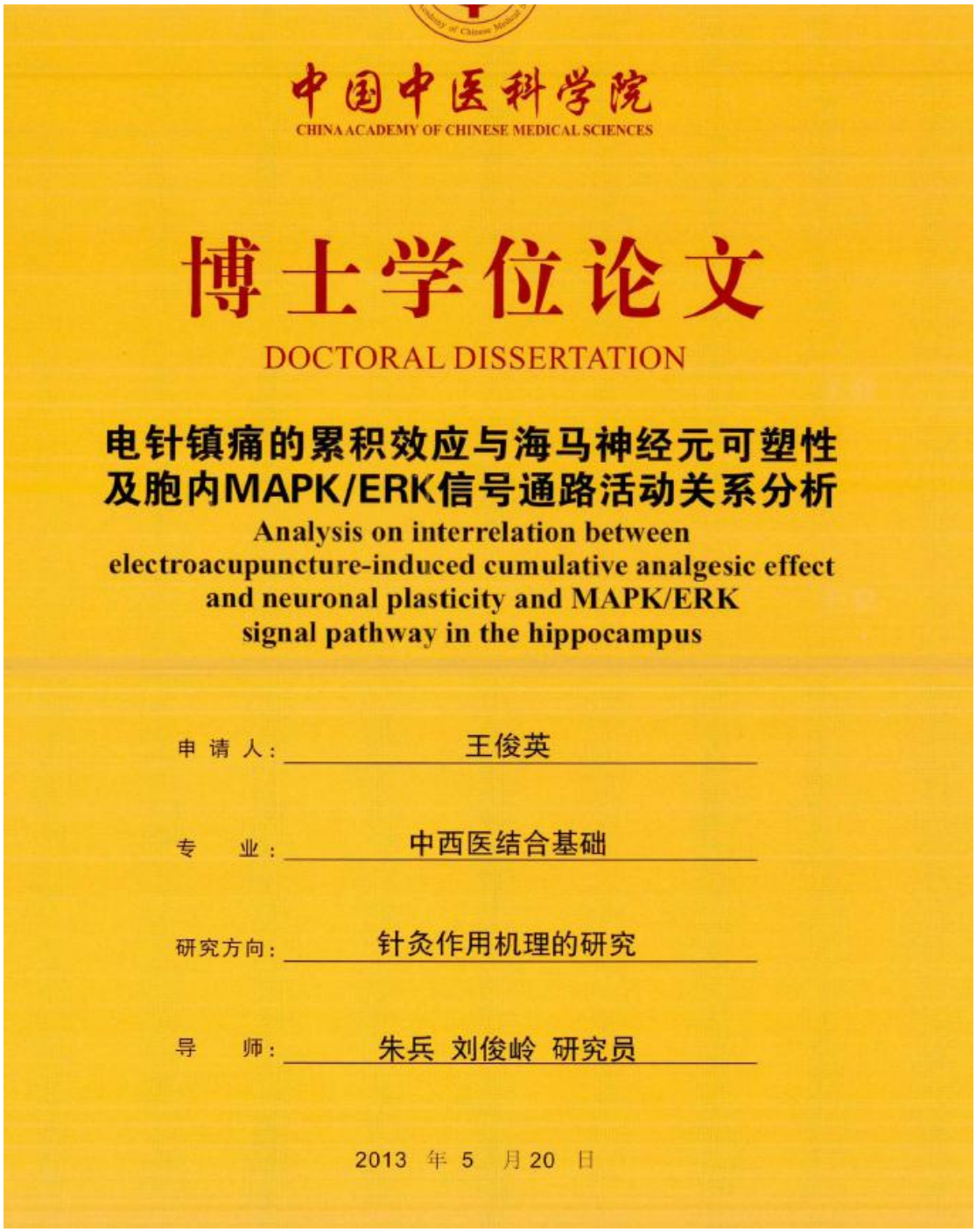

中国中医科学院
CHINA ACADEMY OF CHINESE MEDICAL SCIENCES

博士学位论文

DOCTORAL DISSERTATION

电针镇痛的累积效应与海马神经元可塑性及胞内MAPK/ERK信号通路活动关系分析

Analysis on interrelation between electroacupuncture-induced cumulative analgesic effect and neuronal plasticity and MAPK/ERK signal pathway in the hippocampus

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专　　业：中西医结合基础

研究方向：针灸作用机理的研究

导　　师：朱兵 刘俊岭 研究员

2013 年 5 月 20 日

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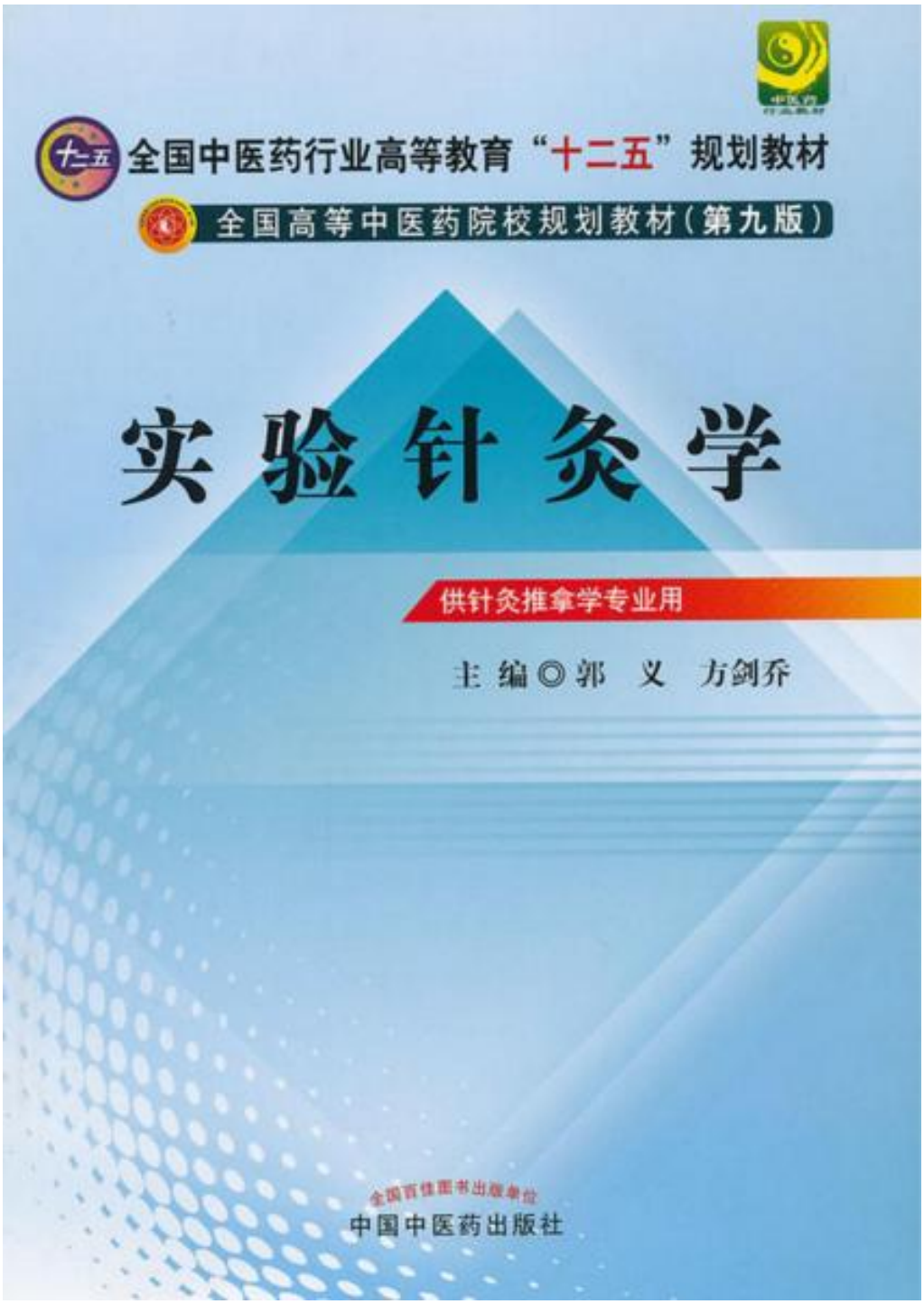

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RESEARCH ARTICLE Open Access

Contributions of p38 and ERK to the antinociceptive effects of TGF-β1 in chronic constriction injury-induced neuropathic rats

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Abstract

Background: Transforming growth factor-βs (TGF-βs) are a group of multifunctional proteins that have neuroprotective roles in various experimental models. We previously reported that intrathecal (i.t.) injections of TGF-β1 significantly inhibit neuropathy-induced thermal hyperalgesia, spinal microglia and astrocyte activation, as well as upregulation of tumor necrosis factor-α. However, additional cellular mechanisms for the antinociceptive effects of TGF-β1, such as the mitogen-activated protein kinase (MAPK) pathway, have not been elucidated. During persistent pain, activation of MAPKs, especially p38 and extracellular signal-regulated kinase (ERK), have crucial roles in the induction and maintenance of pain hypersensitivity, via both nontranscriptional and transcriptional regulation. In the present study, we used a chronic constriction injury (CCI) rat model to explore the role of spinal p38 and ERK in the analgesic effects of TGF-β1.

Methods: We investigated the cellular mechanisms of the antinociceptive effects of i.t. injections of TGF-β1 in CCI induced neuropathic rats by spinal immunohistofluorescence analyses.

Results: The results demonstrated that the antinociceptive effects of TGF-β1 (5 ng) were maintained at greater than 50 % of the maximum possible effect in rats with CCI for at least 6 h after a single i.t. administration. Thus, we further examined these alterations in spinal p38 and ERK from 0.5 to 6 h after i.t. administration of TGF-β1. TGF-β1 significantly attenuated CCI-induced upregulation of phosphorylated p38 (phospho-p38) and phosphorylated ERK (phospho-ERK) expression in the dorsal horn of the lumbar spinal cord. Double immunofluorescence staining illustrated that upregulation of spinal phospho-p38 was localized to neurons, activated microglial cells, and activated astrocytes in rats with CCI. Additionally, increased phospho-ERK occurred in activated microglial cells and activated astrocytes. Furthermore, i.t. administration of TGF-β1 markedly inhibited phospho-p38 upregulation in neurons, microglial cells, and astrocytes. However, i.t. injection of TGF-β1 also reduced phospho-ERK upregulation in microglial cells and astrocytes.

Conclusions: The present results demonstrate that suppressing p38 and ERK activity affects TGF-β1-induced analgesia during neuropathy.

Keywords: Transforming growth factor-β, p38, Extracellular signal-regulated kinase, Chronic constriction injury, Neuropathic pain

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·实验研究·

杏仁核注射 U0126 对芬太尼诱发大鼠痛觉过敏的镇痛效应

罗放　尹平平　李珍

【摘要】 **目的**　探讨杏仁核中央核(CeA)细胞外信号调节蛋白激酶(ERK)在芬太尼诱发痛觉过敏(OIH)发病机制中的作用。**方法**　实验一:雄性 SD 大鼠 12 只,随机分为实验组(OIH 模型组)和对照组,OIH 建模成功后取右侧 CeA 组织用 Western blot 检测 p-ERK 蛋白的表达水平。实验二:另取雄性 SD 大鼠 30 只,随机分为 OIH 组、OIH + U0124 组、OIH + U0126(0.15 nmol)组、OIH + U0126(0.45 nmol)组和 OIH + U0126(1.5 nmol)组,每组 6 只,均杏仁核置管后制作 OIH 模型,成功后向 CeA 内分别注射 0.3 μl DMSO、U0124(1.5 nmol)、U0126(0.15、0.45、1.5 nmol);观测注药前后机械缩足阈值及热缩足潜伏期的变化。取 CeA 组织检测 p-ERK 蛋白的表达水平。**结果**　实验一:与对照组比较,实验组机械缩足阈值和热缩足潜伏期明显降低,CeA 区 p-ERK 蛋白表达明显升高($P < 0.05$)。实验二:建模后各组大鼠机械缩足阈值及热缩足潜伏期均明显降低($P < 0.05$),CeA 区 p-ERK 蛋白表达增加,U0126 剂量依赖性地翻转上述行为学和分子水平的变化($P < 0.05$)。**结论**　CeA区 ERK 参与了芬太尼诱发的痛觉过敏的维持,靶向抑制 CeA 区 ERK 激活可治疗芬太尼诱发的痛觉过敏。

【关键词】　细胞外信号调节蛋白激酶;镇痛药,阿片;痛觉过敏;杏仁核

Analgesic effect of intra-amygdala infusion of U0126 on fentanyl-induced hyperalgesia in rats

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【**Abstract**】 **Objective**　To explore the role of extracellular signal-regulated kinase (ERK) in central nucleus of amygdala (CeA) in the mechanism of fentanyl-induced hyperalgesia (OIH) in rats. **Methods**　Step 1: 12 healthy male Sprague-Dawley rats, weighing 60-100 g, were randomly divided into OIH and Control group. The mechanical paw withdrawal threshold (PWT) and the thermal paw withdrawal latency (PWL) were tested at pre-and post-OIH induction. Then the level of p-ERK in the CeA was analyzed by Western blotting. Step 2: After successful induction of OIH and catheterization in CeA, another 30 SD male rats were randomly divided into 5 groups ($n = 6$ each): Group OIH; Group OIH + U0124; Group OIH + U0126 (0.15 nmol); Group OIH + U0126 (0.45 nmol) and Group OIH + U0126 (1.5 nmol), then 0.3 μl of DMSO, U0124 (1.5 nmol), U0126 (0.15 nmol, 0.45 nmol, 1.5 nmol) was given through the catheter separately. PWT and PWL were tested before catheterization, at pre-OIH induction, post-OIH induction and 0.5 h after CeA drug administration. After the last test of pain threshold, the rats were sacrificed and CeA tissues were sampled for analyzing the expression of p-ERK by western blot. **Results**　In step 1 compared with control group, PWT and PWL of OIH group were sharply decreased post-OIH induction ($P < 0.05$), concomitant increase of the expression of p-ERK in CeA in OIH group was also observed. In step 2, both PWT and PWL were sharply decreased post-OIH induction ($P < 0.05$). Intra-CeA U0126 injection, but not U0124, reversed both behavioral hyperalgesia and molecular activation of ERK in CeA in a dose-dependent manner ($P < 0.05$). **Conclusion**　ERK plays a pivotal role in the maintenance of fentanyl-induced hyperalgesia. Targeting inhibition of ERK activation in CeA can alleviate fentanyl-induced hyperalgesia.

【**Key words**】　Extracellular signal-regulated kinase; Analgesics, opioid; Hyperalgesia; Amygdala

芬太尼是临床麻醉常用药,大量或重复使用芬太尼会引起痛觉敏感性增加,即阿片诱发的痛觉过敏(opioid induced hyperalgesia, OIH)[1],已引起临床重视,其机制尚未完全阐明。近年来,杏仁核在疼痛及疼痛相关反应中的作用正逐步被揭示[2],研究表明,杏仁核细胞外信号调节蛋白激酶(ERK)在福尔马林诱发的外周炎性痛敏中发挥重要作用[3]。杏

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cAMP应答元件结合蛋白与痛觉调制*

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摘要 cAMP应答元件结合蛋白(cAMP response element binding protein, CREB)是刺激诱导的一种转录因子,通过磷酸化实现调节转录功能。疼痛和痛觉过敏是组织损伤或炎症时常伴有的生理病理过程,谷氨酸、P物质等神经递质或神经肽以及细胞内的信号转导途径参与此过程。近年来研究发现 CREB通过自身磷酸化,在炎症、神经损伤等诱发的自发性疼痛、痛觉过敏及痛觉超敏中具有重要作用。本文从 CREB的一般特性及其在脊髓水平的痛觉调制中的作用等方面予以综述。

关键词 cAMP应答元件结合蛋白;脊髓;痛觉调制
中图分类号 R338

cAMP应答元件结合蛋白(cAMP response element binding protein, CREB)是上世纪 80年代后期发现的一种细胞核内调控因子,它通过自身磷酸化实现调节转录功能。cAMP及其下游信号途径参与调节许多不同的细胞内过程(Shaywitz和 Greenberg, 1999; Lonze和 Ginty, 2002; Mayr和 Montminy, 2001; Sakamoto和 Goodyear, 2002; Skaliora等, 2000)。CREB家族成员作为典型的刺激诱导的转录因子已经被广泛接受。许多神经元细胞外刺激均能够激活 CREB家族和依赖 CREB的基因表达,参与中枢神经系统可塑性形成及疾病发生等复杂的生理病理过程[1]。疼痛和痛觉过敏是组织损伤或炎症时常伴有的生理病理现象,谷氨酸、P物质等神经递质或神经肽,以及细胞内的信号转导途径参与此过程。近年来的研究发现,CREB通过自身的磷酸化,在炎症、神经损伤等诱发的自发性疼痛、痛觉过敏的形成过程中具有重要作用,本文将就此方面的研究进展加以综述。

一、CREB的分子结构与调节转录功能

CREB是一种连接于 cAMP反应元件(cAMP response element, CRE)启动子部位的组成性表达转录因子,属具有基本区域和 C端亮氨酸拉链(bZIP)的转录因子大家族成员。bZIP蛋白家族根据其功能分为若干亚家族,其中 CREB, CREM, ATF-1为同一亚家族成员,主要对 cAMP等信号发生应答反应。CREB蛋白家族在诱导所有真核细胞基因表达中起重要作用。CREB磷酸化可启动靶蛋白基因转录,最终提高突触效力。Jun, Fos等早期应答因子亚家族启动子区域包含一个 CRE基序,包括 c-fos, bcl-2, Mcl-1和 interleukin-6(Herdegen和 Leah, 1998)。现已鉴定出 CRE回文序列:5′-TGACGTCA-3′,此序列是转录因子 CREB的结合位点。CREB磷酸化机制仍不清楚,但在这种修饰过程中存在一个将 CREB由不活动状态转变为活性状态的构象改变(Usukura等, 2000)。磷酸化 CREB可能通过补充激活剂(例如 CREB结合蛋白)来加强转录。

CREB可调节与外周损伤和应激刺激后神经元可塑性变化有关的早期即刻基因和一些晚期效应基因功能,因其能够调节基因转录而又被称为调节转录核因子。CREB与即刻早期基因(immediate-early genes, IEGs)编码的蛋白不同,IEGs受刺激诱导可以快速合成新的蛋白(如 Fos, Jun或 Krox),发挥转录因子或转录调节因子的作用;而 CREB受刺激后只需通过活化原有的 CREB发挥作用。细胞内 CREB有两种形式:单体和二聚体,二聚体 DNA亲和力与转录活性均明显高于单体,两者之间可以转化。CREB丝氨酸残基(Ser-133)上进行的磷酸化作用在转录活化中起关键作用(Ji等, 2001)。CREB因磷酸化作用活化后,以二聚体的形式结合到 CRE的目标基因序列上,从而调节基因转录,此过程由与亮氨酸拉链直接相连的氨基末端氨基酸序列介导,这一区域富含赖氨酸和精氨酸。磷酸化与脱磷酸化是调节 CREB的重要机制之一。

二、CREB参与痛觉有关的基因调控

研究表明,CREB作为管家基因,在神经系统中

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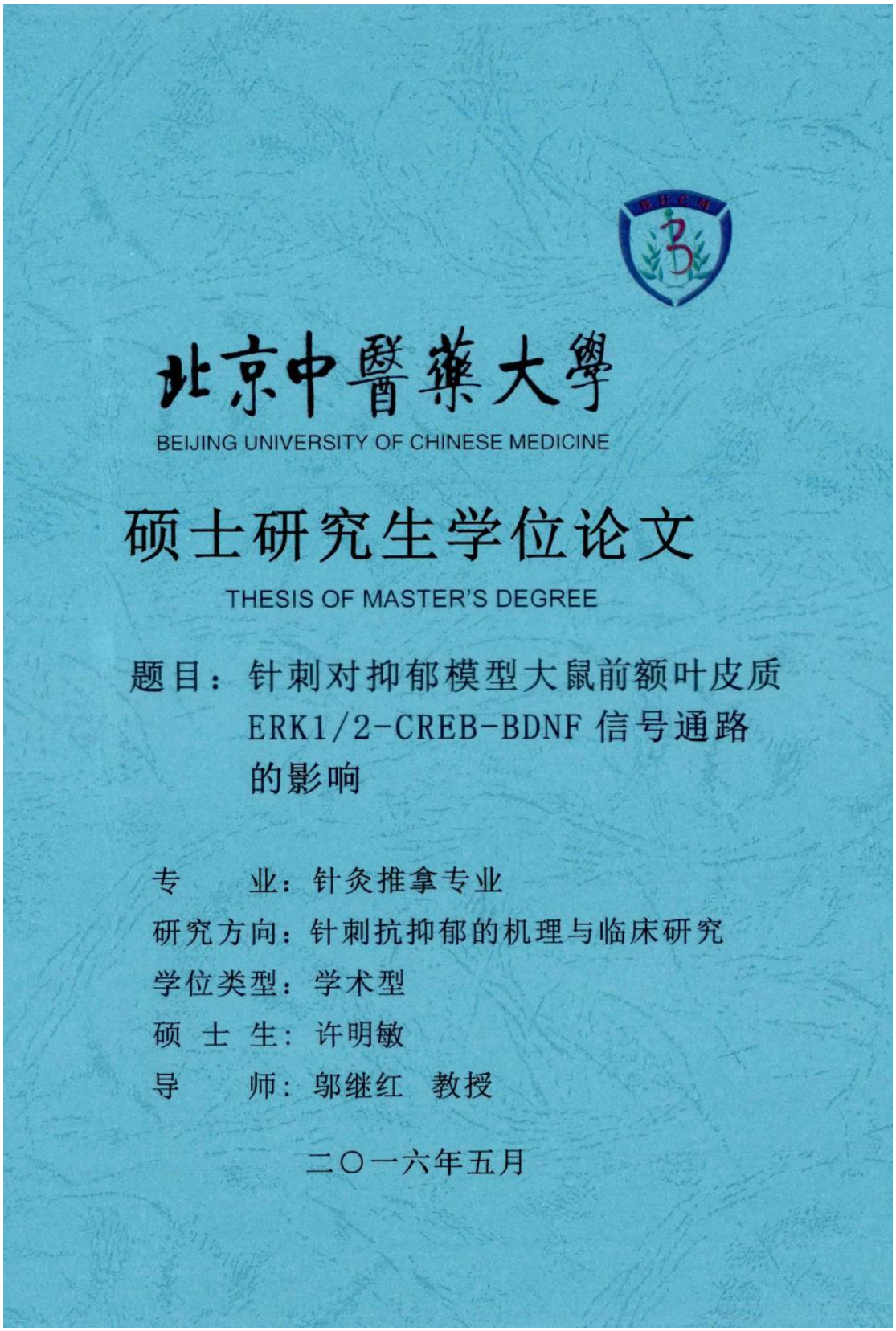

北京中醫藥大學

BEIJING UNIVERSITY OF CHINESE MEDICINE

硕士研究生学位论文

THESIS OF MASTER'S DEGREE

题目：针刺对抑郁模型大鼠前额叶皮质 ERK1/2-CREB-BDNF 信号通路的影响

专　　业：针灸推拿专业

研究方向：针刺抗抑郁的机理与临床研究

学位类型：学术型

硕 士 生：许明敏

导　　师：邬继红　教授

二〇一六年五月

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·综 述·

内脏痛模型的分类及其研究进展

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引言：内脏痛（visceral pain）作为一种主要的内脏感觉，常由内脏受到机械性牵拉、痉挛、缺血或炎症等刺激所引起，在临床上也是一种非常普遍的症状，而且常常伴有不愉快的情绪反应和防御反应。更重要的是，内脏痛可能传达了生命正面临死亡威胁的讯息，例如心肌梗塞、急性肠梗阻、急性胰腺炎或腹膜炎等[1]。如何控制和治疗内脏痛，并防止内脏器官、组织损害的进一步加重，对于临床具有重要的指导意义。而作为研究的基础，建立一个合适的内脏痛模型是研究的首要问题，下面本文将对目前应用的各种模型作一简要论述。

1 内脏痛的特点

内脏痛由内脏器官的功能或器质性障碍所引起，其痛觉传入纤维互有交叉，且传入路径复杂。内脏痛在产生早期比较隐匿，不易觉察。相较于躯体，内脏的感觉支配神经分布相对较少，且在高级中枢有广泛的汇聚现象，导致真实的内脏痛感觉模糊、弥散而难以精确描述。总结内脏痛的特点，具有以下几点：（1）定位不明确，感觉模糊，这是最主要的特点；（2）不是所有的内脏器官都有内脏痛觉，主要是由于一些内脏没有痛觉感受器分布，或是可能缺乏适当的伤害性刺激[2]，如肝、肺、肾等；（3）痛阈较高；（4）常牵涉到体壁，伴有牵涉痛[2]；（5）常伴有运动和（或）自主神经反射；（6）对机械性牵拉、痉挛、缺血、炎症等敏感而对锐器切割、烧灼等不敏感；（7）持续性内脏痛可以引皮肤及深部组织的痛觉过敏。

2 常用的内脏痛模型与分类

一种理想的内脏痛动物模型，首先应该符合所要研究内脏疾病的理论模型，即能够复制其中关键的病理生理特征；其次应当有助于验证该疾病在人体研究中提出的假说等，并能够对关键的病理生理和临床特征予以合理解释；还有就是要具有可重复性、易操作性等细节问题。考虑到内脏痛根据发病急缓与能否缓解分为急性内脏痛和慢性内脏痛的临床意义，现简单的把内脏痛模型也分为急性和慢性两种，分别论述。

2.1 急性内脏痛动物模型

通过急剧的内脏伤害性刺激引起相应的内脏伤害性反应可建立起急性内脏痛动物模型。对内脏的伤害性刺激方式有化学性刺激、机械扩张性刺激、电刺激和缺血性刺激等，其中以化学性刺激和机械扩张性刺激相对较为常用。

2.1.1 炎性内脏痛模型

①扭体实验

又被称为扭动实验，腹部收缩实验[3]。实验中通过向动物腹腔内注射化学刺激物质来引起腹部肌肉收缩，且可伴一侧后肢外伸。常用实验动物为大鼠或小鼠，化学刺激物质可以使用乙酸[4]、硫酸镁[5]、5-羟色胺（5-HT）、缓激肽或乙酰胆碱等。目前使用最多的是乙酸，最早见于 Siegnund[6]等的腹腔怀氏试验，剂量可用 0.6-9%V/V 乙酸溶液 0.2-0.3ml/ 小鼠或 0.5-2.5ml/ 大鼠腹腔注射。这种模型应用很广泛，可以避免麻醉药物的影响，且行为反应变化较明显，故具有一定的特异性。但是由于化学物质在不同个体的腹腔内的扩散程度和速度上可能产生差别，从而影响到动物神经生理和行为的差异，并且可能有广泛腹膜炎症造成的躯体痛的参与，使得其特异性受到很大影响。

②局灶性炎性痛模型

将化学刺激物质注入动物特定部位，如胃、结肠、胆囊、心包腔或膀胱等，引发内脏局部炎症反应，从而使神经纤维产生并传递疼痛。这种模型对操作水平要求较高，但行为学变化显著，特异性较高。

（1）心包炎模型：通过手术将一环形硅导管放入心包内，5d 后，将缓激肽、组胺和前列腺素 E2 通过导管注入清醒大鼠心包内，大鼠迅速出现明显的厌恶反应[7]。在心包炎症产生的同时，炎症也会导致心包内压力升高，从而产生压力性刺激[8]。因此，此模型与临床上心包炎很相似，并且有确切的行为学变化，但是由于手术操作复杂，化学性刺激物质的注入还可能诱发大鼠心律失常，很容易造成动物死亡。

（2）福尔马林（甲醛）诱发结肠直肠痛模型：福尔马林诱发急性局灶性内脏痛模型的应用相对较为成熟和广泛。用乙醚或异氟醚先将大鼠吸入麻醉后，再将 5% 的甲醛 100μl 经过肛门注入直肠粘膜下或者结肠壁内[9,10]。该模型只引起肠壁局限性的炎症反应，重复性好，炎症可逆，且大鼠行为学变化明显，在研究内脏痛

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