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Up-regulation of PKMζ expression in the anterior cingulate cortex following experimental tooth movement in rats

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ABSTRACT

Objective: To explore the involvement of synaptic plasticity in pain induced by experimental tooth movement, we evaluated the expression of protein kinase M zeta (PKMζ), an enzyme necessary for maintaining long-term potentiation (LTP) in the anterior cingulate cortex (ACC).

Methods: Male Sprague-Dawley rats weighing 250–300 g were used. The change of the expression of PKMζ in the ACC was measured by western blot, and the mRNA of PKMζ was detected by quantitative real-time PCR 1, 3, 7 days after experimental tooth movement. The average time spent on mouth-wiping behaviour of rats involved in pain perception was detected. After that a selective PKMζ inhibitor, called myristoylated ζ-pseudosubstrate inhibitory peptide (ZIP) was injected into ACC, and the effects of ZIP were evaluated.

Results: The mouth-wiping behaviour of rats was significantly increased 1, 3, and 7 days after experimental tooth movement. Changes in PKMζ levels were not detected on day 1 but were found to be increased 3 days following the tooth movement, and then declined to the baseline 7 days after tooth movement in the ACC. PKMζ mRNA levels were not significantly different between the experimental and sham-treated groups at the three time points. Time spent on mouth-wiping behaviour was reduced after ZIP was injected into ACC 3 days after tooth movement, and the analgesic effect last for at least 24 h.

Conclusion: PKMζ in the ACC acts to maintain the pain induced by experimental tooth movement. Increased expression of PKMζ protein is attributed to persistent translation of PKMζ mRNA. Synaptic plasticity may be involved in the development of tooth movement pain.

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1. Introduction

Pain is an unpleasant sensory and emotional experience associated with tissue damage. Pathological pain or chronic pain causes major suffering among patients, and there are two common associated pathological conditions: allodynia and hyperalgesia. Orthodontic pain, the most cited side effect arising from orthodontic force application, is a major concern for clinicians, patients, and parents. Ninety-five percent of patients treated with fixed appliances reported pain after 24 h. The pain disrupts patients' daily lives including chewing and sleep, and 8% of a study population even discontinued treatment because of pain.[1–3] The mechanism of the pain caused by orthodontic treatment is still not well known. Furstman and Bernick suggested that periodontal pain is caused by a process of pressure, ischaemia, inflammation, and oedema.[4] Previous studies indicated that pain caused by orthodontic tooth movement involves changes in blood flow in the periodontium and dental pulp, as well as the activation of inflammatory reactions. Many cytokines such as IL-1, IL-6, TNF contribute to pain perception. It has also been found that neuropeptides such as calcitonin gene-related peptide (CGRP) and galanin (GAL) are increased in PDL during experiment tooth movement.[5–9] Further studies suggest that changes occur in mediators and receptors in the trigeminal nerve such as C-fos and $P2X_3$ receptor correlate with orthodontic pain.[10,11] Most studies have mostly focused on peripheral nerves, but less is known about what type of cortical changes in pain after tooth movement. Therefore, we hypothesized that the central nervous system is involved in pain signal regulation during tooth movement.

In recent years, theories have suggested that the mechanisms underlying synaptic plasticity used for learning and memory may also be responsible for chronic pain. Synaptic plasticity, including long-term potentiation (LTP) and long-term depression (LTD), plays a significant role within the brain.[12–19] LTP is a widespread phenomenon exhibited by most excitatory synapses, and it can be divided into two phases: early induction, which triggers potentiation, and maintenance, which commences at least 3 h after the initiating event sustains it over time. Multiple protein kinases have been implicated in LTP induction, such as CaMK II, PI3K, MAPK, PKA, and so on.[20,21] However, the mechanism of the maintenance stage is poorly understood. In the past few years, Todd and colleagues have proved that PKMζ plays a critical role in late-LTP maintenance and memory consolidation.[22–31] PKMζ is a constitutively active, atypical isoform of protein kinase C (PKC), and is produced by a unique PKMζ mRNA. It is expressed exclusively in neural tissue and is enriched in the forebrain.[32] PKMζ maintains the late phase of LTP by increasing the number of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors at post-synaptic sites.[33–35]

Several cortical areas have been reported to contribute to chronic pain, including the anterior cingulate cortex (ACC), which is a key area for pain-related perception.[12] Recent studies from Zhuo Min and colleagues have shown that the protein levels of PKMζ in ACC were increased 3 days after nerve injury. Cumulative results suggest that PKMζ is necessary for maintaining LTP in the ACC and maybe responsible for pathological pain.[12–15,18,19] Therefore, the present study aims to explore whether synaptic plasticity is involved in experimental tooth movement pain by recording changes in time spent on face-grooming behaviour of mouth-wiping and in PKMζ expression in the ACC of rats. Effects of a selective cell-permeable PKMζ inhibitor ZIP were also investigated to further verify the role of PKMζ.

2. Materials and methods

2.1. Animals

Male Sprague-Dawley rats (8–10 weeks old) weighing 250–300 g were obtained from the experimental animal centre of Sun Yat-sen University. The animals were housed individually with stable temperature (23–25 °C) and light/dark cycle (12 h/12 h). Soft food and water were provided ad libitum. All experiments were performed under protocols approved by the Institutional Animal Care and Use Committee of Sun Yat-sen University and steps were taken to minimize the number of animals and their discomfort.

2.2. Appliance for experimental tooth movement

A fixed, Ni-Ti alloy closed-coil spring appliance was constructed for mesial movement of the maxillary first molar, as described by Ashizawa and Sahara.[36] After an intraperitoneal injection of sodium pentobarbital at a dose of 40 mg/kg body wt., the closed-coil spring was hooked between the maxillary first molar and upper incisor through a stainless steel ligature and then cement-wrapped through the stainless steel ligature. A 0.5–1.0 mm groove was produced in the cervical region of the labial and proximal surfaces of the incisor to enhance retention. The appliance provided an initial force of ≈80 g. The sham-treated rats received the same procedure as the experimental rats, but the springs in their mouths were not activated. In all experimental groups, there was no reactivation of the appliance during the experimental periods. The animals were sacrificed for biochemical studies 1, 3, and 7 days after manipulation as noted.

2.3. Brain cannulation surgery and microinjection of ZIP

Rats were anaesthetized by an intraperitoneal injection of sodium pentobarbital (40 mg/kg). Scalp was shaved and sterilized with iodophor. The head of rats was restrained in a stereotaxic apparatus (Benchmark, myNeurolab.com, USA) with the incisor bar set at approximately 3.0 mm below horizontal zero to make the skull position flat. An incision was made at midline to expose the skull. Two holes were drilled in the skull at stereotaxic coordinates: AP: 1.7 mm anterior to the bregma and L: 0.6 mm lateral to the midline. Then two guide cannulas (23 gauge, Plastics One Inc., Roanoke, VA, USA) were implanted bilaterally 1.0 mm above the ACC into the holes (V: 1.6 mm ventral to the surface of the skull).[37] Dummy inner cannulas (Plastics One Inc., Roanoke, VA, USA) of the same extension were positioned inside the guide cannulas to close

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