

ORAL PRESENTATION

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The epigenetic signature of chronic pain in the mouse brain

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From Seventh Scientific Meeting of The TMJ Association, Genetic, Epigenetic, and Mechanistic Studies of Temporomandibular Disorders and Overlapping Pain Conditions
Bethesda, MD, USA. 7-9 September 2014

Background

Peripheral nerve injury can be accompanied by long-term pain-related manifestations, such as affective and cognitive disturbances, suggesting the involvement of supraspinal mechanisms. One particular region of interest is the prefrontal cortex (PFC), an area implicated in depression, anxiety and cognitive impairment, all of which are frequently associated with chronic pain [1-4]. Clinically, pathological pain-related changes in the PFC in individuals with chronic low back pain can be reversed following effective pain management [5]. However, the mechanisms behind pain-induced brain plasticity remain poorly understood.

Epigenetics is a term used to describe modifications to genomic DNA that alter gene expression. DNA methylation is an epigenetic mechanism that is involved in gene regulation mainly by silencing promoter activity. We propose that long-term alterations in DNA methylation could provide a molecular substrate for chronic pain-related changes in the CNS, forming a “memory trace” for pain in the brain.

Materials and methods

Spared nerve injury or sham surgery was performed in male CD1 mice at three months of age. Six months after injury, mechanical hypersensitivity was confirmed, brains were collected and DNA and RNA were extracted. Global DNA methylation was measured by the luminometric methylation assay in various brain regions, including the PFC. Promoter methylation of individual genes was assessed by sodium bisulfite sequencing and functionally validated using an *in vitro* promoter assay. Finally, mRNA levels of the target genes were measured by RT-PCR.

Results

Six months following peripheral nerve injury, abnormal sensory thresholds and increased anxiety were accompanied by significant genomic DNA hypomethylation [6] and transcriptional reprogramming [7]. This was linked to the hypomethylation of individual genes, including (synaptotagmin 2) *syt2*, a known regulator of synaptic function. Furthermore, transcription of *syt2* was regulated by differential methylation of its promoter *in vitro* and *syt2* mRNA was upregulated in the PFC of injured animals. Thus chronic pain-induced changes in the PFC are detected long after the original injury, at a long distance from the site of injury.

Conclusions

We show that peripheral injury produces long-term changes in the PFC methylome and propose that DNA methylation mediates the changes in brain structure and cortical function that are associated with chronic pain.

Disclosures

The authors declare no competing interests.

Acknowledgements

The authors would like to thank Dr. Ziv Machnes and Ms. Stephanie Pierrefelice for technical assistance.

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Published: 15 December 2014

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doi:10.1186/1744-8069-10-S1-O17

Cite this article as: Tajerian et al.: **The epigenetic signature of chronic pain in the mouse brain.** *Molecular Pain* 2014 **10**(Suppl 1):O17.

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