Chronic opioid use is associated with increased DNA met...

Chronic opioid use is associated with increased DNA methylation correlating with increased clinical pain.

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Abstract

Environmentally caused changes in chromosomes that do not alter the DNA sequence but cause phenotypic changes by altering gene transcription are summarized as epigenetics. A major epigenetic mechanism is methylation or demethylation at CpG-rich DNA islands. DNA methylation triggered by drugs has largely unexplored therapeutic consequences. Here we report increased methylation at a CpG rich island in the OPRM1 gene coding for \(\mu\)-opioid receptors and at a global methylation site (LINE-1) in leukocytes of methadone-substituted former opiate addicts compared with matched healthy controls. Higher DNA methylation associated with chronic opioid exposure was reproduced in an independent cohort of opioid-treated as compared to non-opioid-treated pain patients. This suggests that opioids may stimulate DNA methylation. The OPRM1 methylation had no immediate effect on \(\mu\)-opioid receptor transcription and was not associated with opioid dosing requirements. However, the global DNA methylation at LINE-1 was significantly correlated with increased chronic pain. This suggests inhibitory effects on the transcription of still unspecified nocifensive gene products. It further implies that opioids may be causally associated with increased genome-wide DNA methylation, although currently there is no direct evidence of this. This has phenotypic consequences for pain and may provide a new, epigenetics-associated mechanism of opioid-induced hyperalgesia. The results indicate a potential influence of opioid analgesics on the patients' epigenome. They emphasize the need for reliable and cost-effective screening tools and may imply that high-throughput screening for lead compounds in artificial expression systems may not provide the best tools for identifying new pain medications.

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