Mol Pharmacol. 2009 May;75(5):1014-20. doi: 10.1124/mol.108.054346. Epub 2009 Mar 2.

Epigenetic modulation of mGlu2 receptors by histone deacetylase inhibitors in the treatment of inflammatory pain

S Chiechio [1], M Zammataro, M E Morales, C L Busceti, F Drago, R W Gereau 4th, A Copani, F Nicoletti

Affiliations

PMID: 19255242 DOI: 10.1124/mol.108.054346

Abstract

Knowing that expression of metabotropic glutamate 2 (mGlu2) receptors in the dorsal root ganglia is regulated by acetylation mechanisms, we examined the effect of two selective and chemically unrelated histone deacetylase (HDAC) inhibitors, N-(2-aminophenyl)-4-[N-(pyridine-3-ylmethoxy-carbonyl)aminomethyl]benzamide (MS-275) and suberoylanilide hydroamic acid (SAHA), in a mouse model of persistent inflammatory pain. Although a single subcutaneous injection of MS-275 (3 mg/kg) or SAHA (5-50 mg/kg) was ineffective, a 5-day treatment with either of the two HDAC inhibitors substantially reduced the nociceptive response in the second phase of the formalin test, which reflects the development of central sensitization in the dorsal horn of the spinal cord. Analgesia was abrogated by a single injection of the mGlu2/3 receptor antagonist (alphaS)-alpha-amino-alpha-[(1S,2S)-2-carboxycyclopropyl]-9H-xantine-9-propanoic acid (LY341495; 1 mg/kg, i.p.), which was inactive per se. Both MS-275 and SAHA up-regulated the expression of mGlu2 receptors in the dorsal root ganglion (DRG) and spinal cord under conditions in which they caused analgesia, without changing the expression of mGlu1a, mGlu4, or mGlu5 receptors. Induction of DRG mGlu2 receptors in response to SAHA was associated with increased acetylation of p65/RelA on lysine 310, a process that enhances the transcriptional activity of p65/RelA at nuclear factor-kappaB-regulated genes. Transcription of the mGlu2 receptor gene is known to be activated by p65/RelA in DRG neurons. We conclude that HDAC inhibition produces analgesia by up-regulating mGlu2 receptor expression in the DRG, an effect that results from the amplification of NF-kappaB transcriptional activity. These data provide the first evidence that HDAC inhibitors cause analgesia and suggest that HDACs are potential targets for the epigenetic treatment of pain.

Related information

MedGen
PubChem Compound
PubChem Compound (MeSH Keyword)
PubChem Substance

LinkOut - more resources

Full Text Sources

HighWire

Other Literature Sources

The Lens - Patent Citations

Medical

MedlinePlus Health Information