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Cannabinoids in the Descending Pain Modulatory Circuit: Role in Inflammation

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Abstract

The legalization of cannabis in some states has intensified interest in the potential for cannabis and its constituents to lead to novel therapeutics for pain. Our understanding of the cellular mechanisms underlying cannabinoid actions in the brain have lagged behind opioids; however, the current opioid epidemic has also increased attention on the use of cannabinoids as alternatives to opioids for pain, especially chronic pain that requires long-term use. Endogenous cannabinoids are lipid signaling molecules that have complex roles in modulating neuronal function throughout the brain. In this review, we discuss cannabinoid functions in the descending pain modulatory pathway, a brain circuit that integrates cognitive and emotional processing of pain to modulate incoming sensory inputs. In addition, we highlight areas where further studies are necessary to understand cannabinoid regulation of descending pain modulation.

Keywords: Analgesia; Cannabinoid; Endocannabinoid; Pain; Periaqueductal gray; Presynaptic terminals; Rostral ventromedial medulla.

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Conflict of interest statement

Declaration of Competing Interest The authors declare that there are no conflicts of interest.

Similar articles

- [NSAIDs, Opioids, Cannabinoids and the Control of Pain by the Central Nervous System.](#) Vanegas H, Vazquez E, Tortorici V. *Pharmaceuticals (Basel)*. 2010 Apr 29;3(5):1335-1347. doi: 10.3390/ph3051335. PMID: 27713305 Free PMC article. Review.
- [The Role of Cannabinoid Receptors in the Descending Modulation of Pain.](#) Palazzo E, Luongo L, Novellis V, Rossi F, Maione S. *Pharmaceuticals (Basel)*. 2010 Aug 16;3(8):

2661-2673. doi: 10.3390/ph3082661. PMID: 27713370 Free PMC article. Review.

- [The Role of the Brain's Endocannabinoid System in Pain and Its Modulation by Stress.](#) Corcoran L, Roche M, Finn DP. *Int Rev Neurobiol.* 2015;125:203-55. doi: 10.1016/bs.irn.2015.10.003. Epub 2015 Nov 6. PMID: 26638768 Review.
- [Compensatory Activation of Cannabinoid CB2 Receptor Inhibition of GABA Release in the Rostral Ventromedial Medulla in Inflammatory Pain.](#) Li MH, Suchland KL, Ingram SL. *J Neurosci.* 2017 Jan 18;37(3):626-636. doi: 10.1523/JNEUROSCI.1310-16.2016. PMID: 28100744 Free PMC article.
- [Descending modulation of pain: the GABA disinhibition hypothesis of analgesia.](#) Lau BK, Vaughan CW. *Curr Opin Neurobiol.* 2014 Dec;29:159-64. doi: 10.1016/j.conb.2014.07.010. Epub 2014 Jul 26. PMID: 25064178 Review.
- [The Endocannabinoid System Modulating Levels of Consciousness, Emotions and Likely Dream Contents.](#) Murillo-Rodriguez E, Pastrana-Trejo JC, Salas-Crisóstomo M, de-la-Cruz M. *CNS Neurol Disord Drug Targets.* 2017;16(4):370-379. doi: 10.2174/1871527316666170223161908. PMID: 28240187 Review.
- [Cannabinoid Receptor Type 1 and Its Role as an Analgesic: An Opioid Alternative?](#) Milligan AL, Szabo-Pardi TA, Burton MD. *J Dual Diagn.* 2020 Jan-Mar;16(1):106-119. doi: 10.1080/15504263.2019.1668100. Epub 2019 Oct 9. PMID: 31596190
- [Altered Signaling in the Descending Pain-modulatory System after Short-Term Infusion of the \$\mu\$ -Opioid Agonist Remifentanyl.](#) Sprenger C, Eichler IC, Eichler L, Zöllner C, Büchel C. *J Neurosci.* 2018 Mar 7;38(10):2454-2470. doi: 10.1523/JNEUROSCI.2496-17.2018. Epub 2018 Feb 12. PMID: 29440535 Free PMC article.
- [Endogenous opioids acting at a medullary mu-opioid receptor contribute to the behavioral antinociception produced by GABA antagonism in the midbrain periaqueductal gray.](#) Roychowdhury SM, Fields HL. *Neuroscience.* 1996 Oct;74(3):863-72. doi: 10.1016/0306-4522(96)00180-7. PMID: 8884782
- [Inhibition of fatty-acid amide hydrolase enhances cannabinoid stress-induced analgesia: sites of action in the dorsolateral periaqueductal gray and rostral ventromedial medulla.](#) Suplita RL 2nd, Farthing JN, Gutierrez T, Hohmann AG. *Neuropharmacology.* 2005 Dec;49(8):1201-9. doi: 10.1016/j.neuropharm.2005.07.007. Epub 2005 Aug 29. PMID: 16129456
- [Modulatory effects of cannabinoids on brain neurotransmission.](#) Cohen K, Weizman A, Weinstein A. *Eur J Neurosci.* 2019 Aug;50(3):2322-2345. doi: 10.1111/ejn.14407. Epub 2019 Apr 8. PMID: 30882962
- [Non-psychoactive cannabinoids modulate the descending pathway of antinociception in anaesthetized rats through several mechanisms of action.](#) Maione S, Piscitelli F, Gatta L,

Vita D, De Petrocellis L, Palazzo E, de Novellis V, Di Marzo V. Br J Pharmacol. 2011 Feb;162(3):584-96. doi: 10.1111/j.1476-5381.2010.01063.x. PMID: 20942863 Free PMC article.

- [Cortical and subcortical modulation of pain.](#) De Felice M, Ossipov MH. Pain Manag. 2016 Apr;6(2):111-20. doi: 10.2217/pmt.15.63. Epub 2016 Mar 17. PMID: 26984039 Review.
- [Cannabinoids and pain.](#) Walker JM, Strangman NM, Huang SM. Pain Res Manag. 2001 Summer;6(2):74-9. doi: 10.1155/2001/413641. PMID: 11854769 Review.
- [Supraspinal interaction between HIV-1-gp120 and cannabinoid analgesic effectiveness.](#) Palma J, Narasimhan M, Guindon J, Benamar K. Naunyn Schmiedebergs Arch Pharmacol. 2018 Oct;391(10):1157-1161. doi: 10.1007/s00210-018-1533-1. Epub 2018 Jul 15. PMID: 30008083 Free PMC article.
- [Distinct pathways for norepinephrine- and opioid-triggered antinociception from the amygdala.](#) Maire JJ, Close LN, Heinricher MM, Selden NR. Eur J Pain. 2016 Feb;20(2):206-14. doi: 10.1002/ejp.708. Epub 2015 Apr 5. PMID: 25847835 Free PMC article.
- [Cannabinoids and Pain: New Insights From Old Molecules.](#) Vučković S, Srebro D, Vujović KS, Vučetić Č, Prostran M. Front Pharmacol. 2018 Nov 13;9:1259. doi: 10.3389/fphar.2018.01259. eCollection 2018. PMID: 30542280 Free PMC article. Review.
- [Pain Inhibits Pain: an Ascending-Descending Pain Modulation Pathway Linking Mesolimbic and Classical Descending Mechanisms.](#) Tobaldini G, Sardi NF, Guilhen VA, Fischer L. Mol Neurobiol. 2019 Feb;56(2):1000-1013. doi: 10.1007/s12035-018-1116-7. Epub 2018 Jun 1. PMID: 29858776
- [Endogenous opioid-mediated inhibition of putative pain-modulating neurons in rat rostral ventromedial medulla.](#) Pan ZZ, Fields HL. Neuroscience. 1996 Oct;74(3):855-62. doi: 10.1016/0306-4522(96)00179-0. PMID: 8884781
- [Interaction of the cannabinoid and opioid systems in the modulation of nociception.](#) Welch SP. Int Rev Psychiatry. 2009 Apr;21(2):143-51. doi: 10.1080/09540260902782794. PMID: 19367508 Review.
- [An analgesia circuit activated by cannabinoids.](#) Meng ID, Manning BH, Martin WJ, Fields HL. Nature. 1998 Sep 24;395(6700):381-3. doi: 10.1038/26481. PMID: 9759727
- [Neuronal and glial factors contributing to sex differences in opioid modulation of pain.](#) Averitt DL, Eidson LN, Doyle HH, Murphy AZ. Neuropsychopharmacology. 2019 Jan;44(1):155-165. doi: 10.1038/s41386-018-0127-4. Epub 2018 Jun 23. PMID: 29973654 Free PMC article. Review.

- [Molecular Mechanism and Cannabinoid Pharmacology.](#) Schurman LD, Lu D, Kendall DA, Howlett AC, Lichtman AH. *Handb Exp Pharmacol.* 2020 Apr 1. doi: 10.1007/164_2019_298. Online ahead of print. PMID: 32236882
- [The Contribution of the Descending Pain Modulatory Pathway in Opioid Tolerance.](#) Lueptow LM, Fakira AK, Bobeck EN. *Front Neurosci.* 2018 Nov 27;12:886. doi: 10.3389/fnins.2018.00886. eCollection 2018. PMID: 30542261 Free PMC article.
- [Yin-and-yang bifurcation of opioidergic circuits for descending analgesia at the midbrain of the mouse.](#) Kim JH, Gangadharan G, Byun J, Choi EJ, Lee CJ, Shin HS. *Proc Natl Acad Sci U S A.* 2018 Oct 23;115(43):11078-11083. doi: 10.1073/pnas.1806082115. Epub 2018 Oct 8. PMID: 30297409 Free PMC article.
- [Analgesic effects of cannabinoid receptor agonist WIN55,212-2 in the nucleus cuneiformis in animal models of acute and inflammatory pain in rats.](#) Ebrahimzadeh M, Haghparast A. *Brain Res.* 2011 Oct 28;1420:19-28. doi: 10.1016/j.brainres.2011.08.028. Epub 2011 Aug 17. PMID: 21911208
- [The neurobiology and evolution of cannabinoid signalling.](#) Elphick MR, Egertová M. *Philos Trans R Soc Lond B Biol Sci.* 2001 Mar 29;356(1407):381-408. doi: 10.1098/rstb.2000.0787. PMID: 11316486 Free PMC article. Review.
- [Opioids and cannabinoids interactions: involvement in pain management.](#) Desroches J, Beaulieu P. *Curr Drug Targets.* 2010 Apr;11(4):462-73. doi: 10.2174/138945010790980303. PMID: 20017728 Review.
- [The role of descending fibers from the rostral ventromedial medulla in opioid analgesia in rats.](#) Gilbert AK, Franklin KB. *Eur J Pharmacol.* 2002 Aug 2;449(1-2):75-84. doi: 10.1016/s0014-2999(02)01974-x. PMID: 12163109
- [Cannabinoids and Pain: Sites and Mechanisms of Action.](#) Starowicz K, Finn DP. *Adv Pharmacol.* 2017;80:437-475. doi: 10.1016/bs.apha.2017.05.003. Epub 2017 Jun 20. PMID: 28826543 Review.
- [Acetaminophen Relieves Inflammatory Pain through CB₁ Cannabinoid Receptors in the Rostral Ventromedial Medulla.](#) Klinger-Gratz PP, Ralvenius WT, Neumann E, Kato A, Nyilas R, Lele Z, Katona I, Zeilhofer HU. *J Neurosci.* 2018 Jan 10;38(2):322-334. doi: 10.1523/JNEUROSCI.1945-17.2017. Epub 2017 Nov 22. PMID: 29167401 Free PMC article.
- [Cannabinoid disruption of learning mechanisms involved in reward processing.](#) Lupica CR, Hoffman AF. *Learn Mem.* 2018 Aug 16;25(9):435-445. doi: 10.1101/lm.046748.117. Print 2018 Sep. PMID: 30115765 Free PMC article. Review.
- [Pain modulation by release of the endogenous cannabinoid anandamide.](#) Walker JM, Huang SM, Strangman NM, Tsou K, Sañudo-Peña MC. *Proc Natl Acad Sci U S A.* 1999

Oct 12;96(21):12198-203. doi: 10.1073/pnas.96.21.12198. PMID: 10518599 Free PMC article.

- [Morphological evidence for a neurotensinergic periaqueductal gray-rostral ventromedial medulla-spinal dorsal horn descending pathway in rat.](#) Wang J, Zhang H, Feng YP, Meng H, Wu LP, Wang W, Li H, Zhang T, Zhang JS, Li YQ. Front Neuroanat. 2014 Oct 9;8:112. doi: 10.3389/fnana.2014.00112. eCollection 2014. PMID: 25346662 Free PMC article.
- [Sex Differences in GABAA Signaling in the Periaqueductal Gray Induced by Persistent Inflammation.](#) Tonsfeldt KJ, Suchland KL, Beeson KA, Lowe JD, Li MH, Ingram SL. J Neurosci. 2016 Feb 3;36(5):1669-81. doi: 10.1523/JNEUROSCI.1928-15.2016. PMID: 26843648 Free PMC article.
- [Cannabinoid analgesia as a potential new therapeutic option in the treatment of chronic pain.](#) Burns TL, Ineck JR. Ann Pharmacother. 2006 Feb;40(2):251-60. doi: 10.1345/aph.1G217. Epub 2006 Jan 31. PMID: 16449552 Review.
- [Endocannabinoids and pain: spinal and peripheral analgesia in inflammation and neuropathy.](#) Rice AS, Farquhar-Smith WP, Nagy I. Prostaglandins Leukot Essent Fatty Acids. 2002 Feb-Mar;66(2-3):243-56. doi: 10.1054/plaf.2001.0362. PMID: 12052040 Review.
- [The endocannabinoid system and pain.](#) Guindon J, Hohmann AG. CNS Neurol Disord Drug Targets. 2009 Dec;8(6):403-21. doi: 10.2174/187152709789824660. PMID: 19839937 Free PMC article. Review.
- [Stressed-out endogenous cannabinoids relieve pain.](#) Vaughan CW. Trends Pharmacol Sci. 2006 Feb;27(2):69-71. doi: 10.1016/j.tips.2005.11.011. Epub 2005 Dec 20. PMID: 16364458 Review.
- [Endocannabinoid mechanisms of pain modulation.](#) Hohmann AG, Suplita RL 2nd. AAPS J. 2006 Nov 17;8(4):E693-708. doi: 10.1208/aapsj080479. PMID: 17233533 Free PMC article. Review.