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Cannabinoid receptor 1 controls human mucosal-type mast cell degranulation and maturation in situ

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Abstract

Background: Because many chronic inflammatory and allergic disorders are intimately linked to excessive mast cell (MC) numbers and activation, it is clinically important to understand the physiologic mechanisms preventing excess MC accumulation/degranulation in normal human tissues.

Objective: Because endocannabinoids are increasingly recognized as neuroendocrine regulators of MC biology, we investigated how cannabinoid receptor (CB) 1 signaling affects human mucosal-type mast cells (hMMCs).

Methods: Using organ-cultured nasal polyps as a surrogate tissue for human bronchial mucosa, we investigated how CB1 stimulation, inhibition, or knockdown affects hMMC biology using quantitative (immuno)histomorphometry and electron microscopy.

Results: Kit(+) hMMCs express functional CB1 in situ. Blockade of CB1 signaling (with the specific CB1 antagonist N-(piperidin-1-yl)-1-(2,4-dichlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide [AM251] or CB1 gene knockdown) enhanced hMMC degranulation and increased total numbers without affecting their proliferation in situ. This suggests that inhibiting CB1 signaling induces hMMC maturation from resident progenitor cells within human mucosal stroma. hMMC maturation was induced at least in part through upregulating stem cell factor production. Both the prototypic endocannabinoid anandamide and the CB1-selective agonist arachidonyl-2-chloroethylamide effectively counteracted secretagogue-triggered excessive hMMC degranulation.

Conclusions: The current serum-free nasal polyp organ culture model allows physiologically and clinically relevant insights into the biology and pharmacologic responses of primary hMMCs in situ. In human airway mucosa hMMC activation and maturation are subject to a potent inhibitory endocannabinoid tone through CB1 stimulation. This invites one to target the

endocannabinoid system in human airway mucosa as a novel strategy in the future management of allergic diseases.

Similar articles

- Endocannabinoids limit excessive mast cell maturation and activation in human skin. Sugawara K, Bíró T, Tsuruta D, Tóth BI, Kromminga A, Zákány N, Zimmer A, Funk W, Gibbs BF, Zimmer A, Paus R. J Allergy Clin Immunol. 2012 Mar;129(3):726-738.e8. doi: 10.1016/j.jaci.2011.11.009. Epub 2012 Jan 9. PMID: 22226549

- Expression of stem cell factor (SCF) and SCF receptor (c-kit) in synovial membrane in arthritis: correlation with synovial mast cell hyperplasia and inflammation. Ceponis A, Konttinen YT, Takagi M, Xu JW, Sorsa T, Matucci-Cerinic M, Santavirta S, Bankl HC, Valent P. J Rheumatol. 1998 Dec;25(12):2304-14. PMID: 9858422

- Sorafenib stimulates human skin type mast cell degranulation and maturation. Mizukami Y, Sugawara K, Kira Y, Tsuruta D. J Dermatol Sci. 2017 Dec;88(3):308-319. doi: 10.1016/j.jdermsci.2017.08.005. Epub 2017 Aug 12. PMID: 28843624

- Reduced immunostaining for c-kit receptors in mucosal mast cells in inflammatory bowel disease. Farhadi A, Keshavarzian A, Fields JZ, Jakate S, Shaikh M, Banan A. J Gastroenterol Hepatol. 2007 Dec;22(12):2338-43. doi: 10.1111/j.1440-1746.2007.05011.x. Epub 2007 Jul 20. PMID: 17645464

- Effects of Neuroendocrine CB1 Activity on Adult Leydig Cells. Cobellis G, Meccariello R, Chianese R, Chioccarelli T, Fasano S, Pierantoni R. Front Endocrinol (Lausanne). 2016 Jun 3;7:47. doi: 10.3389/fendo.2016.00047. eCollection 2016. PMID: 27375550 Free PMC article. Review.

- Cannabinoid CB1 and cholecystokinin CCK2 receptors modulate, in an opposing way, electrically evoked [3H]GABA efflux from rat cerebral cortex cell cultures: possible relevance for cortical GABA transmission and anxiety. Antonelli T, Tomasini MC, Mazza R, Fuxe K, Gaetani S, Cuomo V, Tanganelli S, Ferraro L. J Pharmacol Exp Ther. 2009 May;329(2):708-17. doi: 10.1124/jpet.109.150649. Epub 2009 Feb 5. PMID: 19197005

- CB1-cannabinoid receptors are involved in the modulation of non-synaptic [3H]serotonin release from the rat hippocampus. Balázsa T, Bíró J, Gullai N, Ledent C, Sperlágh B. Neurochem Int. 2008 Jan;52(1-2):95-102. doi: 10.1016/j.neuint.2007.07.008. Epub 2007 Jul 14. PMID: 17719142

- The CB1 cannabinoid receptor mediates excitotoxicity-induced neural progenitor proliferation and neurogenesis. Aguado T, Romero E, Monory K, Palazuelos J, Sendtner

M, Marsicano G, Lutz B, Guzmán M, Galve-Roperh I. J Biol Chem. 2007 Aug 17;282(33):23892-8. doi: 10.1074/jbc.M700678200. Epub 2007 Jun 7. PMID: 17556369

- Cannabinoid 1 (CB1) receptors coupled to cholinergic motorneurones inhibit neurogenic circular muscle contractility in the human colon. Hinds NM, Ullrich K, Smid SD. Br J Pharmacol. 2006 May;148(2):191-9. doi: 10.1038/sj.bjp.0706710. PMID: 16520743 Free PMC article.

- Differential CB1 and CB2 cannabinoid receptor-inotropic response of rat isolated atria: endogenous signal transduction pathways. Sterin-Borda L, Del Zar CF, Borda E. Biochem Pharmacol. 2005 Jun 15;69(12):1705-13. doi: 10.1016/j.bcp.2005.03.027. PMID: 15885656

- Pharmacological evaluation of cannabinoid receptor ligands in a mouse model of anxiety: further evidence for an anxiolytic role for endogenous cannabinoid signaling. Patel S, Hillard CJ. J Pharmacol Exp Ther. 2006 Jul;318(1):304-11. doi: 10.1124/jpet.106.101287. Epub 2006 Mar 28. PMID: 16569753

- Endocannabinoids contribute to metabotropic glutamate receptor-mediated inhibition of GABA release onto hippocampal CA3 pyramidal neurons in an isolated neuron/bouton preparation. Inada H, Maejima T, Nakahata Y, Yamaguchi J, Nabekura J, Ishibashi H. Neuroscience. 2010 Feb 17;165(4):1377-89. doi: 10.1016/j.neuroscience.2009.11.054. Epub 2009 Dec 1. PMID: 19961906

- Acute overactive endocannabinoid signaling induces glucose intolerance, hepatic steatosis, and novel cannabinoid receptor 1 responsive genes. Ruby MA, Nomura DK, Hudak CS, Barber A, Casida JE, Krauss RM. PLoS One. 2011;6(11):e26415. doi: 10.1371/journal.pone.0026415. Epub 2011 Nov 4. PMID: 22073164 Free PMC article.

- Cannabinoid receptor activation induces apoptosis through tumor necrosis factor alpha-mediated ceramide de novo synthesis in colon cancer cells. Cianchi F, Papucci L, Schiavone N, Lulli M, Magnelli L, Vinci MC, Messerini L, Manera C, Ronconi E, Romagnani P, Donnini M, Perigli G, Trallori G, Tanganelli E, Capaccioli S, Masini E. Clin Cancer Res. 2008 Dec 1;14(23):7691-700. doi: 10.1158/1078-0432.CCR-08-0799. PMID: 19047095

- The role of stem cell factor (c-kit ligand) and inflammatory cytokines in pulmonary mast cell activation. Lukacs NW, Kunkel SL, Strieter RM, Evanoff HL, Kunkel RG, Key ML, Taub DD. Blood. 1996 Mar 15;87(6):2262-8. PMID: 8630386

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Cited by *13 articles*

- The Mast Cell-SCF-CB1 Interaction Is a Key Player in Seborrheic Keratosis. Yamanaka-Takaichi M, Sugawara K, Sumitomo R, Tsuruta D. J Histochem Cytochem. 2020 Jul; 68(7):461-471. doi: 10.1369/0022155420938031. Epub 2020 Jun 24. PMID: 32578480

- Tissue-resident macrophages can be generated de novo in adult human skin from resident progenitor cells during substance P-mediated neurogenic inflammation ex vivo. Gherardini J, Uchida Y, Hardman JA, Chéret J, Mace K, Bertolini M, Paus R. PLoS One. 2020 Jan 23;15(1):e0227817. doi: 10.1371/journal.pone.0227817. eCollection 2020. PMID: 31971954 Free PMC article.

- Endocannabinoid System in the Airways. Bozkurt TE. Molecules. 2019 Dec 17;24(24): 4626. doi: 10.3390/molecules24244626. PMID: 31861200 Free PMC article. Review.

- Modulation of Mast Cell Reactivity by Lipids: The Neglected Side of Allergic Diseases. Hagemann PM, Nsiah-Dosu S, Hundt JE, Hartmann K, Orinska Z. Front Immunol. 2019 May 29;10:1174. doi: 10.3389/fimmu.2019.01174. eCollection 2019. PMID: 31191542 Free PMC article. Review.

- Cannabinoids in Pain Treatment: An Overview. Mallick-Searle T, St Marie B. Pain Manag Nurs. 2019 Apr;20(2):107-112. doi: 10.1016/j.pmn.2018.12.006. PMID: 31036325 Free PMC article. Review.

- Cannabinoid Signaling in the Skin: Therapeutic Potential of the "C(ut)annabinoid" System. Tóth KF, Ádám D, Bíró T, Oláh A. Molecules. 2019 Mar 6;24(5):918. doi: 10.3390/molecules24050918. PMID: 30845666 Free PMC article. Review.

- Human eosinophils and mast cells: Birds of a feather flock together. Robida PA, Puzzovio PG, Pahima H, Levi-Schaffer F, Bochner BS. Immunol Rev. 2018 Mar;282(1):151-167. doi: 10.1111/imr.12638. PMID: 29431215 Free PMC article. Review.

- Cannabis and Pain: A Clinical Review. Hill KP, Palastro MD, Johnson B, Ditre JW. Cannabis Cannabinoid Res. 2017 May 1;2(1):96-104. doi: 10.1089/can.2017.0017. eCollection 2017. PMID: 28861509 Free PMC article. Review.

- Endocannabinoids and Immunity. Chiurchiù V. Cannabis Cannabinoid Res. 2016 Feb 1;1(1):59-66. doi: 10.1089/can.2016.0002. eCollection 2016. PMID: 28861481 Free PMC article. Review.

- Cannabinoid receptor-specific mechanisms to alleviate pain in sickle cell anemia via inhibition of mast cell activation and neurogenic inflammation. Vincent L, Vang D, Nguyen J, Benson B, Lei J, Gupta K. Haematologica. 2016 May;101(5):566-77. doi: 10.3324/haematol.2015.136523. Epub 2015 Dec 24. PMID: 26703965 Free PMC article.

- Human lung-resident macrophages express CB1 and CB2 receptors whose activation inhibits the release of angiogenic and lymphangiogenic factors. Staiano RI, Loffredo S, Borriello F, Iannotti FA, Piscitelli F, Orlando P, Secondo A, Granata F, Lepore MT,

Fiorelli A, Varricchi G, Santini M, Triggiani M, Di Marzo V, Marone G. J Leukoc Biol. 2016 Apr;99(4):531-40. doi: 10.1189/jlb.3HI1214-584R. Epub 2015 Oct 14. PMID: 26467187 Free PMC article.

- Endocannabinoid signalling in innate and adaptive immunity. Chiurchiù V, Battistini L, Maccarrone M. Immunology. 2015 Mar;144(3):352-364. doi: 10.1111/imm.12441. PMID: 25585882 Free PMC article. Review.

- Peripheral gating of pain signals by endogenous lipid mediators. Piomelli D, Sasso O. Nat Neurosci. 2014 Feb;17(2):164-74. doi: 10.1038/nn.3612. Epub 2014 Jan 28. PMID: 24473264 Free PMC article. Review.

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