PAIN MANAGEMENT /INFLAMMATION

Pain is a sensory response to external stimuli and is generally a protective mechanism against tissue damage. It is a natural and ultimately beneficial process. Pain can be caused by injury, inflammation (which is itself a protective mechanism), or any number of internal or external stimuli. It is in situations where pain and inflammation signaling are excessive or inappropriately chronic that “pain management” becomes a focus of intervention.

Neuropathic pain can loosely be described as overactive or abnormally activated sensory signaling in response to a nerve injury. In general, activation of spinal and central circuits is observed in neuropathic pain patients. This type of pain response is not easily treated. Inflammatory responses are observed both at the site of injury as well as in spinal projections, leading to lasting changes, which underlies the chronic nature of neuropathic pain.

Inflammatory pain can loosely be described as enhanced sensory signaling due to increased volume at the site of injury as well as chemically sensitized neuropathic signaling. Inflammation is caused by immune cells sending off chemical alarms alerting the body of injury/infection. First responders rush to the site and the increased volume of fluid/cells/tissue can be painful by pushing on and/or sensitizing the sensory neurons.

Besides causing painful stimuli, overactive inflammatory responses are underlying causes of countless disease states, including multiple sclerosis, rheumatoid arthritis, inflammatory bowel diseases, Alzheimer’s, addiction, depression, and Autism Spectrum Disorder to name a few.

Cannabis manages pain and inflammation effectively and is often the primary reason patients seek out cannabinoid therapy. Cannabis affects nerve and sensory pain through multiple actions. THC is a potent activator of the CB1 receptor. CB1’s natural biological job is to slow down normal forward signaling through a negative feedback loop. Pain, in its most basic form, is an activated forward signaling response, making it an ideal target for cannabis therapy.

It has been shown that the CB2 receptor is a key mediator of inflammation. In fact, the CB2 receptor’s primary biological responsibility is to antagonize or turn off the natural inflammatory response leading to reduced inflammatory “activation” of pain pathways. THC is a potent natural activator of CB2.

CBD reduces pain by an entirely different mechanism than THC. CBD reduces the intensity of pain signaling by interacting with the TRPV1 receptor. Sticking with the fire alarm analogy, CBD turns on a switch that takes fuel/oxygen out of the fire. This effect can be seen without THC but is much more pronounced in combination with THC. We also know that CBD reduces inflammation through multiple non-cannabinoid mechanisms. Of note, CBD activates PPARg, which leads to decreased inflammatory signaling.

Tolerance needs to be monitored when discussing long term pain management. CB1/CB2 receptors are sensitive to the amount of available ligand (THC or naturally occurring endocannabinoids). Higher doses and more chronically available THC will cause the body to decrease the number of receptors available (as a defense mechanism against overactivation.) This causes the need for more and more THC for the same effect. Tolerance can be reset by taking “tolerance breaks” of 2-3 weeks of abstinence.

TERPENES

Humulene and ß-Caryophyllene (BCP) are both known anti-inflammatory agents on their own. BCP, in particular, is a selective CB2 agonist and works through a cannabinoid mechanism in the absence of THC. THC and BCP work together in an additive effect.

Myrcene, Terpinolene, and p-Cymene are known analgesics relieving pain in their own right.

REFERENCES/BIBLIOGRAPHY

Bruni, N., Dosio, F., et al., "Cannabinoid Delivery Systems for Pain and Inflammation Treatment," *Molecules* 23(**2018**), 2478. https://doi.org/10.3390/molecules23102478

Burstein, S., "Cannabidiol (CBD) and its Analogs: A Review of their Effects on Inflammation," *Bioorganic & Medicinal Chemistry* 23(**2015**), 1377. https://doi.org/10.1016/j.bmc.2015.01.059

Ellis, R., Toperoff, W., Vaida, F. et al. "Smoked Medicinal Cannabis for Neuropathic Pain in HIV: A Randomized, Crossover Clinical Trial," *Neuropsychopharmacol* 34(**2009**), 672–680. https://doi.org/10.1038/npp.2008.120

Häuser, W., Finn, D.P., Kalso, E., et al., "European Pain Federation (EFIC) Position Paper on Appropriate Use of Cannabis-Based Medicines and Medical Cannabis for Chronic Pain Management," *Eur J Pain.* 22(**2018**), 1547– 1564. https://doi.org/10.1111/ejp.1297

Häuser, W., Fitzcharles. M.A., Radbruch L, Petzke Fet al., "Cannabinoids in Pain Management and Palliative Medicine—An Overview of Systematic Reviews and Prospective Observational Studies," *Dtsch Arztebl Int* 114(**2017**), 627. https://doi.org/10.3238/arztebl.2017.0627

Klauke, A.L., Racz, I., et al., "The Cannabinoid CB2 Receptor-Selective Phytocannabinoid beta-Caryophyllene Exerts Analgesic Effects in Mouse Models of Inflammatory and Neuropathic Pain," *European Neuropsychopharmacology* 24(**2014**), 608. https://doi.org/10.1016/j.euroneuro.2013.10.008

Lee, G., et al., "Medical Cannabis for Neuropathic Pain," *Curr Pain Headache Rep* 22(**2018**), 8. https://doi.org/10.1007/s11916-018-0658-8

Maayah, Z., Takahara, S., Ferdaoussi, M., and Dyck, J., "The Molecular Mechanisms that Underpin the Biological Benefits of Full-Spectrum Cannabis Extract in the Treatment of Neuropathic Pain and Inflammation," *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease* 1866(**2020**), 165771. https://doi.org/10.1016/j.bbadis.2020.165771

Maldonado, R., Baños, J.E., and Cabañero, D., "The Endocannabinoid System and Neuropathic Pain," *PAIN* 157(**2016**), S23-S32 https://doi:10.1097/j.pain.0000000000000428

Mallick-Searle, T. and St. Marie, B., "Cannabinoids in Pain Treatment: An Overview," *Pain Management Nursing* 20(**2019**), 107. https://doi.org/10.1016/j.pmn.2018.12.006

Meng, H., et al., "Selective Cannabinoids for Chronic Neuropathic Pain: A Systematic Review and Meta-analysis,' *Anesth Analg.* 125(**2017**), 1638-1652. https://doi.org/10.1213/ANE.0000000000002110

Munawar, N., Oriowo, M., and Masocha, W., "Antihyperalgesic Activities of Endocannabinoids in a Mouse Model of Antiretroviral-Induced Neuropathic Pain," *Frontiers in Pharmacology* 8(**2017**), 136. https://doi.org/10.3389/fphar.2017.00136

Oláh. A., Szekanecz, Z., and Bíró, T., "Targeting Cannabinoid Signaling in the Immune System: "High"-ly Exciting Questions, Possibilities, and Challenges," *Frontiers in Immunology* 8(**2017**), 1487. https://doi.org/10.3389/fimmu.2017.01487

Turcotte, C., Blanchet, M., Laviolette, M., et al., "The CB2 Receptor and its Role as a Regulator of Inflammation," *Cell. Mol. Life Sci.* 73(**2016**), 4449. https://doi.org/10.1007/s00018-016-2300-4

Vučković S., et al., "Cannabinoids and Pain: New Insights from Old Molecules," *Frontiers in Pharmacology* 9(**2018**), 1259. https://doi.org/10.3389/fphar.2018.01259

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