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Mechanism of action of Low Dose Naltrexone (LDN)

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- I have no actual or potential conflict of interest in relation to this presentation or program
- Discussions in this presentation are for a general information purposes only. Please discuss with your physician your own particular treatment.
- This presentation or discussion is NOT meant to take the place of your doctor.

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Introduction

- Training and Fellowship, Harvard Medical school
- Pain Medicine specialist
- Assistant Professor – Brown Medical School, Rhode Island

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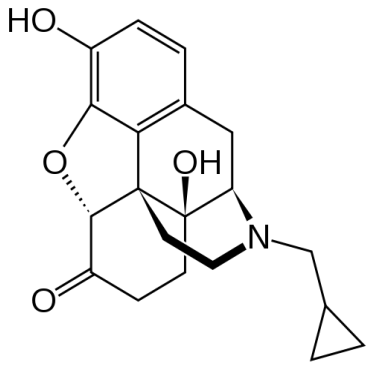
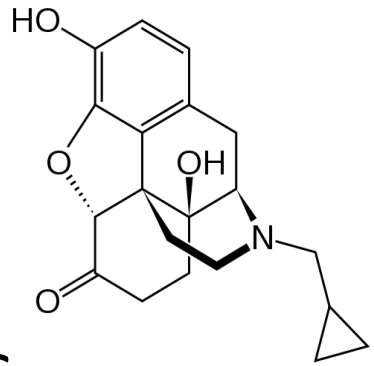
Naltrexone



- Naltrexone is a reversible competitive antagonist at μ and κ receptors
- δ receptor antagonist to a lesser extent
- Its active metabolite 6-β-naltrexol is also reversible competitive antagonist at the μ and κ receptors

Naltrexone



- Plasma half life of Naltrexone is 6 hours
- Plasma half life of its active metabolite 6-β-naltrexol is 13 hours
- Naltrexone is almost fully eliminated in 24 hours.
- Full dose of Naltrexone is 50mg to 150mg per day
- Low Dose Naltrexone (LDN) is 1.75mg to 4.5mg

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Low Dose Naltrexone

- Reversible competitive antagonism of Low Dose Naltrexone blocks the opioid receptor transiently
- This cause a positive feedback mechanism to increase production of endogenous opioids (endorphins)
- The levels of endorphin and enkephalin are raised persistently.

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Bourdette, Dennis. "Spotlight on low dose naltrexone (LDN)". US Department of Veteran Affairs. Archived from the original on 10 February 2010. Retrieved 14 May 2014.

Novella, Steven. "Low Dose Naltrexone – Bogus or Cutting Edge Science?". Retrieved 5 July 2011.

Low Dose Naltrexone

- LDN increases levels of endogenous opioid peptides, which:
  - Promote healing
  - Inhibit cell growth
  - Reduce inflammation

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Opioid Growth Factor [Met(5)]-enkephalin

Opioid Growth Factor (OGF)

- Opioid Growth Factor (OGF) also known as Metkephalin (Met5)
- Its an endogenous pentapepide
- OGF activates a specific receptor called Opioid Growth Factor receptor (OGFr or ζ-opioid receptor).
- OGF and OGFr axis regulates cell growth in normal and abnormal cells

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Low Dose Naltrexone

- LDN blocks the opiate receptor intermittently
- The intermittent block increases production of OGF and OGFr by a positive biofeedback mechanism
- There is an increase in the number and density of OGF receptors

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Glia

Glial cells [1]

- Glia constitute 70% to 80% of all cells in the Central Nervous System

- Perform immune surveillance under basal conditions

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Watkins, Hutchinson, Ledeboer, Milligan et al Brain Behav Immun 2007 Feb; 21(2): 131-146

Activated Glia

- When activated – glia release a variety of substances (proinflammatory cytokines, chemokines, etc.)

- These substances in turn increase the excitability of nearby neurons

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Watkins, Hutchinson, Ledeboer, Milligan et al Brain Behav Immun 2007 Feb; 21(2): 131-146

Toll Like Receptors (TLR)

- Toll Like Receptors are a class of proteins that play a key role in the innate immune system.
- Usually expressed in sentinel cells like macrophages and dendritic cells
- In the face of an infection, the microbes are recognized by TLR which activate the immune system.

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Toll Like Receptors (TLR)

- TLR4 is predominantly expressed by microglia
- Its expression is upregulated under neuroinflammatory conditions.
- Opioids cause glial cell activation by acting on the TLR4 receptors leading to a cascade of pro-inflammatory cytokines
- Opioid antagonists (naloxone, naltrexone) block TLR4 signalling

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LDN and cell growth

- LDN uses the OGF-OGFr pathway to control the cell cycle
- The effects of LDN are dependent on the OGF-OGFr axis. LDN upregulates OGF-OGFr at the translational level
- OGF-OGFr axis regulates cell proliferation by altering the G1/S phase of the cell cycle through the p16 and p21 cyclin – dependent inhibitory kinases
- Metenkephalin production (OGF) stimulates P16 and P21 inhibitory pathways of cancer cell division

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R. N. Donahue, P. J. McLaughlin, I. S. Zagon. Low-dose naltrexone targets the opioid growth factor-opioid growth factor receptor pathway to inhibit cell proliferation: mechanistic evidence from a tissue culture model. Experimental Biology and Medicine, 2011; 236 (9): 1036 DOI: 10.1258/ebm.2011.011121

LDN and Immunity

- LDN blocks release of proinflammatory cytokines including Interleukins IL6 and IL12, TNFα, NF-κB (nuclear factor kappa light chain enhancer of activated B cells)

- Modulates T and B lymphocyte production

- Shift of immune response from TH2 to TH1

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Summary

- Reversible antagonism of the opioid receptors results in an increased production of endogenous opioids
- Upregulates the OGF-OGFr axis
- Blocks TLR signaling which decreases glial cell activation, decreases cytokines, decreases neuroinflammation
- Modulates T and B lymphocyte production

Summary

- LDN blocks release of pro-inflammatory cytokines including Interleukins IL6 and IL12, TNFα, NF-κB (nuclear factor kappa light chain enhancer of activated B cells)
- Regulates cell proliferation through the p16 and p21 cyclin dependent inhibitory kinases.

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Thank you

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