Mechanism of action of Low Dose Naltrexone (LDN)

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- This presentation or discussion is NOT meant to take the place of your doctor.
Introduction

• Training and Fellowship, Harvard Medical school

• Pain Medicine specialist

• Assistant Professor – Brown Medical School, Rhode Island
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
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.


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
Opioid Growth Factor

[Met(5)]-enkephalin
Opioid Growth Factor (OGF)

• Opioid Growth Factor (OGF) also known as Metkephalin (Met5)
• It's an endogenous pentapeptide
• 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
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
Glia
Glial cells

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

- Perform immune surveillance under basal conditions

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

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.
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
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

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
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.
Thank you

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