Low Dose Naltrexone and its Regulatory Effects on Cancer Cell Growth and Autoimmune Disease

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The use of naltrexone for use other than for opiate addiction and alcohol abuse are considered an off label use.

Points to Remember

- 1. Understanding of Low Dose Naltrexone (LDN) Effects on cancer cell growth and autoimmune regulation
- 2. Clinical applications of Low Dose Naltrexone
- 3. How to use Low Dose Naltrexone

Low Dose Naltrexone LDN

- FDA Approved mu opiate receptor antagonist for opiate addiction 1984
- Dosages 50-300 mg per day
- Dr. Bernard Bihari observed AIDS patients on Naltrexone had less fatality rate and opportunistic infections
- Dr Bihari noted Dr. Ian Zagon's studies with opiate antagonists and immune affects. LDN increased beta endorphins 200-300% with 4.5 mg Naltrexone

Beta Endorphin levels in diseases

Human Monocytes

Disease	B endorphin	Th1-Th2 type Response
HIV	↑	Th2
Multiple Sclerosis	↓	Th1
Rheumatoid Arthritis	↓	Th1
Crohn's Disease	↓	Th1

Panerai and Sacerdote, Trends in Immunology Today 19:309, 1997

Beta Endorphins and Multiple Sclerosis

- Baseline levels of BE 40 pg/million cells MS patients
- Controls at 110 pg/million cells
- After treatment with interferon Beta, MS patients BE increased to 80 pg/million

Gironi, M et al., J. Neurol Neurosurg Psychiatry 2003

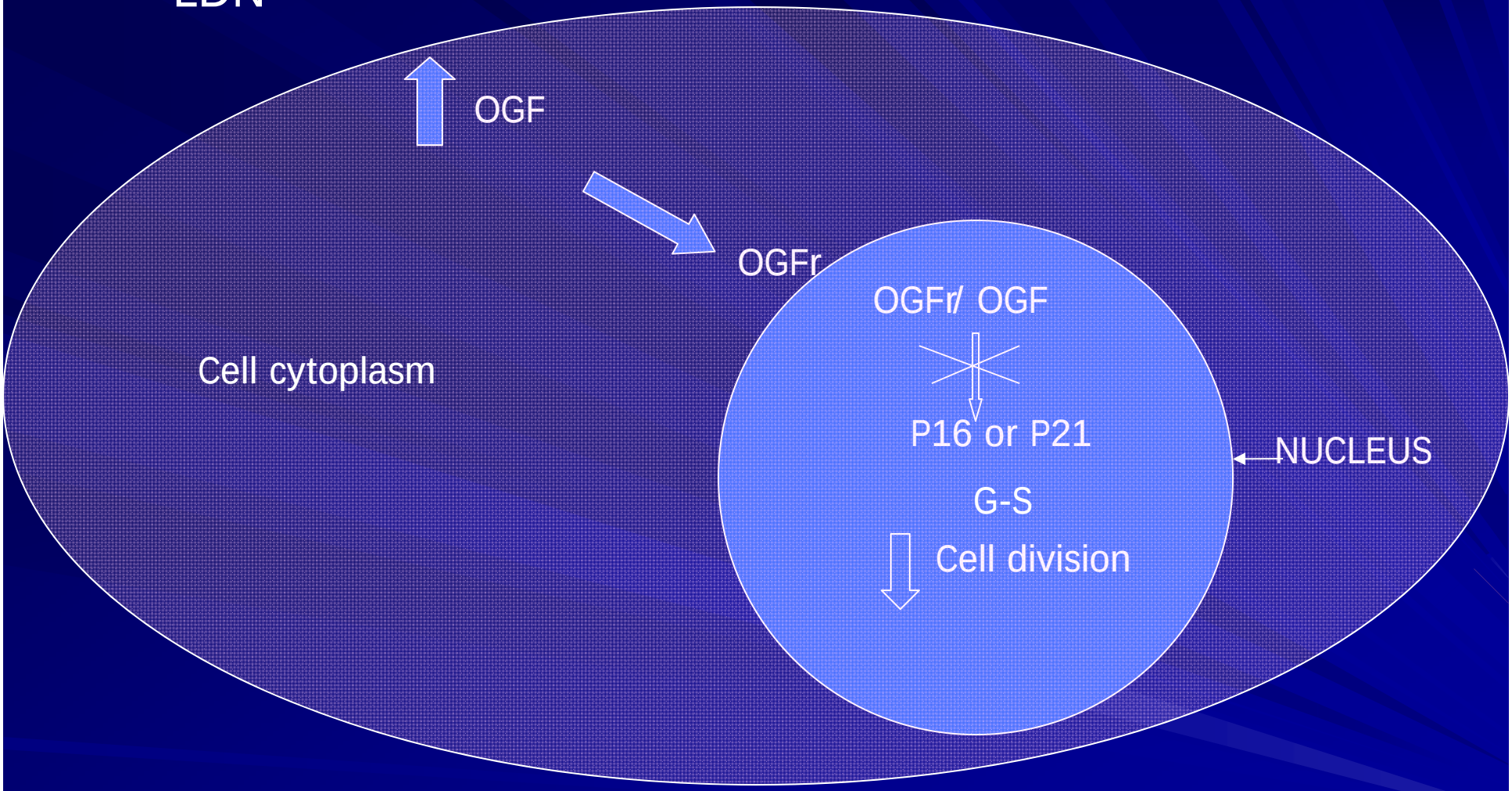
Endorphins and Immunology

- Dr. Ian Zagon Penn State 1981 initial studies on endorphins. Beta endorphins and OGF secreted by brain and adrenals, discovered met-5 enkephalin. OGF (Opiate Growth Factor), autocrine produced peptide that binds to OGFr (Opiate Growth factor receptor)
- OGFr found in nuclear envelope, nucleus, and perinuclear cytoplasm. OGF 7x affinity for OGFr relative to other opiates. No effect on delta,gamma, kappa, opioid receptors

LDN Cellular Effects

- Interacts with cyclin inhibition kinase P21 pathway, which inhibits G1-S phase cell division. In head and neck cancers it inhibits P16 pathway similar to I3C and DIM.
- Increases number of NK cells and improves function increases IL10, Tgf-B
- Increases B cell function, Ifn & IL-2, decreases cytokines, TH-17, TNF alpha

LDN


OGF
OGFr
Cell cytoplasm
OGFr/ OGF
P16 or P21
G-S
Cell division
NUCLEUS

How does it work ?

- Does not act on chemotaxis,adhesion, Zagon documented it with SiRNA blocking binding to OGFr
- Endorphin effects less understood. How does endorphins illicit their effects on T cells, TH1/TH2 balance

OGF and OGFr, Endorphin Effects

- Increased antiviral activity with azt 2-3 fold with HIV disease
- Decreased microglial activation, decreases IL-6, IL-12 to normal levels, decreases peroxynitrites therefore glutamate, neuroexcitatory toxicity related to MS
- Decreases angiogenesis by 30%
- Increases CD4 cell ct.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LDN and OGF in Experimental Autoimmune Encephalomyelitis (EAE) Mice model of MS

Zagon created EAE in Mice gave LDN and OGF and found the following:

1. OGF and LDN reduced T lymphocytes targeting myelin/oligodendrocyte glycoprotein (MOG) stopping disease progression
2. Pretreated mice with LDN prior to EAE reduced the incidence and severity of disease
3. HIGH dosages of naltrexone accelerated disease.

OGF and BE Modulation in tissues

- Chick Chorioallantois membrane reduced blood vessel development 30 %.
- Colitis induced by giving Dextran Sulfate sodium in mice. NTX reduced colon inflammation, reduced wt loss, IL-6 and IL-12 went to normal.
- Nicholas Plotnikoff, Bihari NCI Conference 2007, 12 weeks LDN 46 ARC patients reduced viral virulence, increased CD4,CD56 NK cells, LN size decreased

OGF and OGFr in Cancer Cells

- Zagon found OGF and OGFr in 31 different cancer lines representing 90% of human malignancies.
- Head and neck cancers had less OGF and OGFr which may explain their lower response to therapy

LDN and Fibromyalgia

- Stanford Fibromyalgia pilot study 10 patients 30% reduction in symptoms, Mechanical threshold increased 20%, hot temp threshold increased 0.9 C, no effect on cold threshold.
- Side Effects vivid dreams, insomnia. 90.3% tolerance LDN, 89.7% tolerance placebo peak effects occurred 28 days

Younger J, Mackey S, Pain Med., 2009 May-Jun; 10 (4): 663-72.

UCSF Dr. Bruce Cree M.D. LDN and Multiple Sclerosis

- 70 patients in patient funded study 8 weeks
- MSQLI scores improved measuring mental components, mental health, social support, pain effects
- No impact on fatigue, bowel and bladder control, sexual satisfaction, or vision.

Dr. Skip Lenz PhD Pharmacy Randomized Pharmacy Survey with MS Patients Presentation at 2007 LDN meeting

- 278 patients of varying types of MS
- 83% reported no exacerbations many more than 5 years and longest period was 9 years
- 71% felt their life improved with LDN
- 74 % no side effects
- 20% one side effect mostly sleep
- 6% two side effects sleep and stiffness

LDN in Primary Progressive Multiple Sclerosis

- Gironi, 40 PPM patients pilot study showed over 6 months that use of LDN was safe and tolerable.
- LDN patients had reduced spasticity
- Only one patient had disease progression
- Beta Endorphins increased

Personal Anecdotal Experiences

- 40 year woman with MS on Interferon product, previously 20 hours work per week fatigued. Started LDN April 2008, Sept 2008 off her MS drug Fulltime work riding mountain bike remodeling house
- 40 year old male with severe thoracic neuritis requiring spinal cord stimulator. 4 weeks on the LDN neuritis reduced to 2/10 pain.
- Woman disabled in wheelchair back to work on LDN
- Male who was suicidal due to total body MS neuritis pain, resolved with LDN 4 years later
- 23 yo woman CRPS reduced her pain 25% No Narcs
- 45 yo woman Interstitial cystitis comfortable after 5 yrs

Diseases that have been treated with LDN

- Rheumatoid Arthritis
- Crohn's Disease
- AIDS
- SLE
- Ankylosing Spondylitis
- Fibromyalgia
- ALS
- Autism
- Multiple Sclerosis
- Pancreatic Cancer
- Lung Cancer
- Neuroblastoma
- Parkinsons
- Optic Neuritis
- Breast Cancer
- Multiple Myeloma
- Lymphoma
- Psoriasis

Low Dose Naltrexone and Opiate Growth Factor Formulas

- Compounded Pharmacies create capsules or tablets from 50 mg tablets or powder.
- Naltrexone not to be extended release
- Fillers: calcium carbonate inhibits absorption, avicel good filler, lactose not recommended due to sensitivities
- Opiate Growth Factor given IV or SQ


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Other considerations for LDN use

- Discontinue narcotics for 2 weeks prior to LDN use
- Discontinue LDN 4 days preoperatively
- Not to be used with immunosuppressives ie azathioprine, Tnf inhibitors, prednisone more than 5 mg/day
- MS patients may use copaxone
- Safety: Drs. Hilgren and Boyle in UK infertility clinic without fetal problems. No significant side effects since 1985 including higher dosages of Naltrexone
- Cost: $10- $50 per month vs $5000 with IV biologic Tnf inhibitors for Crohn's, RA and their side effects

Dosing

1.5 mg per day for 4 weeks then increase to 3.0 mg/day for 4 weeks, then up to 4.5 mg/day.

Best time is after 9pm but can take anytime. Opiate blockade effect lasts about 4 hours but the endorphin rise may last 24-72 hours based on Dr. Zagon's studies.

Side Effects: about 15% patients have transient sleep disturbances, insomnia, vivid dreams etc. usually resolves in two weeks. MS patients may have short term exacerbation.

Cancer patients LDN may be complimentary to therapy as in pancreatic cancer with the use of gemicitabine showing enhanced cancer cell growth inhibition

Conclusion

- Metenkephalins inhibit cancer cell growth
- Endorphins impact the immune response in autoimmune disease
- Low dose naltrexone increases beta endorphins, OGF, and OGFr to rebalance the immune response and retard cancer cell growth
- LDN has shown to be safe, economical, and easy to use over the years with minimal side effects
- Further studies need to be conducted to better understand the action of LDN and OGF in different disease states.

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