

Low dose naltrexone therapy in multiple sclerosis

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Abstract

The use of low doses of naltrexone for the treatment of multiple sclerosis (MS) enjoys a worldwide following amongst MS patients. There is overwhelming anecdotal evidence, that in low doses naltrexone not only prevents relapses in MS but also reduces the progression of the disease. It is proposed that naltrexone acts by reducing apoptosis of oligodendrocytes. It does this by reducing inducible nitric oxide synthase activity. This results in a decrease in the formation of peroxynitrites, which in turn prevent the inhibition of the glutamate transporters. Thus, the excitatory neurotoxicity of glutamate on neuronal cells and oligodendrocytes via activation of the α -amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid (AMPA) class of glutamate receptor (GluR) is prevented. It is crucial that the medical community respond to patient needs and investigate this drug in a clinical trial.

INTRODUCTION

Multiple sclerosis (MS) affects thousands of sufferers worldwide. In many cases it is characterized by the relentless progression of disease with increasing disability. Treatment with interferons or with glatiramer acetate necessitates multiple weekly or daily injections, and this can be associated with significant side effects. Furthermore, the drugs are only moderately effective in reducing relapses, while the progression of disease is not much affected (1-2). Thus there is a need for newer therapeutic or neuroprotective agents in MS. The lack of highly effective drugs for MS, may in part reflect the considerable debate regarding the etiology and pathogenesis of MS. There are suggestions in the literature that the widely used animal model of experimental allergic encephalitis may not fully reflect human MS (3-6).

Apoptosis and oxidative damage in multiple sclerosis

Recent work by Barnett and Prineas confirms previous reports and suggests that the developing lesion in MS brains, lacks the inflammatory cells. Instead it shows apoptosis of oligodendrocytes and microglial activation as the prominent pathological finding (4-7). Multiple studies have implicated apoptotic pathway components in the pathogenesis of MS (8-10). There is considerable evidence that the cause of the oligodendrocyte cell apoptosis, demyelination and axonal damage in MS may reflect oxidative stress and or excitatory amino-acid toxicity (11-13). Nitric oxide synthase, nitric oxide and peroxynitrites are the key mediators of oxidative damage in MS lesions (14-18).

Low dose naltrexone in multiple sclerosis

While there are no scientific studies documenting the effects of low dose naltrexone (LDN) therapy in MS, the related drug naloxone has been investigated in a variety of neurodegenerative and inflammatory disorders such as septic shock, injuries to brain and spinal cord, myocardial and cerebral stroke and Alzheimer's disease (15). There is however considerable anecdotal evidence supporting the use of LDN in MS by the lay public.

Anecdotal literature from the United Kingdom and the United States suggests that LDN markedly reduces the frequency of MS relapses and halts the progression of multiple sclerosis. The cult like following of LDN by the lay patient is reflected in the approximately 15000 hits for "low dose naltrexone" on the Google search engine (www.google.com), over 70,000 LDN capsules have been dispensed between Jan-Aug 2004 from just one pharmacy (Dr.Henry Lenz Pharm D, personal communication), an international petition for a clinical trial of LDN in MS has over 5500 signatories (www.thepetitionsite.com), a patent for the use of naltrexone in MS awarded by the U.S.Patent office (#6,586,443) and one ongoing clinical trial of LDN in ulcerative colitis an autoimmune disease (<http://www.hmc.psu.edu/colorectal/research/naltrexone.htm>). Furthermore, MS patients who had been going downhill with conventional therapy have reported their experiences with LDN in five newspaper reports in the British and American press, as well as have organized and participated in a self reported web based survey of 267 LDN users from 16 countries. This patient organized survey, reports an average relapse rate of only 0.2/year in patients with MS. While the patient self-reported

survey cannot be equated with a physician organized clinical trial, it begs the question as to why are there no clinicians investigating this. The patient initiated LDN surveys as well as the media reports have been summarized at www.LDNers.org. (19-24). While naltrexone has been approved by the US Federal Drug Administration at ten fold higher doses, it has not been systematically investigated in MS.

Naltrexone is related to naloxone an opioid antagonist with no opioid agonist properties. The activity of naltrexone is due to the parent drug as well as its metabolite 6-beta-naltrexol. They have a short half-life of 4 and 13 hrs respectively. Naltrexone is used at low doses (3-4.5 mg/day) in clinical practice by private physicians. At these doses, no significant side effects have been reported in the anecdotal literature. Some patients have reported increased stiffness, or increased wakefulness. The increased wakefulness disappears within a few weeks of starting therapy, while decreasing the dose can reduce stiffness.

Hypothesis

The peroxynitrites produced by astrocytes and microglial cells inhibit the glutamate transporters in synaptic clefts of neuronal cells and adjacent oligodendrocytes resulting in excitatory glutamate neurotoxicity. I postulate that naltrexone acts by reducing nitric oxide synthase activity. This results in a decrease in the formation of peroxynitrites, which in turn prevents the inhibition of the glutamate transporters. Thus, the excitatory neurotoxicity of glutamate on neuronal cells and oligodendrocytes via the activation of the α -amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid (AMPA) class of glutamate

receptor (GluR) is prevented. The detailed evidence and reasoning for this hypothesis can be broken down into several steps (Fig.1).

Inducible nitric oxide synthase (iNOS) activity is known to be increased in activated astrocytes and microglia (14,17,18). While the mechanism of the increase in iNOS activity is not the focus of this hypothesis, it could be due to an activation (step 2) of the p38 mitogen activated protein kinase (p38 MAPK), a member of the stress activated superkinase family. The activation of p38 MAPK occurs via opioid receptors or other lipopolysaccharide binding proteins/receptors (step 1) (15,25). In step 1, naltrexone as a mu receptor antagonist can block endogenous opioid receptors as well as prevent the increase (Step3) in iNOS activity (15, 25-27). Significantly, CSF concentrations of glutamate, hypoxanthine and xanthine are all increased in MS (16,28) Nitric oxide (NO) produced by iNOS can combine with superoxide (O_2^-) produced from inflammatory cells by xanthine oxidation to produce peroxynitrites ($ONOO^-$).

The subsequent steps in the hypothesis have been proposed earlier (29). The peroxynitrites inhibit glutamate transport by inhibiting the glutamate transporters (16,30). As a result the accumulated glutamate stimulates excitotoxic death of the adjacent oligodendrocytes by activating the AMPA GluR (12,13, 31). Excitotoxic death can also occur in axons (12,31). Thus, by reducing peroxynitrite formation, LDN would prevent excitotoxic death of oligodendrocytes and neuronal cells.

Testing the hypothesis

It is known that peroxynitrites as well as glutamic acid levels are elevated in the CSF of patients with MS (16). The biochemical basis of LDN therapy can be tested by measuring the decrease in the levels of these analytes in CSF after treatment with LDN. Since the postulated biochemical mechanism may be more complex than envisioned in this hypothesis, it is also crucial to do a clinical trial. This can be achieved by doing a trial of LDN versus placebo in patients receiving glatiramer acetate or other MS frontline therapy. The anecdotal literature suggests that glatiramer acetate but not interferons work well with LDN. Progression of disease could be measured functionally by using the Kurtzke expanded disability status scale and by serial MRI's.

Conclusion

The use of LDN has gained widespread public acceptance, inspite of the lack of enthusiasm from prescribing physicians. It is incumbent upon us to investigate this drug, for it offers the potential of an oral therapy for MS with few side effects. At the very least, by showing a lack of efficacy, patients can be persuaded from using LDN in lieu of the standard therapies of MS.

References

- 1 Munari L, Lovati R, Boiko A. *Cochrane Database Syst Rev* 2004;(2).
- 2 Rice G PA, Incorvaia B, Munari L, et al. *Cochrane Database Syst Rev* 2004;(2).
- 3 Chaudhuri A, Behan PO. Shared scheme for assessing drugs for multiple sclerosis: why are eyes tightly shut to considering causes other than autoimmunity?. *BMJ*. 2003; **326**:1213.
- 4 Barnett MH, Prineas JW. Relapsing and remitting multiple sclerosis: pathology of the newly forming lesion. *Ann Neurol*. 2004; **55**:458-68.
- 5 Behan PO CA, Roep BO. Pathogenesis of multiple sclerosis revisited. *J R Coll Phys Edinb* 2002; **32**:244-65.
- 6 Trapp BD. Pathogenesis of multiple sclerosis: the eyes only see what the mind is prepared to comprehend. *Ann Neurol*. 2004; **55**: 455-7.
- 7 Lucchinetti C, Bruck W, Parisi J, Scheithauer B, Rodriguez M, Lassmann H. Heterogeneity of multiple sclerosis lesions: implications for the pathogenesis of demyelination. *Ann Neurol*. 2000; **47**: 707-17.
- 8 Mycko MP, Papoian R, Boschert U, Raine CS, Selmaj KW. Microarray gene expression profiling of chronic active and inactive lesions in multiple sclerosis. *Clin Neurol Neurosurg*, 2004; **106**: 223-9.
- 9 Ethell DW, Buhler LA. Fas ligand-mediated apoptosis in degenerative disorders of the brain. *J Clin Immunol*. 2003; **23**:363-70.
- 10 Zipp F. Apoptosis in multiple sclerosis. *Cell Tissue Res*. 2000; **301**:163-71.

- 11 Gilgun-Sherki Y, Melamed E, Offen D. The role of oxidative stress in the pathogenesis of multiple sclerosis: the need for effective antioxidant therapy. *J Neurol*. 2004; **251**: 261-8.
- 12 Werner P, Pitt D, Raine CS. Glutamate excitotoxicity--a mechanism for axonal damage and oligodendrocyte death in Multiple Sclerosis? *J Neural Transm Suppl*. 2000; **60**: 375-85.
- 13 Pitt D, Werner P, Raine CS. Glutamate excitotoxicity in a model of multiple sclerosis. *Nat Med*. 2000; **6**: 67-70.
- 14 Chao CC, Hu S, Molitor TW, Shaskan EG, Peterson PK. Activated microglia mediate neuronal cell injury via a nitric oxide mechanism. *J Immunol*. 1992; **149**: 2736-41.
- 15 Liu B, Gao HM, Wang JY, Jeohn GH, Cooper CL, Hong JS. Role of nitric oxide in inflammation-mediated neurodegeneration. *Ann NY Acad Sci*. 2002; **962**: 318-31.
- 16 Gurwitz D, Kloog Y. Peroxynitrite generation might explain elevated glutamate and aspartate levels in multiple sclerosis cerebrospinal fluid. *Eur J Clin Invest*. 1998; **28**: 760-1.
- 17 Hill KE, Zollinger LV, Watt HE, Carlson NG, Rose JW. Inducible nitric oxide synthase in chronic active multiple sclerosis plaques: distribution, cellular expression and association with myelin damage. *J Neuroimmunol*. 2004; **151**:171-9.
- 18 Broholm H, Andersen B, Wanscher B, et al. Nitric oxide synthase expression and enzymatic activity in multiple sclerosis. *Acta Neurol Scand*. 2004;**109**: 261-9.

- 19 Nicholls M. MS sufferers campaign for drug aid. *EDP24* 2004 May 21.
- 20 Calls for the radical treatment. *The Irish Times* 2004 May 18.
- 21 Weiss-Tisman H. Drug offers hope for MS patients. *Brattleboro Reformer* 2004 May 15.
- 22 Carswell S. MS experimental drug 'could save state millions of euros'. *The Sunday Business Post Online* 2003 Oct 5.
- 23 Puttick H. MS victim finds hope in heroin users drug. *The Herald* 2004 April 12.
- 24 Undergrad J. Coping with an unprofitable cure. *Columbia Spectator Online* 2004 May 1.
- 25 Singhal PC, Bhaskaran M, Patel J, et al. Role of p38 mitogen-activated protein kinase phosphorylation and Fas-Fas ligand interaction in morphine-induced macrophage apoptosis. *J Immunol.* 2002; **168**: 4025-33.
- 26 Lysle DT, How T. Heroin modulates the expression of inducible nitric oxide synthase. *Immunopharmacology.* 2000; **46**:181-92.
- 27 Lysle DT, How T. Endogenous opioids regulate the expression of inducible nitric oxide synthase by splenocytes. *J Pharmacol Exp Ther.* 1999; **288**:502-8.
- 28 Stover JF, Lowitzsch K, Kempinski OS. Cerebrospinal fluid hypoxanthine, xanthine and uric acid levels may reflect glutamate-mediated excitotoxicity in different neurological diseases. *Neurosci Lett.* 1997; **238**: 25-8.
- 29 Rose JW, Hill KE, Watt HE, Carlson NG. Inflammatory cell expression of cyclooxygenase-2 in the multiple sclerosis lesion. *J Neuroimmunol.* 2004;**149**: 40-9.

- 30 Trotti D, Rossi D, Gjesdal O, et al. Peroxynitrite inhibits glutamate transporter subtypes. *J Biol Chem.* 1996; **271**: 5976-9.
- 31 Smith T, Groom A, Zhu B, Turski L. Autoimmune encephalomyelitis ameliorated by AMPA antagonists. *Nat Med.* 2000; **6**: 62-6.

Figure Legend

Figure 1. Postulated mechanism of naltrexone mediated prevention of oxidative damage to neuronal cells and oligodendrocytes. **1.** Astrocytes and microglial cells are activated by opioids or other stress signals. **2.** The p38 mitogen activated protein kinase (p38 MAPK) is activated, which increases inducible nitric oxide synthase (iNOS) (15,25). **3.** Naltrexone inhibits the increase in iNOS activity(15, 25-27). This leads to a decrease in the formation of peroxynitrites (ONOO⁻). **4.** The peroxynitrites can inhibit the glutamate transport in synaptic clefts and adjacent oligodendrocytes by inhibiting the glutamate transporters (16,30). As a result, the glutamate does not cause excitotoxic death of neurons and oligodendrocytes via activation of the α -amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid (AMPA) class of glutamate receptor (GluR).

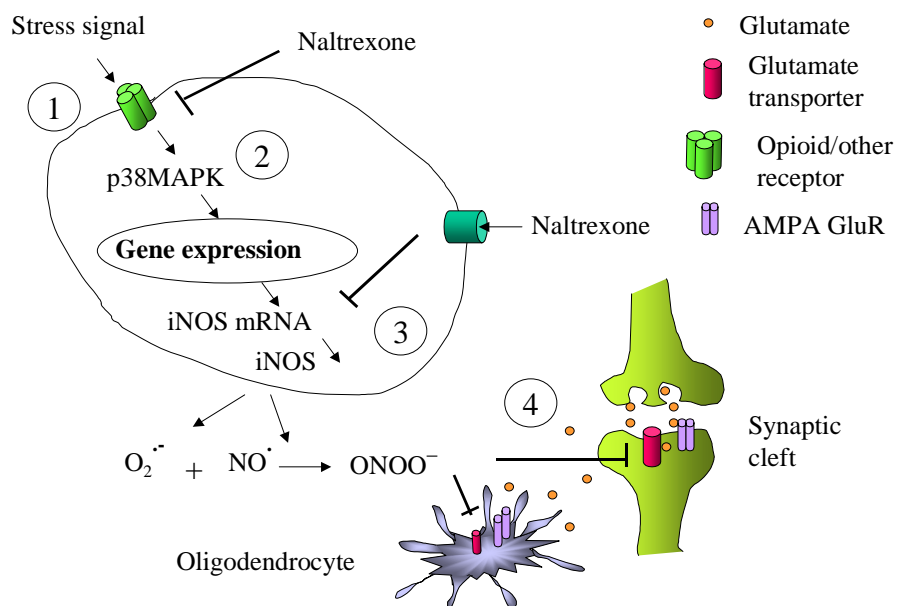


Figure 1.