Medical Hypotheses (2004) x, xxx–xxx

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Low dose naltrexone therapy in multiple sclerosis

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Received 17 September 2004; accepted 22 September 2004

Summary 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 class of glutamate receptor 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 [4–7] 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. 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

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0306-9877/$ - see front matter
doi:10.1016/j.mehy.2004.09.024

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 15,000 hits for ''low dose naltrexone'' on the Google search engine [www.google.com], over 70,000 LDN capsules have been dispensed between Jan and 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 US Patent office (#6,586,4430 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 10-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-β-naltrexol. They have a short half-life of 4 and 13 h, 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. It is postulated 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 (step 3) 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

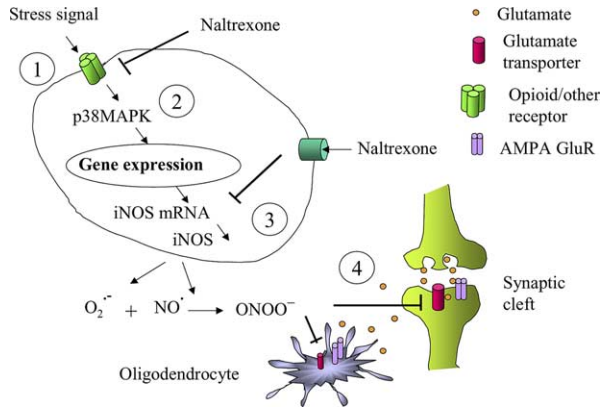

Figure 1 Postulated mechanism of naltrexone mediated prevention of oxidative damage to neuronal cells and oligodendrocytes (1). Astrocytes and microglial cells are activated by opioids or other stress signals. (2). The p38 mitogen activated protein kinase (p38 MAPK) is activated, which increases inducible 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).

formation, LDN would prevent excitotoxic death of oligodendrocytes and neuronal cells.

Testing the hypothesis

This new hypothesis may be tested in the following manner:

(1) 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 therefore be tested by measuring the levels of glutamic acid and peroxynitrites before and then 3–6 months after the start of LDN therapy. A positive response to LDN will be seen by observing the decrease in CSF glutamic acid and peroxynitrite levels following LDN treatment.

(2) Since the postulated biochemical mechanism may be more complex than envisioned in this hypothesis, it is also crucial to do a pilot clinical trial. The two important parameters to monitor during a clinical trial are the number of relapses as well as progression of disease while on LDN. Progression of disease could be measured functionally by using the Kurtzke expanded disability status scale and/or by serial MRI's. Since LDN is not yet approved for MS therapy, it would be unethical to withhold other approved MS therapy during the trial. Therefore, the trial should be designed to provide 3–4.5 mg slow-release LDN or placebo in patients already receiving glatiramer acetate as MS therapy. The anecdotal literature suggests that LDN does not work well in patients taking interferons. Alternatively, LDN or placebo could be given to patients who have refused the standard MS therapy due to its high cost or toxicity.

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.

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