

Enhancing acupuncture by low dose naltrexone

Jan M Keppel Hesselink, David J Kopsky

ABSTRACT

To find appropriate and effective treatment options for chronic pain syndromes is a challenging task. Multimodal treatment approach has been gaining acceptance for chronic pain. However, combining treatments, such as acupuncture, with rational pharmacology is still in its infancy. Acupuncture influences the opioid and cannabinoid system through releasing endogenous receptor ligands. Low dose naltrexone also acts on both these systems, and upregulates the opioid and cannabinoid receptors. The authors hypothesise that low dose naltrexone could enhance the pain-relieving effect of acupuncture.

INTRODUCTION

Chronic pain syndromes are difficult to treat and besides drugs, non-pharmacological therapies, such as acupuncture, are available as treatment modalities. There is enough clinical evidence supporting the role of acupuncture to relieve pain in a great variety of chronic pain syndromes—such as migraine, low back pain, cervical pain and headache.^{1–4} However, a number of randomised clinical trials have failed to show superiority of acupuncture compared to sham acupuncture due to either a high placebo response or relatively small clinical effects, or both.⁵ Considering some studies show that acupuncture and sham acupuncture show superiority to standard care,⁶ one might question whether acupuncture can be blinded or not, because it is a hands-on technique. Moreover, the more invasive a therapy is, the more placebo response it will evoke.⁷ Because acupuncture has a very low incidence of adverse effects, the risk benefit ratio of this intervention remains positive. Indeed, many patients prefer acupuncture over treatment with analgesics, due to the dose-limiting side effects of these drugs. Acupuncture is an intervention that exerts its clinical effect most probably via modulation of endogenous analgesic pathways based on opioids and cannabinoids. Recently, there has been growing interest in the enhancement of the analgesic effects of opiates by low doses (nanomolar to

picomolar) of naltrexone, an opioid antagonist. Furthermore, there is significant crosstalk between the opioid and the cannabinoid systems, and low dose naltrexone (LDN) might facilitate this crosstalk. In addition, LDN also enhances cannabinoid-induced analgesia.

Based on these facts we will discuss a theoretical framework of boosting acupuncture analgesic effects by adding LDN in order to modulate further the endogenous cannabinoid and opioid systems.

THE ENDOGENOUS OPIOID AND CANNABINOID SYSTEMS, AND THEIR CROSS TALK

Opioid and cannabinoid receptors are expressed in our brain and our peripheral nervous system, as well as in other tissues, such as cells of the immune system. These receptors can be activated by endogenous ligands, and for the opioid system alone around 30 opioid peptides have already been identified. All these ligands are synthesised on the base of three opioid peptide precursors: proenkephalin, prodynorphin and proopioidmelanocortin. Many endogenous opioid peptides and fatty acids are produced by the body as biological relevant answers to inflammation and pain. Moreover, inflammation and pain increase the synthesis of opioid receptors. The four classical opioid receptors— μ opioid receptor (MOR), δ opioid receptor (DOR),

κ opioid receptor and the opioid receptor ligand 1—are expressed through the entire central and peripheral nervous system, and on cells of the immune system. In all these cells, the locally produced opioid peptides play an important role in the modulation of chronic pain. Cross talk between the opioid system and other systems, such as the N-methyl-D-aspartate system, exists, and this can be modulated by dynorphins.

Just as our body produces opioids, endocannabinoids are synthesised. At least five different endocannabinoids have been characterised, such as anandamide, palmitoylethanolamide and 2-arachidonglycerol. These lipid-signalling molecules are produced in the cell membrane from phospholipids acting as precursors. The most researched cannabinoid receptors are the cannabinoid receptors 1 and 2 (CB1 and the CB2 receptors). Other receptors for endocannabinoids exist, such as the transient receptor potential vanilloid 1 (TRPV1). One of the endocannabinoids, N-arachidonyldopamine, has a high affinity for the TRPV1, and capsaicin shares the same binding site on this receptor. The endocannabinoid system can modulate various other neurotransmitter systems, also relevant in pain, such as the glutamate and the GABAergic systems. Just as described for the opioid system, cannabinoid receptors can be found in central supraspinal pathways, in the spinal cord, the dorsal root ganglia and in the primary afferents, as well as on many cells belonging to the immune system. The CB1 receptor is one of the most densely expressed receptors in the central nervous system. CB1 (and CB2) receptors are even present in membranes of small unmyelinated nerve fibres in the skin.⁸

Thus, the anatomical distribution of both the opioid and the cannabinoid system show great overlap. It might not be a surprise, therefore, that various functional interactions between the cannabinoid and opioid system exist, such as the release of endogenous opioids by cannabinoid agonists.⁹ Noxious stimulation leads to an enhanced production of endocannabinoids via

endocannabinoid mobilisation from the cell membranes.¹⁰ In line with these findings we expect that acupuncture as a minor noxious stimulus has comparable effects and might induce the production of anandamide and 2-arachidonylglycerol, though to a lesser extent. Literature discussed in the section below supports this idea, as well as the hypothesis that we can boost the analgesic effects of acupuncture by adding LDN to the treatment regime.

ACUPUNCTURE INFLUENCES THE CANNABINOID AND OPIOID SYSTEM

Over the last 40 years we have gained a much better understanding of the biological effects of acupuncture. In the past, the efficacy of acupuncture was thought to be dependent on imaginary acupuncture points and hypothetical meridians. This might have been a sufficient metaphor in the Orient, but scientists felt the necessity to understand the analgesic effects of acupuncture based on scientific concepts rooted in our understanding of neurobiology and neurophysiology.

In the 1970s, research revealed that naloxone blocked acupuncture-analgesia, suggesting that the analgesic effects of acupuncture are mediated by endogenous opioids.¹¹ Research on the mechanism of action of acupuncture was greatly enhanced by the availability of radioimmunoassays for the endogenous opioids. Studies into the mechanism of the actions of electroacupuncture demonstrated clear frequency dependent effects on the level of endogenous opiates: 2 Hz stimulated the release of enkephalin, β -endorphin and endomorphin, while 100 Hz electrostimulation selectively increased the release of dynorphin. A combination of these two frequencies produce simultaneous release of all four opioid peptides, and a improved therapeutic effect could be obtained.¹² These preclinical observations are now confirmed in clinical studies of low back pain and diabetic neuropathic pain.¹³ Other studies showed that both serotonergic descending and ascending pathways originating from the nucleus raphe magnus are implicated in mediating acupuncture analgesia.¹⁴ Acupuncture

also influences other brain nuclei belonging to the structures of the pain matrix, such as the periaqueductal grey, locus coeruleus, hypothalamic paraventricular nucleus and their predominant neurotransmitters as neurotensin, norepinephrine, arginine vasopressin.¹⁵ A positron emission tomograph-scanning study showed that acupuncture evoked short-term and long-term increases in MOR binding potential, in multiple pain and sensory processing regions including the cingulate, caudate and amygdale nuclei, whereas sham acupuncture did not show any increases.¹⁶

Electroacupuncture also has effects on the release of peripheral neurotransmitters, as it increases peripheral anandamide levels, acting on CB2 receptors, and this clearly leads to analgesic effects.¹⁷ A neuromodulator, adenosine, which is a degradation product of ATP, has been found to be 24 times increased in concentration in the peripheral interstitium after manual acupuncture.¹⁸ Suppression of pain mediated by acupuncture required adenosine as well as sufficient A1 receptor expression.

All this suggests that interventions modifying the various mentioned neurotransmitter systems can create synergies leading to enhanced analgesic effects of acupuncture. This suggestion is supported by experimental research providing evidence that pharmacological active agents can potentiate the analgesic effect of acupuncture. We will now focus in detail on the analgesic enhancing properties of the opiate antagonist naltrexone in a low dose.

LOW DOSE NALTREXONE

Naltrexone hydrochloride is an antagonist of opioid receptors, and has been used clinically for over 30 years to treat opioid addiction. It is a well-characterised competitive opioid receptor antagonist with high affinity for the MOR.¹⁹ The dose administered in clinical settings to treat opiate addiction is 50 mg daily. The dose we suggest to boost the analgesic effects of acupuncture is 3–4.5 mg daily. This dose is in line with recent literature on the use of LDN.²⁰

Naltrexone is a drug with a low propensity for side effects in this advised dose. In animal models researchers recently explored the effects of LDN in picomolar to nanomolar dose levels, revealing measurable and relevant biological effects.²¹

For instance, studies show a significant potentiation of opioid-induced analgesia by low doses of opioid receptor antagonists.²² This analgesic activity involves direct opioid receptor antagonism. These findings, coupled with the fact that blockade of opioid receptors causes upregulation of the endogenous opioid receptors as well as upregulation of adenosine A1 receptors, makes LDN an attractive tool for enhancing analgesic effects of acupuncture. LDN prevents analgesic tolerance to opioids.²¹ Moreover, LDN seems to inhibit detrimental gliosis in spinal tissue, which has been identified as an important pathogenetic aspect in neuropathic pain.²³ That is why the term gliopathic pain has been recently introduced.²⁴

Chronic naltrexone treatment also leads to an increase in the density of opioid receptors, particularly the MOR but also the DOR subtype in the brain.²⁵

In some experimental human studies, the administration of naltrexone reduces pain measured on numerical pain ratings as well as the nociceptive flexion reflex in response to noxious electrical stimulation of the skin.²⁶ LDN reduces also relevant biological readouts for neuropathic pain, restores the analgesic effects of morphine and suppresses spinal neuroinflammation. Low doses of opioid antagonists enhance the analgesic effects of opioid agonists such as morphine in various animal models of chronic pain.²⁷ Furthermore, seizure threshold in mice is increased by LDN and thus potentiates the anticonvulsant effect of low dose morphine on clonic seizures in a mouse model for epilepsy.²⁸ The analgesic effects of cannabinoid ligands are enhanced by LDN too.²⁹

All these findings point out that LDN can enhance the analgesic effects of opioids (and cannabinoids), a fact that seems counter intuitive, given the

opioid antagonistic properties of naltrexone.

The hypothesised boosting effects of LDN on acupuncture might be explained by a relatively short opioid receptor blockade during peak dose, resulting in a compensatory rise in opioid peptides, as well as opioid receptors. Between these peak dose periods, LDN no longer blocks the opioid receptors, and thus both the reactive elevated levels of endogenous opioids, and the acupuncture-induced endorphins and dynorphins, will exert their analgesic effects. Furthermore, due to the repeated short phases of opioid receptor blockade an increased density of opioid receptors will result in super sensitivity for the endogenous opioid. This again will be the basis of a decrease in pain perception.

Apart from the effects on the above discussed endogenous neurotransmitter systems, LDN has additional mechanisms of action. The first relevant action is via the adenosine receptors.³⁰ It is well known that adenosine A1 receptors are implicated in pain, shown, for example, in an experiment that intrathecal adenosine suppresses pain.³¹ Intrathecal injection of the A (2A) receptor agonist ATL313 produced a long-duration reversal of mechanical allodynia and thermal hyperalgesia.³²

Furthermore, naltrexone has a high affinity for filamin A, a protein that serves as a modulator of the MOR. Naltrexone also influences the toll-like receptor 4, which plays a role in glia activation, neuropathic pain and the production of nitric oxide.

Naltrexone therefore seems a pleiotropic wonder molecule, a molecule with 'dirty pharmacology' and that might just be the reason why LDN might be used to enhance opioid and cannabinoid mediated analgesic effects of acupuncture.

New clinical data also support the safety and usefulness of LDN. Recently, LDN appeared to improve the quality of life in patients suffering from multiple sclerosis (MS).³³ Based on interviews with five North American pharmacies known to compound LDN, it was estimated that several thousand MS patients in the USA are

currently using LDN. Some MS patients suffering from severe (central) neuropathic pain claim on the internet that LDN drastically decreased pain. In addition to case descriptions of patients suffering from central neuropathic pain in MS, preclinical work has also indicated a putative role of LDN in neuropathic pain.³⁴

Furthermore, a pilot trial was reported on the efficacy and safety of LDN (4.5 mg) on pain in fibromyalgia.³⁵ These clinical studies all supported the safety of LDN up to 4.5 mg/day. Vivid dreams, sleep disturbances and slight nausea were the only reported adverse effects.

CONCLUSION

Acupuncture exerts its analgesic activity mainly via the stimulation of endogenous opioids and cannabinoids. LDN has a variety of pharmacological actions, leading to an enhancement of the analgesic effects of our endogenous opioids and cannabinoids. Furthermore, naltrexone modulates a number of subsystems related to pain physiology, such as the toll-like receptor 4, NO and filamin A. Low dose of naltrexone has been found to be safe, with very few side effects, and recent clinical pilot trials in fibromyalgia and MS showed pain reducing and quality of life enhancing effects.

Therefore we postulate that LDN (3–4.5 mg/day) might be a useful adjunct for acupuncture and will enhance its analgesic properties.

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Education and practice

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