D-CYCLOSERINE FOR THE TREATMENT OF CHRONIC PAIN

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Abstract

N-methyl-d-aspartate (NMDA) receptors play fundamental roles in pain processing, pain sensitization, and chronic-pain induced depression. The NMDA receptor antagonist, ketamine, is used off-label to treat various chronic pain syndromes. However, because of its risks for causing physical and psychological dependance, psychomimetic side effects, and neurotoxicity, ketamine is of limited clinical usefulness. D-cycloserine (DCS) is a partial agonist of the NMDA receptor, and antagonizes the NMDA receptor when administered at higher doses. Unlike ketamine, DCS does not carry a propensity for dependance or abuse is not neurotoxic, and has extensive history of long term use as an anti-infective agent. These factors suggest that DCS is potentially suitable for treatment of chronic pain.

Anecdotal reports suggest that high doses of DCS can cause psychotomimetic side effects, which is a potential barrier to development as monotherapy. However, preclinical and clinical work suggests that when DCS is administered with a serotonin (5HT) 2A receptor antagonist such as lurasidone, it reduces the risk of these adverse effects. In turn, DCS reduces lurasidone's propensity to cause akathisia. When DCS and lurasidone are considered as a combined treatment for chronic pain, additional synergies become apparent. 5HT receptor antagonism may block inflammation that underlies peripheral sensitization. Blocking NMDA receptors can stop the development of central sensitization in the dorsal horn of the spinal cord. Moreover, DCS may act at the thalamus, amygdala, and higher brain levels to alter the perception of pain. CS and lurasidone may also act synergistically to treat chronic-pain induced depression. We describe the rationale for the development of DCS and lurasidone as a treatment for chronic pain.

Chronic Pain

Drugs that modulate the N-methyl-d-aspartate (NMDA) may decrease perception of chronic pain, treat the depression often associated with chronic pain, and decrease craving for opioids. However, NMDA antagonist

drugs have not been introduced as a mainstream approach to treating chronic pain because of the potential for many drugs in this class to cause addiction, neurotoxicity, and hallucinations. Extensive laboratory evidence and early human data suggest that D-cycloserine, a mixed NMDA agonist/antagonist drug, has the potential to provide clinical benefit with no potential to cause addiction or neurotoxicity. Off label use of ketamine demonstrates proof of concept that NMDA antagonist use ameliorates chronic pain in patients.[1] Ketamine is toxic, addictive, and likely not suitable for long term use. Consequently, safe, oral, nonaddictive drugs that act at the NMDA receptor are needed.

Two in five adults suffer from chronic pain and represents the most common reason for seeking medical care.[2,3,4] Estimates from 2010 indicate that medical costs and lost productivity from chronic pain costs Americans between $560 and $635 billion each year.[5] Treatments include physical therapy/exercise, anti-convulsants, non-steroidal anti-inflammatory drugs (NSAIDs), analgesic antidepressants, targeted injections, neuromodulation, psychotherapy, and – all too often – opioids. None of these treatments is ideal. The safest treatments tend to be least effective, while the most potent analgesics, particularly opioids, lead to physical and psychological dependence, use disorders, and increasingly death. More than 100,000 Americans will die next year from opioids.[6]

From Acute Pain to Chronic Pain

Chronic pain is a consequence of both peripheral and central sensitization (Figure 1). Peripheral sensitization is often driven by inflammation around the site of tissue damage. Mast cells, basophils, platelets, macrophages, neutrophils, endothelial cells, keratinocytes, and fibroblasts release numerous proalgesic compounds including neurotransmitters, peptides, eicosanoids, prostaglandins, thromboxanes, leukotrienes, neurotrophins, cytokines, and chemokines.[7] Nociceptors sense these molecules through specific cell surface receptors.[7] The peripheral nerves become far more sensitive than in their native state, sending a steady stream of abnormal stimuli to the spinal cord.

Repeated, abnormal stimuli from peripheral nerves cause changes at the level of the spinal cord in a process called central sensitization. The theory of central sensitization was articulated by Woolf and King in 1989 when they demonstrated that neurons in the spinal cord become hyperexcitable after injury.[8] Central sensitization may produce hyperalgesia, a greater-than-usual pain sensation from a stimulus that usually provokes pain and/or allodynia, a sensation of pain from a stimulus that does not normally cause pain. Moreover, central sensitization can be maintained with *or without* ongoing input from the periphery. Neuroplastic changes cause a persistent, heightened state of neural reactivity.[9,10] Higher order neurons and circuits can certainly adapt and maladapt to chronic pain, e.g., catastrophizing, avoidance, anxiety, depression, analgesic self-administration, etc. Indeed, the insula, which participates in role in multisensory integration, is hyperactive in most individuals with central sensitization in the spinal cord.[10-12]

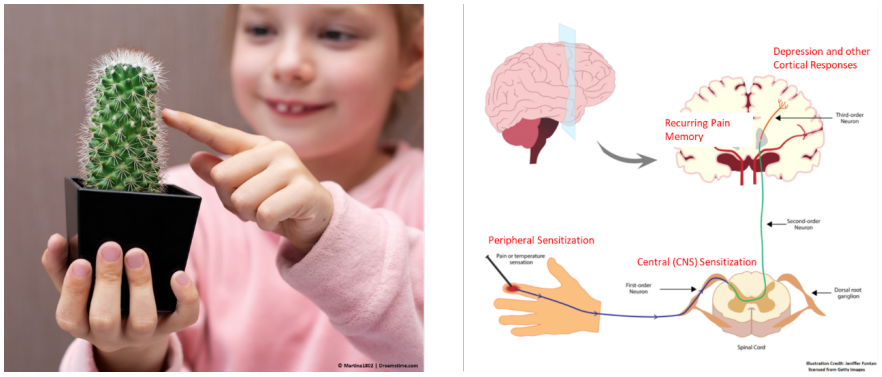

Figure : The nociceptive pain pathway. Sensitization in both the peripheral and central nervous system,

together with thalamic and cortical contributions to chronic pain are all regulated by NMDA receptor activation.

NMDA Receptors and Chronic Pain

NMDA Receptors Regulate Spinal Cord Hyperexcitability

NMDA receptors (NMDARs) are critical regulators of neuroplasticity and excitability in the spinal dorsal horn.[13] NMDARs are abundant in the dorsal horn, with GluN1 and GluN2A subunits expressed throughout the gray matter, whereas GluN2B subunits are distributed mainly in laminae I–II.[14] Repeatedly stimulating C fibers results in a phenomenon called "windup" in which depolarization of neurons in the dorsal horn increases in amplitude.[15] Both non-competitive (MK-801) and a competitive (D-CPP) NMDAR antagonists block windup.[16]Subcutaneous injection of formalin, a model of chronic pain, results in a biphasic pain response in animals. Neural activity generated during the first phase produces changes in CNS function that influence pain processing in the second phase.[17] The increased excitability in the spinal dorsal horn caused by formalin can be blocked by NMDAR antagonists.[18] Local injection of an adeno-associated virus into the dorsal horn of the spinal cord that results in >80% of NR1 NMDA receptor subunit expression and a corresponding loss of NMDA, but not AMPA currents, almost completely blocked pain hypersensitivity caused by formalin in mice.[19] Moreover, NR1 subunit knockdown using intrathecal viral injections blocks the induction of pain hypersensitivity caused by formalin injection, but does not affect pain thresholds in the absence of injury.[20] These results indicate that NMDA receptors are critical for central hypersensitivity.

Presynaptic NMDA receptors

Postsynaptic NMDA receptors are blocked by Mg^{2+} at rest, which is displaced with glutamate binding and neuronal depolarization. Presynaptic NMDA receptors are able to achieve tonic neurotransmitter release without neuronal depolarization.[21,22] Unlike classical postsynaptic NMDA receptor, magnesium ions do not inhibit spontaneous neurotransmitter release brought on by presynaptic terminals exposed to glutamate and in the absence of neuronal depolarization.[23,24] Consequently, presynaptic NMDARs become tonically active. In opioid-induced hyperalgesia and chronic neuropathic pain conditions, endogenous glutamate activates presynaptic NMDARs.[25] Spinal nerve ligation, a model of neuropathic pain, increased evoked EPSC amplitudes compared to sham and increased the probability of neurotransmitter release from presynaptic terminals.[26] Activation of presynaptic NMDA receptors increases the release of substance P, the frequency of miniature EPSCs, and pain hypersensitivity in chronic constriction injury and spinal nerve ligation models and a model of calcineurin inhibitor-induced pain syndrome[27-29] but does not affect glutamate release in in sham-treated animals. Thus, neuropathic injury changes the regulation of presynaptic NMDA receptors to enhance glutamate release and drive excitability in the spinal dorsal horn. This is consistent with formalin-induced pain discussed above—NMDA receptor antagonism blocks phase 2 of the pain reaction but does not affect phase 1. Furthermore, selective knockdown of primary afferent NMDA receptors does not affect phase 1 of the formalin model of pain, only phase 2.[30]Likewise, local injections of NMDA receptor antagonists, namely dextrorphan, ketamine and memantine, inhibits phase 2 but not phase 1 response to subcutaneous formalin.[31,32]

NMDA Receptor-mediated Excitotoxicity Leads to Chronic Neuropathic Pain

Afferent signals from injured nerves cause apoptosis in dorsal horn neurons via glutamate excito-toxicity.[33] Peripheral nerve injury leads to an irreversible loss of GABAergic interneurons, which in turn leads to persistent pain hypersensitivity. Targeted deletion of NMDA receptors using a spatially restricted Grin1 knockout or proapoptotic Bcl2-associated X (Bax) knockout prevents this loss of GABAergic inhibition.[34]

These findings indicate that NMDA receptor-mediated excitotoxicity leads to chronic neuropathic pain, and neuroprotection through genetic alteration of the NMDA receptor blocks the transition to chronic pain.

NMDA Receptors Affect Higher Pain Processing Centers in the Brain

Part of the survival benefit of pain is that it creates a persistent memory of the pain-inducing event. Painful stimuli can be used in mammalian fear conditioning to study learning and memory. The more painful the unconditioned stimulus, the fewer presentations of the stimulus are required to create an aversive association.[35] Likewise, extinguishing the conditioned stimulus is critical to overcome the fear associated with conditioned stimuli. Indeed, disorders such as PTSD, specific phobia, social anxiety disorder, and chronic pain have been conceptualized as disorders of impaired fear extinction.[36,37] The NMDA receptor is critical to the formation and extinction of fear memories.[38-42]

D-Cycloserine in Chronic Pain

: Preclinical Studies

Millecamps et al. showed that d-cycloserine (DCS), a partial agonist at the NMDA receptor and a component of NRX-101, dose-dependently reduced mechanical sensitivity in rats with spared nerve injury.[43] Infusions of DCS directly into the medial prefrontal cortex or amygdala (but not into other brain regions) induced antinociception in rats subjected to spared nerve injury. This antinociceptive effect was mimicked by a combination of NMDA and glycine and blocked by a selective antagonist of the glycine site of the NMDA receptor, HA-966. Moreover, spared nerve injury caused a down-regulation of NR2B subunit expression in the medial prefrontal cortex, which was reversed with repeated oral administration of DCS. In addition, repeated oral DCS administration also reduced cancer chemotherapy drug-induced neuropathic pain behavior.[43] Importantly, infusions of DCS into mPFC reversed place avoidance behavior induced by mechanical stimulation of the injured paw rats with spared nerve injury. DCS reduced pain-like symptoms by about 50%, but the rats behaved as if the remaining pain does not bother them, suggesting that DCS reduced the emotional impact of the neuropathic pain.[43,44]

In separate work, Walker et al. showed that DCS facilitates extinction of conditioned fear (fear-potentiated startle) after either systemic injections or intra-amygdala infusions.[45] This facilitation was blocked by HA-966. The criticality of NMDA receptors in the prelimbic cortex for the maintenance of neuropathic pain has been confirmed through the use of a selective NMDA receptor antagonist, LY235959.[46] These findings have been confirmed by intraperitoneal administration of DCS in the Wistar Kyoto (WKY) rodent model of conditioned fear (NRx Pharmaceuticals, data on file).

D-cycloserine potentially decreases opioid cravings

Opioid withdrawal involves both physical and psychological components, similar to other substance use disorders. Patients may be able to overcome physiological effects of withdrawal, only to relapse after being exposed to drug-taking triggers.[47]Naloxone-induced conditioned place aversion is an animal model of this form of opioid craving.[48] When the opioid antagonist, naloxone, is given to opioid-dependent rats, it triggers an immediate withdrawal syndrome. If rats are confined to a specific area on the test apparatus during acute withdrawal, they develop an aversion to that location. When allowed to move freely in the test apparatus, they will avoid the area that is now associated with withdrawal. Extinction is a means of reducing conditioned responses and involves exposure to the conditioned stimulus in the absence of the unconditioned stimulus with which it was paired previously. Using this model, Myers and Carlezon showed that opioid-dependent animals were slow to extinguish their memory of the conditioned stimulus; however, administration of DCS accelerated this extinction. The authors conclude that DCS facilitates extinction of morphine withdrawal-associated place aversion.[49]

Clinical Experience with DCS and Chronic Pain

Schnitzer et al. performed randomized, double-blind, placebo-controlled pilot study of the efficacy and safety of D-cycloserine in 41 people with chronic back pain.[44] Patients in the active arm received daily oral doses of D-cycloserine. Participants sequentially received 100 mg, 200 mg, and 400 mg for two weeks. Various pain scales were assessed before and after the six-week study. The primary endpoint (Numeric Rating Scale) improved by 1.05±3.1 units in the DCS group than in placebo. The results failed to reach statistical significance (p=0.14) overall, though the effect size was 0.4. However, at the highest administered dose of DCS (400mg/day), a statistically-significant (P=0.02) reduction in pain was seen compared to placebo (Figure 2). This threshold dosage corresponds to the 25μg/ml blood level identified by Javitt as the threshold at which DCS saturates the glycine modulatory sites on the NMDA receptor and begins functioning as an NMDA antagonist. Based on these results, the Schnitzer group has embarked on a larger clinical trial using the 400 mg dose of DCS in over 200 patients with chronic pain (NCT03535688).

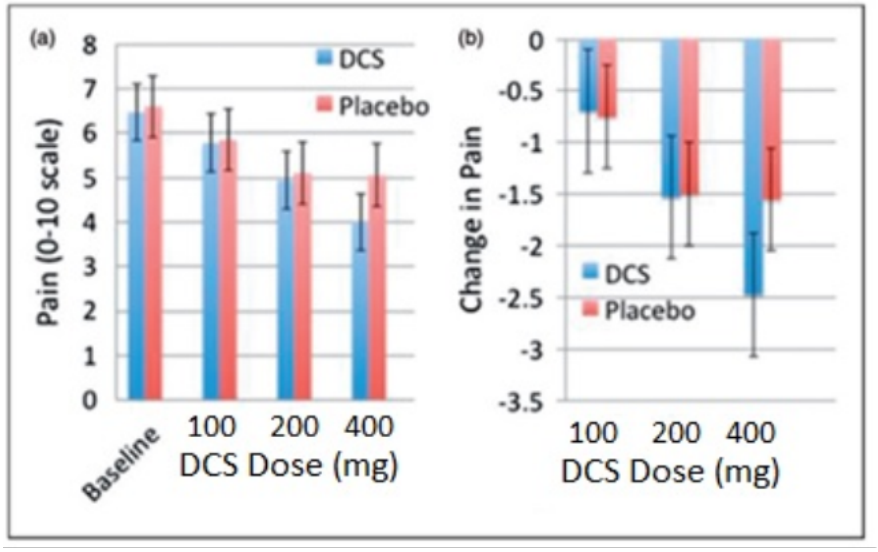

Figure 2: Back pain intensity ratings over a six-week, dose escalating, placebo or DCS treatment. (a) Across subject average back pain, assessed on the primary outcome measure of 0–10 numeric rating scale. (b) Within subject change in pain, relative to baseline, using the 0–10 numeric rating scale. Adapted from Schnitzer [44]. Note that the trial did not meet its primary endpoint because separation from placebo was not seen at all dosages/timepoints.

Can DCS be Clinically Useful in Chronic Pain?

DCS has been used as an antituberculosis agent for at least sixty years. In 2018, the World Health Organization (WHO) recommended DCS as one of the Group B drugs for tuberculosis (TB). In multidrug-resistant TB, the WHO recommends DCS as one of group of antituberculosis drugs to be used in the first-line longer term, treatment regimen.[50]While DCS has a multi-decade history of safe use in patients, chronic use of higher doses can be associated with neuropsychiatric symptoms[51] of which, hallucination and mania are by far the most concerning.[52,53] Since DCS would presumably need to be administered sub-acutely or chronically to effectively treat chronic pain, this toxicity could potentially be treatment-limiting.

One approach to minimize neuropsychiatric symptoms is to combine DCS with serotonergic drugs, including SSRI and 5-HT_{2A}antagonist antidepressants. Both classes of drugs are routinely used on a long-term basis

in the treatment of depression and 5-HT_{2A} antagonists at higher doses are used as atypical antipsychotics. Lurasidone has one of the most favorable side-effect profiles among 5-HT_{2A} antagonist drugs, lacking anticholinergic or metabolic side effects that are otherwise common in the drug class.[54] However, it must be acknowledged that lurasidone is associated with potential for akathisia.[55] Interestingly, DCS and lurasidone appear to mitigate the most common side effects of the other; lurasidone reduces the risk of psychosis and mania while DCS reduces the occurrence of akathisia.[56] Thus, when lurasidone and DCS are administered together, the risk of the treatment-limiting toxicities is diminished.

Lurasidone in Chronic Pain

Aside from its role in modulating the hallucinations that may be induced by DCS and other NMDA antagonists, lurasidone may be useful as a treatment for chronic pain in its own right. Lurasidone is a full antagonist at dopamine D2 and serotonin 5-HT_{2A} and 5-HT_7 receptors.[57] Compared to other antipsychotics, lurasidone has the highest binding affinity for 5-HT_7 receptors.[54] Peripheral serotonin (5-HT) mediates and potentiates pain[58,59]whether through direct tissue injection[60,61] or through the use of pain models that raise serotonin levels.[62,63] Using peripheral 5-HT as a model of pain, Abbott et al. showed 5-HT_{2A} antagonists may be effective as peripherally acting analgesic agents and/or analgesic adjuncts.[64] Using chronic constriction injury of the sciatic nerve in rats, Nitada et al. demonstrated that the 5-HT_{2A} receptor antagonist sarpogrelate, specifically ameliorated hyperalgesia without affecting the normal nociception.[65] 5-HT_{2A} receptors are involved in the sensitization of peripheral nociceptors and spinal nociceptive processing in chemotherapeutic-induced neuropathy, an effect that is blocked by the 5-HT_{2A} receptor antagonist, MDL 11,939.[66]

The role of 5-HT_7 receptors in acute and chronic pain processing is complex.[67] Evidence suggests 5-HT_7 receptors play a pronociceptive role in chronic pain models and that blocking 5-HT_7 receptors may be therapeutic in chronic pain. For example, tactile allodynia induced by L5/L6 spinal nerve ligation could be dose-dependently blocked by the selective 5-HT_7 receptor antagonist, SB-269970.[68] Peripheral activation of 5-HT_7 receptors increases c-Fos levels in rat dorsal horn of spinal cord of rats, a process that is blocked by pre-administration of a selective 5-HT_7 antagonist.[69] The selective 5-HT_7 antagonist SB 269970 reduces nociceptive behavior induced by formalin[70] and inhibits mechanical allodynia induced by 5-HT.[71] Likewise, 5-HT_{2A} antagonists spiperone, ketanserin and ritanserin effectively blocked the pain response produced by α-methyl-5-HT and prostaglandin E2, suggesting that 5-HT2A antagonists may be effective as analgesics or analgesic adjuncts.[64]

Growing evidence shows that antipsychotics play a role in chronic pain management. Reports since the 1970s indicate haloperidol can relieve chronic lower back pain[72] or refractory chronic facial pain.[73] In a review of the published clinical literature, Jimenez et al. reported that various atypical antipsychotics are effective in treating various forms of chronic pain.[74]

Additional Synergies of DCS and Lurasidone: Chronic Pain and Depression

Chronic pain and depression are frequently comorbid. Studies in psychiatry[75] and neurology[76] clinics show that the prevalence of pain in depressed patients is 60 to 75%. The mean prevalence for major depression in patients is 52% in pain clinics, 56% in orthopedic clinics, and 85% in dental/facial pain clinics.[77] In a review of over 30,000 adults across four continents, patients who have experienced pain for greater than 6 months are more than 4 times as likely to have a depressive disorder than those without chronic pain.[78] When pain is moderate or severe or refractory to treatment it is more strongly associated with depression and poorer depression outcomes.[77,79] Conversely, the treatment of depression can improve chronic pain outcomes,[80,81] an effect that further highlights the close relationship between the two clinical entities.

Not only do pain and depression often co-occur, each tends to exacerbate the other, both subjectively and objectively. Severe depression intensifies the perception of pain[82] and makes traditional treatments less effective.[83] On the other hand, chronic pain influences the severity and treatment of depression.[84] It is often more difficult to treat depression in someone with chronic pain than someone who is without pain.[85]

Depression is an independent risk factor for poor quality of life in people with chronic musculoskeletal pain.[86] Importantly, the risk of suicide is very high in patients with both chronic pain and depression.[87]

Chronic pain and depression are so strongly linked that it is unclear which process begets the other.[79,84,88] Indeed, the two conditions share common neurobiological pathways.[77] Higher pain processing centers include the anterior cingulate cortex, prefrontal cortex, insular cortex, amygdala, thalamus, cerebellum, and periaqueductal gray. The emotional aspects of pain are served by these areas along with the ventral tegmental area and nucleus accumbens.[89] The amygdala is critical for the processing of stress, depression, and persistent pain.[90,91]

Given the strong neurobiological and clinical link between depression and chronic pain, several groups have argued that the treatment of depression should be considered part of a comprehensive strategy for the treatment of chronic pain.[81,88,92] In light of this, the combination of DCS and lurasidone may not only treat chronic pain at various levels of the peripheral and central nervous systems, but the combination may also reduce symptoms of depression that worsen the course and complicate the treatment of chronic pain. Consider that lurasidone is FDA-approved for the treatment of bipolar depression[55] and has been shown to be effective in treating major depressive disorder with mixed features.[93] Moreover, the antidepressant effects of high-dose DCS were first noted in the late 1950s, which has been confirmed in several small-scale clinical studies.[94-96] Thus, a combination of lurasidone and DCS could be useful as a treatment for chronic pain alone, or in the many patients who have chronic pain comorbid with depression.

Conclusion

NMDA antagonists in general and D-cycloserine (DCS) in specific have demonstrated extensive promise in the laboratory for the treatment of chronic pain and early promise in a clinical trial. Similarly, 5-HT_{2A} antagonists show promise in the treatment of chronic pain. However, the well-known psychotogenic side effects of NMDA drugs and the potential for akathisia associated with chronic 5-HT2A antagonist drugs have limited their respective use in patients with chronic pain. The combined administration of DCS and lurasidone has been demonstrated in psychiatry-focused clinical trials to be nontoxic and the psychotogenic side effects of DCS appear to be blocked by lurasidone. The extensive body of nonclinical evidence combined with early clinical evidence supports the advancement of this drug combination to broader clinical study.

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