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Commentary

## Peripheral NMDA receptors revisited – Hope floats

Neuropathic pain patients, especially those with complex regional pain syndrome (CRPS), remain in the category of “poorly treated” in the clinic. Many currently used therapies for these patients have a low success rate, inconsistent results and/or are based on anecdotal evidence. Therefore, the search for novel treatments and therapies is on-going. In a paper published in this volume by Finch et al. [6] the group revisits the use of ketamine, an N-methyl-D-aspartate (NMDA) antagonist for the treatment of CRPS. The use of topical 10% ketamine cream and a double-blind, placebo-controlled crossover trial sets this study apart from those that came before (see [6] for references). Patients were tested on the symptomatic and contralateral, healthy limb for sensitivity to light touch, light brushing, pressure, as well as punctate and thermal stimulation. Testing was done before and 30 min after application of ketamine cream or placebo, on either the symptomatic or healthy limb. Application of the cream reduced the allodynia to light brushing and hyperalgesia to punctate stimulation. Because ketamine levels in venous blood were below detectable limits, a systemic effect of ketamine was ruled out. The targets – peripheral NMDA receptors – were discovered/described in the 1980s but the location and function of these receptors in pain transmission have not been exploited to any great extent. Given the decades of data confirming a role for NMDA receptors in pain, why have we not capitalized on these peripheral receptors? Are there too few NMDA receptors to make an impact? Are they expressed by the wrong fiber types? Is peripheral glutamate even involved in the mediation of neuropathic pain or have we just overlooked these receptors and missed the boat?

### 1. Widespread expression of NMDA receptors in sensory neurons

A variety of techniques have confirmed NMDA receptor expression in the cell bodies, as well as peripheral and central processes of primary sensory neurons in rodents [3,11,14] and humans [8,16]. In lumbar dorsal root ganglia (DRG), virtually all cells express the NR1 subunit [14]. In the periphery, analysis of the plantar (mixed motor and sensory) and sural (purely sensory) nerves show approximately 50% of the myelinated and 20–30% of the unmyelinated axons label for NR1 [4]. In the same study, measurements of axonal diameters of myelinated fibers indicate that all sizes including A $\delta$  and A $\beta$  are labeled, along with unmyelinated C fibers. Thus, there is no shortage of NMDA receptors expressed by primary sensory neurons.

### 2. Nociceptors express NMDA receptors

Expression of NMDA receptors by nociceptive C and A $\delta$  fibers is confirmed by single fiber recordings from plantar nerves [5].

Behavioral studies demonstrate that local injection of NMDA agonists produce pain behaviors while NMDA antagonists block the pain [17]. Local administration of NMDA antagonists block mechanical sensitivity due to inflammation [5] or nerve injury [7]. Finally, there is co-localization of the NR2B subunit with markers of small diameter and/or nociceptive DRG cells (i.e. wheat germ agglutinin horse radish peroxidase [WGA-HRP], isolectin B4 [IB4], calcitonin gene-related peptide [CGRP]) [12]. Thus, it is clear that NMDA receptors are expressed by a population of nociceptors. Since many NMDA receptors are autoreceptors, they could control the release of glutamate from primary afferents, as well as modulate the release of CGRP and substance P. There is evidence for this NMDA-induced modulation at central terminals of primary afferents [9,10] and there is no reason to doubt it can occur in peripheral terminals as well.

### 3. Peripheral glutamate is important in the mediation of neuropathic pain

If glutamate release is critical to the development of neuropathic pain in a nerve-injured region, then it would follow that glutamate receptor activation plays a prominent role in the pain that develops. The data indicate that the peripheral release of glutamate and subsequent activation of NMDA receptors, (but not AMPA or kainate receptors), contributes to the mechanical hyperalgesia following nerve injury [7]. Furthermore, the data indicate that local injection of NMDA antagonists will alter the induction and the maintenance of neuropathic pain [7]. Thus, it has been hypothesized that an increased level of peripheral glutamate (through injury discharge and/or ectopic discharge of primary afferents), is critical to the induction of neuropathic pain. This being the case, peripheral administration of glutamate antagonists should alter neuropathic pain symptoms.

### 4. Are peripheral NMDA receptors an attractive target?

The main ingredients are present in the periphery that would predict successful analgesia following treatment with NMDA antagonists: an abundance of NMDA receptors, location of the receptors on nociceptors, a confirmed role for glutamate in peripheral pain. One might postulate that the key to success when using NMDA antagonists lies in activating enough peripheral NMDA receptors to block pain transmission, but keeping the systemic concentration low enough to avoid unwanted CNS side effects (which include memory impairment, psychotomimetic effects, ataxia, motor incoordination). Surprisingly in rat, intradermal MK-801 (an NMDA antagonist) did not have good effect in reducing hyperalgesia in four different models of neuropathic pain which included models of nerve trauma- and metabolic-induced

neuropathic pain [1]. These data would indicate that NMDA receptors are not crucial to the development/maintenance of peripheral sensitization in these situations. However, the human studies by Finch et al. [6] and Sigtermans et al. [15], provide rays of hope. As described above, 10% ketamine applied locally had good effect, relieving some of the sensory abnormalities of CRPS [6]. Sigtermans et al. [15] also reported decreased pain scores in CRPS using prolonged infusion (4.2 days) of low dose ketamine. Small fiber changes in the periphery have been described in CRPS [13] and as Borsook reviews [2], there are a number of plastic changes throughout the CNS in chronic pain patients. Thus, combining the two approaches, topical + low dose infusion, may lead to superior pain relief because both peripheral and central NMDA receptors are affected. Alternatively, targeting NR2B expressing cells with selective NMDA antagonists may provide analgesia with reduced side-effects and improved efficacy. There is overwhelming anatomical and physiological data to support the use of peripheral NMDA antagonists in treatment of neuropathic pain as well as other pain states. It is too soon to abandon this "ship".

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