



Topical review

# Translational pain research: bridging the gap between basic and clinical research

Jianren Mao\*

*Department of Anesthesia and Critical Care, MGH Pain Center, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114, USA*

Accepted 9 April 2002

## 1. Introduction

Basic research on pain and pain modulation is unique among many branches of biomedical research in that objective measures such as nociceptive responses to thermal or mechanical stimulation in experimental animals are used to investigate only the sensory discriminative aspect of the subjective pain sensation. While this approach is indispensable in preclinical pain research for obvious reasons, information generated from such research is inevitably limited for addressing multi-facet aspects of clinical pain. This inherent gap between basic pain research and clinical pain could be further widened if the clinical application of bench information deviates from the scope and limitation of preclinical pain research. Likewise, basic pain research is unlikely to be informative if experimental pain (nociception) fails to represent features of clinical pain.

Over the last decade, the role of the central glutamatergic system in general, and the *N*-methyl-D-aspartate (NMDA) receptor in particular, in neural mechanisms of persistent pain has been extensively investigated in experimental animals. Accordingly, a considerable number of clinical studies have been carried out to evaluate the potential application of this mechanism in clinical pain management. However, significant discrepancies exist between basic and clinical research with regard to the therapeutic role of NMDA receptor antagonists in managing persistent pain states. Taking the NMDA receptor mechanism as an example, this article will discuss several issues concerning translational pain research and the urgent need for bridging the gap between basic and clinical pain research.

## 2. Preclinical research on the NMDA receptor mechanism

A large body of convincing evidence has emerged from basic research indicating a critical role of NMDA receptors in both development and maintenance of persistent pain states including neuropathic and inflammatory pain (Dickenson, 1990; Woolf and Thompson, 1991; Dubner, 1991; Mao et al., 1995; Chaplan et al., 1997; Woolf and Mannion, 1999). Several fundamental features of these studies may be summarized. First, nerve injury induced by either partial or complete nerve ligation or persistent inflammation induced by inflammatory agents was often used as experimental pain models. Second, both experimental (AP-5, MK-801) and clinically available (ketamine, amantadine, dextrophan – an active metabolite of dextromethorphan) NMDA receptor antagonists were effective in preventing and reversing an experimental persistent pain state. Third, except for a few studies in which changes in spontaneous pain behaviors were observed, thermal hyperalgesia and mechanical allodynia were largely used as the behavioral endpoints to assess the effectiveness of the NMDA receptor blockade in experimental persistent pain states.

In general, preclinical evidence regarding the role of NMDA receptors in prolonged nociception is reproducible and reliable. Such preclinical evidence suggests that blockade of NMDA receptors using clinically available agents would prevent the development of a persistent pain state in a clinical setting. Because NMDA receptor antagonists also effectively reverse signs of persistent pain in experimental animals, NMDA receptor antagonists would be expected to have a therapeutic role in treating clinical persistent pain resulting from a neuropathic or inflammatory pain condition.

## 3. Clinical research on the NMDA receptor mechanism

A considerable number of clinical studies (both

\* Tel.: +1-617-726-2338; fax: +1-617-724-2719.

E-mail address: jmao@partners.org (J. Mao).

controlled randomized studies and case observations) have been conducted to test the above hypotheses (Sindrup and Jensen, 1999; also see Table 1). Three clinically available agents (ketamine, dextromethorphan, amantadine) with the NMDA receptor antagonist property were commonly used in these studies. Unlike unequivocal results from the basic research, however, clinical outcomes of pain relief using NMDA receptor antagonists vary substantially among different studies. As shown in a small sample in Table 1, these studies may be generally divided into two categories, i.e. negative and positive outcome studies.

A closer look at these clinical studies reveals several critical differences between these two categories. First, post-operative pain such as that following abdominal or knee surgery was generally used as the clinical pain condition in the negative outcome studies, whereas neuropathic pain (e.g. complex regional pain syndrome or postherpetic neuralgia) was primarily examined in the positive outcome studies. Second, a single dose of an NMDA receptor antagonist given preoperatively or intraoperatively was often used in the negative outcome studies. In contrast, either multiple doses or continuous intravenous/subcutaneous infusion over hours, days or weeks were employed for the medication delivery in the positive outcome studies. Third, except for few studies in which hyperalgesia was specifically examined, in both categories the visual analog scale was used to report changes in pain intensity after the treatment. The potential influence of these differences on the clinical outcome is discussed below in relation to the issues of translational pain research.

#### 4. Issues from bench to bedside

As mentioned above, the role of the NMDA receptor mechanism in persistent pain states is overwhelmingly supported by the data from a huge number of preclinical studies. Yet, outcomes from clinical studies are sharply

divided in supporting the use of NMDA receptor antagonists for pain management. One clear limitation in assessing the role of the NMDA receptor mechanism in clinical pain management is the lack of highly selective NMDA receptor antagonists that are suitable for the clinical use. However, clinical outcomes do indeed vary in different pain conditions when the same clinically available NMDA receptor antagonist (such as ketamine or dextromethorphan) was used (see Table 1). The following issues may have contributed to the discrepancies between basic and clinical research with regard to the NMDA receptor mechanism.

A basic tenet of the NMDA receptor mechanism supported by the basic research is that NMDA receptors are implicated in central sensitization that may occur following tissue damage such as that after nerve injury or persistent inflammation (Dubner, 1991; Mao et al., 1995; Woolf and Mannion, 1999). Central sensitization may increase the gain of pain intensity via both cellular and molecular mechanisms (Woolf and Mannion, 1999). What is not supported by the NMDA receptor mechanism is normal (physiological) pain response such as that following transient noxious stimulation and tissue damage (Mao, 1999). In general, blockade of NMDA receptors does not change baseline nociceptive response to either heat or mechanical stimulation or baseline spontaneous pain behaviors in experimental animals. Thus, NMDA receptor antagonists are most likely to reduce the gain of pain intensity but not to remove a normal pain response. That is, an NMDA receptor antagonist per se is unlikely to act as an analgesic. Conceivably, a mismatch in pain conditions can be a fundamental cause of discrepancies between basic and clinical research.

##### 4.1. Is there a mismatch in treatment regimens between basic and clinical research?

Another basic tenet of the NMDA receptor mechanism supported by basic research is that activation of central NMDA receptors is initiated and modulated by peripheral

Table 1  
A sample of clinical studies<sup>a</sup>

| Pain type         | Drug | Dose regimen          | Outcome  | Ref.                            |
|-------------------|------|-----------------------|----------|---------------------------------|
| Hysterectomy      | Ama  | 200 mg, i.v., pre-op  | Negative | Gottschalk et al., 2001         |
| Hysterectomy      | Dex  | 150 mg, p.o., pre-op  | Negative | Ilkjaer et al., 2000            |
| Knee surgery      | Dex  | 40 mg, i.m., pre-op   | Negative | Yeh et al., 2000                |
| Knee surgery      | Dex  | 200 mg, p.o., pre-op  | Negative | Wadhwa et al., 2001             |
| Abdominal surgery | Dex  | 120 mg, i.m., pre-op  | Negative | Helmy and Bali, 2001            |
| Hysterectomy      | Dex  | 27 mg, p.o., peri-op  | Negative | McConaghy et al., 1998          |
| CNP               | Ket  | > 100 mg/day, p.o.    | Positive | Enarson et al., 1999            |
| PHN               | Dex  | 125 mg/day, p.o.      | Positive | Klepstad and Borchgrevink, 1997 |
| Hyperalgesia      | Ket  | 2 µg/kg/min × 72 h    | Positive | Stubhaug et al., 1997           |
| PHN               | Ket  | 0.15 mg/kg/h × 7 days | Positive | Eide et al., 1995               |
| NCP               | Ket  | 400 mg/day, s.c.      | Positive | Mercadante et al., 1995         |
| NCP               | Ama  | 200 mg/3 h, i.v.      | Positive | Pud et al., 1998                |

<sup>a</sup> Note that only a small sample of clinical studies on the NMDA receptor mechanism is included to demonstrate the differences in pain type and dose regimens between two categories of clinical outcomes. CNP, chronic neuropathic pain; PHN, postherpetic neuralgia; NCP, neuropathic cancer pain; Ama, amantadine; Dex, dextromethorphan; Ket, ketamine; Pre-op, pre-operative; Peri-op, peri-operative; VAS, visual analog scale.

nociceptive input (Thompson and Woolf, 1991; Gracely et al., 1992). As such, blocking peripheral nociceptive input and/or central NMDA receptors before tissue damage should then inhibit the NMDA receptor activation, hence the concept of preemptive analgesia. Indeed, a single treatment with an NMDA receptor antagonist often blocks elements of central sensitization when a stimulus is transient under certain experimental conditions (Dickenson and Sullivan, 1987; Woolf and Thompson, 1991). In contrast, repeated doses of an NMDA receptor antagonist are required to prevent the development of a persistent pain state in animal models of nerve injury or inflammation in which a constant barrage of peripheral nociceptive input is expected (Mao et al., 1992a; Ren et al., 1992).

Given that a single dose and multiple doses were respectively used in the negative and positive outcome clinical studies (Table 1), it is not difficult to realize why outcomes from those single dose studies are often unfavorable. When a single dose of an NMDA receptor antagonist is given in these clinical studies, at best the effects would last for a few hours according to the pharmacokinetics of individual agents assuming that the dose is adequate for blocking the NMDA receptor. However, peripheral nociceptive input continues during the perioperative period, which could constantly drive the process of central sensitization (Gracely et al., 1992), in part via the activation of NMDA receptors. Thus, preemptive analgesia should not be considered as a time point but a dynamic process. It could only become effective to block the NMDA receptor mechanism, as suggested by the basic research, if clinical treatment regimens correlate temporally with the underlying NMDA receptor mechanism. Conceivably, the combination of a local anesthetic (peripheral blockade) and a central NMDA receptor antagonist for a sufficient duration of action would be most effective as suggested by the basic research (Mao et al., 1992b).

#### *4.2. Is there a mismatch in pain evaluation tools between basic and clinical research?*

The commonly used behavioral endpoint in basic research is a withdrawal response to a thermal or mechanical stimulus, whereas a prevalent method of pain assessment in clinical research is a self-reporting system using the visual analog (or numerical) pain scale. This mismatch may have enormous impact on discrepancies between basic and clinical research for several reasons. First, even if the pain condition and dosing regimen were compatible between preclinical and clinical studies, different pain assessment tools would address different aspects of the same pain condition. The tools used in basic research are primarily for the assessment of stimulus-induced pain, whereas the pain assessment tools commonly used in clinical research focus on the overall pain evaluation that is readily influenced by many factors including psychosocial issues and the physician–patient relationship. Second, data from the

basic research suggest that the NMDA receptor mechanism may be more sensitive to thermal hyperalgesia than mechanical allodynia (Tal and Bennett, 1994). As such, lacking the pain assessment tools that could differentiate different elements of a pain state would considerably hamper the ability to evaluate a distinct treatment outcome in the clinical setting. Third, NMDA receptor antagonists are considered as antihyperalgesic (bringing nociceptive threshold back to baseline) but not antinociceptive (raising the threshold above baseline) in the basic research. This distinction is almost impossible in those clinical studies using the visual analog scale.

In many cases, a negative clinical outcome study does not necessarily indicate that information from basic research is not applicable to clinical pain conditions. Knowing the limitation and scope of basic research provides a practical guidance for carrying out truly meaningful clinical studies. Although the issues discussed above have focused on the NMDA receptor mechanism, these issues would be vital to other examples of translational pain research.

### **5. Issues from bedside to bench**

A thoughtful design of clinical studies clearly is key to an authentic translation of bench information into clinical application. However, the premise is that basic research would truly address clinical pain issues. Thus, translational pain research is not synonymous with ‘from bench to bedside’. Translational pain research should be considered as a two-way approach, one being from bedside to bench and the other from bench to bedside. Just as critical as designing meaningful clinical studies, translating clinical pain into testable laboratory pain models certainly is the very first step that might lead to the development of new therapeutic tools. Meaningful translation from bench to bedside could not take place without assuring the authenticity of the first translation from bedside to bench. While some aspects of clinical pain are difficult to be reproduced in experimental animals, other issues may be addressed in future basic research. The following are examples of such issues.

#### *5.1. Spontaneous versus stimulus-induced pain*

A vast majority of persistent pain conditions may be considered as spontaneous pain in the clinical setting, because such pain experience is often described as constant and is present without overt peripheral stimulation. Simply avoiding certain stimuli (thermal or mechanical) often is insufficient to stop the pain. For instance, a persistent pain condition almost never results from heat stimulation in the clinical setting. Yet, stimulus-induced nociception such as thermal hyperalgesia is the most predominant test method used in basic research to assess a persistent pain state. To date, no reliable pain measurement methods with reasonable predictive values have been developed in basic research to

assess pain behaviors, including spontaneous pain behaviors, which would better resemble pain conditions observed in pain patients. In many cases, thermal hyperalgesia itself, which is hardly an issue in the clinical setting, becomes the target of extensive investigation in basic research besides being used as a behavioral test endpoint. While such investigations may add depth into the neurobiology of the sensory system, unfiltered translation of such information into clinical application has often proven to be less fruitful.

### 5.2. Early versus persistent pain state

Clinically, acute pain such as uncomplicated postoperative pain is rather manageable with a predictable time course. It is the persistent pain such as neuropathic pain that is most dreadful and challenging. A pressing issue is to understand why and how tissue injury can lead to a persistent pain state even after the initial injury is resolved. Here, mechanisms of central sensitization may be used as an example. To date, much of the preclinical pain research on central sensitization has been focusing on the cellular and molecular changes during the early stage after nerve injury or inflammation. Although such changes may reflect the cellular adaptation mechanisms, hence neural plasticity, they are largely driven by a constant peripheral nociceptive input from a live nerve injury or inflammatory condition in animal models. The vast majority of preclinical research stop short at this stage assuming that what has happened during this early stage would reflect the cellular basis of a persistent pain state. As such, it has been suggested that targeting those changes seen in this early stage would provide a therapeutic tool for a clinical persistent pain state. However, these early responses extensively investigated in basic research may not necessarily represent persistent pain seen in clinical pain patients at weeks, months or years after an initial injury. Conceivably, some of these early cellular and molecular changes may just accompany an ongoing injury. In fact, under many circumstances such early cellular and molecular changes subside before pain signs do even in experimental animals. The implication is that the strategy of blocking such early cellular and molecular changes for the prevention of a persistent pain state would only work if those early changes truly lead to a persistent pain state following recovery from an initial injury. Similarly, an established persistent pain state might be treated in the clinical setting only if the therapeutic targets are those factors that indeed play a role in sustaining a persistent pain state in the absence of the initial tissue injury.

## 6. Future directions of translational pain research

Preclinical pain research is facing an enormous challenge, because what is being studied in experimental animals may only reflect a part, sometimes a very small part, of clinical pain (Fields, 1999; Price, 2000). In several ways, translational pain research could make important contributions to

basic pain research and its clinical application. First, translational pain research may examine the effectiveness and relevance of both basic and clinical research by using the method of evidence-based data analysis. Second, translational pain research could play a critical role in integrating information from both basic and clinical research and coordinate research efforts between these two ends of pain research. Third, although not all basic research should be expected to lead to direct clinical applications and indeed basic research is a process of data accumulation, translational pain research may help maximize the utilization of our limited research resources and shorten the cycle between bench findings and clinical applications.

## Acknowledgements

A portion of this work was supported by NIH RO1 DA08835.

## References

- Chaplan SR, Malmberg AB, Yaksh TL. Efficacy of spinal NMDA receptor antagonism in formalin hyperalgesia and nerve injury evoked allodynia in the rat. *J Pharmacol Exp Ther* 1997;280:829–838.
- Dickenson AH. A cure for windup: NMDA receptor antagonists as potential analgesics. *Trends Pharmacol Sci* 1990;11:307–309.
- Dickenson AH, Sullivan AF. Evidence for a role of the NMDA receptor in the frequency dependent potentiation of deep rat dorsal horn nociceptive neurons following C fiber stimulation. *Neuropharmacology* 1987;26:1235–1238.
- Dubner R. Neuronal plasticity and pain following peripheral tissue inflammation or nerve injury. In: Bond M, Charlton E, Woolf CJ, editors. *Proceedings of Vth world congress on pain, Pain research and clinical management*, vol. 5. Amsterdam: Elsevier, 1991. pp. 263–276.
- Eide PK, Stubhaug A, Stenehjem AE. Central dysesthesia pain after traumatic spinal cord injury is dependent on *N*-methyl-D-aspartate receptor activation. *Neurosurgery* 1995;37:1080–1087.
- Enarson MC, Hays H, Woodroffe MA. Clinical experience with oral ketamine. *J Pain Symptom Manage* 1999;17:384–386.
- Fields HL. Pain: an unpleasant topic. *Pain Suppl* 1999;6:S61–S69.
- Gottschalk A, Schroeder F, Ufer M, Oncu A, Buerkle H, Standl T. Amanatadine, a *N*-methyl-D-aspartate receptor antagonist, does not enhance postoperative analgesia in women undergoing abdominal hysterectomy. *Anesth Analg* 2001;93:192–196.
- Gracely RH, Lynch SA, Bennett GJ. Painful neuropathy: altered central processing maintained dynamically by peripheral input. *Pain* 1992;51:175–194.
- Helmy SA, Bali A. The effect of the preemptive use of the NMDA receptor antagonist dextromethorphan on postoperative analgesic requirements. *Anesth Analg* 2001;92:739–744.
- Ilkjaer S, Bach LF, Nielsen PA, Wernberg M, Dahl JB. Effect of preoperative oral dextromethorphan on immediate and late postoperative pain and hyperalgesia after total abdominal hysterectomy. *Pain* 2000;86:19–24.
- Klepstad P, Borchgrevink PC. Four years' treatment with ketamine and a trial of dextromethorphan in a patient with severe postherpetic neuralgia. *Acta Anaesthesiol Scand* 1997;41:422–426.
- Mao J. NMDA and opioid receptors: their interactions in antinociception, tolerance and neuroplasticity. *Brain Res Rev* 1999;30:289–304.
- Mao J, Mayer DJ, Hayes RL, Lu J, Price DD. Differential roles of NMDA and non-NMDA receptor activation in induction and maintenance of

- thermal hyperalgesia in rats with painful peripheral mononeuropathy. *Brain Res* 1992a;598:271–278.
- Mao J, Price DD, Mayer DJ, Lu J, Hayes RL. Intrathecal MK-801 and local nerve anesthesia synergistically reduce nociceptive behaviors in rats with experimental peripheral mononeuropathy. *Brain Res* 1992b;576:254–262.
- Mao J, Price DD, Mayer DJ. Mechanisms of hyperalgesia and opiate tolerance: a current view of their possible interactions. *Pain* 1995;62:259–274.
- McConaghy PM, McSorley P, McCaughey W, Campbell WI. Dextromethorphan and pain after total abdominal hysterectomy. *Br J Anaesth* 1998;81:731–736.
- Mercadante S, Lodi F, Sapio M, Calligara M, Serretta R. Long-term ketamine subcutaneous continuous infusion in neuropathic cancer pain. *J Pain Symptom Manage* 1995;10:564–568.
- Price DD. Psychological and neural mechanisms of the affective dimension of pain. *Science* 2000;288:1769–1772.
- Pud D, Eisenberg E, Spitzer A, Adler R, Fried G, Yarnitsky D. The NMDA receptor antagonist amantadine reduces surgical neuropathic pain in cancer patients: a double blind, randomized, placebo controlled trial. *Pain* 1998;75:349–354.
- Ren K, Williams GM, Hylden JL, Ruda MA, Dubner R. The intrathecal administration of excitatory amino acid receptor antagonists selectively attenuated carrageenan induced behavioral hyperalgesia in rats. *Eur J Pharmacol* 1992;219:235–243.
- Sindrup SH, Jensen TS. Efficacy of pharmacological treatment of neuropathic pain: an update and effect related to mechanism of drug action. *Pain* 1999;83:389–400.
- Stubhaug A, Breivik H, Eide PK, Kreunen M, Foss A. Mapping of punctuate hyperalgesia around a surgical incision demonstrates that ketamine is a powerful suppressor of central sensitization to pain following surgery. *Acta Anaesthesiol Scand* 1997;41:1124–1132.
- Tal M, Bennett GJ. Neuropathic pain sensations are differentially sensitive to dextrophan. *Neuroreport* 1994;5:1438–1440.
- Thompson SWN, Woolf CJ. Primary afferent-evoked prolonged potentials in the spinal cord and their central summation: role of the NMDA receptor. In: Bond MR, Carlton JE, Woolf CJ, editors. *Proceedings of the Vth world congress on pain, Pain research and clinical management*, vol. 5. Amsterdam: Elsevier, 1991. pp. 291–298.
- Wadhwa A, Clarke D, Goodchild CS, Young D. Large-dose oral dextromethorphan as an adjunct to patient-controlled analgesia with morphine after knee surgery. *Anesth Analg* 2001;92:448–454.
- Woolf CJ, Mannion RJ. Neuropathic pain: aetiology, symptoms, mechanisms, and management. *Lancet* 1999;353:1959–1964.
- Woolf CJ, Thompson SWN. The induction and maintenance of central sensitization is dependent on *N*-methyl-D-aspartic acid receptor activation: implications for the treatment of post-injury pain hypersensitivity states. *Pain* 1991;44:293–299.
- Yeh CC, Ho ST, Kong SS, Wu CT, Wong CS. Absence of the preemptive analgesic effect of dextromethorphan in total knee replacement under epidural anesthesia. *Acta Anaesthesiol Sin* 2000;38:187–193.