Red-Hot Chili Peppers: A Spicy New Approach to Preventing Postoperative Pain

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Despite the increasing emphasis on the need to improve pain management,[1] the search continues for effective analgesic therapies that are devoid of side effects.[2,3] Many naturally occurring antinociceptive plant substances (e.g., papaversomniferum salix, cannabis sativa, capsicum species) are being evaluated for the treatment of acute and chronic pain.[4–6] Although one or more of these compounds may eventually emerge as a useful analgesic,[6] the findings to date have been disappointing, as clinical utility has been limited by poor efficacy or unacceptable side effects.

Purified capsaicin, the "hot" ingredient in chili peppers, is considered to be a safe and effective external (topical) analgesic that also possess antiarthritic, antioxidant, and even anticancer properties.[7] Capsaicin produces prolonged inhibition of C-fibers by interacting with the transient receptor potential vanilloid 1 (TRPV1) binding sites on small sensory nerves.[7–9] The mechanism of TRPV1 (formerly the vanilloid receptor-1) polymodal nociceptor activation has been described in the comprehensive review article by Kissin in the current issue of this Journal.[10] Intercellular calcium accumulation desensitizes nerves, producing prolonged hypoanalgesia until the sensory nerve endings regenerate (Fig. 1).[11] The TRPV-1 receptor is a ligand-gated ion channel, which is activated by heat, acidosis, and both endogenous and exogenous agonists (Fig. 2).[11] TRPV-1 is one of the most important transduction proteins expressed by peripheral nociceptors.

Kim et al. reported that application of capsaicin plaster at the Zusanli (ST-36) acupoint decreased the postoperative opioid analgesic requirement and/or opioid-related side effects (e.g., postoperative nausea and vomiting) after abdominal hysterectomy,[12,13] and inguinal hernia repair in children.[14] In this issue of *Anesthesia & Analgesia*, Aasvang et al.[15] demonstrate that wound instillation of purified capsaicin (Adlea®) can reduce incisional pain for up to 3 days after inguinal hernia repair procedure. These findings are even more impressive because the investigational drug was found to enhance the efficacy of a state-of-the-art "multimodal analgesic" regimen[16] consisting of local anesthetic infiltration, systemic administration of a nonsteroidal antiinflammatory drug, and acetaminophen,[2] which would be expected to minimize the need for opioid analgesic medication.[3]

Interestingly, their initial data analysis failed to find a significant difference when the pain scores were averaged over the first 7 day after surgery. However, the use of a more sensitive NONMEM analysis found significant differences in the pain scores for the first 3 days after this superficial surgical procedure, as discussed in the accompanying editorial by Shafer and Struys.[17] Of concern, a transient elevation in some of the patients' liver function tests was observed. Another potential concern is the theoretical possibility that capsaicin instillation could lead to long-term neuropathic symptoms secondary to neuromas after regeneration of the sensory nerve endings. Finally, when capsaicin is used in the perioperative setting, the clinician must administer the drug well before the end of anesthesia to allow for resolution of the acute burning sensation that

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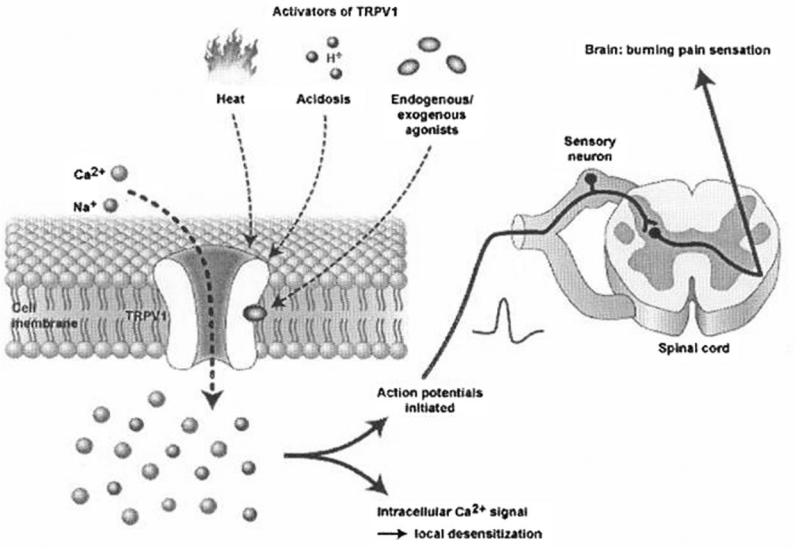

Figure 1. Mechanism for burning pain associated with capsaicin induced activation of the transient receptor potential vanilloid-1 (TRPV-1) receptor binding site.[11]

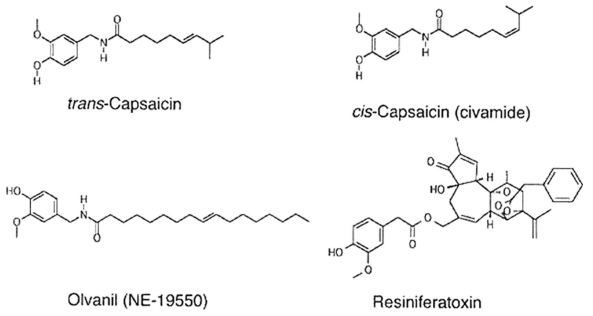

Figure 2. Structure of capsaicin and related transient receptor potential vaniolloid-1 (TRPV-1) receptor agonist and antagonists.[11]

occurs immediately after its topical administration and before the onset of its sustained analgesic effect (Fig. 1).[11] For example, Cantillon et al.[18] reported the onset of acute pain <5 min after capsaicin administration, with a duration lasting from 13 to 180 min. The onset of analgesia after the burning sensation is triggered by the acute influx of calcium molecules.

The prolonged duration of analgesia produced by capsaicin could be extremely valuable in facilitating earlier rehabilitation after painful orthopedic surgery procedures.[19,20] In contrast to local anesthetics, capsaicin does not affect motor or autonomic functioning, and therefore should not interfere with early postoperative ambulation. Although the effects of capsaicin on the TRPV1 receptor are completely reversible, the possibility of longer-lasting neurotoxicity due to the 4–16 week interval required for nociceptive C-fiber regeneration must be thoroughly investigated to exclude the possibility of an increase in the incidence of acute pain becoming chronic pain.[21] Theoretically, these compounds may be capable of causing inflammatory hyperalgesia. On the other hand, reduced C-fiber nociceptive input to the spinal cord might reduce secondary hyperalgesia, with a potential beneficial impact on neuronal mechanisms responsible for chronic pain.[22,23]

Since the early 1990s when the capsaicin "vanilloid" receptor was first described, scientists have been searching for specific TRPV1 receptor antagonists that could reversibly block C-fiber nociception without the acute discomfort associated with capsaicin-induced TRPV1 receptor activation.[24] TRPV1 receptor antagonists might alleviate the concern about potential neurotoxicity due to the desensitization process and subsequent nerve regeneration.[22,23] Although a large number of potential antagonist molecules have been investigated in animals and volunteer studies,[24] no clinically useful analgesic compounds in the TRPV1 receptor antagonist class have been identified.

An analog of capsaicin, resiniferatoxin (a phorbol-related diterpene), is an ultra-potent and highly selective for the TRPV1 receptor. Resiniferatoxin has been extensively evaluated as a potential alternative to capsaicin (Fig. 2).[11] A charged, membrane-impermeable lidocaine derivative (QX-314) when administered in combination with capsaicin also produced long-lasting decreases in the response to painful mechanical and thermal stimuli.[25] The regional analgesia produced by this mechanism was without the motor or tactile deficits produced by conventional local anesthetics. This strategy for blocking pain would be advantageous in producing local analgesia while preserving both motor and autonomic responses. Although this investigational compound is similar to capsaicin with respect to induction of pain, it is more effective in producing sensory nerve desensitization. Clearly, this is an exciting area for both basic and clinical pain research in the future.

In summary, there may be a role for capsaicin and other TRPV-1 agonists in the management of acute and chronic pain. Knotkova et al.[26] have further suggested that the "TRPV-1 agonist and antagonists are not mutually exclusive but rather complimentary pharmacologic approaches for (achieving) pain relief." In addition to the liquid formulation of capsaicin, a cutaneous patch formulation (NGX-4010) containing a synthetic capsaicin, also known as trans-capsaicin, is

currently in clinical development. The pungent ingredient in "red hot" chili peppers may eventually prove to be a valuable adjuvant for improving the management of acute and chronic pain.

REFERENCES

1. Brennan F, Carr DB, Cousins M. Pain management: a fundamental human right. Anesth Analg 2007;105:205–21
2. White PF. The changing role of non-opioid analgesic techniques in the management of postoperative pain. Anesth Analg 2005;101:S5–22
3. White PF, Kehlet H. Postoperative pain management and patient outcome: time to return to work! Anesth Analg 2007;104:487–9
4. Calixto JB, Beirith A, Ferreira J, Santos AR, Filho VC, Yunes RA. Naturally occurring antinociceptive substances from plants. Phytother Res 2000;14:401–18
5. Calixto JB, Kassuya CA, André E. Ferreira J. Contributions of natural products to discovery of the transient receptor potential (TRP) channels family and their functions. Pharmocol Ther 2005;106:179–208
6. White PF. Use of alternative medical therapies in the perioperative period: is it time to get on board? Anesth Analg 2007;104:251–4
7. Prasad BC, Kumar V, Gururaj HB, Parimalan R, Giridhar P, Ravishankar GA. Characterization of capsaicin synthase and identification of its gene (csy1) for pungency factor capsaicin in pepper (Capsicum sp.). Proc Natl Acad Sci 2006;103:13315–20
8. Biro T, Acs G, Acs P, Modarres S, Blumberg PM. Recent advances in understanding of vanilloid receptors: a therapeutic target for treatment of pain and inflammation in skin. J Investig Dermatol Symp Proc 1997;2:56–60
9. Caterina MJ, Schumacher MA, Tominaga M, Rosen TA, Levine JD, Julius D. The capsaicin receptor: a heat-activated ion channel in the pain pathway. Nature 1997;23:389:816–24
10. Kissin I. Vanilloid-induced conduction analgesia: Selective, dose-dependant, long-lasting, with a low level of potential neurotoxicity. Anesth Analg 2008;107:271–81
11. Bley KR. Recent developments in transient receptor potential vanilloid receptor 1 agonist-based therapies. Expert Opin Investig Drugs 2004;13:1445–56
12. Kim KS, Koo MS, Jeon JW, Park HS, Seung IS. Capsicum plaster at the Korean hand acupuncture point reduces postoperative nausea and vomiting after abdominal hysterectomy. Anesth Analg 2002;95:1103–7
13. Kim KS, Nam YM. The analgesic effects of capsicum plaster at the Zusanli point after abdominal hysterectomy. Anesth Analg 2006;103:709–13
14. Kim KS, Kim DW, Yu YK. The effect of capsicum plaster in pain after inguinal hernia repair in children. Paediatr Anaesth 2006;16:1036–41
15. Aasvang EK, Hansen JB, Malmstrom J, Asmussen T, Gennevois D, Struys MRF, Kehlet H. The effect of wound instillation of a novel purified capsaicin formulation on postherniotomy pain: a double-blind, randomized, placebo-controlled study. Anesth Analg 2008;107:282–91
16. White PF. Multimodal analgesia: Its role in preventing postoperative pain. Curr Opin Investig Drugs 2008;9:76–82
17. Shafer SL, Struys MM. Mixed effect modeling in analgesia trials. Anesth Analg 2008;107:9–10
18. Cantillon M, Hughes S, Moon A, Vause E, Sykes D. Safety, tolerability and efficacy of ALGRX 4975 in osteoarthritis of the knee. J Pain 2005;6:S39
19. Davis J, Williams H, Bramlett K, Powell T, Schuster A, Yu KP, Gennevois D. Enduring and well-tolerated analgesia for total knee arthroplasty postsurgical pain produced by a single, rapidly-eliminated, intra-operative instillation of 4975. J Pain 2007;8:S46
20. Cantillon M, Tagoe M, Vause E, Sykes D. Safety, tolerability and efficacy of intraoperative ALGRX 4975 in subjects undergoing bunionectomy. J Pain 2005;6:S48
21. Brennan TJ, Kehlet H. Preventive analgesia to reduce wound hyperalgesia and persistent postsurgical pain: not an easy path. Anesthesiology 2005;103:681–3
22. Romundstad L, Stubhaug A. Glucocorticoids for acute and persistent postoperative neuropathic pain: what is the evidence? Anesthesiology 2007;107:371–3
23. Jang JH, Kim KH, Nam TS, Lee WT, Park KA, Kim DW, Leem JW. The role of uninjured C-afferents in the generation of mechanical hypersensitivity after partial peripheral nerve injury in the rat. Exp Neurol 2007;204:288–98
24. Szallasi A, Cortright DN, Blum CA, Eid SR. The vanilloid receptor TRPV1: 10 years from channel cloning to antagonist proof-of-concept. Nat Rev Drug Discov 2007;6:357–72
25. Binshtok AM, Bean BP, Woolf CJ. Inhibition of nociceptors by TRPV1-mediated entry of impermeant sodium channel blockers. Nature 2007;449:607–11
26. Knotkova H, Pappagallo M, Szallasi A. Capsaicin (TRPV1 Agonist) therapy for pain relief: fairwell or revival? Clin J Pain 2008;24:142–54