

Capsaicin and Resiniferatoxin: A Review of the Literature for the Potential of Vanilla Alkaloids as an Alternative for Analgesia

Joseph Levinson, D.O.

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INTRODUCTION

Analgesia has progressed to the point where we have a variety of different drugs to achieve our desired goal. However, a good way of providing analgesia has been growing in fields and gardens for thousands of years. A safe and effective analgesic can be found in the pods of chile peppers, namely in the chemical formulation of capsaicin.

Capsaicin is the predominant alkaloid present in chile peppers and is the active ingredient which supplies gustatory heat when consumed. The medicinal and analgesic uses of peppers go back several hundred, perhaps thousands, of years. Native Americans would rub the flesh of chile peppers against their gums to relieve tooth pain. Peppers have been prescribed as a cure for cold and flu for centuries.

Peppers were not always used for such noble purposes, though. The Incas, in an attempt to deter invading Spaniards, burned mounds of dried peppers in the path of the Spaniards to blind them.

“The Mayans rubbed fresh peppers into the sexual organs of unchaste women as a punitive measure.”¹ and numerous cultures have used the caustic properties of chile peppers in injurious and punishing fashion.¹

The active ingredient in chile peppers was first isolated in 1816, and was given its name by the chemist L.T. Thresh in 1846, who predicted that the structures of capsaicin and vanillin were related.² Wilbur Scoville in 1912 created a way to quantify the capsaicin content of capsaicin, which is now done by high performance liquid chromatography (HPLC). After the chemical characterization of capsaicin began in earnest, its use for medicinal purposes in Western society

proliferated. Capsaicin is now currently considered to be a safe and effective topical analgesic that produces anti-arthritis, anti-oxidant and even anti-cancer properties. Analgesic uses for capsaicin have increased over the past century, where a major breakthrough was made in the treatment of herpes zoster. This breakthrough led to further research into the structure and mechanism of action of capsaicin to determine its method of providing analgesia.

The mainstays of analgesia are opiates. Used intravenously, intrathecally, or within the epidural space, opioids provide analgesia through their interaction with opioid receptors within the central nervous system. Their efficacy is limited due to their side effect profile which includes but is not limited to; respiratory depression, pruritus, allergic reactions, decreased in gastrointestinal motility, CNS effects, and tolerance with increased usage. For local and regional anesthesia, the mainstays are local anesthetics. While they can provide adequate analgesia, they are limited by their necessity to be placed at the site of action and their systemic toxicity. There are numerous additives used to prolong the duration of action of local anesthetics. These include epinephrine, ephedrine, and steroids such as dexamethasone. While lengthening the duration of local and regional anesthesia these additives do not in themselves provide any analgesia. This is an important distinction because capsaicin does, and will, prolong analgesia.

Based on research done on capsaicin, and its ultra-potent analog, resiniferatoxin, these substances could be used to provide intra-operative and post-operative analgesia potentially better than our current regimen of pharmacologic options.

MECHANISM OF ACTION

The mechanism of analgesia that capsaicin and resiniferatoxin supplies seems at first to be counter-intuitive. For example, capsaicin that is applied to the skin or injected intradermally induces both hyperalgesia and allodynia. Capsaicin excites certain subsets of dorsal root ganglia

which give rise to thinly myelinated A-delta and unmyelinated C fibers.² These nerve fibers, which are specific for transmission of pain signals, seem to be sensitive to vanilloids such as capsaicin centrally where they block the transmission of noxious stimuli. However, the terminal ends of the peripheral nerves are affected differently, where capsaicin blocks the release of several proinflammatory neuropeptides such as Substance P, calcitonin gene-related peptide, and somatostatin.² Of particular importance is the effect on Substance P, where prolonged stimulation of these neurons by capsaicin will deplete the nerve's capacity to supply presynaptic amounts of this neuropeptide.

HOW CAPSAICIN IS CURRENTLY UTILIZED

Given the above-described mechanism of action, capsaicin has some current clinical uses for evaluating regional analgesia and for enhancing the effectiveness of treatment for certain painful disorders and neural dysfunction. Capsaicin is known to induce hyperalgesia and allodynia, which are present in certain acute and chronic pain states, so capsaicin has been one of the chemicals used in studies to evaluate hyperalgesia. "Primary hyperalgesia (i.e. hyperalgesia at the site of injury) can be studied by determining pain thresholds after heat and mechanical stimulation. Secondary hyperalgesia can be determined by brush and pinprick stimulation of the skin surrounding the injury."³ Because this mechanism obviously involves pain mediators, it became the source of interest in pursuing alkaloids such as capsaicin and resiniferatoxin for analgesia.

In addition to evaluation of analgesia, capsaicin is also currently used as a safe and effective adjunct treatment for treatment of rheumatoid arthritis, osteoarthritis, neuralgias, and diabetic neuropathy.⁴ Current efforts are ongoing to evaluate the effectiveness of capsaicin to treat a wide variety of conditions including: pruritus, psoriasis, cluster headache, postmastectomy pain

syndrome, oral mucositis, rhinopathy, cutaneous allergies, detrusor hyperreflexia, loin pain and hematuria syndrome, neck pain, amputation stump pain, reflex sympathetic dystrophy, and the pain of skin tumors. While many of these do not involve specific pain syndromes, it does demonstrate the capacity of capsaicin to modulate important neuropeptides to affect a beneficial change in neurologic function.

SUPPORTING RESEARCH

With continued research concerning the use of the vanilla alkaloids capsaicin and resiniferatoxin, it was observed that they “show structure-function relationships and evoke responses in a dose-dependent manner, [and that] the existence of a receptor site represents the most likely mechanism.”⁵ Research with capsaicin has been done for much of the past half-century, but there was a dramatic increase of interest with the cloning of the first vanilloid receptor in 1997.⁵ This receptor is known as TRPV1, and is characterized by Kissin as:

TRPV1 (transient receptor potential vanilloid type 1 receptor) was initially identified as the receptor for capsaicin, the pungent ingredient in peppers. It is a nonselective cation channel, predominantly expressed by sensory neurons. TRPV1 is activated by a diverse range of chemical ligands (capsaicin, resiniferatoxin, endogenous lipid anandamide, and other endogenous capsaicin-like substances), as well as protons, and heat, and it can behave as an integrator of the effects of many pain-producing agents.⁶

It is noteworthy that the TRPV1 is found in more than one part of the primary afferent sensory neuron, and has been found in the dorsal root ganglion, central terminals, peripheral terminals, and the axons. However, the effects of the vanilla alkaloids have on these sensory neurons are dependent on the substance that has been tested. Szallasi’s testing in 1996 demonstrated that capsaicin will primarily deplete neurotransmitters from neurons while resiniferatoxin tends to be up-or-down regulated. Both substances were shown to have a depletive effect on the vanilloid receptor.⁷

EVIDENCE IN FAVOR OF USE OF CAPSAICIN AND RESINIFERATOXIN

The evidence for the beneficial uses of capsaicin and resiniferatoxin is growing. Baranowski had theorized that capsaicin had potential as a local anesthetic agent due to its depletion of Substance P and other neuropeptides. This research was key in proving not only the immediate blockade of afferent C-fibers but also the long-term action on peptides levels *in vivo*.⁸

Xu worked with capsaicin and resiniferatoxin with mechanisms of spinal nociception. It was found that “following capsaicin-induced excitation, the neuronal responses exhibit a refractory state traditionally referred to as desensitization, the extent and duration of which is related to the dose of capsaicin used and duration and frequency of its application.”⁹ It was found that resiniferatoxin mimics nearly all of the actions of capsaicin, including specificity, but with enhanced potency in most testing.

Kohane et al. observed a synergistic effect of vanilloid compounds with site 1 sodium channel blockers (namely, local anesthetics). While the potentiation of this analgesic effect was not done using capsaicin, an analogous vanilloid showed some promise. These interactions may provide not only clues on how to prolong regional anesthesia with local anesthetics but may help elucidate mechanisms of selective nerve blockade using vanilloid compounds that are specific for a given receptor.¹⁰

In an article by Kissin, resiniferatoxin is tested as an ultra-potent vanilloid agonist. Its excitatory component was less pronounced than capsaicin, but had a prolonged inactivating effect. When used with bupivacaine for regional anesthesia, the hypoalgesic effect lasted more than an order of magnitude longer than the effect of bupivacaine alone.¹¹

Kissin’s later research into the TRPV1 receptors shows that the analysis of the studies with systemic administration of capsaicin indicates that the drug does have the potential for the

suppression of responses to noxious stimuli.⁶ Their results were also favorable to the use of percutaneous resiniferatoxin to suppress motor responses to noxious stimulation in a manner similar to capsaicin. Testing was also done to peripheral nerves with capsaicin and the observed blockade of C-fibers. This step was necessary to prove the selective nature of these vanilloid agonists, and their lack of impairment of motor function. The selectivity is important, because Kissin postulates that vanilloid agonists could be used for other types of peripheral analgesia, such as topical, intra-articular, intra-vesicular, and infiltrative. Because the peripheral terminals are different than those of nerve fibers, synergism in analgesia is possible.

White's research further evaluated the use of resiniferatoxin as a potential alternative to capsaicin for use in regional anesthesia. Using a labeled lidocaine molecule, the TRPV1 receptor was analyzed for its role in mediating activation of anti-nociceptive activity. It was noted that the regional anesthesia produced by this mechanism was without the motor or tactile deficits produced by conventional anesthetics.¹² If this model works, then it was suggested that this could be a way of providing analgesia that would preserve both motor and autonomic function. Gerner went further with the combination of vanilloid agonists and local anesthetics, and showed that when capsaicin was used in combination with local anesthetics that an enhanced and longer-lasting differential block was obtained. Using more hydrophobic drugs provided an even larger differential block.¹³ This research is significant because this may allow for not only more effective analgesia and duration of blockade, but the very real possibility of increased efficacy by using much lower doses of local anesthetics. While not specifically stated, the evidence suggests that vanilloid agonists, such as capsaicin and resiniferatoxin, could be used as parent compounds of a sole analgesic.

EVIDENCE AGAINST THE USE OF CAPSAICIN AND RESINIFERATOXIN

The flip side of the coin with the vanilloid agonists is that their use is still not well-characterized in all studies, and many of these have shown some concerning results.

While Baranowski showed a depletion of Substance P with use of capsaicin, it was observed that “peptide depletion is slow, becoming significant only 24-96 hours after treatment, whilst reductions in nociceptive reactions and in neurogenic inflammatory reactions may occur within a few hours.”⁸ If peptide depletion plays a significant role in analgesia, this may be a tangible issue.

Szallasi’s literature analysis reveals that the increasing cytoplasmic calcium concentrations caused by vanilloid agonists impairs neuronal function, through desensitization, and can ultimately kill affected neurons.⁷ This desensitization comes with an initial irritation that may be difficult for patients to initially endure. Szallasi also suggests that any level of receptor heterogeneity may select against the use of capsaicin in all patients. Along the same lines, Xu observes that the low potency of capsaicin has limited the therapeutic potential because of the same issues of toxicity and initial stimulation.⁹

Caterina noticed that the decreased sensitivity to noxious stimuli came as a result of reversible changes to the nociceptor itself, and that long-term loss of responsiveness could actually be explained by the actual destruction of the peripheral nerve terminals themselves.⁵ This is just one of the paradoxical effects that vanilloid alkaloids can provide: effective analgesia but potentially at the cost of the nerve fibers themselves.

Simone’s research with epidermal nerve fibers did not provide a clear mechanism of analgesia. The supposition was that “desensitization of capsaicin-sensitive afferent fibers involves a continuum of physiological and morphological changes that are dependent on capsaicin dose and

route of administration.”¹⁴ When a range of effects occur, further evidence of the mechanism versus dosage must be obtained. Robbins went further to suggest that nociceptor desensitization, regardless of mechanism, may be highly dependent on the use of large-dose capsaicin.¹⁵

Resiniferatoxin may be a better use for analgesia, because capsaicin applied to peripheral nerves in large concentrations permanently damages nerve fibers, resulting in sensory deficits that last for months.¹¹ This is due to degeneration of nerve fibers which may take months to reinnervate. White notes that trials of capsaicin used in the perioperative period results in timing issues in its administration. The clinician must administer the drug well before the end of anesthesia to allow for resolution of the acute burning sensation that occurs immediately after its [topical] administration and before the onset of its sustained analgesic effect.¹² This conduction blockade is desired for peripheral nerves as well. Vanilloid agonists are selective in their conduction analgesia to A-delta and C-fibers, and any nociceptive signals provided by mechanisms outside this system may be missed by this application.⁶

CONCLUSION

The use of peripheral neural blockade with local anesthetics is utilized in local and regional anesthesia to maintain postoperative analgesia. Some practitioners utilize a continuous blockade technique to achieve this, but the research suggests that vanilloid alkaloids could provide more efficacious and long-lasting analgesia to potentially rival that of other methods. Research into the area of vanilloid receptors (VR's) indicate that an agonist may be available from among the current candidates to provide selective and long-lasting nociceptive blockade without either the issues of toxicity or motor blockade that come from local anesthetics. When local anesthetics are

used, the adjunct usage of vanilloid agonists could significantly lengthen the duration of analgesia.

Clinical trials are ongoing with resiniferatoxin and capsaicin. Emphasis on doing more trials with animal models will be necessary to get an idea of *in vivo* testing in human subjects. Human disorders that would benefit from expanded usage of vanilloid agonists include:

1. disease states for which vanilloid alkaloids are beneficial, such as capsaicin creams for chronic painful cutaneous pain syndromes,
2. conditions for which vanilloid agonists are currently used, but require more potency with their current formulation
3. conditions that would benefit from receptor subtype-selective alkaloids for analgesia

The use of receptor subtype-selective alkaloids is where this author would like to see more focus, to improve the quality of regional anesthesia or even to provide a novel sole analgesic that avoids the pitfalls currently seen with the widespread usage of opioids.

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