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Capsacin and Analgesia

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Abstract

Capsaicin is the active compound responsible for the pungency of hot chilli. Research has discovered its ability to desensitize peripheral nociceptive fibers which is useful in treating chronic pain disorders, specifically neuropathic pain syndromes. Capsaicin treatment comes in a variety of mediums including patches and creams and has been clinically proven to bring relief to patients with disorders such as post herpetic neuralgia, chronic regional pain syndrome and HIV related neuralgia. Exciting new forms of treatment are also in development and promise breakthroughs in the near future in this relatively young field of capsaicin-based analgesia.

Introduction

Chronic pain syndromes are debilitating, robbing many of their quality of life and productivity while putting them at additional risk of mental health disorders. Many do not find relief despite extensive treatments. This has prompted research into finding a compound that will present a viable alternative to traditional analgesics, especially opiates which carry an additional risk of addiction. Capsaicin, the compound responsible for the pungency of the capsicum family and an example of a vanilloid, has been used as an analgesic agent for thousands of years. Recent research has proven just how well suited it is as a treatment for a subset of chronic pain disorders especially neuropathic pain.

This paper will look at the mechanisms of nociception that are targeted by this treatment, the properties of capsaicin and its receptor, TRPV1, that make it so effective. Its clinical applications and limitations will also be examined to give a glimpse of what research has discovered and where it is taking us.

Mechanisms of Subcutaneous Primary Nociception

Nociception is the sensation of noxious stimuli perceived by nociceptive receptors which are usually found in the skin (Caterina & Julius, 2001), although they can also be found viscerally. It is the first step toward the sensation of pain which is the result of a complicated multilayered process including central gating controls and peripheral activity (Hunt, 2009). Nociception itself is a complex process with aspects that take place in both the central (CNS) and peripheral nervous systems (PNS).

There are two general categories of subcutaneous nociceptive primary afferent neurons, myelinated A-fibers and unmyelinated C-fibers. Not all A-fibers are sensitive to nociceptive stimuli, Aβ fibers are large rapidly conducting fibers responsible for touch and proprioception, and only Aδ fibers which are smaller and slower conductors are involved in nociception (Khalid & Tubbs, 2017). Lightly-myelinated Aδ fibers are associated with acute pain or first pain which is characterized by lancinating, stabbing, or pricking pain that is felt immediately after exposure a noxious stimulus. Unmyelinated C-fibers are very slow conductors and are responsible for second pain which is characterized by the more global sensations of throbbing, burning or cramping pain (Hunt, 2009; Dubin & Patapoutian, 2010).

Noxious stimuli are usually categorized as either heat (H), cold (C), or mechanical (M). Primary nociceptive afferent fibers are further classified according to the type of stimuli that they respond to, for example C-MH, A- MH. The most common C fibers are polymodal, meaning they respond to multiple types of stimulation such as C-MC, C-MH and C-MHC. There is also a subgroup of C-fibers known as silent C-MiHi that only become sensitive to noxious mechanical or thermal stimuli after he area has become sensitized by inflammation. Most A-fibers are heat- or mechano- sensitive (A-H, A-M, A-HM) (Dubin & Patapoutian, 2010).

Nociceptors have a variety of voltage gated channels that encode the intensity of the stimulus (Dubin & Patapoutian, 2010). They also release neuropeptides that transmit input further up the neural axis. For example, when C-fibers are triggered they release glutamate and substance P (Hanpaa & Treede, 2012).

When the skin is injured it undergoes physiological changes that protect it from further damage and promote healing, known as inflammation. There are two subgroups of C-fibers. One of them expresses the trkA receptor which binds to nerve growth factor (NGF) and synthesizes neuropeptides such as CGRP and substance P. When they are triggered they contribute to inflammation and healing at the site of the injury (Hunt, 2009). Symptoms of the inflammatory state include flare or reddening of the immediate area and increased sensitivity to both innocuous and noxious stimul,i both in the immediate and surrounding area. The increased sensitivity is due to a reduced threshold of excitation in the C-fibers (Dubin & Patapoutian, 2010) and increased receptor expression and excitation (Lebovitz, et al., 2012).

There is a second subgroup of C-fibers that do not have a role in inflammation, instead they display the Ret receptor that binds to GDNF and express PAP that breaks down ATP to produce adenosine that, in turn, binds to the A1 receptor and reduces nociception. In fact, intrathecal application of GDNF has been shown to reduce neuropathic pain symptoms (Hunt, 2009).

C-fibers that are constantly in a state of excitation, such as those in a chronic pain state, will release a constant flow of glutamate known as a glutamate barrage. This barrage may result in physiological changes to the dorsal root ganglion and higher pain areas of the brain that increases their sensitivity and excitability which is known as central sensitization. Descending controls may also have an impact on determining the sensitization of dorsal root neurons (Hunt, 2009). Central sensitization may also impact the sensitivity of A-fiber neurons, which don't usually become sensitized, causing even innocuous stimuli to register as painful (Baron, 2006). This may be a result of synapses that they form with neurons that have been sensitized by C-fiber barrage (Hunt, 2009).

Peripheral sensitization may also occur post-injury as a result of physiological changes which may contribute to the development of neuropathic pain syndromes (Gilron, Baron, & Jensen, 2015)

The role that C-fibers and Aδ- fibers play in the process of nociception is definitely an important one which makes them a worthwhile target in the field of analgesia. These afferent neurons share a receptor TRPV1 which is expressed on all C-fibers and a subset of Aδ fibers (Hunt, 2009; (Lebovitz, et al., 2012), this means that if it can be shut off of blocked then peripheral nociceptive input can be greatly minimized or even neutralized.

Targeting TRPV1 is especially prized because it allows a two-pronged strategy against pain. Not only does targeting it , target the beginning of the pain pathway (Trevisani & Szallasi, 2011; Wagner, Roth-Daniek, Sell, England, & Kern, 2012), but it also blocks the glutamate barrage which allows the body to break the pain cycle common in chronic pain patients.

TRPV1

In 1990, the study of a more potent capsaicin analog, resiniferatoxin (RTX), led to the discovery of a new receptor known as TRPV1. It's name comes from the amino acid sequence that designates it's membership in a family of receptors first identified in fruit flies. In 1969 a mutation was identified on a visual receptor of a fruit fly, instead of a sustained depolarizing after exposure to light, these mutated receptors showed only transient depolarizing response to light, giving the family of receptors the name transient receptor potential or TRP. The second part of its name, V1, comes from the amino acid sequence that was identified that marked it as a vanilloid receptor (Caterina & Julius, 2001). The amino acid strain was first designated VR1 but when it was joined to the receptor family it was abbreviated to TRPV1.

The discovery of TRPV1 led to the discovery of a subset of thermal-sensitive TRP-type receptors which are also called thermoTRPs (Trevisani & Szallasi, 2011). Other members of this family include TRPV2, TRPV3 and TRPV4. TRPV1 is highly expressed on normal nociceptive C-fibers and Aδ-fibers and after inflammation show increased upregulation and sensitivity (Lebovitz, et al., 2012). It is part of the nociceptive pathway and is activated by a variety of stimuli including protons, noxious heat, phorbol esters, fatty acids as well as vanilloids like capsaicin and RTX. The receptor only experiences maximum activation when activated by multiple types of stimuli (Vyklicky, et al., 2008), which is consistent with the polymodal nature of the C-fibers that are involved in nociception.

TRPV1 has been proved to be involved in many forms of pathophysiology including inflammatory bowel syndrome (IBS), osteoarthritis, rheumatoid arthritis, post herpetic neuralgia (PHN) and cystitis amongst others (Andreev, et al., 2013). This makes understanding this receptor necessary for the treatment of many different disorders.

There are two ways that TRPV1 can be targeted pharmacologically, either it can be desensitized by vanilloids or blocked by antagonists. There are two types of desensitization, acute desensitization and tachyphylaxis, which is a reduction in response to noxious stimuli as a result of repeated application (Vyklicky, et al., 2008). There is also a difference between high dosage and low dosage desensitization such as between the short-term refractory period that takes place after any application of a vanilloid and longer lasting defunctionalization that takes place after the administration of a high dosage application (Finch & Drummond, 2015) (Trevisani & Szallasi, 2011).

Multiple biomechanisms have been discovered by researchers to have a role in the process of sensitization and desensitization of the TRPV1 receptor including the phosphorylation and dephosphorylation of the receptor (Trevisani & Szallasi, 2011), although the process isn't fully understood. The dramatic influx of Ca2+ ions in the primary afferent neurons that takes place during vanilloid applications have also proved to be a part of the long-term desensitization mechanism (Vyklicky, et al., 2008). Vanilloid induced messenger plasticity, which refers to changes in the expression of neuropeptides on the receptor such as a decrease of the proinflammatory neuropeptide SP and the increase of analgesic peptide galanin, and is also part of the long-term desensitization or 'defunctionalization' associated with the application of high dosage capsaicin.

Antagonists that block the TRPV1 receptor are a popular avenue of research, but many promising leads often lead to disaster. These compounds often induce spontaneous hypothermia in humans making them impractical for use. However, there have been promising breakthroughs by a group in Russia with a compound that only partially blocked the receptor which shows that partial blockage of the receptor may be a better outcome than a full blockage (Andreev, et al., 2013). This is backed up by research that has shown that partial binding is enough to activate the TRPV1 receptor and that there are multiple levels of activation based on the state of binding of the receptor (Hui, Liu, & Qin, 2003).

There used to be a theory that the main function of TRPV1 is thermoregulation. This was based on its role in thermal sensitivity and the hypothermic effect of capsaicin and TRPV1 antagonists, but this was later mostly debunked (Trevisani & Szallasi, 2011). Other studies have also shown that the gene deletion of TRPV1 in mice still allowed for a level of noxious thermal sensitization (Dubin & Patapoutian, 2010).

TRPV1 is the therapeutic focus of a common analgesic and other drugs on the market. Paracetamol or acetaminophen is thought to interact with TRPV1 as part of its analgesic mechanism. Also drugs such as Taramidol which is used to treat fibromyalgia and nefopam, a benzoxazocine analgesic, also interact with TRPV1. There are also compounds in Eastern medicine that may target TRPV1 (Trevisani & Szallasi, 2011).

Capsaicin

Capsaicin, or 8-methyl-N-vanillyl-noneamid, is the compound responsible for the pungency of hot chili peppers (Factor, et al.,

2011) which are of the genus capsicum (Finch & Drummond, 2015). Any ingestion of hot chili will cause a painful burning sensation. However, perhaps ironically, capsaicin has been proved to have extensive analgesic qualities. It is also a potential neurotoxin and large doses can cause permanent nerve damage (Trevisani & Szallasi, 2011).

For thousands of years capsaicin extracts were used as part of native medicine as a primitive analgesic. Aztec physicians may have used it to treat tooth ache and sources show that RTX, which is derived from the latex of the palm Euphoria Resinifera, may have been used in Ancient Rome to treat the arthritis of the Emperor Augustus. In Northern India a native plant containing capsaicin called bhut jolokial has been used by the people who live there to treat arthritis (Finch & Drummond, 2015). Modern pharmacy, however, was late to discover its qualities and did not recognize it's potential until the year1878 (Trevisani & Szallasi, 2011).

The Hungarian chemist Endre Högyes is credited with the discovery of the effect of capsaicin on sensory fibers but his find remained lost until the turbulent years and scientific innovation of World War Two. Another Hungarian chemist, Nicholas (Miklós) Jancsó further developed the use of capsaicin by developing its potential as a promising analgesic. In the 1970's capsaicin research exploded, with the number of papers on record jumping exponentially. Capsaicin continues to be of a topic of interest for the general scientific community and continues to be extensively researched until today (Trevisani & Szallasi, 2011).

Originally the analgesic properties of capsaicin were though to come from its counterirritant and warming properties (Hanpaa & Treede, 2012) but now we know that there are many mechanisms involved (Vyklicky, et al., 2008). It is a TRPV1 agonist (Factor, et al., 2011) and it is the complex interaction between TRPV1 and capsaicin that is the crux of its analgesic abilities.

Initial exposure to capsaicin activates the TRPV1 ligand gated channels on the primary afferent nociceptive neurons which cause depolarization, the initiation of an action potential and transmission of a pain signal to the spinal cord (Backonja, et al., 2008). This is followed by a lasting refractory period know as desensitization (Factor, et al., 2011) and if the dose is high enough it generates a longer lasting local desensitization which is also known as defunctionalization (Finch & Drummond, 2015).

In high dose applications when TRPV1 is activated, high levels of calcium enter the cell overwhelming the mitochondria and causing apoptosis. The nociceptive nerve fibers in the area where the capsaicin is administered begin to die which prevents the initiation of new nociceptive input, causing a defunctionalization of the nociceptive ability in that area.) After the application of a high dose capsaicin patch for one week there was an 80% decrease in the density of epidermal nerve fibers (ENFs). However, if the dosage is not too high the damage is reversible, which was corroborated by the study. Partial regeneration was present twelve weeks after the treatment and complete regeneration at twenty-four weeks (Wallace & Pappagallo, 2011). This is consistent with the pain relief that patients who use high dosage capsaicin treatment experience, often pain relief lasts for up to three months per application (Finch & Drummond, 2015).

This is one of the reasons that capsaicin is so well suited to treating chronic pain, especially neuropathic pain. Long lasting, comprehensive relief without daily drug use is very attractive for chronic pain sufferers. Also, the ability of capsaicin to temporarily destroy nociceptive nerve endings provides a way to cut off nociceptive input, the glutamate barrage to the spinal cord. This allows the spinal cord and higher pain areas to minimize or perhaps extinguish the effects of central sensitization or 'windup,' which is the hyperactivity of neurons in the spinal cord and brain, due to neuroplasticity that makes them extra sensitive to pain input. Central sensitization is characteristic of neuropathic pain and extremely hard to treat. Doctors who have been using the high dose capsaicin patch have reported anecdotally a reduction in the symptoms of windup in their patients (Wagner, Roth-Daniek, Sell, England, & Kern, 2012).

Medications

There are many forms of capsaicin based pharmacological treatments. Initially, low dose, topical creams were the form of choice, but studies found them to have a disappointing effect. In a comprehensive study they were found, at best, to have a moderate effect and many subjects reported poor or no effect (Trevisani & Szallasi, 2011). The creams come in two different strengths 0.075% under the name Zostrix® (Finch & Drummond, 2015) and 0.025% with lidocaine under the name Axain® (Trevisani & Szallasi, 2011).

The most popular form of capsaicin-based treatment is the Quetenza® 8% patch. The dosage of the patch is significantly higher than the creams which allows the treatment to enable long-term desensitization within the treatment area. The patch promises relief for up to three months (Wallace & Pappagallo, 2011) which is consistent with capsaicin mediated nerve fiber death.. This means that the patch only needs to be reapplied every three months, which greatly increases patient compliance.

The potential for capsaicin to cause irreversible nerve damage may make physicians wary of using the high potency patch. However, a study shows that the recommended dosage of up to four patches per application (Wallace & Pappagallo, 2011) is within estimated dietary consumption of cultures that consume a diet heavy in capsaicin such as Mexico, Thailand and India (Hanpaa & Treede, 2012).

The patch has shown to be effective for a variety of syndromes and can be cut to size so that it can be applied almost anywhere on the body. Capsaicin's unique mechanism of analgesia means that it has no known drug interactions which allows it to be incorporated into a treatment plan that includes other analgesics too (Wallace & Pappagallo, 2011).

Other forms of capsaicin include an injectable form that can be used to treat osteoarthritis, tendonitis and some forms of neuropathic pain. There is also an intranasal form that has been clinically proven to be effective in the treatment of migraines (Trevisani & Szallasi, 2011).

Clinical Applications

Capsaicin treatment has been adapted for the treatment of many disorders. The most obvious of these are pain related including PHN, stump pain, headaches, trigeminal neuralgia and osteoarthritis amongst others (Wagner, Roth-Daniek, Sell, England, & Kern, 2012). Interestingly, capsaicin has also been used for the treatment of urinary incontinence as well (Trevisani & Szallasi, 2011).

The treatment of PHN by capsaicin has been the focus of many studies into the efficacy of capsaicin- based analgesia. PHN is one of the most common forms of neuropathic pain after chronic back pain and painful diabetic neuropathy (Wallace & Pappagallo, 2011). PHN is a chronic pain disorder that develops the varicella zoster (shingles) virus comes out of dormancy. The treatment options of PHN are limited and often poorly tolerated which makes the disorder very hard to treat (Backonja, et al., 2008). However, multiple studies that have investigated the outcome of using a capsaicin patch have seen favorable results with minimal side effects and marked relief experienced by the patient (Backonja, et al., 2008; Wallace & Pappagallo, 2011). Some patients with HIV associated neuropathy have also reported relief from capsaicin patch treatments (Capsaicin dermal patch: a guide to its use in non-diabetic peripheral neuropathic pain, 2011).

A tertiary hospital studied the results of their hospital-wide adoption of capsaicin patches to treat non-diabetic patients with a variety of neuropathic pains. These included PHN, CRPS-I, knee arthroplasty related pain, painful scaring, femoral cutaneous neuropathy, HIV related neuropathy and neuroma. They found a 23% reduction of pain in a population of twenty patients that had been treated with the patches. They also noted that six of the patients had not found relief with any other treatment that they had tried so far. They also found that patients that had a higher basal quality of life experienced a better response to the drug (Gimenez-Mila, et al., 2014).

A novel way that capsaicin is being used is to facilitate rehabilitation for knee arthroplasty patients. Often pain following knee arthroplasty surgery can impede recovery and rehabilitation, leading to prolonged hospital stays and a more painful, prolonged recovery. Capsaicin has been introduced as a novel way to dull the pain through temporary desensitization of the local area for the duration of the initial recovery. This allows the patient to proceed with exercises and activities that will improve their function and help them get back on their feet quicker. It was expected that patients may report increased post-operative pain because the capsaicin had been applied, but pain scores were found to be well within range (Hartrick, Pestan, Carlson, & Hartrick, 2011).

Trials of capsaicin being used as 'molecular scalpels' for the treatment of cancer-related neuropathic pain are showing promising signs (Trevisani & Szallasi, 2011). The principle behind this method of treatment is that physicians can use the neurotoxic ability of capsaicin to target very specific cells to treat chronic, intractable pain that cancer patients experience. The treatment carries obvious risks which is probably why the clinical applications that are being pursued right now are very limited, but the potential of this technique is very exciting.

Drawbacks

Although capsaicin is an exciting new frontier in analgesia it has some risks and limitations that must be addressed. Exposure of the mucosa of the throat to capsaicin can cause coughing and bronchoconstriction. However, bronchoconstriction from such a scenario is very rare and even coughing had a very low incidence rate during the clinical trials (Wallace & Pappagallo, 2011).

Capsaicin can only be applied to a local area. In high doses that would be needed to give systemic relief it can cause a drop in body temperature and may be cardiotoxic (Lebovitz, et al., 2012). The hypothermic effect of capsaicin is posited to be a result of the defunctionalization of the TRPV1 receptor. This warps the thermosensitivity of the preoptic heat sensors and fools the animal into thinking that they are warm. This is reflected in the animal's loss of ability to regulate their own body temperature (Trevisani & Szallasi, 2011).

Researchers have also found a correlation between a diet high in spicy food and an elevated risk of cancer. However, further research needs to be done to see if this is applicable to all forms of capsaicin exposure or just ingestion of capsaicin. Capsaicin is poorly metabolized by the skin (Wallace & Pappagallo, 2011) so topical application may not carry the same risk of ingestion.

The patch system, despite having many advantages, has the drawback of needing a minimal infrastructure and attending medical personnel to a be able to incorporate them into a treatment plan (Gimenez-Mila, et al., 2014). Also, they often require the administration of a local topical anesthetic such as Lidocaine before application due to the sensation of painful burning that is experienced during the hour long application time (Wagner, Roth-Daniek, Sell, England, & Kern, 2012).

The disadvantage of the creams is that they require multiple, daily applications which greatly decreases patient compliance. It may also induce a painful burning sensation that will discourage its application and hasn't even been proven to be an effective analgesic because of its low dosage (Backonja, et al., 2008).

Conclusions

The ingenuity that is being employed to find pathology and techniques suited to capsaicin treatment is astounding and there is no doubt that the scientific community will continue to come up with new ways to use the unique capabilities of capsaicin

to treat other pathologies. However, there is a need for the development of a standardized schedule of treatment for using capsaicin in a clinical setting (Factor, et al., 2011).

A better understanding of the biology of neuropathic pain would also be an advantage for the development of capsaicin-based pharmacology. If the mechanisms of pain disorders were better understood, treatments could be targeted to directly counteract them in a technique similar to the molecular scalpel being used for cancer-related neuropathic pain.

Perhaps capsaicin could also be adapted for the treatment of phantom limb pain (PLP). The source of PLP is a combination of sensitization and inflammation that takes place in both the central and peripheral nervous systems. Perhaps the desensitizing ability of capsaicin could be effective in this scenario by reducing peripheral sensitization and central nervous system input.

Capsaicin is a novel pharmacological agent that promises an alternative to traditional analgesics and opioids in the treatment of neuropathic pain and other pain syndromes. Research into capsaicin is fairly recent but clinical data has yielded favorable results and new research seems hopeful of making new breakthroughs in techniques and applications of capsaicin in medicine.

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