Resiniferatoxin: Mechanism in Treating Osteoarthritis Pain and Slowing Osteoarthritis Progression, Safety, and Efficacy

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Abstract

Resiniferatoxin is a diterpene found in *E. resinifera* and *E. poissonii*, and is a more potent functional analog of capsaicin. Resiniferatoxin provides pain relief by binding as an agonist to transient vanilloid receptor 1 (TRPV1), a nociceptive ion channel. Resiniferatoxin targets the TRPV1 channel and activates it, allowing calcium cations to flow in and desensitize the TRPV1 receptors, producing an analgesic effect. Resiniferatoxin was recently designated as a Breakthrough Therapy by the FDA for the treatment of the pain caused by knee osteoarthritis, a common degenerative joint disease caused by aging, joint injury, and obesity. Studies suggest that osteoarthritis is linked with chronic inflammation through a cycle of injury, inflammation, and repair. Multiple studies involving TRPV1 agonists have shown anti-inflammatory properties, presenting TRPV1 agonists as a potential inhibitor for the progression of osteoarthritis. This review highlights the mechanism of resiniferatoxin in treating pain caused by knee osteoarthritis, its potential in treating inflammation in osteoarthritis, its efficacy, and its safety.

Introduction

Osteoarthritis is the most common joint disease in the United States. It is a degenerative joint disease predominantly in the hands, hips, and knees, leading to a decrease in joint mobility.

Osteoarthritis is caused by factors including aging, obesity, and past joint injuries. There is currently no cure for osteoarthritis, but there are treatments for its symptoms of pain and mobility (Chen et al., 2017).

One treatment option for osteoarthritis pain is resiniferatoxin, a capsaicin analog and currently the most potent agonist for transient receptor potential vanilloid type 1 (TRPV1) a non-selective nociceptive ion channel that can be activated by capsaicin, heat, and acid. Resiniferatoxin is found in *E. resinifera* and *E. poissonii*. Resiniferatoxin was recently granted Breakthrough Therapy by the FDA for pain caused by osteoarthritis in the knee, increasing mobility. As a TRPV1 agonist, it provides prolonged pain relief by allowing calcium cations to permeate through the TRPV1 ion channel, and this large influx of cations desensitizes the TRPV1 receptors.

Besides pain, studies have shown the potential for resiniferatoxin and other TRPV1 agonists to treat inflammation, a major cause of further cartilage degeneration in osteoarthritis.

How Resiniferatoxin Treats Pain

Resiniferatoxin targets the TRPV1 ion channel, a cation channel on C-fiber sensory neurons that causes pain. As an ultrapotent TRPV1 vanilloid, resiniferatoxin activates and opens TRPV1 for a prolonged period of time, allowing calcium cations to flow in, causing calcium cytotoxicity and desensitization to TRPV1 pain receptors (Raisinghani et al., 2005). Researchers hypothesize that 2 key amino acids of TRPV1, Arg-114 in the N-cytosolic tail and Glu-761 in the C-cytosolic tail, form a binding pocket for resiniferatoxin and capsaicin (Jung et al., 2002).

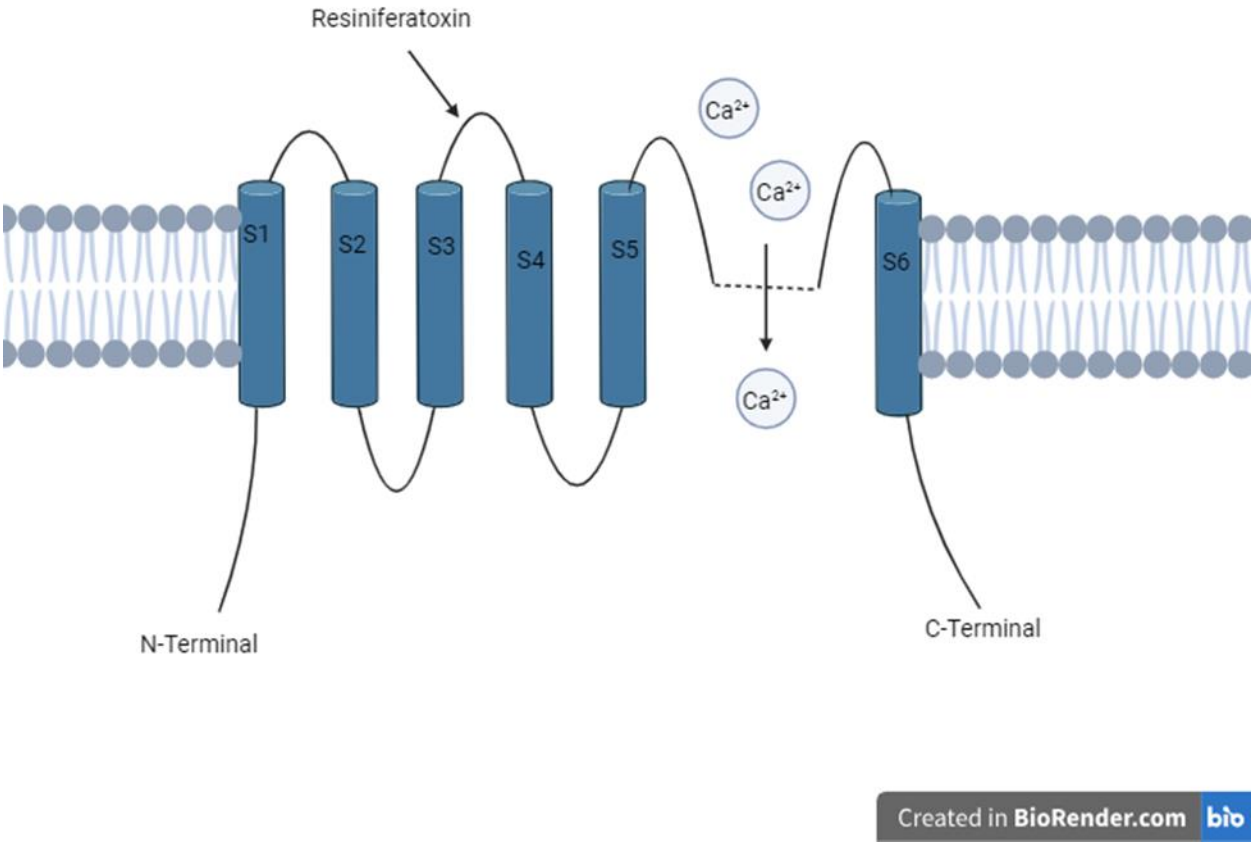

Fig. 1. Diagram of the transmembrane domains of the TRPV1 channel and label of Resiniferatoxin binding pocket.

TRPV1 has 6 transmembrane domains, and a calcium-permeable pore is formed between the 5th and 6th domains (Rosenbaum & Simon, 2007). TRPV1 agonists bind to 2 residues located between the second loop and the S3 domain (Tyr 511 and Ser 512) and a residue beneath the 5th domain (Tyr 550), creating the pore and allowing calcium cations to flow in (Rosenbaum & Simon, 2007).

How Osteoarthritis is Caused

Osteoarthritis is caused by numerous factors including aging, obesity, and injury, but the mechanisms are not fully understood. However, studies suggest that the link between these factors and the disease is chronic inflammation.

Chronic inflammation from osteoarthritis is thought to be caused by a continuing cycle of tissue damage, inflammation, and then repair. The initial damage causing osteoarthritis induces an inflammatory response that may cause further cartilage degeneration, pain, and dysfunction (Sokolove & Lepus, 2013).

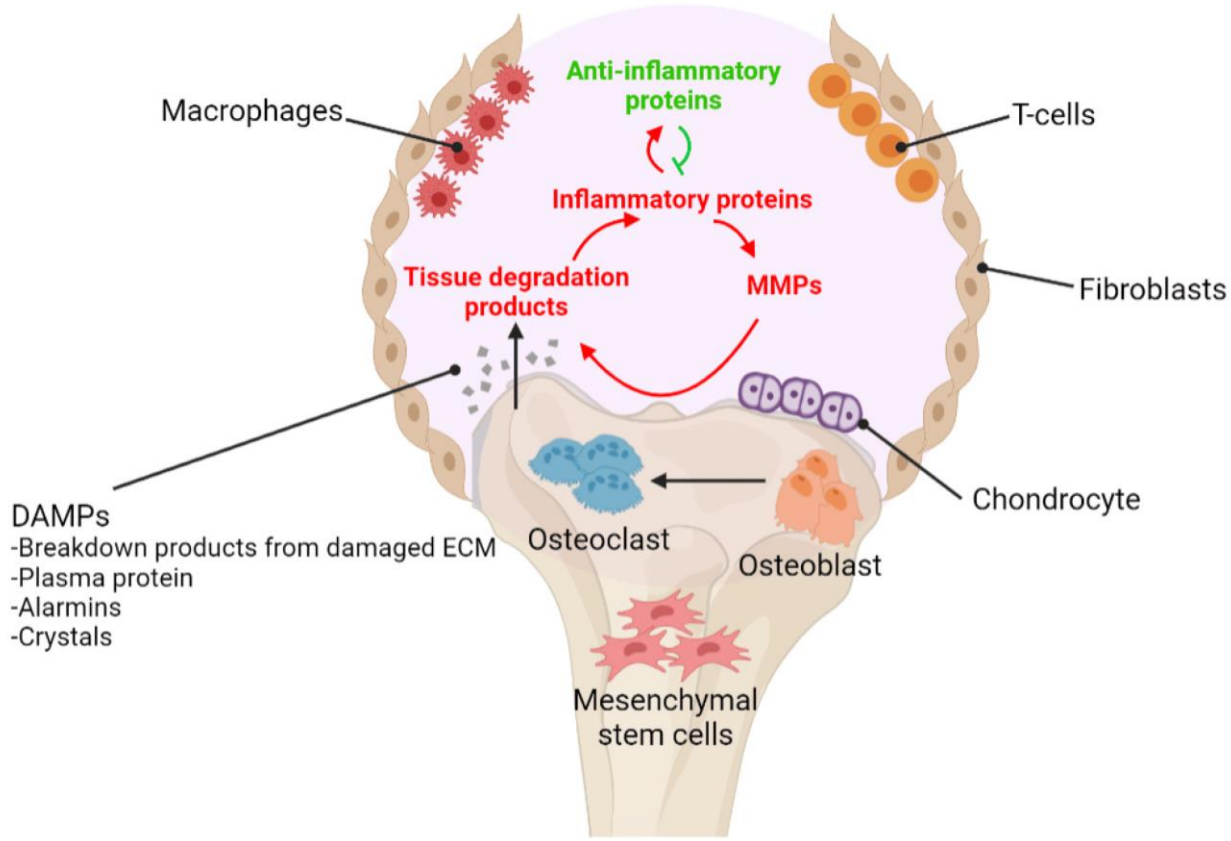

Fig. 2. Retrieved from (Nurul et al., 2021). Diagram showing the cycle of inflammation in osteoarthritis. After initial damage to the joint, damage-associated molecular patterns (DAMPs) like breakdown products of the cartilage extracellular matrix (ECM) are produced. These DAMPs go through pattern-recognition receptors on synovial macrophages, fibroblasts, or chondrocytes, leading to the production of inflammatory mediators. Inflammation causes angiogenesis, the formation of new blood vessels, resulting in an influx of plasma proteins that can serve as DAMPs, leading to more inflammation. Chronic inflammation directly causes cartilage degradation, but it also results in the induction of proteolytic enzymes, accelerating cartilage degradation in osteoarthritis (Sokolove & Lepus, 2013).

Additionally, reactive oxygen species (ROS) play a role in inducing inflammatory responses. ROS can activate cell signaling pathways and increase the release of proinflammatory cytokines, enhancing and prolonging the inflammatory responses. (Li et al., 2016). This can create a cycle where inflammation produces more ROS, which sequentially causes even more inflammation (Li et al., 2016). The cycle continues until the cellular defense mechanism against oxidative stress removes the ROS molecules from the cells (Ansari et al., 2020). Although a greater amount of ROS can help deal with infections effectively, prolonged and excessive inflammatory responses can cause tissue damage, which are major factors in the mechanisms of certain diseases, including osteoarthritis (Li et al., 2016).

Excessive ROS production can cause irreversible damage and oxidative stress in the chondrocytes and induce cell death by necrosis. ROS levels exhibit a high upregulation in the human osteoarthritis cartilage and chondrocytes. Stimulation of human osteoarthritis chondrocytes increases the production of ROS, which promotes chondrocyte cell death. Inflammation is induced when chondrocytes are exposed to pro-oxidants, meaning that oxidative stress in chondrocytes causes inflammation. Oxidative stress also relates to collagen degradation, and since ROS causes oxidative stress, excessive ROS production can lead to cartilage deterioration, which is associated with osteoarthritis (Ansari et al., 2020).

Resiniferatoxin has the potential to prevent this cycle of inflammation since the activation of TRPV1 has proven to be associated with an increase in inflammation. Desensitizing TRPV1 through resiniferatoxin can therefore provide a long-lasting decrease in inflammation.

How Resiniferatoxin Treats Inflammation

TRPV1 agonists have been shown to reduce inflammation. For example, the injection of capsaicin reduced mortality in rats with induced abdominal sepsis (Bryant et al., 2003). In addition, the injection of capsaicin in mice with lipopolysaccharide stimulation (LPS)-induced bone inflammation inhibited prostaglandin E2 production by osteoblasts. Prostaglandin E2 induces inflammation and bone resorption, so inhibiting prostaglandin E2 production also inhibits inflammation and bone resorption associated with the inflammation (Kobayashi et al., 2012).

Human umbilical vein endothelial cells cultured in the presence of capsaicin before LPS showed an increase in nitric oxide (NO) production and endothelial nitric oxide synthase (eNOS) phosphorylation and a decrease in LPS-induced cytokine and chemokine production. This led the authors to conclude that TRPV1 reduces inflammation in endothelial cells through the activation of the Ca^{2+}/eNOS/NO pathway (Wang et al., 2017).

Resiniferatoxin has demonstrated anti-inflammatory effects in multiple diseases. For example, resiniferatoxin prevented renal damage in rats induced with ischemic acute renal failure by inhibiting inflammation (Muñoz-Carrillo et al., 2017; Ueda et al., 2008). Also, resiniferatoxin demonstrates anti-inflammatory activity by inhibiting Th1 cytokines and forming a protective response against *T.spiralis* infection (Muñoz-Carrillo et al., 2017).

While capsaicin has been a TRPV1 agonist that has been more thoroughly studied, resiniferatoxin has proven to be a much more potent TRPV1 agonist, being over 1000 times more effective in neuropathic pain treatment (Singla et al., 2020). The long-lasting desensitization of TRPV1 with resiniferatoxin allows for a long-lasting analgesic effect, and with

studies proving TRPV1's association with inflammation as well, resiniferatoxin might very well be able to reduce inflammation in its activation of TRPV1, as well.

Safety and Efficacy

In a study on the effects of resiniferatoxin on dogs, dogs with osteoarthritis had a persistent lowering in pain and also an improvement in limb use after an intra-articular injection of resiniferatoxin (Iadarola et al., 2018). In dog studies involving the injection of resiniferatoxin to cerebrospinal fluid, measurements proved that resiniferatoxin's half-life in cerebrospinal fluid is between 5 to 15 minutes, which is relatively quick (Iadarola & Mannes, 2011). The scientists who conducted the study also predicted resiniferatoxin would have the same half-life in humans, and this rapid decrease in resiniferatoxin concentration after injection helps limit any possible side effects that could be caused by the resiniferatoxin staying in the human body. The results of these studies set a basis for the clinical trials on humans that came afterward.

Further, resiniferatoxin was shown to be safe in a Phase 1b double-blind study for the treatment of pain from knee osteoarthritis in humans when given as a one-time intra-articular injection with a dose of up to 30mcg (Leiman et al., 2020).

Resiniferatoxin is a capsaicin analog, and both resiniferatoxin and capsaicin bind to TRPV1 and desensitize it through calcium cytotoxicity. Resiniferatoxin is 3 orders of magnitude more potent than capsaicin in pain relief, thermoregulation, and neurogenic inflammation (Singla et al., 2020; Szallasi & Blumberg, 1989). This is because resiniferatoxin binds to TRPV1 for a

prolonged period of time, allowing more calcium cations to flow through than capsaicin does. Resiniferatoxin is able to achieve this with just 1/500th the dose of capsaicin, proving its potency.

A study was conducted regarding the pain-related genes and non-pain-related genes that capsaicin and resiniferatoxin upregulate and downregulate in rats. The scientists found that resiniferatoxin not only downregulates more target pain genes than capsaicin but also pain genes that weren't targeted, which might be a reason for the overwhelming difference in potency of pain relief between resiniferatoxin and capsaicin (Singla et al., 2020). Resiniferatoxin downregulated more than capsaicin off-target pain genes associated with nociception or those related to hypersensitivity. These off-target pain genes *Kcnk2*, *Kcnj5*, *Gal*, *Nt5e*, *Gfra2*, *Comt,* and *Ptgdr*, which are pain genes associated with nociception, and *Kcnk2*, *Acpp*, *Nt5e*, *Kcnt1*, which are pain genes associated with hypersensitivity (Singla et al., 2020). Resiniferatoxin's ability to downregulate effectively both target pain genes and off-target pain genes reveals a reason behind its potency. However, resiniferatoxin further inhibits desired genes, which alleviates nociception and hypersensitivity. These desirable genes include *Iapp*, *Trpv1*, *Adcyap1*, *Grik1*, *Tac1*, *Hrh2*, and *Gnaq* (Singla et al., 2020).

Phase 2a Clinical Trial Results for resiniferatoxin in treating knee osteoarthritis pain were recently released by Sorrento Therapeutics in September 2023. In the study, all doses of resiniferatoxin from 7.5 to 20 µg were well tolerated, with few severe adverse events and side effects. The 20 µg dose provided the best results, having the best efficacy and a durability of over 26 weeks after treatment. Future studies like Phase 2 pivotal trials and Phase 3 clinical trials may potentially allow resiniferatoxin to become a key treatment for knee osteoarthritis pain.

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