Bee Venom Therapy: a Sting in the Tale of Rheumatoid Arthritis?

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CLINICAL POINTS

Bee venom has been utilised in Asia and the USA as a therapy for treating rheumatoid arthritis.

Recent studies have shown that bee venom produces both anti-inflammatory and anti-nociceptive effects via different mechanisms.

Components of the venom inhibit expression of inflammatory mediators, such as cyclooygenase-2 and phospholipase A2, which decrease the production of pro-inflammatory molecules.

Interaction with adrenergic receptors produces analgesic effects.

Bee venom therapy may be useful for symptomatic control in patients with rheumatoid arthritis

Peptide contents of bee venom adapted from 1

Melittin

Molecular weight
2840

Contents (% dry bee venom)
40-50

Effects
Inhibits PLA_2 activity
Anti-inflammatory effects

Apamin

Molecular weight
2036

Contents (% dry bee venom)
2-3

Effects
Inhibits Ca^{2+}-activated K^+ channels
Anti-inflammatory & analgesic activity

Adolapin

Molecular weight
11,500

Contents (% dry bee venom)
1

Effects
Inhibits PLA_2 & COX activity
Anti-inflammatory activity

PLA_2 = Phospholipase A_2
Ca^{2+} = Calcium
K^+ = Potassium
COX = Cyclooxygenase

Abstract

Bee venom therapy (BVT) has been used in Asian alternative medicine for many years to treat rheumatoid conditions. BVT involves the administration of bee sting venom through injections at certain points in the body. BV exhibits anti-inflammatory and anti-nociceptive effects, which are attributable to bioactive constituents including peptides (melittin, adolapin and apamin), enzymes (phospholipase A2), and amines. It is thought that the anti-inflammatory effect is produced by inhibiting expression of inflammatory mediators, such as cyclooxygenase-2 and phospholipase A2. This results in decreased production of pro-inflammatory signalling molecules (interleukins, nitric oxide, prostaglandins). BVT administration at specific rheumatoid-affected locations also elicits an anti-nociceptive effect via interaction with adrenergic receptors and the descending serotonergic pathway of the central nervous system. BVT offers an alternative therapy for symptomatic control in rheumatoid arthritis.

Introduction

Bee venom therapy (BVT) has been used since ancient times as a treatment for arthritic pain and inflammation[1]. BVT involves the injection of purified and diluted bee venom into certain areas on the body, called acupoints. It is used in some Asian countries, including Korea, for the treatment of arthritis and rheumatoid diseases. In the Western world, including the USA, BVT has been used to treat multiple sclerosis, arthritis and chronic inflammation[2,3,4]. Bee venom itself contains at least 18 active components (including enzymes, peptides, and biogenic amines), which give it analgesic and anti-inflammatory properties. These properties make it an interesting therapy for symptomatic control in patients with rheumatoid arthritis (RA).

Mouse models of rheumatoid arthritis have suggested that BVT is an effective analgesic and is useful in improving the symptoms of RA[4,5,6]. Human clinical trials have been conducted in which BVT reduced chronic inflammation and pain[1].
This review discusses the pathophysiology of rheumatoid arthritis. It also aims to summarise the evidence to date elucidating the anti-inflammatory and analgesic effects of BVT, and its potential as an alternative therapy for patients with RA.

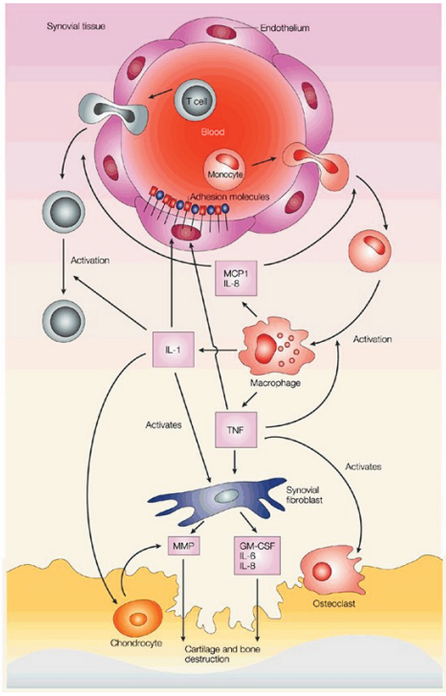
Pathophysiology of rheumatoid arthritis

RA is an autoimmune disease that causes chronic inflammation of the joints, the tissue around the joints, and other organs in the body. Although much remains uncertain, it is thought to occur when a person's body tissues are mistakenly attacked by their own immune system[7]. After initial injury, a continuing autoimmune reaction ensues. The cascade of immunological and inflammatory reactions involved has been determined (see Fig. 1). These reactions produce inflammatory synovitis and tissue swelling. Furthermore, fibroblasts that reside in the synovial lining significantly increase in number and display phenotypic transformations[8]. This leads to irreversible destruction of adjacent cartilage and bone (see Fig. 2). Often, as part of the reparative process, RA patients develop bone spurs (osteophytes), which are formed by remaining joint cartilage[9]. These cause further pain and inflammation, and may require surgical intervention.

In RA, fibroblast-like synoviocytes, macrophages, and other cells involved in inflammation infiltrate the synovial tissue[10]. The complex mechanisms that lead to inflammation include signalling mediators such as nitric oxide (NO) and prostaglandins (PG). PGs are derived from fatty acids by the family of cyclooxygenase (COX) enzymes, and the COX-2 isoenzyme is considered to be a pro-inflammatory mediator. Indeed, elevated levels of PG have been found in synovial cells treated with inflammatory mediators in vitro, and in patients with RA in vivo[11,12]. Pro-inflammatory cytokines, such as interleukin-1 (IL-1) and tumour necrosis factor-α (TNF-α), activate the inducible NO synthase (iNOS) pathway in bone cells. NO derived from this pathway potentiates the cytokine- and inflammation-induced bone loss. Therefore, agents that can inhibit COX-2 activity as well as the iNOS pathway have potential as anti-inflammatory drugs. Phospholipase A_2 (PLA_2), an upstream regulator of many inflammatory processes, also plays an important role in the pathophysiological state of RA[13,14,15].

Bee venom peptides and their effects

BV contains numerous peptides (including melittin, adolapin, and apamin), enzymes (PLA_2, hyaluronidase), biogenic amines (histamine, adrenaline), and other non-peptide components (lipids, carbohydrates, free amino acids)[1,17,18,19,20].
Melittin is a small protein and is the principle toxin in BV. However, in RA, melittin reduces pro-inflammatory COX-2 and PLA_2 expression[18], which affects the expression of TNF-α, IL-1, IL-6, and NO. These effects are suggested to be associated with the anti-inflammatory effect of melittin[1].
The effects of adolapin are thought to be due to its ability to inhibit the prostaglandin (PG) synthesis system via pro-inflammatory cyclooxygenase (COX) enzyme inhibition. In rat models of polyarthritis, adolapin has been shown to have anti-inflammatory activity[19].
Apamin, the smallest peptide found in bee venom, is a small conductance Ca^{2+}-activated K^+ channel blocker. Though not much is known about its role in RA, it is thought that apamin may have anti-inflammatory and analgesic properties. ➔



▲ ***Fig. 1. Inflammatory cascade involved in a rheumatoid arthritis joint.*** *Monocytes are attracted to the RA joint, where they differentiate into macrophages, become active, and secrete TNF and IL-1. TNF increases the expression of adhesion molecules on endothelial cells, which recruit more cells to the joint. IL-1 and TNF induce synovial fibroblasts to express cytokines (such as IL-6), chemokines (such as IL-8), growth factors (such as granulocyte–macrophage colony-stimulating factor; GM-CSF) and matrix metalloproteinases (MMPs), which contribute to cartilage and bone destruction. TNF contributes to osteoclast activation and differentiation. In addition, IL-1 mediates cartilage degradation directly by inducing the expression of MMPs by chondrocytes l 6.*

Anti-inflammatory effects of BVT

Many studies have reported a variety of mechanisms for the anti-inflammatory effect of BV and its constituents. In 2003, Nam et al.[20] examined the activity of BV from European honey bees (Apis mellifera) on mouse macrophage cell line (J774A.1 cells), human airway epithelial cell line (A549 cells) and the human myelomonocytic cell line (U937 cells) in vitro. Their results showed inhibition of COX-2 and PLA_2 activity, as well as decreased levels of pro-inflammatory TNF-α, IL-1, IL-6 and NO. This indicated that BV had anti-inflammatory properties. Indeed, their results were the first to suggest the pharmacological activities of BV on the inflammatory process of RA.

In order to gain a better insight into the mechanism of action of BV, another group[21] re-evaluated the anti-arthritic effect of BV using animal models. They examined the mechanisms behind the effect of BV and melittin using mouse macrophages, as well as synoviocytes obtained from (human) RA patients. Similar to other findings in the literature to date[1], this group found that BVT decreased the level of tissue swelling and osteophyte formation in both acute and chronic animal models of oedema[21]. They also compared the anti-inflammatory effects of BVT to those of indomethacin (a well-known COX-2 inhibitor), and found that BV had comparable results[1].

Though the anti-inflammatory effect of BV in arthritis is a compelling explanation of the symptom relief experienced by RA patients another mechanism of action is noted in recent literature. Hong et al.[22] examined cell growth inhibition and induction of apoptosis in human rheumatoid synovial fibroblasts. Their efforts suggested that rheumatoid synovial cells treated with BV exhibited apoptotic activity, and that through an apoptotic mechanism, BVT inhibits synovial fibroblast proliferation, reducing the destruction of bone and cartilage.

Anti-nociceptive effects of BVT

Nociception is defined as the "neural processes of encoding and processing noxious stimuli"[23]. It is produced in the peripheral and central nervous systems by stimuli that have the potential to damage tissues. Nociceptors (pain receptors) detect mechanical, thermal and chemical changes, and relay these changes from peripheral "afferent" neurons to the brain via ascending tracts in the spine. The brain then triggers a variety of autonomic responses, which result in a "fight-or-flight" response. It is thought that adrenergic receptor activation in the locus coeruleus (LC) of the central nervous system, however, causes depression of nociceptive transmission from afferent fibres to spinal nociceptive neurons. This results in reduced signalling to higher brain regions, and an anti-nociceptive effect[24,25].

Although an injection of BV has been reported to cause increased sensitivity to pain (hyperalgaesia), there is also evidence suggesting that BV has anti-nociceptive effects on the thermal, visceral, and inflammatory pain responses. In this regard, BV has been used traditionally to treat RA-associated pain[26].

The precise anti-nociceptive mechanisms of BV are unclear but different theories have been suggested. Subcutaneous injection of BV at a specific site has been used in Chinese medicine to produce a potent analgesic effect[1]. Kwon et al.[27] reported the anti-nociceptive effect of BV injections into a specific point ("Zusanli acupoint") located at the medial aspect of the proximal tibia. Using an animal model of chronic arthritis, they compared subcutaneous injection at this site with subcutaneous injection into a non-acupoint distal to the knee joint. BVT at the Zusanli acupoint significantly reduced the arthritis-induced nociception (mechanical and thermal pain) compared to BVT at the non-acupoint[27].

It has been hypothesized that the activation of the adrenergic pathway might be associated with the anti-nociceptive effect of BVT in RA. Baek et al. (2006) observed the activation of adrenergic receptors in BV Zusanli acupuncture in a rat model of chronic arthritis[28]. An injection of BV into the Zusanli acupoint showed a significant decrease in hyperalgaesia induced by this disease. This effect was reported to be associated specifically with the activation of α2-adrenergic receptors. Following on from this, they suggested that BVT is an effective alternative therapy for patients with joint pain, particularly for those who respond poorly to current analgesic medications.

Conclusion

In vitro and in vivo animal experiments have demonstrated that BVT can alleviate RA-related inflammation and pain. Recent studies have demonstrated mechanisms for the anti-inflammatory effect of BV and its constituents. Importantly, inhibition of COX-2 and PLA2 expression, as well as the generation of TNF-α, IL-1, IL-6, and NO (1,21) has been described. ➔

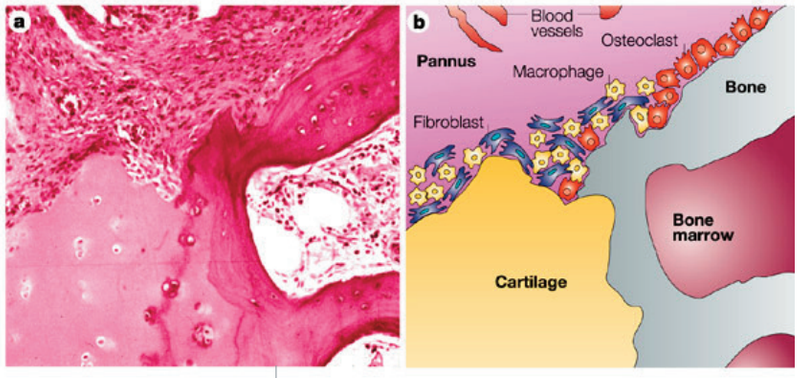
BVT - A patient's story

The account of Mr X, a 60 year old Management Consultant

My Father (a bee-keeper) was diagnosed with RA. The condition affected his movement and fine motor function. Shortly after he was diagnosed, he was stung multiple times and found that the inflammation and pain associated with his condition was relieved. As the disease progressed, he began to intentionally sting himself subcutaneously from April to October (when the bees were active). Each time, the outcome was the same – improved symptoms.

When I was in my mid-20s, a physician told me I had "Traumatic Arthritis" – caused by repeated impact trauma to my joints from sports. Over the years, my symptoms have worsened – swelling, pain, stiffness and a burning sensation in my hips, knees, left hand, and left foot near the lateral malleolus. In general, the pain is mild, but on moderate exertion (running) I feel a sharp stabbing. This reduces in a few hours, but may linger for 48-72hrs.

I do not like to take any pain medication and have taken an aspirin perhaps only a dozen times in the past 25 years. Instead, to relieve my symptoms, I sting subcutaneously at the affected joint (knees, hips, etc.) with bee stings. I usually sting the joints 2-4 times at the same location. Similar to what my father experienced, my symptoms improve significantly.



▲ ***Fig. 2. Rheumatoid arthritis.***
A: *A section through the ankle joint of a patient with rheumatoid arthritis.*
B: *Schematic representation of (A):The region of the synovial lining that erodes into the bone (known as the pannus) contains macrophages, fibroblasts and osteoclasts, which contribute to the cartilage and bone destruction. The sublining region of the rheumatoid joint is replete with blood vessels, which are important for delivering inflammatory cells, such as monocytes and lymphocytes, to the joint16.*

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Though the anti-nociceptive effect of BVT is not well understood, α2-adrenergic receptor modulation in the central nervous system has been revealed as one possible mechanism. Acupuncture at sites proximal to joints affected with RA seems to produce better analgesia to sites more distally.

There are still many concerns regarding the dose, mode of delivery, and side effects which need to be elucidated before BVT becomes widely used in the clinical setting. However, the data from recent studies have shown that BVT has the potential to be used as an alternative therapy to control inflammation and pain associated with RA. ■

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