Bee Venom Therapy as an Alternative Treatment for Neurodegenerative Disorders

Clarissa Otto

Writer's Comment: After discovering my bee allergy at a high school swim meet, I became fascinated by the healing and debilitating effects of bee venom. I had heard of bee sting acupuncture treatment for Lyme's Disease patients that resulted in miraculous recovery, and chose to research the unknown properties of bee venom in the field of medicine. My initial search yielded diverse results, with research articles suggesting that bee venom could potentially treat everything from cancer to arthritis to HIV. Counteracting my desire to research all of these, I chose to focus on neurodegenerative disorders because of the complete lack of an effective treatment available for patients, despite the devastating effects these diseases cause on memory, personality, and function in affected individuals. My continued research made it clear that major gaps in the research on bee venom therapy exist, preventing clinical trials and a possible cure for these diseases. My review discusses these gaps in the literature and suggests future topics of research that can aid in the urgent development of bee venom treatment.

Instructor's Comment: In my UWP 102B: Writing in the Biological Sciences course, students spend most of the term researching and writing a literature review. They choose their own topics, with the requirements that the topic must connect to biological sciences in some way (a pretty broad guideline) and that the topic must be timely and relevant, helping to answer some of the big questions of our time. Selecting a topic is often the most difficult part of the project, but Clarissa knew from early

in the term that she wanted to research bee venom. It's an exciting review because Clarissa explores how we can take an old idea (bee venom) and apply it in new ways (as treatment for neurodegenerative diseases). Writing a strong review is no easy feat, however. It requires discipline, motivation, and persistence. Clarissa put in a lot of time doing the research and doing extensive revision, building on what she had learned from our class community. By the end of the term, her goal had shifted from understanding what was happening in the research to finding the clearest and most engaging way to share her discoveries with readers. This final version is the result. I'm thrilled to see it published here, representing excellent undergraduate research and writing.

—Amy Goodman-Bide, University Writing Program

Introduction

Over the past 200 years, average human life expectancy has doubled in most developed countries due to improved food and water quality, better living conditions, and advanced medical services. However, this increase in lifespan does not align with an increase in health, and many neurodegenerative diseases associated with age, such as Alzheimer's disease (AD), Parkinson's disease (PD), and dementia are increasing in the general population.[1] These diseases account for 12% of deaths worldwide and are stigmatized because they cause social incapacitation, behavioral disorders, cognitive impairment, and even depression and suicide.[14] Additionally, no cure has been found for any of these disorders, and current treatments solely alleviate symptoms and slow degenerative progress. Researchers have begun to focus on bee venom therapy (BVT), a branch of alternative medicine dating back to 3000 BC, as a potential treatment for these diseases, as well as other neurodegenerative disorders, such as epilepsy and amyotrophic lateral sclerosis (ALS).

In recent years, researchers have begun to explore the biochemical mechanisms, components, and applications of this

ancient form of therapy in order to develop treatments that can cure or counteract degenerative progress. However, due to the potential of adverse effects and limited research, most studies are in preclinical stages. Nevertheless, awareness of this treatment is expanding, and the urgent need for a cure is pushing researchers to begin clinical trials. This review will evaluate the current literature on bee venom therapy and its potential to treat neurodegenerative diseases. It will also recommend future prioritization of research of components, administration, clinical applications, and safety.

Biomolecular Components and their Applications

Bee venom (BV) is a transparent, odorless mixture of various biologically active compounds that contains peptides such as melittin, adolapin, and apamin, as well as enzymes such as phospholipase A2 (PLA2).[13] It is slightly acidic with a pH that ranges from 4.5 to 5.5, and one drop consists primarily of water (88%) with only 0.1 μg of dry venom.[13] The use of whole bee venom is risky due to its inconsistent and potential adverse effects, and thus exploration into single components might provide safer and more specified care for patients.[15]

Melittin constitutes 40-60% of dry BV and is believed to be the major biologically active component.[4] In large doses, it causes pain, itching, and swelling, but in small doses, carries anti-inflammatory and antinociceptive properties.[13] Melittin has been found to cause neural plastic changes in pain-signaling pathways in the brain. These changes activate and sensitize nociceptor cells, thus producing its antinociceptive effects.[13] Researchers also found that melittin decreases signaling pathways that activate inflammatory cytokines, which leads to a reduction of inflammation in liver, skin, joint, and neuronal tissues, as well as in the lungs and spleen[13,17]. Additional properties associated with melittin are an increase in capillary permeability, decrease in blood pressure,[14] and a binding to the enzyme PLA2 to create a complex and inhibit the enzyme's activity.[9] Overall, melittin may be the most promising component

for treatment of neurodegenerative diseases, as its cytokine activation and PLA2 deactivation are critical components involved in neurodegeneration healing.

The enzyme PLA2 constitutes 10-12% of dry bee venom and is the most lethal enzyme found in BV.[4] However, it does have beneficial applications, some of which include nerve regeneration, nociception, and delayed neurotoxic effects,[4] as well as inactivation of microglia and reduced T-cell infiltration[8]. The complex it forms with melittin is beneficial in that it occurs during erythrocyte lysis, and melittin can help expose membrane phospholipids by opening melittin-induced channels.[13] A study conducted in 2018 found that PLA2 reduced accumulation of Aβ peptides and hippocampal neuroinflammation, thus improving cognitive function, as well as increased glucose metabolism in the brain.[18] Two smaller peptides include apamin, which constitutes 2-3% of dry bee venom and is primarily known for its inhibitive action on calcium/potassium channels in the CNS,[4] as well as adolapin. This peptide constitutes about 1% of dry bee venom and is the only peptide in BV that has anti-inflammatory, antinociceptive, and antipyretic properties, though minimal research has been done in its precise effects on the brain.[13]

Modes of Administration

The administration of bee venom includes a variety of methods, one of which is bee venom acupuncture (BVA). This method involves directly applying venom to the tip of a small needle, and inserting the needle into an acupoint in the skin.[8] Many studies have found that direct application to acupuncture points increases the benefits of bee venom due to combined biochemical mechanisms and acupuncture stimulation.[8,9,11] Researchers studying rheumatoid arthritis found that BV acupuncture of the Zusanli acupoint greatly improved anti-nociceptive and anti-inflammatory effects when compared to injection.[9] Studies have also shown that BVA as a potential mechanism of treatment may a safer method.[11] BVA is the primary mechanism used in human studies, and its

effectiveness thus far shows it may be the best method for clinical trials. Additionally, future research should study the mechanisms of acupuncture and investigate specific acupoints pertaining to BVT.

Live bee sting acupuncture is performed by directly inserting the stinger of a live bee into the patient's skin using tweezers to hold the bee in place.[8] Researchers utilized this tactic and found that this treatment did not improve disability, fatigue, or quality of life in patients with multiple sclerosis (MS), or produce any serious adverse effects.[12] However, another study suggests that this method increases the risk of fatal allergic reactions[8]. Overall, this method appears to be largely ineffective and potentially dangerous. BV injection involves administering the venom into the skin with a syringe, allowing for accurate collection and injection of venom.[8] This form of administration is less effective than BVA in decreasing pain and inflammation for neurodegenerative diseases, and may not be the most effective mode of administration.[9]

Clinical Applications

Parkinson's Disease

Parkinson's disease (PD) involves the loss of dopaminergic neurons and motor function, yet the mechanisms underlying the death of dopaminergic cells are unknown. However, mounting evidence points to neuroinflammation as the cause.[21] Bee venom has been shown to protect dopaminergic neurons from degeneration and injury [10,19] by modulation of Treg cells and reinstatement of TNF-α and IL-1β in brain tissues.[20] A possible mechanism by which BV protects these neurons is via interactions with proinflammatory cytokine pathways. A study found that this interaction reduces inflammation in the brain associated with PD.[21] BV was also found to increase neurotransmitter levels, ameliorate neuroexcitation, and protect against neurotoxicity, all of which could aid in PD treatment.[16] A preclinical study involving mice subjects induced with Parkinson's-like symptoms found the

enzyme PLA2 to be effective in treatment.[13] Additionally, a clinical study demonstrated the benefits of bee venom acupuncture over injection in participants with PD,[11] suggesting that acupuncture may be the best method to utilize in clinical settings and specifically in PD patients. Bee venom is extremely promising in the treatment of PD, and future studies should expand on this information, including PLA2 and BVA in the treatment of PD, while also moving into clinical settings.

Alzheimer's Disease and Dementia

Alzheimer's disease and dementia are characterized by progressive cognitive decline and inflammation in the brain. Researchers have proposed that the modulation of Treg cells is vital in research because of their anti-inflammatory effects in the brain.[18] Multiple preclinical studies have used bee venom as a method to regulate these cells and found it to be successful.[10,18,20] One of these studies simultaneously found that the enzyme PLA2 halted progressive decline in rat models induced with Alzheimer-like symptoms through its anti-inflammatory mechanisms mentioned previously. Alternatively, another study showed that the peptide apamin increased hippocampal neuronal-excitability and synaptic plasticity in rodent models, suggesting its potential to treat AD in clinical settings. Dementia affects the brain in similar ways, and a study on vascular dementia found that treatment with BV improved spatial memory, increased neurons in the hippocampus, reduced damage to microglial cells, and reduced brain inflammation.[23] While BVT shows promise in treating both neurodegenerative diseases, most if not all studies have yet to advance to the clinical stage. Before this can happen, researchers should explore which specific components of BV will have the best result and design a treatment that produces consistently beneficial results.

Amyotrophic Lateral Sclerosis

ALS is a progressive and severe paralytic disease characterized by the death of upper and lower neurons in the motor cortex, brainstem, and spinal cord.[14] Current clinical treatments focus on blocking the release of glutamate in the brain, which extends patient survival and alleviates symptoms.[22] However, the various properties of bee venom could potentially benefit patients more effectively than these treatments. Preclinical studies have found that melittin in BV reduced lung, spleen, and neuronal tissue inflammation by blocking cytokine signaling pathways in the brains of mice induced with ALS.[13,17] Because many ALS patients suffer from decreased spleen size and respiratory insufficiency, which often leads to death, these findings are crucial to ALS treatment research.[17] It's even possible that BV administration at a precise stage in ALS can block activated microglia.[13] Unfortunately, most studies involving BV treatment of ALS models are currently preclinical due to the uncertainty of the mechanisms and lack of research. Future studies should evaluate components such as melittin and their precise mechanisms in order to move toward clinical trials.

Epilepsy

Epilepsy is a neurodegenerative disease that causes recurrent seizures through imbalances in GABA (inhibitory) and glutamate (excitatory) neurotransmissions in the brain.[24] Current treatments involve antiepileptic drugs (AEDs), which are largely ineffective. However, a preclinical study found that BV acupuncture ameliorated changes in expression of blood electrolytes, neurotransmitters, and voltage-gated channels and prevented consequences associated with increased levels of glutamate and DOPA in the hippocampus. The researchers concluded that BVA could be successful in treating epilepsy in conjunction with AEDs.[10] Another preclinical study found melittin effective in decreasing seizure severity and astrocyte activation (which plays a role in glutamate uptake) in the hippocampus.[24] Overall, BV research on epilepsy is limited but

has great potential, and more research is needed to ascertain the mechanisms and effects of BV before clinical practice.

Safety Implications

Bee venom therapy can elicit immune responses that range from mild skin irritation to life-threatening anaphylaxis and should therefore be treated as a potentially dangerous form of treatment.[2] Adverse reactions consist of difficulty breathing, skin reactions (hives), swelling of the throat, weak pulse, dizziness, and loss of consciousness. A systematic review and meta-analysis of 145 studies found that adverse reactions from BVT occurred in 28.8% of all participants.[2] Additionally, patient deaths caused by BVT have been reported, including a woman who experienced adverse reactions during a second treatment of BVA and died of hypovolemic shock the next day,[5] as well as another woman who died of anaphylaxis two years into BV treatment, with no previous record of adverse reactions.[3] Because adverse reaction are so unpredictable in patients, the key to institutionalizing this treatment in medicine lies in competent and overly-cautious care.

The same meta-analysis found that BVT is often given without an initial skin test for an adverse reaction, which accounts for a significant proportion of these negative effects, and is also often administered by unqualified professionals, which can have fatal consequences for patients.[2] Additionally, it is difficult to determine the optimum dose, method of administration, and frequency of dose to succeed in effect and safety.[3] Recent research has proposed that administration through acupuncture needles could be a safer route of therapy. One study found that treatment with acupuncture needles reduced adverse effects, though participants did not experience less pain.[7] It is clear that great caution should precede any study or treatment, and BVT should possibly be considered as a last-resort option for less-severe cases of neurodegenerative disorders.[4] Its unpredictability and poor administration are

problems which need to be solved through further research and more rigid regulation in medicine.

Conclusion

The purpose of this review was to evaluate the safety, components, and applications of bee venom therapy for neurodegenerative disorders such as Alzheimer's, dementia, Parkinson's, epilepsy, and amyotrophic lateral sclerosis. The current research on the topic reveals that BV and its individual components have significant anti-inflammatory and overall beneficial effects on the brain when in small doses, and the key to specialized treatments may lie in utilizing the mechanisms and characteristics of specific components, of which melittin and PLA2 seem the most promising thus far. However, as studies are primarily in the preclinical stage, further research is needed to advance to clinical settings, especially regarding the safest methods, properties of the components, and the most effective way to apply in conjunction. Bee venom therapy has great potential to change the field of neuro-medicine, yet inconsistent results and insufficient research limits its applicability, and there is much research to be done before these benefits can be utilized and potentially treat neurodegenerative diseases.

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