

Bee venom acupuncture in different neurological illness and its immune modulation

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Introduction

Bee venom have been widely used in Oriental medicine to relieve pain and to treat inflammatory diseases.

Other potential bee venom-related treatments are currently under investigation.

In this review, attention will be focused on the most recent and innovative therapeutic applications of the bee venom in some neurological illness.

Bee Venom Components & Mode Of Action

The amount of bee venom protein released in a sting is variable, ranging between 50 to 140 micrograms.

Enzymes, Proteins and peptides are the main components including phospholipases, hyaluronidase, serotonin, histamine, dopamine, noradrenaline, adrenaline, melittin, apamin, adolapin and mast cell degranulating (MCD) peptide.

MELETTIN

Approximately 50% of honey bee venom is comprised of melettin, which has a profound neuro-hormonal and immunological effect on the body.

- ❖ It primarily stimulates the hypothalamus in the brain to release corticotropin releasing hormone which triggers the pituitary gland to secrete adrenocorticotrophic hormone (ACTH), which stimulate the adrenal cortex to reproduces cortisol.

Cortisol is:-

- A potent anti-inflammatory,
- stimulates gluconeogenesis,
- activates anti-stress pathways.

❖ Melittin also stabilizes lysosomal cell membrane, protecting against inflammation and slows the production of interleukin-1 which has been correlated to both arthritic pain and inflammation.

Apamin

Apamin is an 18 amino acid peptide neurotoxin. Dry bee venom consists of 2-3% of apamin. It selectively blocks Small conductance calcium-activated potassium channels (SK channels) , *a type of Ca^{2+} activated K^+ channel expressed in the central nervous system.*

These channels are a type of ion channel allowing potassium cations to cross the cell membrane and are activated (opened) by an increase in intracellular calcium.

Their activation limits the firing frequency of action potentials and is important for regulating after-hyperpolarization in the neurons of the central nervous system as well as many other types of electrically excitable cells. This hyperpolarization causes the membrane potential to become more negative.

ADOLAPIN

Adolapin has an anti-inflammatory and pain killing effect. It inhibits microsomal cyclooxygenase, platelet lipoxygenase, thromboxane and prostacycline which are activated during inflammation.

DOPAMINE: controls different brain center.

NOREPINEPHRINE: important neurotransmitter regulating heart rate, suppresses neuro-inflammation, and increases blood flow to skeletal muscles.

MAST-CELL DEGRANULATION PEPTIDE

Mast cell degranulation peptide is a potent anti-inflammatory, 100 times more effective than hydrocortisone in reducing inflammation, it blocks arachidonic acid production and inhibits prostaglandin synthesis.

Administering Bee Venom

In some cases, the venom administered directly from bees via the bee's stinger.

The lived bee is held by the person, who then places the bee on the part of the patient's body to be treated, at which point the bee reflexively stings.



Also the venom could be given via a syringe,
rather than directly from the bee.

Allergic reactions with Bee Venom Therapy

Generally, treatment is well tolerated. Swelling, tenderness, and redness at the sting sites are the most common complaints.



However the most sever risk of bee venom therapy is anaphylactic shock.

Although only a small percentage of the population is allergic to bee venom, it is very important to test for a bee sting allergy before the treatment.

Therapeutic Value of Bee Venom In Different Illness

There are numerous conditions that bee venom has been proposed to treat, such as:

- **Joint pain, arthritis,**
- **Chronic injuries, such as bursitis and tendonitis,**
- **Removal of scar tissue,**
- **Gout,**
- **Shingles&**
- **Burns.**

There are different therapeutic applications of Bee venom in neurological illness,

Parkinson's Disease,

Multiple sclerosis,

Learning Deficit and Alzheimer's disease

Bee venom therapy and Parkinson disease

Parkinson's disease (PD) is a neurodegenerative disorder of the central nervous system characterized by the progressive loss of dopaminergic (DA) neurons in the substantia nigra, *a region of the midbrain.*

Activated microglia, *innate immune cells in the CNS*, are known to be a key mediator of neuro-inflammation in PD.

Symptoms of Parkinson's disease include:

- **Rest tremors** : Slight shaking of a finger, hand, leg,
- **Rigidity**: Stiffness or difficulty walking,
- **Gait abnormality**,
- **Stooped posture**&
- **A 'masked' face**, frozen in a serious expression

Many studies reported that Bee venom therapy has anti-inflammatory and anti-neurodegenerative effects, that improve PD symptoms.

How Is BV Supposed to Work in PD?

Apamine and other bee venom components have a neuroprotective effect on dopaminergic neurons in the experimental PD model as:

- ❖ Improves the survival percentage of tyrosine hydroxylase, which is the enzyme responsible for the conversion of the amino acid L-tyrosine to L-3,4-dihydroxyphenylalanine (L-DOPA),

- ❖ Also it attenuates the activation of the microglial response, and reduce expression of the inflammation markers.
- ❖ BV might be helpful in reducing glutamatergic cell toxicity, which has been reported in many neurodegenerative including PD,

- ❖ increasing the efflux of dopamine and overcome the drawbacks of drugs used in PD treatment &
- ❖ Apamin not only protects undamaged neurons but also restores the function of silent neurons.

There are different studies that support this hypothesis :-

- *In 2011 Kim JI et al,* conducted a study on Bee venom and possible reduction of neuro-inflammation in animal model of Parkinson's Disease, the results of which suggested that BV injection may have a neuro-protective effect that attenuates the activation of the microglial response, which has implications for the treatment of PD.

- **Two more studies in 2012 & 2013** conducted by **DOO, A R et al & Alvarez-Fischer D et al**, suggested that bee venom can induce protection of dopaminergic neurons in an animal model with PD. The results of the studies suggest that not only apamin is responsible for this but there may be other bee venom components with the same protective effect.

- **In 2014**, another study revealed that Bee venom acupuncture might be beneficial in Parkinson's disease by increasing the efflux of dopamine. It has also been suggested to enhance the benefits of L-dopa and alleviate its adverse effects.

Bee venom therapy and MS

Multiple sclerosis (MS), is a demyelinating disorder in which the myelin sheath (insulating covers) of nerve cells in the central nervous system are damaged.

This damage disrupts the ability of parts of the nervous system to communicate, resulting in a wide range of signs and symptoms including physical, mental, and psychiatric problems.

Symptoms and signs of MS

- Hemiparesis, paraparesis
- Spasticity
- Sensory deficits
- Lhermitte phenomenon
- Monocular central
scotoma
- Diplopia
- Vertigo

- Ataxia
- Tremor
- Neurogenic bladder
- Sexual dysfunction
- Fatigue
- Depression
- Cognitive impairment

There are multiple theories considering the cause of lesions in patients with MS, including immune mediated theory. As it has been shown that T helper cells, specifically Th1 and Th17, play a significant role in the development of the brain lesion.

Overproduction of the Interleukin 12 has been found to transform CD4+ autoreactive T cells into inflammatory Th1 and Th17 cells in the brain.

Normally, T cells can distinguish between harmful and harmless cells, but in the case of MS patients, these cells will attack healthy tissues of the central nervous systems (CNS). This process triggers inflammation and the formation of subsequent lesions.

How Is BV Supposed to Work in MS?

❖ The theory is that because the stings produce inflammation, the body mounts an anti-inflammatory response. This would then work to reduce inflammation where the myelin is being attacked by the immune system.

❖ Also the anti-inflammatory constituents of bee venom have been identified. Melittin is the most abundant of these substances and is known to be 100 times more potent than hydrocortisone.

There are different studies that support this hypothesis including:-

- **A Case Report by *Huang* “ Effect of Apitherapy on Multiple Sclerosis “ concluded that apitherapy plays an important curable role in MS.**

- ***Also in Egypt Suzette et al, 2014 and Hegazi et al, 2015;*** concluded that, although Apitherapy is not curative in MS, but it can be used to minimize the clinical symptoms and can be included among programs of MS therapy.

However there are other studies against this hypothesis:-

- *“A randomized crossover study of bee sting therapy for multiple sclerosis”* concluded that Bee sting therapy *didn't improve the MS, nor improve the quality of daily activity.*

- ***Another study testing the same hypothesis was held in Netherlands in 2004***, the effectiveness of the bee venom therapy in the MS patients was assessed extensively by both clinical and radiological measures. . Although the participants tolerated the treatment well, no benefits were seen on MRI measures, the frequency and severity of the attacks, progression of disability, fatigue, or quality of life.

Bee venom therapy in learning deficit & Alzheimer's disease

As was illustrated before Small conductance calcium-activated potassium channels (SK channel) stimulation make a state of hyperpolarization that causes the membrane potential to become more negative.

increasing SK channel activity serves to impair learning.

The increase in SK channel activity, that occurs over time, may be related to decreases in plasticity and memory that is seen with aging.

How Is BV Supposed to affect learning & memory?

❖ Experiments using apamin have shown that it specifically blocks SK channels, so it was hypothesized that apamin can increase learning and long term potentiation.

- ❖ In addition, SK channels blocking, can increase brain-derived neurotrophic factor (BDNF), which facilitates long-term potentiation.
- ❖ BV might be helpful in reducing glutamatergic cell toxicity, which has been reported in many neurodegenerative diseases, including Alzheimer's disease.

Conclusion

In this review, we introduced the therapeutic effects of some bee venom component on some neurological diseases, and discussed its underlying mechanisms.

More studies are needed to clarify the effect of other different bee venom component on other neurological illness.

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