Review Article

Role of Cannabis in Diabetic Neuropathy: Is This the Therapeutic Agent?

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ABSTRACT

Diabetic peripheral neuropathy (DPN) is a common presentation in Type 2 diabetes in the long run. Neuropathic pain is the most common disabling symptom of DPN. Previous studies suggest beneficial role of cannabis in animal model for neuropathic pain. Cannabinoid receptors (CB1 and CB2) are found at sites associated with pain processing and they also modulate release of proalgesic and pro-inflammatory factors by peripheral cells. This review explored few available studies to assess role of cannabis in diabetic neuropathic pain. Extracts of cannabis have strong antioxidant effect through nerve growth factor in chemically pancreatectomised rats as supported by various studies. A human study concluded that inhalation of cannabis in a dose dependent regimen reduces pain intensity in patients of DPN while another study didn't support the role of cannabis in painful DPN. Progressive studies are required to establish the beneficial role of cannabis in diabetic neuropathic pain.

Keywords: Cannabis, Type 2 Diabetes Mellitus, Diabetic peripheral neuropathy, Cannabinoid receptors, Oxidative stress.

INTRODUCTION

Diabetes is a leading cause of morbidity and mortality worldwide. The incidence of diabetes is expected to double in the span between 2000 and 2030.[1] Diabetic peripheral neuropathy (DPN) is the leading cause of peripheral neuropathies in patients of diabetes. Nearly half of patients of diabetes are prone to DPN in near future.[2,3]

Most common symptoms in these patients are hyperalgesia and pain in their feet which gets worse at night. Numbness, sensitivity to touch, paresthesia, weakness and unsteadiness are the other symptoms of the complications.[4] DPN can disrupt the quality of life, increase morbidity and can lead to various disabilities like amputation, foot ulceration and others. Neuropathic painis the most common symptoms suffered by DPN patients constituting approximately 20 to 30% of all the symptoms.[5-8] It increases the socioeconomic burden on the patients and lowers the quality of life.[9] Metabolic, autoimmune, vascular, neurohormonal growth factor deficiency and oxidative stress are the contributing factors leading to the pathogenesis of diabetic neuropathy.[10]

Management of Diabetic Neuropathy

Diabetes Mellitus and its complication affect the quality of life and suitable therapy is not present to change the course of its pathogenesis. DPN management is critical as the symptoms are progressive and also there is lack of therapy. Aggressive glycemic control for patients of Type 1 diabetes demonstrate to decrease the progression of DPN and reduce its complications as seen in the Diabetes Controls and Complications Trial (DCCT).[11] Contrary to DCCT, various studies quotes that aggressive management of type 2 diabetes did not impact the risk and progression of DPN as compared to standard glycemic control.[12] It has been documented in various studies that lifestyle changes helps in regeneration of small nerve fiber and slow down the progression of neuropathy in diabetes and prediabetes.[13]

In the pathogenesis of DPN, various metabolic pathways have been implicated and could be the potential targets for new molecules. The assumptive pathways for the future targets are reactive oxygen species, aldose reductase, protein kinase C-beta, angiotensinogen pathway and hexosamine pathway.[14,15] Till date, in spite of promising clinical studies, none of these have been found to have progressive lead in the field.

Neuropathic pain is the most common disabling symptom of DPN. The class of drugs effective for the pain management of DPN are tricyclic antidepressants (most commonly used are amitriptyline and nortriptyline), anticonvulsants (most commonly used in DPN are gabapentin and pregabalin), and serotonin-norepinephrine reuptake inhibitors (SNRIs).[14] Duloxetine and pregabalin are the only approved for the management of neuropathic pain in diabetesdespite availability and evidence of effectiveness of these first-

line agents.[16] One of the disadvantages are that the approved agents are more expensive than other available agents for neuropathic pain. Current approved treatments were not found to achieve satisfactory results in many DPN patients. The objective of treating diabetic neuropathy is for complete pain relief. Thus to achieve the objective of complete remission from neuropathic pain, there is a need to find out new molecule which can achieve the therapeutic objective of this condition.

Cannabis and its Pharmacological Effects

Cannabis is derived from the Cannabis sativa plant which is composed of dried and shredded flowers and leaves of the plant. Tetrahydrocannabinol (THC) is the active ingredient of cannabis has been found to have psychoactive action by stimulating cannabinoid receptors and activating the endocannabinoid system.[17] Cognitive impairment, euphoria, sedation, orthostatic hypotension, tachycardia and anxiety are some of the pharmacological action of THC. Apart from THC, Cannabidiol is another constituent of cannabis that has limited psychotropic effects.[17]

CB1 and CB2 receptors are two G-coupled protein receptors of the endocannabinoid signaling system. It gets activated by their endogenous ligands (e.g., anandamide, etc.) and the bioavailability of the endocannabinoids are controlled by the synthetic and hydrolytic enzymes.[18,19]

The activation of CB1 receptors suppresses the excitability of neuronand decrease transmitter release. They execute the depressive action by reducing the action potential across the neurons. On the other hand; CB2 receptor activation stimulates MAPK activity.[20]

Role of Cannabis in Neuropathic Pain

The anatomical distribution of CB1 receptors are mostly in the brain whereas CB2 receptors are mainly expressed in the peripheral tissues and immune cells. Glial cells in the central nervous system also have CB2 receptors.[21] The distribution of CB1 receptors are mostly found in pain processing sites of the brain like the periaqueductal gray, thalamus, amygdala, cortex, etc.[22-24]

Dorsal root ganglia, brainstem, thalamus, periaqueductal gray and cerebellum are the common sites for CB2 receptor protein.[25-27]Although the number of CB2 receptor are in low amount for detectionin the brain but they get up regulated in presence of immunoreactivity or increase in mRNA due to the nociceptive action of neuropathy.[28]

On injury or trauma, the peripheral cells like mast cell, macrophage, endothelial cells, etc release the proalgesic and proinflammatory factors which are modulated by cannabinoids.[29-32] These factors sensitize the peripheral nociceptor and contribute to peripheral pain. Cannabinoid receptor gets activated by these factors which lead to modulation of the latter production resulting in analgesic effects.

Studies on Neuropathic pain

As observed from various animal studies, injury to nerve leads to neuropathic pain which in turn leads toupregulation of cannabinoid receptors suggesting the possible role of cannabinoids agonists as antihyperalgesic in the treatment of neuropathic pain.[33-39] More recent studies on animal model on neuropathic pain have found the effect of inhaled cannabis more promising but it has not found to be specifically useful in diabetic neuropathy.[40-42] Therefore, we are reviewing the effect of cannabis in diabetic neuropathy.

Studies on Diabetic Neuropathy

A study on chemically pancreatectomised rats, repeated treatment with cannabis extract has significantly reduced the physiological perception of thermal pain without affecting the blood sugar level. Cannabis extract have also additional benefit of decreasing oxidative stress and modulates nerve growth factor which will have neuroprotection against development of neuropathy and thus attenuate diabetic neuropathic pain.[43]

A randomized, double-blinded, placebo controlled crossover study was conducted in which each participant was exposed to a single dosing session of aerosolized placebo, low, medium and high doses of THC. At baseline, the intensity of spontaneous and evoked pain, and cognitive testing were recorded and subjective highness score was measured. It was observed that a significant difference was found in spontaneous pain scores between the different aerosolized doses of THC ($p<0.001$). In the average pain intensity score, significant difference was observed between placebo and the high dose of THC. Among the different doses of THC, high dose was found to have a significant improvement in average pain intensity score as compared to medium and low dose of THC. High dose of THC has significant effect on foam brush and von Frey evoked pain. On the contrary, high dose of THC has a significant negative effect on performance. In the study, it was concluded that inhaled cannabis has dose dependent reduction in pain intensity in patients of DPN.[44]

In another study, a randomized controlled trial showed that subjects receiving Sativex (cannabis based medicinal extract) or placebo had significant improves pain scores but there was no significant improvement in quality of life. The study concluded that the efficacy of cannabis has no major role in painful DPN as compared to placebo.[45]

CONCLUSION

Few previous studies have suggested that the antioxidant effect and modulatory effect on nerve growth factor of cannabinoids have unleashed its anti-hyperalgesic effects in a number of neuropathic pain models of animal. On the other hand, results from two human studies were contradictory as in one study, inhaled cannabis had dose dependent reduction in pain intensity in patients of DPN while another study showed cannabis to be no more

efficacious than placebo in painful DPN. These studies included small number of subjects and could be underpowered. Further studies with appropriate design and adequate sample size are required to explore real potential of cannabis in therapy of painful diabetic neuropathy.

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