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Research Article

Effect of Nobiletin on Diabetic Neuropathy in Experimental Rats

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Abstract

A microvascular consequence of diabetes called diabetic neuropathy (DN) causes allodynia, slowed nerve transmission, and gradual sensory loss. DN has a high prevalence and is very severe, but there is currently no cure. The purpose of the current study was to assess nobiletin's effectiveness in treating diabetic neuropathy in rats. Rats were given a single dosage of streptozotocin (50 mg/kg i.p.) to cause diabetes. Treatment with nobiletin (10mg/kg and 25mg/kg) continued for a further four weeks following the introduction of diabetes. A hot plate and tail flick test was used to determine the nociception latency after eight weeks. Also, the sciatic nerve's histology was researched together with the nerve conduction velocity measurement. The outcomes showed that nobiletin was improvement in the histology of the sciatic nerve and nerve conduction velocity at a dose of 25mg/kg (42.58 2.02** vs. control 30.00 1.51). Moreover, the nociception latency was improved. As a result, the study demonstrated nobiletin's effectiveness in the management of diabetic neuropathy in rats.

Introduction

A chronic metabolic disease that affects the vast majority of people globally is diabetes mellitus (DM). The prevalence of diabetes is rising due to a number of variables, including changing dietary and exercise habits, sedentary lifestyles, and a rise in obesity. The ratio of affected people's morbidity and mortality rises as a result of many vascular problems that people with persistent hyperglycemia experience. More than 50% of diabetics experience diabetic peripheral neuropathy (DN), which is a complex and potentially serious consequence of diabetes and the main reason for non-traumatic amputation and anatomic failure [1,2]. Alternate pathogenetic mechanisms for the circulating glucose are activated by hyperglycemia, including aldol reductase [3], non-enzymatic glycation [4], protein kinase C (PKC) [5, mitogen activated protein kinases [6], and poly ADP ribose.To mention a few, try polymerase (PARP) [7]. The activation of these alternative pathways results in the formation of a number of hazardous compounds, which negatively damage the affected people's various biological systems. Nerve conduction velocity slowing, axonal degeneration, paranodal demyelination, and fibre loss are early signs of nerve dysfunction [8]. The more severe effects of long-term neuropathy include severe pain, loss of sensation, foot ulceration and amputation, burns, infection, cellulites, sleep disorder, impaired daily functioning, mood disorders, gangrene, and involvement of various systems, including the cardiovascular, gastrointestinal, and reproductive systems [9,10].There are now relatively few medications available to cure this condition, and those that are available only provide symptomatic relief, despite efforts to make an early diagnosis and stop the progression of DN [11]. To lessen neuropathic pain, a number of medication combinations with organic compounds, such as vitamin E, have been tested [12]. According to an ethnobotany report, over 800 medicinal plants have the potential to treat diabetes, and bioactive substances such glycosides, alkaloids, terpenoids, and flavonoids (phenols) have been shown to be effective medicines in both preclinical and clinical investigations [13,14]. A class of secondary metabolites from natural sources known as flavonoids has been researched for its range of functions [15]. Citrus fruit peels contain a flavonoid called nobiletin, which has been discovered to be a potential molecule with a number of biological actions.an MMP-2 and MMP-9 inhibitor in cancer cells [16]. We postulate that nobiletin may be a promising molecule in reducing the diabetes complications since MMPs are involved in the pathophysiology of diabetic vascular

problems. Using STZ diabetic rats as a model, the current study sought to assess nobiletin's impact on diabetic neuropathy.

Discussion

Diabetes frequently results in peripheral neuropathy, which ultimately raises mortality. The current investigation examined the impact of chronic nobiletin administration on diabetic neuropathy in STZ-diabetic rats. In 48 hours, STZ-induced diabetes led to hyperglycemia, which persisted until the end of the trial. The animals' total body weight was significantly reduced. Over the course of the eight-week investigation, nobiletin treatment had no effect on the animals' body weights or blood sugar levels. This study shows that nobiletin, an MMP-2 and MMP-9 inhibitor, has a protective effect in experimental diabetic neuropathy. In addition to neuropathic pain and altered sensory perceptions, experimental diabetic neuropathy is typically characterised by abnormalities in nerve blood flow and poor nerve conduction [19,20]. We discovered important MNCV, hyperalgesia, and allodynia in diabetic rats receiving nobiletin therapy were reduced. A DN-related symptom is neuropathic pain and unusual sensory impressions. Examining an animal with diabetes' behavioural reactions to external stimuli can reveal important details about the ways in which diabetes-related pain and altered sensation are produced [21]. Using the tail flick and hot plate tests, we evaluated sensory reactions to thermal stimuli in the current study. Diabetes caused by STZ was associated with altered nociception. Several pathophysiological symptoms associated with STZ-induced hyperalgesia have been observed in various animal models to be capable of altering nociceptive responses [22–24]. Rats with diabetes that were eight weeks old showed decreased latencies in the hot plate and tail flick tests.

According to the current study's findings, a four-week course of In test animals, nobiletin reduced thermal hyperalgesia. Nobiletin treatments helped to partially restore decreased tail-flick latencies. In diabetic rats, nobiletin had a strong antinociceptive impact; the level of antinociception was more pronounced in the higher dose group (NOB25).Our examination of the sciatic nerve's morphology revealed that diabetes causes endoneurial edoema, axonal degeneration, and occasionally secondary segmental demyelination, which results in histological damage to the nerve fibres. These findings are consistent with past research [25–27]. It is understood that MMP-2 and MMP-9 contribute to the breakdown of the basement membrane's ECM elements. Type IV collagen, fibronectin, elastin, and denatured interstitial collagen are a few of the substrates they function on [28]. The basement membrane thickens and the ECM is degraded as a result of elevated levels of MMP-2 and MMP-9 [29]. Atherosclerosis and artery constriction may result from ECM deterioration.

This could ultimately result in the loss of neural cells due to ischemia of the affected nerve tissue. For what Nobiletin is well known its restraining effect on MMP-2 to MMP-9. According to the histology of the neurons in our investigation, the inhibition of MMP-2 and MMP-9 may have improved their state. Other measures including MNCV, hot plate latency, and tail flick latency may also have decreased as a result of this improvement in nerve histology.It was clear from the current study that streptozotocin-induced diabetes in rats resulted in a decrease in the conduction velocity of the sciatic motor neuron and nociception. The MNCV in animals treated for four weeks with nobiletin improved. Histology of the sciatic nerve revealed that the treatment group's nerve structure was better than the control group's. These results happened even when the hyperglycemia was unaffected. Hence, it is possible to say that nobiletin causes diabetic neuropathy via It was clear from the current study that streptozotocin-induced diabetes in rats resulted in a decrease in the conduction velocity of the sciatic motor neuron and nociception. The MNCV in animals treated for four weeks with nobiletin improved. Histology of the sciatic nerve revealed that the treatment group's nerve structure was better than the control group's. These results happened even when the hyperglycemia was unaffected. So, it can be said that nobiletin functions in diabetic neuropathy by a mechanism other than reducing blood glucose. The most likely cause of this improvement could be nobiletin's inhibition of MMP-2 and MMP-9.

Conclusions

Nobiletin therapy, in conclusion, improved nociceptive latency and nerve conduction velocity in STZ rats with diabetic neuropathy. Hence, the findings of the present investigation imply that nobiletin may play a protective function in STZ-induced diabetic neuropathy.

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