Finding a Novel Dual Active Agonist of the Adiponectin and Opioid Receptors as a Potential Therapy for Diabetic Neuropathy

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Introduction

One of the most common complications of diabetes mellitus is diabetic neuropathy (DN), which affects more than half of diabetic patients, including those with type 1 diabetes and type 2 diabetes. Without displaying any obvious symptoms, diabetic patients may suffer from extensive peripheral nerve damage and dysfunction. Patients commonly experience sensory symptoms like pain, prickling, and tingling as a result of DN, which mostly affects sensory nerves [1]. Additionally, it affects motor neurons, resulting in ankle and toe weakness. Motor weakness and sensory loss in the lower extremities are two effects of the progressive impairment. It is difficult to fully comprehend the molecular mechanisms that lie behind DN and the onset and progression of nerve damage. Additionally, it is regrettable that diabetic neuropathy does not respond to other than strict glycemic control [2].

Neuropathic pain is a common symptom of DN, which is caused by multifactorial impairment of the peripheral sensory neurons caused by oxidative stress, inflammation, and neuronal apoptosis. Opioid analgesics are actually less effective at treating diabetic neuropathy, and tolerance develops quickly after prolonged use [3]. In many cases, neuropathies cause excessive sensitivity to nociceptive stimuli or render normal stimuli perceptible as painful. However, diabetic pain has been treated with opioid analgesics. The -opioid receptor (MOR), the -opioid receptor (DOR), and the -opioid receptor (KOR) are the three GPCRs that control opioid analgesia [4]. Opioids that combine MOR agonist–DOR antagonist activity may be more effective as an antinociceptive and less likely to cause MOR-mediated side effects. The decrease of narcotic analgesics viability and aftereffects in this sort of agony may be because of MOR in the spinal line. Some of us have recently described benzomorphan derivatives that are -opioid receptor ligands but do not possess any affinity for the other opioid receptor subclasses delta and kappa in our search for alternative antinociceptive pathways distinct from the well-known signal transduction mediated [5]. However, while an agent with only an analgesic effect may be able to alleviate DN pain symptoms, it may not be able to treat DN. Due to the disease's multifactorial pathogenesis and complex etiology, multi-target medications have emerged to treat diabetic neuropathy [6].

Description

Adiponectin (APN) is an insulin-sensitizing, anti-inflammatory, and anti-oxidative circulatory adipokine that is primarily secreted by adipocytes and the liver. It has been linked to diabetes complications and type 2 diabetes mellitus (T2DM). APN ties to adiponectin receptors (ADIPOR1 and ADIPOR2) to sharpen insulin flagging and tweak fat digestion. A low APN level in the bloodstream can accelerate the onset of diabetes symptoms and lead to insulin resistance. Adiponectin polymorphisms linked to lower APN levels in the blood increase the risk of developing diabetic neuropathy, according to studies [7]. There is growing evidence that APN protects neurons in both the central and peripheral nervous systems. Retinal ganglion cells, hippocampal neurons, and sensory neurons in the hypothalamus are all protected from neuronal death by APN. Subclinical inflammation and sensorimotor nerve conduction have also been linked to APN in T1DM and T2DM patients, according to a clinical study [8]. All the more critically, APN manages warm nociception in a mouse model of neuropathic torment. Neurons in the somatosensory cortex, the spinal cord dorsal horn, and glial cells in the spinal cord all express adiponectin receptors. In mice, the loss of APN increased thermal insensitivity, which is linked to an increase in the levels of proinflammatory cytokines (TNF and IL1) in the spinal cord's dorsal horn [9]. These suggest that APN may inhibit neuroinflammation in the somatosensory nervous system to regulate nociception. Neuronal loss and degeneration have also been observed in the motor system of diabetic patients and rodent models, most likely as a result of oxidative stress in the motor neurons. Antioxidant and neuroprotective properties of adiponectin have been demonstrated. The sensorimotor system may be protected from neuronal loss by activating adiponectin signaling. In obese diabetic mice, AdipoRon was found to be an orally active adiponectin receptor agonist with anti-diabetic effects and a shorter lifespan. It has also been used to prevent neurodegeneration in mouse models [10- 12]. However, it may worsen neuropathic pain by inhibiting mitochondrial functions and reducing ATP production, similar to some AMPK activators. Therefore, the adiponectin-based treatment plan for diabetic neuropathy is dependent on the discovery of a novel adiponectin receptor agonist [13].

Benzomorphan derivatives with opioid activity emerged as potential binders to ADIPO-R1 and -R2 following a virtual screening repositioning campaign that included previously reported benzomorphan derivatives and adipoRon-like piperidine derivatives by docking into ADIPO-R1 and -R2. 1). Compound (+)-MML1017 was ultimately selected for further testing as ADIPO-R ligand on the basis of the docking score, the structural similarities with AdipoRon (unpublished results), and the good functional in vivo pharmacological profile [14]. Compound (+)- MML1017 could address a praiseworthy double acting exceptionally unambiguous compound that can adjust the action of the MOR framework to oversee neuropathic torment and ready to enact adiponectin receptors for neuroprotection. (+)-MML1017 has been shown to increase cell viability in hyperglycemic neurons and AMPK phosphorylation through ADIPO-R1 and ADIPO-R2 in motor neuron NSC-34 in vitro [15].

Conclusion

We have distinguished an original double acting μ-narcotic receptor and adiponectin receptor agonist, (+)- MML1017, a benzomorphan subsidiary, with likely neuroprotective impacts. The compound increases neuronal survival in hyperglycemic conditions, activates ADIPOR-AMPK signaling, and activates MOR-mediated calcium influx. For (+)-MML1017's potential analgesic and therapeutic benefits in diabetic neuropathy, additional biochemical and pharmacological studies on preclinical models are necessary.

Acknowledgement

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Conflict of Interest

None

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