Letters to the editor: Nicotinic acetylcholine receptor ligands as potential targets for managing neuropathic pain induced by diabetic peripheral neuropathy

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ABSTRACT

Diabetic peripheral neuropathy (DPN) is a medical condition that is progressively becoming more prevalent. The underlying cause of DPN is still unknown, although there have been several hypothesized mechanisms. There are current pharmaceutical treatments used to manage the pain, but their efficacy is largely unsatisfactory and are often associated with serious adverse effects. This review will explore the evidence of a new potential target for treating DPN, the ligands for nicotinic acetylcholine receptors (nAChRs), specifically α4β2 agonists and α9α10 antagonists.

1. Nicotinic AChRs and their subtypes

Nicotinic AChRs are pentameric ligand gated non-selective cation channels found in abundance in the nervous system and immune cells such as macrophages, cochlear hair cells, or keratinocytes. Among the various subunits discovered so far, α4β2 and α9α10 are potentially useful to regulate nociception and inflammation [1,2]. The exact mechanisms of action remain elusive, but both nAChR ligands seem to play important roles in modulating inflammation and immune cell functions (Fig. 1). The results of their preclinical and clinical studies are listed in Table 1.

2. α4β2 subunit

The α4β2 subunit is one of the predominant subtypes of nAChRs in the brain. Activation of brainstem α4β2 nAChRs may engage the descending inhibitory mechanisms, such as release of serotonin (5-HT) and norepinephrine to reduce pain neurotransmission in the spinal cord [3]. It may also increase gamma aminobutyric acid (GABA) release in the rostral ventromedial medulla to promote descending inhibition. Moreover, activation of α4β2 nAChRs can suppress peripheral macrophages and possibly microglia in the CNS to decrease neuropathic pain.

Epibatidine is a toxic alkaloid and natural α4β2 agonist from the skin of the Epipedobates tricolor frog. The analgesic effects of epibatidine are 200 times higher than morphine and 30 times higher than nicotine [4]. Unfortunately, it failed the clinical trial due to adverse effects such as toxicity in the CNS, gastrointestinal, respiratory and cardiovascular systems likely due to epibatidine’s ability to activate ganglionic α3β4 subunits [4].

Despite failing clinical trials, epibatidine has garnered great interest because of its non-opioid superior analgesic effects. Derivatives with better selectivity have since been made from this natural compound and shown promising results. ABT-594, also known as Tebanicline, showed very potent analgesic and anxiolytic effects in rat and mouse models with little to no adverse effects at the effective antinociceptive dose [5]. It was then studied in a phase II randomized, multicenter, double-blind, placebo-controlled study in 266 patients with DPN and showed pain reduction across all doses of the treatment groups. However, the ratio of patients dropping out due to adverse effects were significantly higher than placebo. The therapeutic window is small as higher doses of ABT-594 activate the α3 nAChR as well, causing adverse autonomic effects such as decreased body temperature and impaired motor coordination, nausea, vomiting, and abnormal dreams [4].
Another α4β2 selective agonist, Cris-104, showed better selectivity for α4β2 subunit with a much lower affinity for other nAChR subunits [6]. In diabetic mice, it reduced mechanical allodynia and thermal hyperalgesia, common symptoms associated with DPN [6]. In diabetic mice, it reduced mechanical allodynia and thermal hyperalgesia, common symptoms associated with DPN [6]. In diabetic mice, it reduced mechanical allodynia and thermal hyperalgesia, common symptoms associated with DPN [6]. In diabetic mice, it reduced mechanical allodynia and thermal hyperalgesia, common symptoms associated with DPN [6]. In diabetic mice, it reduced mechanical allodynia and thermal hyperalgesia, common symptoms associated with DPN [6]. In diabetic mice, it reduced mechanical allodynia and thermal hyperalgesia, common symptoms associated with DPN [6].

Recently, S-(1R,5S)-3,6-Diazabicyclo[3.2.0]heptan-6-yl nicotinonitrile (A-366833), showed even higher selectivity for the α4β2 subunit (Ki = 3.2 nM) vs. the α3 subunit. It reduced mechanical hyperalgesia and produced antinociception in rat models of diabetes and chemotherapy-induced neuropathic pain [7,8]. Although they have not been studied clinically, improved selectivity of the α4β2 subunit over the α3 subunit indicates great potential to alleviate DPN pain without concurrent side effects.

### 3. α9α10 subunit

The α9 subunit was first identified in the inner hair cells of rodents. Later on, α10 subunits are found to be assembled together with α9 to form the α9α10 subunit in the DRG, immune cells, and immune cell derivatives. Existing evidence indicates that they are involved in immune responses and processes including nociception and inflammation. When activated, α9α10 subunit can promote the release of IL-1β, interferon γ (IFN-γ), and monocyte infiltration [1]. Multiple α9α10 nAChR agonists, such as cone snail venom toxins Vc1.1, RglIA, and RglIA4, have been studied in various pain models [2].

Vc1.1 was the first compound of this class to advance to clinical trials after showing significant reduction of neuropathic pain following partial sciatic nerve ligation in rodents [7]. It blocked the development of tactile allodynia and mechanical hyperalgesia that lasted 10 days post discontinuation of treatment in streptozotocin-induced diabetic rodents [9]. In the Phase I clinical trial no drug related adverse effects was observed with single or multiple systemic doses [2]. Unfortunately, the drug failed to show therapeutic effect in Phase II clinical trials [10]. Later on, it has been discovered that Vc1.1 has much lower affinity for human α9α10 nAChRs than its rodent counterparts [11]. Another conopeptide, RglIA, showed great efficacy in alleviating chronic neuropathic pain induced by nerve injury and chemotherapy in mice possibly via inhibition of inflammation and activation of peripheral macrophage and/or central microglia and astrocytes in the dorsal horn [9]. However, similar to Vc1.1, RglIA is about 300 fold less potent against human α9α10 nAChRs than the rodent receptors.

More recently, McIntosh group created RglIA4 [12], a derivative of RglIA, that have significantly higher affinity to human α9α10 nAChRs than its predecessors. It has equal potency to both receptors with half-maximal inhibitory concentrations (IC50) of 0.9 and 1.5 nM for rodent and human receptors, respectively [13]. RglIA4 has been shown to produce remarkable “disease-modifying” effects for the prevention and treatment of neuropathic pain in rodents without observable tolerance effects [2].

While these newer α9α10 nAChR antagonists haven’t been tested directly in DPN patients, they have been shown to decrease the degeneration of the DRG and nuclear alterations associated with DPN [10], reduce the activation of macrophages and T cell infiltration following a nerve injury, which may contribute to their anti-neuropathic properties.

In summary, DPN is a growing problem worldwide. α4β2 agonists and α9α10 antagonists have shown promising results in rodent models in alleviating several types of neuropathic pain. The selective ligands of these subtypes that have been tested in clinical trials seemed to be well tolerated. Based on the current research, α4β2 nAChR agonists and...
a9α10 nAChR antagonists hold great potentials to relieve neuropathic pain induced by DPN with less adverse side effects than the current available therapies.

**Declaration of Competing Interest**

None of the authors has any conflict of interest.

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