

Treating neuropathic pain and nicotine dependence: Epibatidine derivatives as potential therapeutics

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Lance R. McMahon, Ph.D. and Jenny L. Wilkerson, Ph.D. from Texas Tech University Health Sciences Center, describe the search for the magic bullet to treat both neuropathic pain and nicotine dependence using novel epibatidine derivatives as potential therapeutics

Nicotinic acetylcholine receptors (nAChR), specifically nAChR containing $\alpha 4\beta 2^*$ subunits (* denotes additional receptor subunits), are known for their role in nicotine dependence and addiction ⁽¹⁾. These receptors are found throughout the central and peripheral nervous systems on neuronal, glial, and immune cells ⁽²⁾. Although varenicline, an $\alpha 4\beta 2$ nAChR* partial agonist, is a useful smoking cessation pharmacotherapy, the largest individual cause of preventable death continues to be cigarette smoking. ⁽¹⁾

Nicotine dependence and chronic neuropathic pain

Up to 17% of the global population live with neuropathic pain, which is produced from injury to the nervous system and is associated with significant impairment in quality of life. ^(2,3) Conditions producing neuropathic pain are increasingly prevalent in tobacco-dependent individuals, e.g., lung and other cancers, which, when treated with chemotherapy, often result in peripheral neuropathy, as well as peripheral neuropathies in diabetic patients (Figure 1). ⁽³⁾

Neuropathic pain is poorly controlled by current pharmacotherapeutics, which include tricyclic antidepressants, serotonin and noradrenaline reuptake inhibitors, antiepileptic drugs, and opioids, all of which have significant side effect profiles ⁽³⁾. A compound that can successfully treat both chronic neuropathic pain and nicotine dependence would be extraordinary.

$\alpha 4\beta 2^*$ nAChR agonists as pain therapeutics

Many nAChR agonists, including those acting on $\alpha 4\beta 2^*$ and $\alpha 7$ nAChR, have pain-alleviating effects in preclinical studies ⁽³⁾; however, the potential for $\alpha 4\beta 2^*$ nAChR agonists to be viable pain medications has yet to be realized. Epibatidine, one such $\alpha 4\beta 2$ nAChR agonist, initially garnered interest for both its analgesic and anti-nicotine dependence effects, yet a low therapeutic index due to toxicities has limited its development as a safe therapeutic ⁽³⁾.

Medicinal chemistry of novel epibatidine derivatives

Epibatidine (chemical name (\pm)-exo-2-(6-Chloro-3-pyridinyl)-7-azabicyclo[2.2.1]heptane) has become an important chemical scaffold used by several independent laboratories to further investigate $\alpha 4\beta 2^*$ nAChR pharmacological activity. Dr. F. Ivy Carroll, Distinguished Fellow for Medicinal Chemistry and Lead Medicinal Chemist at Research Triangle Institute (RTI) International's Center for Drug Discovery, spearheaded such a campaign, which led to the synthesis of numerous novel epibatidine derivatives that act as $\alpha 4\beta 2^*$ nAChR agonists and antagonists. Previous studies have described the synthesis, nAChR binding affinity, and pharmacological properties of numerous novel epibatidine analogues produced by Dr. Carroll and his laboratory. ^(4,5)

Exploration of novel epibatidine derivatives for nicotine dependence and neuropathic pain

Approved nicotine dependence medications like varenicline share similar but not identical pharmacological activity to the targeted abused drug nicotine. ⁽³⁾ To determine whether a novel compound shares pharmacological properties with nicotine, behavioral assays, referred to as nicotine discrimination assays, have proven useful in developing pharmacotherapies for nicotine dependence. A compound that shares effects with nicotine in this assay is likely to include $\alpha 4\beta 2^*$ nAChR as a major part of the mechanism of action.

Three epibatidine derivatives, 2'-fluoro-3'-(4-nitrophenyl) deschloroepibatidine (RTI-7527-102; i.e., RTI-102), 2'-fluorodeschloroepibatidine (RTI-7527-36; i.e., RTI-36), and 3'-(3"-dimethylaminophenyl)-epibatidine (RTI-7527-76; i.e., RTI-76) were tested in both the rat nicotine drug discrimination assay as well as in the rat chronic constriction injury (CCI) of the sciatic nerve neuropathic pain model. ⁽³⁾ In the nicotine discrimination assay, the rank order potency (i.e., the amount of drug required to produce a specified amount of effect, usually half the full effect) was RTI-36 > nicotine > RTI-102 > RTI-76.

In a separate cohort, Sprague-Dawley rats underwent nerve ligation surgery and tested for light touch sensitivity, termed mechanical allodynia, which is a surrogate for peripheral neuropathy. RTI-36, RTI-102, and RTI-76 reduced the mechanical allodynia at doses that did not produce unwanted effects. ⁽³⁾ Each compound produced mechanical allodynia reversal at doses that fully substituted for nicotine, which suggests that at therapeutically active doses, these compounds produce a subjective experience similar to that produced by nicotine. ⁽³⁾

Conclusions and future perspectives of $\alpha 4\beta 2^*$ nAChR-targeted therapeutics

Although epibatidine is not an ideal clinical candidate, its $\alpha 4\beta 2^*$ nAChR agonist derivatives described here may be useful analgesics if they display analgesic-like effects at doses that do not produce toxicity or other side effects. As nicotine is highly addictive, the abuse and dependence potential of these compounds should be further explored before these derivatives are considered as viable potential novel analgesics. Additional

work on the receptor selectivity and binding activity of these and related analogues may yield better therapeutic leads. However, $\alpha 4\beta 2^*$ nAChR agonists could serve the dual purpose of a smoking cessation aid and analgesic.

References

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