INNOVATION PARTNERSHIPS
UNIVERSITY OF MICHIGAN

Methods for the Treatment of Nicotine Dependence

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OVERVIEW

A novel improvement of a therapeutic method to aid smoking cessation

- A cofactor CycN that increases the turnover rate of NicA2 to decrease nicotine reaching the brain
- Recognition and isolation of mutated NicA2 variants that may also improve nicotine inhibition

BACKGROUND

Tobacco use has long been correlated with potentially serious health consequences, leading to nearly 20% of annual deaths in the United States. Nicotine addiction serves as the primary reason that people are unable to discontinue tobacco use, in spite of the availability of smoking cessation aids that deliver nicotine by other routes such as gum, patches, and lozenges. The success of these existing supportive methods leading to the desired goal of smoking cessation rarely reach above 1.5-2 times greater than efforts undertaken in their absence. Nicotine holds impressive addictive properties, and there exist few other pharmaceuticals that modulate nicotine receptors in the brain and which could therefore serve as therapeutic agents. One new approach to treatment is the use of a nicotine degrading enzyme, nicotine oxidoreductase (NicA2), to intercept nicotine in the bloodstream and prevent its passage into the brain. NicA2 is a protein produced in bacteria that has been shown to prevent nicotine cravings when given to rats. Unfortunately, the positive effects of Nic2A would require a prohibitively high dose to serve as feasible treatment option in humans, due to the low rate of activity of this agent in the bloodstream. So, a need exists for a method to increase the metabolic turnover rate of Nic2A in patients seeking smoking cessation.

INNOVATION

Researchers have invented a method to address the slow turnover rate and high level of nicotine oxidoreductase (NicA2) required to treat nicotine addiction, providing an improved therapeutic approach to aid smoking cessation. Though the slow turnover rate of NicA2 results from a rate limiting step whereby it reacts with molecular oxygen, this innovation provides a means by which to increase the speed of NicA2 turnover 10,000-fold by co-administration of a novel cytochrome c cofactor (CycN). Additionally, the invention utilizes a screening approach to detect mutated variants of NicA2 in vitro that are capable of bypassing the need for CycN co-administration while increasing turnover rate. Through the use of a novel genetic selection process, the investigators were able to screen through mutated variants of NicA2 in a very high-throughput growth assay. This approach permitted screening of millions of mutations for

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variants that perform better than wild-type NicA2, which would then be more suitable for use as treatment. A pathway might also exist for creation of mutated variants of NicA2 to increase the intrinsic ability of this enzyme to react with O2, increasing the in vitro turnover rate without the need for additional cofactors. Overall, the invention provides a promising approach for fostering smoking cessation and decreasing the diseases which result from tobacco use.