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Involvement of neuronal Nicotinic cholinergic α4β2 receptors in alcohol and Nicotine addiction and cognition: Preclinical studies

Amir H. Rezvani
Duke University Medical Center, USA

Neuronal nicotinic cholinergic receptors have been implicated in alcohol drinking behavior, nicotine addiction and cognitive function. Manipulations of these receptors have been shown to influence both alcohol consumption and cognition. Sazetidine-A [6-(5(((S)-azetidine-2-yl)methoxy)pyridine-3-yl)hex-5-yn-1-ol] and VMY-2-95 are novel compounds that potently and selectively desensitizes neuronal α4β2 nicotinic receptors. The goal of the present study was to examine the effects of these compounds on alcohol consumption in alcohol preferring (P) rats, and on nicotine self-administration and attention in Sprague Dawley rats. In alcohol studies, alcohol preferring rats were given the choice of water or alcohol. Once stable baselines were established, the acute and chronic effects of sazetidine-A and acute effects of VMY-2-95 on alcohol intake were assessed. In addition, the acute effects of sazetidine-A, VMY-2-95 and naltrexone on alcohol intake after alcohol deprivation were evaluated. Our results show that sazetidine-A and VMY-2-95 caused a dose-dependent reduction in alcohol intake. Chronic sazetidine-A also effectively reduced alcohol intake. In the post-deprivation experiment, when the urge for drinking is enhanced, similar to naltrexone, sazetidine-A and VMY-2-95 significantly reduced alcohol intake and preference. In the sustained attention study, using an operant visual signal detection task it was shown that dizocilpine and scopolamine caused significant impairments in performance, which were significantly reversed by an acute dose sazetidine-A. These studies imply an important role for α4β2 nicotinic receptors in improving sustained attention under conditions that disrupt it. Both sazetidine-A and VMY-2-95 when given acutely significantly reduced nicotine intake.

In conclusion, very low doses of sazetidine-A and VMY-2-95 may hold promise for the treatment of heavy drinking and nicotine self-administration and sazetidine-A provides therapeutic benefit for reversing attentional impairment in patients with mental disorders suffering from cognitive impairment. (Supported by NIDA U19 grant DA027990 and NIAAAR25-AA015512-02).

Biography

Amir H. Rezvani earned his Ph.D. in neurophysiology from University of Illinois in 1983. After finishing his Post-doc training at the University of North Carolina in Chapel Hill he worked as a faculty in the Dept. of Psychiatry and Center for Alcohol Studies till 1999 when he joined the Department of Psychiatry and Behavioral Sciences at Duke University. Currently, as a professor of Psychiatry and Psychology and Neuroscience he both teaches and does research. His research mainly is focused on alcohol and nicotine addictions, cognition and drug development for these disorders. He has authored more than 160 scientific articles and book chapters. He is well known internationally for his scholarly works.

azadi@duke.edu