sufficient affinity to block nicotine's reinforcing effect by preventing binding of nicotine at α4β2 nAChRs when smoking.

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**3.11**

### Low efficacy partial agonists of the α4β2 nicotinic acetylcholine receptor (nAChR). Does functional efficacy govern in vivo response?

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Nicotinic acetylcholine receptor (nAChR) partial agonists are promising medicinal targets as treatments for cognition, pain, schizophrenia, addiction and depression. As mediators of cholinergic signaling, partial agonists with differing functional efficacies are of interest as this property could be a critical variable in determining treatment effectiveness. Here, we describe an enantiomeric pair of molecules closely related to varenicline, the first approved nAChR partial agonist, and their evaluation in in vitro and in vivo preclinical models relevant to nicotine addiction and other indications.

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**3.12**

### The nAChR agonist AMOP-H-OH ('sazetidine-A') exhibits reinforcing, but not withdrawal-alleviating, properties in rats

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The novel nAChR ligand AMOP-H-OH ('sazetidine-A') has been reported as either a full or partial agonist at high-affinity nicotinic acetylcholine receptors (nAChRs). The present studies aimed to test the hypothesis that if AMOP-H-OH is an agonist at high-affinity nAChRs, it will exhibit reinforcing and perhaps withdrawal-alleviating properties in rats trained to self-administer nicotine or chronically exposed to nicotine via subcutaneous osmotic minipumps, respectively. Rats were trained to self-administer nicotine under a fixed-ratio 3 schedule of reinforcement, and a nicotine dose–response function (0, 0.01, 0.03, 0.06, 0.1 mg/kg/inf) was determined. Nicotine-trained rats were then allowed to self-administer a range of doses of AMOP-H-OH (0.01, 0.03, 0.06, 0.1, 0.3 mg/kg/inf). The effects of AMOP-H-OH, the non-competitive neuronal nAChR antagonist mecamylamine or the high-affinity nAChR partial agonist varenicline on the reinforcing effects of nicotine were determined. Finally, naive rats were prepared with subcutaneous osmotic minipumps containing either nicotine (3.16 mg/kg/day, free base) or saline. Six days later, the minipumps were removed and the effects of acute pre-treatment with AMOP-H-OH, varenicline and nicotine on the somatic signs of nicotine withdrawal were assessed. AMOP-H-OH exhibited a dose-response function that was shifted to the right compared to nicotine. The reinforcing effects of nicotine were attenuated by AMOP-H-OH, mecamylamine and varenicline. Varenicline and nicotine, but not AMOP-H-OH, attenuated somatic signs of nicotine withdrawal in rats. The present studies observed dose-sensitive changes in AMOP-H-OH self-administration similar to nicotine, thereby indicating that AMOP-H-OH is an agonist at high-affinity nAChRs *in vivo*. Interestingly, AMOP-H-OH failed to attenuate the somatic signs of nicotine withdrawal, most likely due to a lack of efficacy at β4-containing nAChRs. The present studies confirmed previously reported effects of varenicline on nicotine self-administration, and extended the varenicline literature by demonstrating varenicline-induced attenuation of somatic signs of nicotine withdrawal. Future studies should further characterize the reinforcing properties of AMOP-H-OH, assess the effects of AMOP-H-OH on nicotine withdrawal-associated changes in brain reward function and neurochemistry, and assess the effects of AMOP-H-OH in preclinical models of relapse.

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## Section 4. Pain and other indications

**4.1**

### In vitro pharmacological profile of a novel α4β2 positive allosteric modulator NS9283 (A-969933)

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Nicotinic agonists of the α4β2 nAChR subtype are considered as potential therapeutic agents for treating pain with supporting evidence provided by compounds such as ABT-594 and ABT-894. An approach to enhance the function of α4β2 nAChRs is by positive allosteric modulation. In this study, we describe the in vitro pharmacological profile of a novel positive allosteric modulator (PAM) of α4β2 nAChRs, NS9283 (A-969933), based on radioligand binding, $Ca^{2+}$ imaging, and electrophysiology. NS9283 (at ≤10 μM) did not displace the binding of orthosteric ligands including [$^3$H]cytisine at rat α4β2* (cortex), [$^3$H]A-585539 at rat α7* (cortex), or [$^3$H]epibatidine at human α3* (IMR-32). NS9283 did not directly evoke $Ca^{2+}$ responses in HEK-293 cells expressing hα4β2 nAChRs but potentiated the submaximum agonist evoked (nicotine or ABT-594) responses ($EC_{50}$ ~ 0.4 μM). In the presence NS9283 (3 or 10 μM), the agonist concentration-responses, in HEK-293 α4β2 cells, were also potentiated by increases in potency, maximum efficacy, and Hill slope. Interestingly, the agonist responses to ACh and nicotine were affected more robustly than for ABT-594 and ABT-894. Effects of NS9283 were also examined at human and rat α4β2 nAChRs expressed in oocytes by two electrode voltage clamp (POETs) where the submaximum agonist evoked responses were enhanced concentration-dependently ($EC_{50}$ ~ 0.3 μM) as well as were the agonist evoked concentration-responses in the presence of NS9283 (10 μM). NS9283 did not potentiate the responses at human α3β4 ($Ca^{2+}$ imaging in HEK-293/α3β4 cells or IMR-32 cells, $IC_{50}$ ~ 10 μM, and expressed in oocytes, TEVC, $IC_{50}$ ~ 70 μM),