the conditioning amplitude (response to the first of paired identical auditory stimuli) but failed to significantly alter test amplitude (response to the second of paired identical auditory stimuli) or TC ratio, the measure of sensory inhibition. These data suggest that the $\alpha4\beta2$ nicotinic receptor, but not the $\alpha7^*$ receptor, is involved in the effect of cotinine, at the doses tested. The apparent efficacy of cotinine at $\alpha4\beta2$ receptors coupled with its longer half-life than nicotine may explain the fact that the increase in conditioning amplitude with nicotine administration in this mouse model, outlasts the effect on test amplitude, i.e., cotinine is responsible for the longer duration of the conditioning effect. These data may have implications for the use of cotinine in schizophrenia patients.

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2.13

The alpha-7 receptor agonist EVP-6124 increases dopamine and glutamate efflux in rat medial prefrontal cortex and nucleus accumbens

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Stimulation of nicotinic alpha-7 and alpha-4-beta-2 receptor agonists has been postulated to be of value to improve some elements of the cognitive impairment in Alzheimer's disease, schizophrenia and attention deficit hyperactivity disorder and negative symptoms in schizophrenia. The mechanism of action of these beneficial effects may include increased release of dopamine (DA), acetylcholine (ACh), glutamate (Glu) and GABA in cortical, hippocampal, and nucleus accumbens (NAC) regions of the brain. In the present study, we assessed the effects of EVP-6124, a high affinity, nicotinic alpha-7 receptor agonist, on DA, Glu and GABA release in rat medial prefrontal cortex (mPFC) and NAC in awake, freely moving Sprague–Dawley male rats. EVP-6124, at the dose of 0.1 mg/kg, s.c., increased DA efflux in both the mPFC and the NAC. The effect of this dose was greater than that of 0.03 and 0.3 mg/kg. Similarly, EVP 6124, 0.1 mg/kg but not 0.03 and 0.3 mg/kg, significantly increased cortical Glu efflux, with no effect in the NAC. Thus, there is an inverted U-shaped curve for DA and Glu release with EVP 6124, as previously reported for other alpha-7 nicotinic receptor agonists. None of the three doses of EVP 6124 had any effect on GABA efflux in either region. Pre-treatment with the selective alpha-7 antagonist methyllycaconitine (MLA, 1.0 mg/kg, s.c.) significantly and completely blocked the cortical Glu efflux induced by EVP 6124 (0.1 mg/kg). These results provide a possible mechanism for the nicotinic alpha-7 receptor agonist EVP-6124, to treat cognitive impairment and the negative symptoms of schizophrenia.

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2.14

In vitro pharmacological characterization and pro-cognitive effects of the novel alpha-7 nicotinic acetylcholine receptor partial agonist, SKL-A4R

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Enhancement of cognitive performance via activation of the alpha7 nAChR represents a promising new approach to treating cognitive disorders such as Alzheimer's disease and cognitive impairment associated with Schizophrenia. Here, we report the pharmacological properties of SKL-A4R, a novel selective alpha7 nAChR agonist. KL-A4R selectively binds to rat alpha7 receptor (Ki 828 nM) and acts as partial agonist in functional Ca^{2+} influx assay (EC_{50} 100 nM). Experiments with human alpha7 receptors expressed in *Xenopus* oocytes confirmed that SKL-A4R is a partial agonist of alpha7 nAChR with an EC_{50} of 2.3 ± 0.2 μM and I_{max} of approximately 60% relative to ACh. The compound showed high selectivity against other nicotinic receptors and did not interact with other receptors, transporters, and enzymes. SKL-A4R treatment (MED 0.01 mg/kg, *po*) improved episodic memory in a novel object recognition task in mice in which cognitive functions have been disrupted by MK-801 or scopolamine. This improvement was blocked by the alpha7 selective antagonist methyllycaconitine indicating that it is mediated by the activation of alpha7 receptor. SKL-A4R (0.01 mg/kg, *po*) also improved a MK-801-induced deficit in a Y-maze task. Furthermore, SKL-A4R (0.01 mg/kg/day, *po*) reversed scopolamine-induced deficits in the Morris water maze repeated acquisition task model. In models targeting other cognitive domains including attention and perceptual processing, SKL-A4R normalized the phencyclidine-induced deficit of auditory evoked potential at 0.03 mg/kg, *ip*. Neuroprotection of SKL-A4R was demonstrated in NBM-lesioned rats in which treatment with SKL-A4R (0.01 and 0.1 mg/kg/day, *po*) resulted in a significant protection of choline acetyltransferase-positive neurons in the lesioned hemisphere. The pro-cognitive effects of SKL-A4R described may also be mediated by pre- and post-synaptic activation of alpha7 nAChRs via metabotrophic actions. In support of this concept, we have confirmed that SKL-A4R activates the ERK1/2 pathway and subsequent downstream phosphorylation of cAMP response element binding (CREB) protein, and also JAK2 pathway at therapeutically relevant concentrations. Taken together, the current results indicate that SKL-A4R exhibits robust pro-cognitive and neuroprotective properties.

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2.15

Attentional improvement in rats with the nicotinic agonist AZ12564698 (AZD3480)

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Nicotinic acetylcholine systems have been shown to play major roles in cognition. Nicotine and nicotinic analogs improve attention and nicotinic antagonists impair it. This study was conducted to investigate the effect of a novel nicotinic agonist (AZD 3480)

on sustained attention and reversal of pharmacologically-induced attentional impairment in rats produced by the NMDA glutamate antagonist dizocilpine (MK-801). *Methods:* Adult female Sprague–Dawley rats were trained to perform an operant visual signal detection task to a stable baseline of accuracy. The rats then were injected in a repeated measures, counter-balanced design with saline, AZD3480 (0.01, 0.1, 1 mg/kg), dizocilpine (0.05 mg/kg) or their combinations 15 min before the test. In another experiment, as a positive control the effect of donepezil, on pharmacologically-induced attentional impairment was tested. After training for the sustained attention, rats were injected with donezepil (0.01, 0.1 and 1 mg/kg), dizocilpine (0.05 mg/kg) or their combinations and their sustained attention was assessed. *Results*: The NMDA glutamate antagonist dizocilpine caused a significant ($p < 0.0005$) impairment in percent correct. This attentional impairment was significantly ($p < 0.0005$) reversed by 0.01 and 0.1 mg/kg of AZD3480. There was evidence for an inverted U-shaped dose-effect curve inasmuch as the higher 1.0 mg/kg AZD3480 dose did not effectively reverse the dizocilpine-induced impairment. AZD3480 by itself did not alter the already high baseline control performance. Donepezil (0.01-1.0 mg/kg) also caused a significant (0.005) effect by attenuating the dizocilpine-induced attentional impairment. *Conclusions*: AZD3480, similar to donepezil, showed significant efficacy for counteracting the attentional impairment caused by the NMDA glutamate antagonist dizocilpine. We have previously shown with this signal detection attentional task that methylphenidate also effectively reversed the attentional impairment caused by dizocilpine. Very low doses of AZD3480 may provide therapeutic benefit for reversing attentional impairment in patients suffering from cognitive impairment.

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2.16

Neuronal nicotinic receptor agonists ameliorate 3-acetylpyridine-induced ataxia

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Recent clinical studies have indicated that the neuronal nicotinic receptor agonist varenicline improves balance and coordination in patients with ataxia of distinct pathogenic etiologies, but the mechanisms involved are not readily apparent. Studies in our laboratory sought proof of concept for the use of nicotinic agonists in an animal model of human olivocerebellar degeneration. To accomplish this, male Sprague–Dawley rats (225–250 g) were acclimatized to an open field and trained to maintain their balance on a rotorod for 3 min. One week later, performance in the open field and on the rotorod was quantified, and animals were placed on a narrow runway to assess gait parameters. Following establishment of baseline on these 3 measures, rats received injections of 3-acetylpyridine (3-AP, 70 mg/kg, i.p.) followed at 3.5 h by nicotinamide (300 mg/kg, i.p.) to destroy the primary afferent input to the cerebellum, and performance was determined one week later for 2 consecutive days. Rats were then randomly assigned to one of 3 treatment groups: saline; varenicline dihydrochloride (1.0 mg/kg/day); or nicotine hydrogen bitartrate (1.0 mg/kg/day). Drugs were administered (s.c.) once daily for 1 week after which time performance was again determined. Immunohistochemical analyses (NeuN for neuronal nuclei and calbindin for Purkinje cells) verified that the 3-AP injections destroyed neurons in the inferior olive and led to the degeneration of Purkinje cells in the cerebellum. The 3-AP-induced lesion led to a decrement in locomotor activity, the inability of animals to maintain their balance on a rotating rod, and an increase in hind limb stride width. All measures remained impaired or worsened in animals who received saline for one week. In contrast, all measures improved towards baseline values in animals receiving either varenicline or nicotine for 1 week. Results indicate that both varenicline and nicotine improve motor behavior impaired by the administration of 3-AP. These findings provide proof-of-concept that in this animal model of human olivocerebellar degeneration, nicotinic receptor modulation tempers the expression of cerebellar-mediated motor deficits, and thus, these and related nicotinic receptor agonists may have therapeutic benefit for the treatment of ataxias in humans. Further studies are necessary to elucidate the specific subtype of nicotinic receptor involved and cellular and molecular mechanisms mediating the observed effects.

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2.17

Chronic treatment with nicotine metabolite, cotinine, improves sustained attention and recognition memory in rats and attenuates glutamate (NMDA) antagonist-related impairments

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The neuropharmacological and behavioral properties of the tobacco alkaloid nicotine have been investigated extensively; however, the most predominant metabolite of nicotine in humans and other mammalians, cotinine, has received considerably less attention. Cotinine has a long pharmacological half-life with a range of ~15–20 h (depending on the body fluid analyzed) relative to nicotine which has a range of ~30 min to 3 h. Thus, after nicotine consumption, cotinine levels in vivo greatly exceed that of nicotine over time. However, until recently, few studies had been conducted to systematically characterize the behavioral pharmacology of cotinine, an issue that may be particularly relevant to the study of neuropsychiatric disorders such as schizophrenia (i.e., given the high percentage of patients who smoke tobacco). Previous work in our laboratories indicated that acute cotinine treatment improves prepulse inhibition of the auditory startle response in rats in pharmacological impairment models and that it improves working memory in non-human primates. The objective of the experiments described here was to test the hypothesis that chronic treatment with cotinine improves sustained attention and recognition memory in rodents and attenuates the deficits in performance induced by the glutamate (NMDA) antagonist MK-801 (i.e., studies potentially reflective of cognitive deficits observed in schizophrenia). The effects of chronic administration of cotinine (2.0 mg/kg/day in drinking water) were evaluated in a five choice serial reaction time task (5C-SRTT) and a spontaneous novel object recognition