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)