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

(NOR) task. In the 5C-SRTT, cotinine attenuated MK-801-related impairments of accuracy, and it reduced impulsive-like behaviors (elevated premature responses) when the demands of the task were increased (i.e., by varying the stimulus durations and administering MK-801). Cotinine also improved the discrimination ratio in 48 hr retention sessions in the NOR task. Studies are currently underway to evaluate chronic cotinine for its ability to attenuate MK-801-related impairments of NOR. These data suggest that cotinine may have therapeutic potential for neuropsychiatric disorders, especially in conditions where sustained attention and recognition memory are impaired.

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2.18

In Vitro neuroprotective effects of ABT-779, a positive allosteric modulator of α7 nAChRs

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ABT-779 is a novel positive allosteric modulator (PAM) of α7 nAChRs that selectively potentiates responses to acetylcholine at recombinant and native α7 nAChRs with a type II profile. ABT-779 itself did not show any intrinsic effects at the α7 nAChRs, but selectively potentiated responses to both choline or acetylcholine at human and rodent α7 nAChRs in a concentration-dependent manner. Acute administration of ABT-779 in mice increased dose-dependent phosphorylation of the downstream signaling protein, CREB (see Kohlhaas et al., abstract 2.19). Since α7 agonists have been previously shown to have in vitro neuroprotective effects following various insults, we examined whether a PAM could exhibit such effects. The effect of ABT-779 was examined *in vitro* in a cellular model (NGF-differentiated PC12 cells) where increased p-tau levels were trigged by application of the toxic $A\beta_{1-42}$ peptide. In this model, ABT-779 prevented tau phosphorylation induced by $A\beta_{1-42}$ in a concentration-dependent manner with maximal inhibition (~60%) comparable to that of α7 NNR agonists and GSK3β inhibitors. ABT-779 also attenuated NGF-withdrawal induced loss of neuron numbers and neurite outgrowth in differentiated PC12 with maximal 70% and 36% protection effects, respectively. It is likely that the effects of ABT-779 could be mediated via amplification of α7 nAChR responses to choline present in cell culture media, although additional studies to further elucidate this remain to be been conducted. ABT-779 did not show any cytotoxic effects at any of the concentrations tested. Our studies demonstrate that ABT-779, like other α7 agonists, could activate biochemical pathways important for cognitive and neuroprotective processes in vitro.

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2.19

α7 NNR allosteric modulation in behavioral models of cognition

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Targeting α7 nicotinic acetylcholine receptors (α7 nAChRs) through orthosteric agonism has demonstrated a potential for enhancement of cognitive function in psychiatric and neurological diseases such as schizophrenia and Alzheimer's disease. Another way to target α7 nAChR function is by enhancing effects of the endogenous neurotransmitter acetylcholine via positive allosteric modulation. In the present study, we utilized ABT-779, a selective α7 nAChR positive allosteric modulator (PAM) (see abstracts 2.18 and 1.20) to improve preclinical behavioral measures in various animal models to address multiple cognitive domains across different species. In DBA2 mouse N40 auditory sensory gating, a model of pre-attention, ABT-779 was efficacious in the dose range of 0.001–0.01 μmol/kg i.p. Using 24-h recall inhibitory avoidance in CD-1 mice as a model of memory consolidation and recall, ABT-779 showed efficacy at the same dose range of 0.001–0.1 μmol/kg i.p. In rat social recognition, a model of short-term recognition memory, significant efficacy was seen for ABT-779 at 0.01 and 0.1 μmol/kg. Similar efficacy was retained using a rat lesion model of cholinergic hypofunction. Studies in Rhesus monkey using delayed-matching-to-sample (DMTS) as a measure of working memory, showed an effect for ABT-779 in long-delay performance in a dose range of 0.001–0.1 μmol/kg. Immunohistochemistry evaluation showed ABT-779 enhanced the phosphorylation of CREB, an important biochemical event in memory processes at behaviorally effective dose range. Taken together, these results suggest that positive allosteric modulation of the α7 nAChR with ABT-779 has the potential to improve aspects of cognitive function, including those deficiencies that may underlie various neurological and neuropsychiatric disorders.

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2.20

The α7 nicotinic acetylcholine receptor (nAChR) allosteric modulator UCI-40083 differentially increases dopamine (DA) and norepinephrine (NE) release in adolescent rat brain

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The selective α7 nAChR positive allosteric modulator UCI-40083 (N-(4-chlorophenyl)-α-[[(4-chlorophenyl)amino]methylene]-3-methyl-5-isoxazolacet-amide), has been shown to evoke robust positive modulation of agonist-induced currents at α7 nAChRs. In order to evaluate its pharmacological potential in cognition disorders such as the attention deficit with hyperactivity disorder (ADHD), we assessed the effect of systemic UCI-40083 administration on DA and NE release in the medial prefrontal cortex (PFC) of adolescent spontaneous hypertensive (SHR) and Sprague Dawley (SD) rats, by using a microdialysis technique in freely moving animals. We also assessed the effect on DA and NE release in the nucleus accumbens (NAcc) shell to gain insight into potential motivational properties of UCI-40083. Our results show that UCI-40083 (1 mg/kg i.p.) increases NE and DA in the PFC of both SD and SHR rats. This effect yielded an optimum dose as the effect of 3 mg/kg was not significantly different (NE) or was lower (DA) when compared to 1 mg/kg in both strains. In addition, our results show that UCI-40083 significantly increased DA and NE output in the NAcc shell of both SD and SHR rats. The stimulant effect on DA and NE levels in the PFC was blocked by the selective α7 nAChR antagonist methyllycaconitine (MLA) at 3 mg/kg i.p. In summary our results suggest that UCI-40083 has the potential of modulating catecholamine transmission in the PFC and in the NAcc shell and thus may possess cognitive and motivational properties, features that are shown also by stimulant drugs currently used in ADHD therapy such as amphetamine and methylphenidate.