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.

Acknowledgments: This work was supported by AstraZeneca.

doi:10.1016/j.bcp.2011.07.046

2.16

Neuronal nicotinic receptor agonists ameliorate 3-acetylpyridine-induced ataxia

L. Wecker*, M.E. Engberg, R.M. Philpot, C.S. Lambert, P.C. Bickford, C. Hudson

Department of Psychiatry and Neuroscience, University of South Florida College of Medicine, Tampa, FL, USA

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.

Acknowledgments: This work was supported by the Florida Center of Excellence for Biomolecular Identification and Targeted Therapeutics and the USF Neuroscience Collaborative, and NIH #NS072114 to L.W.

doi:10.1016/j.bcp.2011.07.047

2.17

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

Alvin V. Terry Jr.[1,2,*], Rosann Schade[2], Patrick M. Callahan[1,2], James M. Chapman[3], Michael G. Bartlett[4]

[1] *Dept. of Pharmacology and Toxicology, Georgia Health Sciences University, Augusta, GA, USA*
[2] *Small Animal Behavior Core, Georgia Health Sciences University, Augusta, GA, USA*
[3] *Department of Pharmaceutical and Biomedical Sciences, South Carolina College of Pharmacy, Columbia, SC, USA*
[4] *Department of Pharmaceutical and Biomedical Sciences, University of Georgia, College of Pharmacy, Athens, GA, USA*

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