has similar effects in zebrafish as in rodents and humans. These studies point to the value of zebrafish as models of human neurobehavioral function. Zebrafish models of behavioral pharmacology can be useful to efficiently screen test compounds for drug development and can be useful for helping determine the mechanisms critical for new therapeutic treatments of neurobehavioral impairments.

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2.10

The nicotinic alpha7 receptor partial agonist GTS-21 ameliorates dopaminergic- and glutamatergic-related sensorimotor gating deficits in Wistar rats

Patrick M. Callahan[1,2,*], Alvin V. Terry Jr.[1,2], Ashok Tehim[3]

[1] *Department of Pharmacology and Toxicology, Georgia Health Sciences University, Augusta, GA, USA*
[2] *Small Animal Behavioral Core, Georgia Health Sciences University, Augusta, GA, USA*
[3] *Dr. Reddy's Laboratories, Bridgewater, NJ, USA*

One feature associated with schizophrenia is an inability to focus attention on relevant information and to exclude extraneous irrelevant information. This deficiency in filtering or gating sensory information can be assessed in humans as well as laboratory animals by using either P50 auditory-evoked potentials or prepulse startle inhibition (PPI) techniques thus serving as translational tools for drug discovery efforts. Alterations in nicotinic acetylcholine alpha 7 receptors (α7nAChRs) are believed to play an important role in the information processing deficits associated with schizophrenia and α7nAChR agonists have been shown to ameliorate these deficits. In the present study, we determined the effects of the partial α7nAChR agonist GTS-21 (1–10 mg/kg, ip) on PPI in two pharmacological impairment models, dopamine receptor agonism by apomorphine (0.5 mg/kg, sc) and NMDA receptor antagonism by MK-801 (0.1 mg/kg, sc) in male Wistar rats. For comparison, the antipsychotics haloperidol (0.03–0.3 mg/kg, ip), clozapine (0.5–5 mg/kg, ip) and risperidone (0.1–1 mg/kg, ip) were assessed as potential positive controls for model validation. Under vehicle conditions, the prepulse stimuli (75, 80 and 85 dB) inhibited the startle response to a 120 dB auditory stimulus in a graded fashion. Apomorphine and MK-801 reduced the effects of the prepulse stimuli on the acoustic startle response. Of the antipsychotics, risperidone was the most efficacious; reversing the PPI deficits elicited by both apomorphine and MK-801, whereas the positive effects of haloperidol and clozapine were limited to one model (i.e., the apomorphine and MK-801 models, respectively). These observations support previous findings and provide model validation. Administration of the partial α7nAChR agonist GTS-21 resulted in a dose-dependent and complete restoration of the PPI-induced deficits elicited by apomorphine as well as MK-801. GTS-21 has previously been shown to normalize auditory-evoked gating deficits in schizophrenic patients as well as in model systems and the present results extend those positive findings to include sensorimotor gating (i.e., via PPI of the auditory startle response) in animals. The ability of GTS-21 to regulate perceptual processing may, in part, contribute to its ability to restore cognitive function in schizophrenic patients.

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2.11

Deviance-based negativity in the conscious rat: Modulation by nicotinic agonists

Siva Digavalli*, Ping Chen, Nick Lodge

Neuroscience Biology, Bristol Myers Squibb Co., Wallingford, CT, USA

When repeated discrete sensory stimuli are interrupted by a novel stimulus that differs in pitch, duration or intensity, a slow negative excursion is noted in the event related potential (ERP) to the novel stimulus following N100. This late onset negativity in response to a deviant expressed as deviant ERP-standard ERP, is called mismatch negativity (MMN). MMN has been found to be deficient in schizophrenia patients and is known to correlate inversely with global functioning deficits in patients. MMN has been recently used as a functional biomarker to predict drug response in early discovery. To date, nicotinic cholinergic agonists are one of the few drugs known to improve MMN in normal subjects as well as in patients. Analogous mismatch related slow positive or negative deflections that happen after N40 have been reported in the rodent literature. Using CA3 hippocampal field recordings in SD rats referred to a cerebellar lead, we saw a robust negative excursion following N40 in ERP after duration as well as pitch deviants. When the difference between the standard and the deviant stimuli were such that it elicited a robust negativity under vehicle condition, nicotine (0.1 and 0.3 mpk, sc) made the response unchanged or worse. On the other hand, when stimulus conditions were altered to reduce the MMN-like response to sub-maximal levels under vehicle treatment, nicotine (0.1 mpk, sc) significantly improved the MMN-like negativity. A novel alpha7 partial agonist (compound A; 1 mg/kg, sc) also improved MMN-like negativity to both duration and pitch deviance in normal unimpaired rats. These findings have utility in preclinical as well as in early clinical discovery.

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2.12

Acute administration of cotinine to DBA/2 mice increases conditioning amplitude in the sensory inhibition model

K.E. Stevens[1,2,*], L. Zheng[2]

[1] *Medical Research Service, Department of Veterans Affairs Medical Center, Denver, CO, USA*
[2] *Department of Psychiatry, University of Colorado, Denver, School of Medicine, Aurora, CO, USA*

It has long been observed that the effect of nicotine on a number of behaviors, in both rodents and man, lasts longer than the half-life of nicotine. Recent studies have shown that cotinine, a major metabolite of nicotine, is also active in behavioral assays in both rodents and non-human primates. Cotinine has a dramatically longer half-life than nicotine (15–19 h versus 2–3 h) and thus may account for some of the long-term effects previously thought to be mediated by nicotine. Studies have shown improvement in cognition in non-human primates and improvement in rodent pharmacological models of deficits analogous to those observed in schizophrenia suggesting an "antipsychotic-like" role for cotinine. The DBA/2 mouse models a sensory inhibition deficit observed in schizophrenia and has shown predictive validity for the effects of nicotinic agonists in schizophrenia patients, including both nicotine and the partial α7 nicotinic agonist, DMXB-A. We tested acute cotinine administration in this mouse model at 3 doses, 0.033, 0.33 and 1 mg/kg, ip, doses previously found to be active in reversing MK801-induced deficits in accuracy in the 5-choice serial reaction time task in rats. We found that all three doses significantly increased

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

Mei Huang[1,*], Anna R. Felix[1], Chaya Bhuvaneswaran[2], Dana Hilt[2], Gerhard König[2], Herbert Y. Meltzer[1]

[1] *Division of Psychopharmacology, Vanderbilt University School of Medicine, Nashville, TN, USA*
[2] *EnVivo Pharmaceuticals Inc., Watertown, MA, USA*

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

C.Y. Maeng*, C.M. Joung, H.W. Shin, Y.K. Jang, S.B. Cha, H.R. Cha, E.J. Yi, C.H. Park

Discovery Laboratory, SK biopharmaceuticals, SK R&D Park, Yuseong-gu, Daejeon 305-712, Republic of Korea

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)

Amir H. Rezvani[1], Marty Cauley[1], Edwin Johnson[2], Edward D. Levin[1]

[1] *Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC, USA*
[2] *AstraZeneca, Research and Development, Innovative Medicines, Södertälje, Sweden*

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)