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