brain, but densely localized in both pre-and postsynaptic sites on interneurons innervating hippocampal pyramidal cell dendrites. In an effort to understand possible structural changes that might be related to learning-related behavioral deficits known to occur in alpha7 knockouts, we quantified several measures of dendritic morphology in the CA1 region of the mouse hippocampus in wild-type and knockout alpha7 mice. Measurements were made in Golgi-stained material from formalin fixed brains in mice at 60 days of age. The most significant difference was a 63% increase in thin (L-type) dendritic spines on the CA1 basilar tree in knockout mice ($p = 0.0005$) and a small but significant decrease in N-type (Nubby) basilar dendritic spines (−15%, $p = 0.02$). There was no difference in the total number of spines per neuron and per brain between wild-type and knockout animals nor was there a difference in M-type and D-type spines in the basilar dendrites. In the apical CA1 dendritic tree, there was a significant increase number of total spines in knockouts (+11%, $p = 0.01$). In the Parietal Cortex, layers II–II, there was a trend toward decreased dendritic branching between in knockout mice. No differences were found in measurements of dendritic branching of the granule cells of the dentate gyrus. In sum, the data suggests that the alpha7 nAChR knockout genotype results in an alteration in brain circuitry in cortical and hippocampal regions which could disrupt normal cognitive function.

doi:10.1016/j.bcp.2011.07.038

2.8

Mice lacking the β4 subunit of the nicotinic acetylcholine receptor show memory deficits, altered anxiety- and depression-like behavior, and diminished nicotine-induced analgesia

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Nicotine binds to nicotinic acetylcholine receptors (nAChRs) throughout the brain and elicits a range of behavioral responses related to cognition, anxiety, depression and analgesia. However, the role of specific nAChRs subtypes in regulating behavior in the absence of nicotine is still not clear. We investigated the role of β4-containing nAChRs in behavioral tests assessing cognitive function, affective behaviors, and nociception using wildtype ($\beta4^{+/+}$) and knockout ($\beta4^{-/-}$) mice for the nAChR β4 subunit. Mice were tested in a battery of cognitive tasks including the Y-maze (spontaneous alternations), the novel object and novel location recognition tasks, the Barnes maze, and the contextual and cued fear conditioning tasks. Anxiety- and depression-like behaviors were evaluated in the light-dark box, forced swim, tail suspension and marble burying tests. The analgesic effect of nicotine was investigated using the tail immersion and hot plate tests. There were no significant learning and memory deficits in $\beta4^{-/-}$ mice compared to $\beta4^{+/+}$ mice during acquisition of the Barnes maze, contextual fear conditioning, Y-maze, and the novel object recognition tasks. In the Barnes maze memory retention test, male $\beta4^{-/-}$ mice showed reduced use of the spatial search strategy, indicating small spatial memory deficits compared to $\beta4^{+/+}$ mice. In the cue-induced fear conditioning memory retention test, both male and female $\beta4^{-/-}$ mice exhibited reduced freezing time compared to $\beta4^{+/+}$ mice, reflecting decreased memory retention, while during task acquisition memory deficits were observed only in male $\beta4^{-/-}$ mice. Small memory deficits were detected in a subset of $\beta4^{-/-}$ male mice compared to the $\beta4^{+/+}$ male mice in the novel location, but not the novel object, recognition task. Compared to $\beta4^{+/+}$ mice, $\beta4^{-/-}$ mice exhibited decreased anxiety-like behavior in the light-dark box; while depression-like behavior in $\beta4^{-/-}$ mice was decreased in the tail suspension test (females only) and increased in the forced swim test (males only) compared to $\beta4^{+/+}$ mice. In nociception tests, male and female $\beta4^{-/-}$ mice did not differ from their $\beta4^{+/+}$ counterparts in basal nociception, but were less sensitive to the antinociceptive effect of nicotine in two tests of acute thermal pain, indicating that β4-containing nAChRs are involved in the modulation of nicotine-induced analgesia. In conclusion, the results indicate that (a) lack of the β4-containing nAChRs resulted in deficits in hippocampus- and amygdala-dependent short- and long-term memory functions; (b) β4-containing nAChRs are involved in anxiety- and depression-like behaviors, and (c) contribute to the analgesic effects of nicotine.

Acknowledgments: This work was supported by NIDA grant DA023209 to AM.

doi:10.1016/j.bcp.2011.07.039

2.9

Using zebrafish to fill the gap between *in vitro* and rodent models for nicotinic drug development

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Zebrafish can provide a valuable animal model to screen potential cognitive enhancing and anxiolytic nicotinic drugs. Zebrafish are economical and can provide a relatively quick indication of possible functional efficacy. With a complex nervous system and elaborate behavioral repertoire, zebrafish can provide a good intermediate model between in vitro receptor and cell-based assays and classic mammalian models for drug screening. In addition, the variety of molecular tools available in zebrafish makes them outstanding models for helping to determine the neuromolecular mechanisms for nicotinic drugs. In a series of studies, our lab has developed tests of cognitive function and stress response, which are sensitive to drug effects in a similar fashion as rodent models and humans for cognitive enhancement and alleviating stress response. We have determined the effects of nicotine, the prototypic nicotinic agonist, and nicotinic antagonists on cognitive function, exploratory behavior and stress response in a series of behavioral tests we have developed to reliably index these behavioral functions. The overall hypothesis of this line of investigation was that nicotine would have similar behavioral effects in zebrafish as in mammals when analogous tests of behavioral function are used. In particular, the 3-chamber task for learning and memory was shown to be sensitive to the cognitive enhancing effects of nicotine and has been useful in helping to determine neural mechanisms critical for nicotinic-induced cognitive enhancement. The novel tank diving test was shown to be a valid and efficient test of stress response. It is sensitive to the reduction of stress-related behaviors of the anxiolytic drugs diazepam and buspirone. Nicotine also causes stress-alleviating effects which can be interpreted as anxiolytic effects. As with mammalian species, nicotine significantly improves learning and memory at low to moderate doses with an inverted J-shaped dose-effect function. The nicotine-induced learning improvement in zebrafish is reversed with the nicotinic antagonist mecamylamine and is accompanied by increased brain dopamine levels, an effect which is also reversed with mecamylamine. Also as in mammals nicotine has anxiolytic effects in zebrafish. Nicotine significantly reduces bottom dwelling in the novel tank diving task. This effect is reversed by either α7 or α4β2 nicotinic antagonist co-administration. In many respects nicotine

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.

doi:10.1016/j.bcp.2011.07.040

2.10

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

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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.

doi:10.1016/j.bcp.2011.07.041

2.11

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

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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.

doi:10.1016/j.bcp.2011.07.042

2.12

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

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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