(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.

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2.21

The use of the scopolamine-induced cognitive impairment model to translate on-target activity for ABT-894 from rodents/monkeys to humans: Preclinical evidences

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Demonstrating the successful translation of a pharmacodynamic signal from preclinical species to humans has become an active focus of drug discovery research as a means to facilitate decision making early in the drug development process. Scopolamine-induced cognitive impairment has been proposed to be a useful tool to demonstrate the pharmacodynamic effect across species for multiple mechanisms such as acetylcholinesterase inhibitors, neuronal nicotinic receptor (NNR) ligands, stimulants and glycine analogs. The present preclinical study investigated whether this model could be used to advance the NNR α4ß2 agonist ABT-894 more rapidly to key PhII efficacy trials in the target patient population by providing a means to establish proof of pharmacological activity in humans. Scopolamine was used to induce deficits in the rat two-platform water maze (WM) assay of spatial reference memory (0.3 mg/kg, i.p.), in the rat T-maze assay of working memory (0.3 mg/kg, i.p.), in the rat passive avoidance response (PAR) assay of memory consolidation (0.1 mg/kg, s.c.) and in the monkey delayed matching-to-sample (DMTS) assay of short term/working memory (0.02 mg/kg, i.m.). ABT-894 was given 10-15 minutes prior to scopolamine, and the behavioral testing occurred 15–20 min after scopolamine administration. ABT-894 dose-dependently blocked scopolamine-induced deficits in WM (0.0062, 0.019 and 0.19 μmol/kg, i.p.). In T-maze, ABT-894 (0.019 μmol/kg, i.p.) significantly attenuated scopolamine-induced deficits at the short delay only. ABT-894 dose-dependently attenuated scopolamine-induced deficits in PAR, reaching significance at the dose of 0.03 μmol/kg, i.p.. Finally in DMTS, ABT-894 attenuated scopolamine-induced deficits at the dose of 0.03 but not at 0.01 or 0.1 μmol/kg, i.m.. Together, these data suggest that ABT-894 can attenuate scopolamine-induced deficits across multiple cognitive domains in preclinical species. As such, the translational model may be of use to demonstrate proof of pharmacological activity in humans and thereby allow more rapid advancement into the key PhII clinical efficacy trials. This hypothesis is being tested in human studies using the scopolamine-induced cognitive impairment model.

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2.22

A randomized, double-blind, placebo-controlled Phase 2 study of α4β2 agonist ABT-894 in adults with ADHD

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ABT-894 is a novel α4β2 neuronal nicotinic acetylcholine receptor agonist that displays consistent and robust activity in preclinical models of cognition and is generally well tolerated in healthy adults. Attention-deficit/hyperactivity disorder (ADHD) is characterized by core symptoms of hyperactivity, inattentiveness, and impulsivity, with 15–65% of diagnosed children continuing to experience symptoms into adulthood. There is a need for novel treatments that address the unmet medical need associated with ADHD. A randomized, double-blind, placebo-controlled, 2 period, crossover Phase 2 study was designed to determine the safety and efficacy of ABT-894 and atomoxetine in adults with ADHD. For each dose group, subjects received, in random order, placebo treatment and ABT-894 (1 mg, 2 mg, 4 mg PO QD, or 4 mg PO BID) or active comparator atomoxetine (40 mg PO BID) treatment for 28 days. The washout period between treatment periods was approximately 2 weeks. Subjects were assessed weekly and the primary efficacy variable was the Conners' Adult ADHD Rating Scale – Investigator Rated (CAARS:Inv) Total score at the final evaluation of each 4-week treatment period. Data were analyzed by analysis of covariance with baseline score from each period as a covariate. An expanded period by period analysis examined the consistency of ABT-894 effects. A total of 238 subjects were assessed for safety endpoints, 236 patients included in the intent-to-treat (ITT) dataset, and 196 included in the completers dataset, which was the pre-specified, primary dataset for efficacy. Administration of 4 mg BID ABT-894 resulted in a significant improvement compared with placebo in CAARS:Inv Total score (LS mean ± SE = −6.69 ± 2.30, $p = 0.003$). This effect was similar to atomoxetine treatment (−7.98 ± 2.65, $p = 0.002$). Results from secondary outcome measures were similar to those for the primary outcome measure. In analysis of Period 1, the response on the CAARS:Inv Total score to 4 mg BID ABT-894 was significantly improved vs placebo ($p = 0.041$). For subjects who received placebo in Period 1 and 4 mg BID ABT-894 or atomoxetine in Period 2, the change in CAARS:Inv total score for 4 mg BID ABT-894 was equivalent to that of atomoxetine in Period 2. Overall, ABT-894 was well tolerated at all dose levels, and the 4 mg BID dose was found to be efficacious compared with placebo and generally well tolerated in this Phase 2 trial in adults with ADHD. Evidence of efficacy for this dose was observed during both periods of this crossover study, suggesting that the results were not biased by carryover effects of the crossover design. A better efficacy and adverse event profile was observed for 4 mg BID vs 4 mg QD ABT-894, suggesting that consistently higher plasma levels of ABT-894 could improve its therapeutic potential. Further investigation of ABT-894, including doses higher than those tested in the current study, would be needed to determine its potential as a safe and effective treatment for adults with ADHD.

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