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R3487/MEM 3454, a novel nicotinic alpha 7 receptor partial agonist, improves attention and working memory performance in cynomolgus macaques

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The nicotinic alpha 7 (nic α_7) receptor plays an important role in cognitive function, and selective nic α_7 agonists have been proposed as novel therapeutic agents for treating cognitive impairments associated with schizophrenia (CIAS) and Alzheimer's disease (AD). R3487 / MEM3454 (R3487) is a novel nic α_7 receptor partial agonist with 5-HT_3 antagonist properties that is being developed for the treatment of both CIAS and AD. R3487 exhibits pro-cognitive effects in rodents, healthy volunteers and, more recently, in a Phase IIa AD population. In attempt to further understand the cognitive enhancing and antidepressant-like effects of R3487 and to improve on translatability between preclinical and clinical studies, additional characterization was conducted using nonhuman primate (NHP) efficacy methods. Following acute administration, R3487 (0.3–10 mg/kg, p.o.) was studied in the NHP object retrieval model of attention (response inhibition) in which the compound improved percent-correct first reaches in the difficult trials with a minimally effective dose (MED) of 1.0 mg/kg. In addition to improving attentional measures, R3487 (0.1–10 mg/kg, p.o.) was assessed in the delayed match to sample (DMTS) NHP model of working memory. In this procedure, R3487 (MED, 1.0 mg/kg) significantly improved accuracy in the long delay of this task, similar to effects observed with the non-selective nicotinic agonist, nicotine. In both the object retrieval and DMTS procedures, R3487 exhibited a characteristic inverted U-shaped dose-response function that is often reported with nicotinic agonists. In addition to further assessing the effects of R3487 for cognitive improvements, R3487 was also evaluated in the differential reinforcement of low-rate (DRL) behavior model to examine potential antidepressant-like properties. Unlike nicotine (0.03–0.3 mg/kg), which increased the number of reinforcers obtained (MED, 0.1 mg/kg, i.m.), R3487 (0.3–10 mg/kg, p.o.) did not exhibit this effect at the doses tested. Similarly, the nicotinic $\alpha4\beta2/\alpha_7$ agonist, varenicline (0.03–0.3 mg/kg, p.o.), had no effect on reinforcers obtained in the DRL procedure. Overall, the data from these studies indicate that R3487 improves attention and working memory function in line with clinical data suggesting that the NHP models may be useful in advancing drug discovery efforts.

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Characterization of JNJ-1930942, a novel positive allosteric modulator of the α_7 nicotinic acetylcholine receptor

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The α_7 nicotinic acetylcholine receptor (α_7 nAChR) is a therapeutic target for the treatment of cognitive deficits associated with schizophrenia, Alzheimer's disease, Parkinson's disease and ADHD. Activation of these receptors with α_7 agonists improves sensory gating and memory and attention in animal models, and early clinical trials have shown a beneficial effect on cognitive function in schizophrenia and Alzheimer's disease patients. Here, we describe the novel highly selective α_7 nAChR positive allosteric modulator (PAM), JNJ-1930942. This compound enhances choline-evoked rise in intracellular Ca^{2+} in the GH4C1 cell line stably transfected with cloned human α7 nAChRs. JNJ-1930942 does not act on α4β2, α3β4 nAChRs nor on the related 5-HT_3 channel. Electrophysiological assessment in the GH4C1 cell line shows that JNJ-1930942 increases the peak and net charge response to choline, acetylcholine and PNU-282987. The potentiation is obtained mainly by affecting the receptor desensitisation characteristics, leaving activation and deactivation kinetics as well as recovery from desensitisation fairly unchanged. The choline efficacy is increased over its full concentration response range and its potency is increased more than ten-fold. The potentiating effect is α7 channel-dependent, since it is blocked by the α7 antagonist methyllycaconitine. Moreover, in hippocampal slices, JNJ-1930942 enhances in a dose dependent manner neurotransmission at hippocampal synapses and facilitates the induction of long term potentiation of electrically evoked synaptic responses in the dentate gyrus. Hence, with these properties, JNJ1930492 is able to improve a genetically based auditory gating deficit in DBA/2 mice. These results support the potential of an α_7 nAChR PAM as a pharmacotherapy for cognitive dysfunction.

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Profile of A-716096, a novel thiazolylidine positive allosteric modulator of the α7 nicotinic acetylcholine receptor

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Targeting α7 neuronal nicotinic receptors (α7 nAChRs) via selective α7 NNR agonism has potential to treat cognitive deficits of schizophrenia and Alzheimer's disease. An alternative approach is modulation of α7 NNR function to enhance effects of the endogenous neurotransmitter acetylcholine via positive allosteric modulators (PAMs). Structurally distinct small molecules continue to be identified as viable tools to explore this novel pharmacology.