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Postive allosteric modulators of muscarinic acetylcholine receptors subtype 1 and 4 for treatment of central nervous system disorders

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Abstract

Previous clinical studies as well as a large number of cellular and animal behavioral studies suggest that selective activators of M1 and/or M4 subtypes of muscarinic acetylcholine receptors (mAChRs) could provide a novel approach to improving cognitive function and reducing psychotic symptoms in patients suffering from Alzheimer's disease. In addition, mAChR agonists have efficacy in treatment of all major symptom clusters (positive, negative, and cognitive) in schizophrenia patients. Unfortunately, previous efforts to develop mAChR subtypes selective agonists have not been successful and previous compounds have failed in development because of adverse effects due to activation of multiple mAChR subtypes. We have been highly successful in developing selective positive allosteric modulators (PAMs) of both M1 and M4 that have excellent properties for in vivo studies and potential development as drug candidates. Interestingly, selective M1 PAMs have robust efficacy in enhancing synaptic plasticity in the hippocampus and increasing synaptic activation of the medial prefrontal cortex (mPFC) in rodents and induce robust improvements in specific domains of cognitive function in animal models that are dependent of hippocampal and mPFC function. Additionally, highly selective M4 PAMs induce profound reductions in dopamine release in the nucleus accumbens and other regions that are relevant to psychosis and have robust antipsychotic-like effects in animal models. These studies provide an exciting new approach to discovery of novel highly selective activators of individual mAChR subtypes and suggest that subtype specific mAChR PAMs may provide a novel approach for treatment of multiple CNS disorders.

Biography

Dr. Jerri M. Rook is an Instructor of Pharmacology at Vanderbilt University and the Vanderbilt Center for Neuroscience Drug Discovery. Dr. Rook completed her Ph.D. in Pharmacology from the University of Kansas Medical Center in 2008 and her postdoctoral studies at Vanderbilt University. Dr. Rook has received multiple awards including the Ruth L. Kirschstein National Research Service Award from the National Institute of Mental Health in 2009 and was the recipient of The Alzheimer's Drug Discovery Foundation (ADDF) 2012 and 2013 awards program to accelerate the discovery of new drugs for cognitive aging and Alzheimer's disease.

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