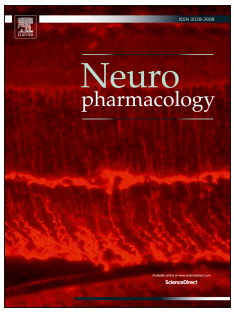
Accepted Manuscript



Cognitive enhancement and antipsychotic-like activity following repeated dosing with the selective M_4 PAM VU0467154

Robert W. Gould, Michael D. Grannan, Barak W. Gunter, Jacob Ball, Michael Bubser, Thomas M. Bridges, Jurgen Wess, Michael W. Wood, Nicholas J. Brandon, Mark E. Duggan, Colleen M. Niswender, Craig W. Lindsley, P. Jeffrey Conn, Carrie K. Jones

PII: S0028-3908(17)30343-X

DOI: 10.1016/j.neuropharm.2017.07.013

Reference: NP 6782

To appear in: *Neuropharmacology*

Received Date: 9 March 2017

Revised Date: 6 July 2017

Accepted Date: 14 July 2017

Please cite this article as: Gould, R.W., Grannan, M.D., Gunter, B.W., Ball, J., Bubser, M., Bridges, T.M., Wess, J., Wood, M.W., Brandon, N.J., Duggan, M.E., Niswender, C.M., Lindsley, C.W., Conn, P.J., Jones, C.K., Cognitive enhancement and antipsychotic-like activity following repeated dosing with the selective M_4 PAM VU0467154, *Neuropharmacology* (2017), doi: 10.1016/j.neuropharm.2017.07.013.

ABSTRACT

Although selective activation of the M_1 muscarinic acetylcholine receptor (mAChR) subtype has been shown to improve cognitive function in animal models of neuropsychiatric disorders, recent evidence suggests that enhancing M_4 mAChR function can also improve memory performance. Positive allosteric modulators (PAMs) targeting the M_4 mAChR subtype have shown therapeutic potential for the treatment of multiple symptoms observed in schizophrenia, including positive and cognitive symptoms when assessed in acute preclinical dosing paradigms. Since the cholinergic system has been implicated in multiple stages of learning and memory, we evaluated the effects of repeated dosing with the highly selective M_4 PAM VU0467154 on either acquisition and/or consolidation of learning and memory when dosed alone or after pharmacologic challenge with the N-methyl-D-aspartate subtype of glutamate receptors (NMDAR) antagonist MK-801. In animals, MK-801 challenge represents a well-documented model of NMDAR hypofunction that is thought to underlie some of the positive and cognitive symptoms observed in schizophrenia. In wildtype mice, 10-day, once-daily dosing of VU0467154 either prior to, or immediately after daily testing enhanced the rate of learning in a touchscreen visual pairwise discrimination task; these effects were absent in M_4 mAChR knockout mice. Following a similar 10-day, once-daily dosing regimen of VU0467154, we also observed 1) improved acquisition of memory in a cue-mediated conditioned freezing paradigm, 2) attenuation of MK-801-induced disruptions in the acquisition of memory in a context-mediated conditioned freezing paradigm and 3) reversal of MK-801-induced hyperlocomotion. Comparable efficacy and plasma and brain concentrations of VU0467154 were observed after repeated dosing as those previously reported with an acute, single dose administration of this M_4 PAM. Together, these studies are the first to demonstrate that cognitive enhancing and antipsychotic-like activity are not subject to the development of tolerance following repeated dosing with a selective M_4 PAM in mice and further suggest that activation of M_4 mAChRs may modulate both acquisition and consolidation of memory functions.