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Abstract (word count: 344):

Acetylcholine (ACh) is a neurotransmitter known to modulate cognitive functions, including learning and memory. Many cholinergic drugs bind to highly conserved orthosteric binding sites of muscarinic receptors (mAChRs) and are therefore likely to activate all mAChR subtypes (M<sub>1</sub>-M<sub>5</sub>) to some degree, including M<sub>3</sub>, which is primarily thought to mediate most of the adverse peripheral side effects associated with cholinergic agonists. Drugs that bind to allosteric sites, however, have shown promise for targeting specific muscarinic receptor subtypes. There are two broad classes of allosteric activators: allosteric agonists, which can act to enhance memory in the absence of ACh, and positive allosteric modulators (PAMs), which enhance the ability of ACh to activate mAChRs and thus depend on ACh to produce a similar effect. In the present study, we sought to identify the contribution of M<sub>1</sub> and M<sub>4</sub> receptor subtypes to hippocampal memory, since these receptors are profusely found in memory related structures such as the hippocampus and believed to be crucial for memory. We therefore hypothesized that selective M<sub>1</sub> or M<sub>4</sub> activators would act to enhance memory in an object recognition task. To this end we utilized low, medium and high doses of the novel M<sub>1</sub> allosteric agonist, VU0364572, M<sub>1</sub> PAM, BQCA, or the novel M<sub>4</sub> PAM, VU0152100. Importantly, experimenters were blind to drug condition and drug order was randomized for subcutaneous injection to rats 30 minutes before they performed an object recognition memory task. Interestingly, the results suggested that the efficacy of the drugs might depend on a rat's baseline level of memory performance. In particular, when drug effects in low baseline performers (discrimination indices < 0.60) and high baseline performers (discrimination indices > 0.60) were analyzed separately, simple comparisons indicated that a low dose of VU0152100 increased memory performance in rats with low baseline performance. To our knowledge, this is the first demonstration that potentiating the M<sub>4</sub> mAChR subtype can increase memory performance. Fully understanding the behavioral effects of activating mAChR subtypes in the brain will be essential for developing drugs for memory deficits associated with disorders such as Alzheimer's disease and schizophrenia.