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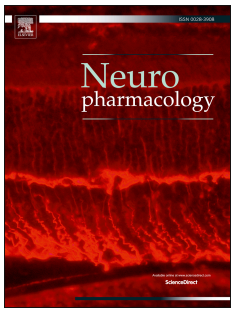

Current status of muscarinic M1 and M4 receptors as drug targets for neurodegenerative diseases

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Current Status of Muscarinic M1 and M4 Receptors as Drug Targets for Neurodegenerative Diseases

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Abstract

The cholinergic signalling system has been an attractive pathway to seek targets for modulation of arousal, cognition, and attention which are compromised in neurodegenerative and neuropsychiatric diseases. The acetylcholine muscarinic receptor M1 and M4 subtypes which are highly expressed in the central nervous system, in cortex, hippocampus and striatum, key areas of cognitive and neuropsychiatric control, have received particular attention. Historical muscarinic drug development yielded first generation agonists with modest selectivity for these two receptor targets over M2 and M3 receptors, the major peripheral sub-types hypothesised to underlie the dose-limiting clinical side effects. More recent compound screening and medicinal chemistry optimization of orthosteric and allosteric agonists, and positive allosteric modulators binding to sites distinct from the highly homologous acetylcholine binding pocket have yielded a collection of highly selective tool compounds for preclinical validation studies. Several M1 selective ligands have progressed to early clinical development and in time will hopefully lead to useful therapeutics for treating symptoms of Alzheimer's disease and related disorders.

Introduction

The search for neurosymptomatic treatment options for neurodegenerative and neuropsychiatric diseases has achieved modest gains in success after many decades of intense work (Szeto et al, 2016). Alzheimer's disease (AD) is one of the fastest growing patient populations and the current standards of care for AD-related dementia and cognitive decline are limited to modulators of the cholinergic and glutamatergic systems. Cognitive symptoms such as memory loss, confusion, and problems with thinking and reasoning are poorly managed with cholinesterase inhibitors (e.g. donepezil, rivastigmine and galantamine) or the glutamate receptor blocker memantine (Namenda) as the overall efficacy of these therapeutics is modest (Tan et al., 2014). These agents are generally perceived to lose efficacy over