Poster
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Therapeutic Efficacy of Xanomeline on Psychotropic Drug-Induced Cognitive Dysfunction in Rats

Cheng Peng, Zonghao Yu, Zhen Li, Lifeng Zhang, Juan Tan, *In Vivo* Pharmacology Unit, WuXi Biology, WuXi AppTec

WuXi Biology

Introduction

Psychotropic drug abuse, particularly with amphetamine and ketamine, has been shown to induce alterations in dopaminergic innervation, neuronal structure, and cognitive function. Previous studies demonstrated that the M1R/M4R agonist xanomeline could reverse cognitive abnormalities induced by methamphetamine and MK801, suggesting its potential therapeutic value in addressing psychotropic drug abuse. The aim of the present study was to investigate whether xanomeline, an M1R/M4R agonist, could ameliorate cognitive dysfunction induced by amphetamine and ketamine abuse.

Experimental design

Male Long-Evans rats (n=50) were randomly divided into five groups to evaluate the therapeutic efficacy of xanomeline on psychotropic drug-induced cognitive dysfunction. The novel object recognition (NOR) task, a behavioral paradigm used to assess recognition memory in rodents, was employed. The groups included: Vehicle group (n=10), which received saline injection; Amphetamine group (n=9), which received four injections of amphetamine (2 mg/kg, administered every 2 hours, 72 hours before NOR); Ketamine group (n=10), which received a single injection of ketamine (20 mg/kg, subcutaneously, 30 minutes before NOR); Xanomeline plus Amphetamine group (n=9); and Xanomeline plus Ketamine group (n=10), both of which were administered xanomeline (30 mg/kg, intraperitoneally) 30 minutes before each drug administration.

Results

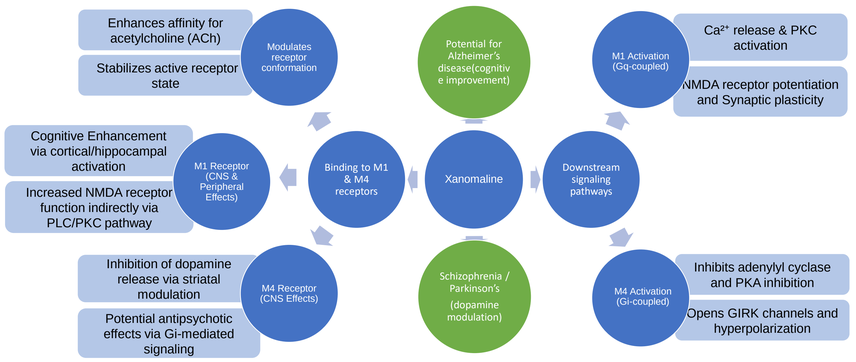

Figure 1. Xanomeline Mechanism of Action (Flow Chart)

Xanomaline is a selective positive allosteric modulator (PAM) of muscarinic M1 and M4 receptors, enhancing their sensitivity to endogenous acetylcholine (ACh) without directly activating them. By binding to allosteric sites, it stabilizes active receptor conformations—potentiating M1-mediated Gq signaling (boosting cognition via cortical/hippocampal PLC/PKC pathways and NMDA receptor modulation) and M4-mediated Gi signaling (inhibiting striatal dopamine release, offering potential antipsychotic effects). This subtype selectivity (M1/M4 over M2/M3) aims to improve cognitive and neuropsychiatric symptoms (e.g., in Alzheimer's or schizophrenia) while minimizing peripheral side effects linked to other muscarinic receptors.

Results

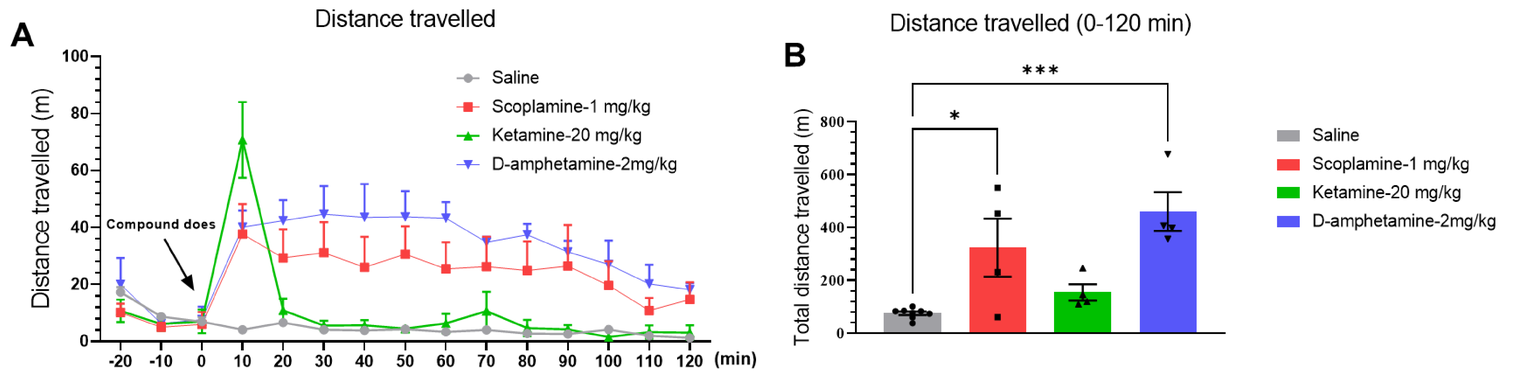

Figure 2. Robust Hyperactivity Induced by Distinct Pathways

Drugs that increase hyperlocomotion, scopolamine, ketamine, amphetamine) often impair NOR performance. We used psychotropic drugs to induce a rat model of cognitive impairment and observed the locomotion activities of rats. (A) is the distance travelled of rats 30 minutes before administration of psychotropic drugs and 120 minutes after administration. (B) represents the total distance travelled of rats 120 minutes after administration of psychotropic drugs . Data were expressed as Mean ± SEM and analyzed by Kruskal-Wallis test, *p<0.05, ***p<0.001.

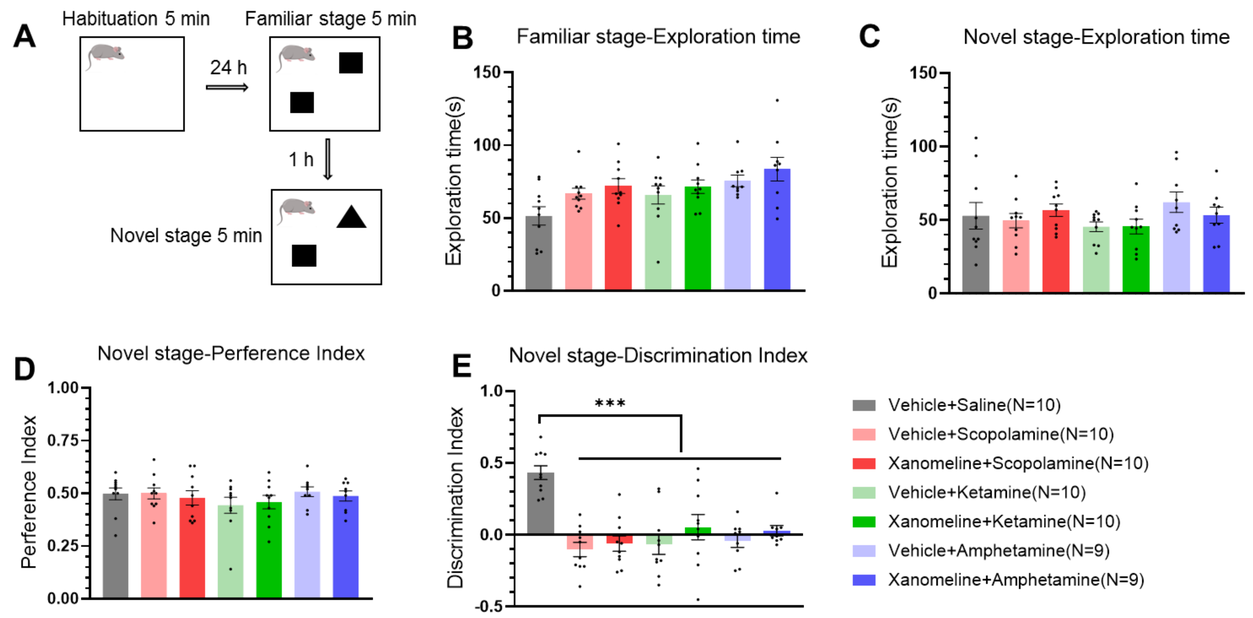

Figure 3. Xanomeline Enhances Object Recognition Memory in Cognitive Impairment Models

Xanomeline can potentially reverse ketamine-induced cognitive deficit as observed in novel object recognition (NOR) task. **(A)** is a schematic diagram of NOR. We tested the total exploration time of the animals in the Familiar stage **(B)**, the total exploration time in the novel stage **(C)**, the preference index (Time $_{\text{Familiar object}}$ / (Time $_{\text{Familiar object}}$ + Time $_{\text{Novel object}}$)) **(D)** and discrimination index (Time $_{\text{Familiar object}}$ - Time $_{\text{Novel object}}$) / (Time $_{\text{Familiar object}}$ + Time $_{\text{Novel object}}$)) **(E)**. Data were expressed as Mean ± SEM and analyzed by Kruskal-Wallis test,***p<0.001.

Summary

These findings suggest a functional interaction between the muscarinic cholinergic and dopaminergic/NMDA systems in modulating recognition memory. Muscarinic cholinergic agonists, such as xanomeline, may hold therapeutic potential for treating cognitive impairments associated with psychotropic drug abuse.

References

1. Bridges TM, et al. (2018). *"Xanomeline and the M1/M4 PAMs: Preclinical Mechanisms Supporting Therapeutic Potential for Schizophrenia and Alzheimer's Disease." ACS Chem Neurosci. 2204-2216.