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Effects of co-administration of ketamine and ethanol on the dopamine system via the cortex-striatum circuitry

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ABSTRACT

Aim: Ketamine and ethanol are increasingly being used together as recreational drugs in rave parties. Their effects on the dopamine (DA) system remain largely unknown. This study aimed to investigate the effects of consuming two different concentrations of ketamine with and without alcohol on the DA system.
Materials and methods: We employed the conditioned place preference (CPP) paradigm to evaluate the rewarding effects of the combined administration of two different doses of ketamine (30 mg/kg and 60 mg/kg) with ethanol (0.3156 g/kg). We evaluated the effects of the combined drug treatment on the transcriptional output of tyrosine hydroxylase (TH), dopa decarboxylase (DDC), synaptosomal-associated protein 25 (SNAP25), and vesicular monoamine transporter 2 (VMAT2) as well as protein expression level of brain-derived neurotrophic factor (BDNF) in rat prefrontal cortex (PFC) and striatum.
Key findings: We found that rats exhibited a dose-dependent, drug-paired, place preference to ketamine and ethanol associated with an elevated DA level in the striatum but not in the PFC. Moreover, treatment involving low- or high-dose ketamine with or without ethanol caused a differential regulatory response in the mRNA levels of the four DA metabolism genes and the cellular protein abundance of BDNF via the cortex-striatum circuitry.
Significance: This study investigated the molecular mechanisms that occur following the combined administration of ketamine and ethanol in the DA system, which could potentially lead to alterations in the mental status and behavior of ketamine/ethanol users. Our findings may aid the development of therapeutic strategies for substance abuse patients.

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1. Introduction

Ketamine, a noncompetitive and nonselective high-affinity *N*-methyl-D-aspartate (NMDA) antagonist, is a commonly used anesthetic in clinical and veterinary applications [1–3]. It is also illegally consumed as a recreational drug. Abusive use of ketamine could damage the nervous system, resulting in cognitive impairment, perceptual alteration, impaired vision, and schizophrenia [4–7]. Previous studies have indicated that chronic ketamine consumption can lead to deregulated cerebellum activity in both mice and humans; additionally, it can cause kidney dysfunction with reduced urinary bladder capacity, liver fibrosis, and deteriorated cardiac function in humans [6,8–10]. The number of ketamine abusers has considerably increased worldwide [11–16]. According to the Central Registry of Drug Abuse (CRDA), from among all psychotropic substances, ketamine was consumed by 28.2% of the reported substance abusers in Hong Kong in 2013 [17]. Abusive use of ketamine is also rampant in China. There were >190,000 registered ketamine abusers in 2013; the majority of them were from the southeastern coastal area. The reported figures may have underestimated the true extent of this social problem [18].

The mesocorticolimbic dopaminergic system plays an essential role in motivated behaviors, reward system, and addiction [19,20]. The dopaminergic projections to the prefrontal cortex (PFC) were highly sensitive to ketamine administration. A sub-anesthetic dose (30 mg/kg) of

Abbreviations: BDNF, brain-derived neurotrophic factor; CNS, central nervous system; CPP, conditioned place preference; DA, dopamine; DDC, dopa decarboxylase; GABA, gamma-aminobutyric acid; NAc, nucleus accumbens; NMDA, *N*-methyl-D-aspartate; PFC, prefrontal cortex; qRT-PCR, quantitative real-time polymerase chain reaction; SNAP25, synaptosomal-associated protein 25; TH, tyrosine hydroxylase; VMAT2, vesicular monoamine transporter 2.

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ketamine induced drastic dopamine (DA) release in the rats' PFC by modulating neurotransmission at the postsynaptic receptors, including NMDA glutamate receptors and gamma-aminobutyric acid receptors (GABA) [21,22]. Additionally, a previous study has shown the midbrain to be a potential hub for dopaminergic activity [23]. Tan et al. reported that chronic ketamine administration strongly promoted DA production in the midbrain, and this was associated with enhanced tyrosine hydroxylase (TH) expression [24].

In the central nervous system, DA metabolism is mainly regulated by the DA-associated synthesis and transport genes [25,26]. TH hydroxylates tyrosine to L-3,4-dihydroxyphenylalanine (L-DOPA), which then undergoes decarboxylation by dopa decarboxylase (DDC) to form DA [27]. Vesicular monoamine transporter 2 (VMAT2) then transports the cytosolic DA pool to the synaptic vesicles. Synaptosomal-associated protein 25 (SNAP25), predominately distributed in the axons and nerve terminals, is necessary for establishing neural circuits and regulating neurotransmitter release into the synaptic clefts [28]. SNAP25 is also associated with heritable neurocognitive and behavioral abnormalities [29].

Ketamine users, primarily young adults, usually consume ketamine with ethanol in "rave parties" for its hallucinogenic and short-term effects [30]. However, the combined effects of ketamine and ethanol on the neuronal system are largely unexplored. We employed a rat model to study the conditioned place preference (CPP) in response to the co-administration of ketamine and ethanol. Moreover, we examined their combined interactions on the dopaminergic activity and expression profiling of the DA-related genes (TH, DDC, SNAP25, and VMAT2) and BDNF protein in the PFC and striatum, two important brain areas in the mesocorticolimbic dopaminergic system. Our findings provide a novel understanding of the underlying mechanism of the ketamine-ethanol interaction in the DA system and the development of therapeutic strategies for substance abuse patients.

2. Materials and methods

2.1. Animals and drugs administration

All animal experiments were performed according to the Principles of Laboratory Animals Care as per the law in China. The study was also approved by the Ethics Committee of Kunming Medicine University (KMU). Male Sprague-Dawley (SD) rats weighing 200–250 g were obtained from the Laboratory Animal Centre (LAC) of KMU and housed at 22–24 °C with 45–55% humidity and a 12-hour alternating light-dark cycle. Standard diet (Beijing Ke-ao Xie-li Feed Co., LTD, SPF Rat Feed) and water were given ad libitum. Four experimental groups were created. Each group had 13 rats; we randomly selected 6 for the conditioned place-preference experiment (N = 6). Simple randomization was used to ensure that each rat had an equal chance of being chosen for each treatment in the study. Two rat groups were administrated ketamine (Cat# H35020148, Ketamine Hydrochloride Injection, Fujian Gutian Pharmaceutical Co, LTD) intraperitoneally once per day at a sub-anesthetic dose of either 30 mg/kg (K30) or a higher dose of 60 mg/kg (K60), the suggested dosage for chronic administration [31,32]. The other two experimental groups were administered ketamine intraperitoneally at a dose of 30 mg/kg (K30 + E) and 60 mg/kg (K60 + E), immediately followed by oral gavage of 20% ethanol (Cat# GB/678-2002, Changshu Yangyuan Chemical Industry Co., LTD, AR) at a dose of 0.3156 g/kg once a day. The control groups received the same dose of ethanol and saline for 30 days. Body weights of the rats were measured weekly for dose adjustment. At this dosage, ethanol did not induce CPP [33].

2.2. Conditioned place preference procedure

2.2.1. Apparatus

The rewarding effect was assessed using CPP testing with a three-compartment CPP apparatus (Cat# RD1111-CPP-R-2, Shanghai Mobile datum Co., LTD). One compartment had a grid floor and black walls (L × W × H: 30 cm × 30 cm × 34 cm). The other, same-sized compartment had a mesh floor and white walls. The middle compartment had a flat gray floor and gray walls (L × W × H: 10 cm × 30 cm × 34 cm) and was connected to the other two compartments via removable doors. Both, black and white compartments had a ceiling lamp. General activity was monitored via video recording, and the time spent in each compartment was recorded using Dr. Rat Video Analysis Software 2.20.

2.2.2. Pre-conditioning test

As shown in Fig. 1A, the pre-conditioning testing session consisted of three phases as previously described, with minor modifications [34,35]. To identify any pre-existing bias towards the individual compartments, each rat was initially placed in the middle chamber and allowed to freely explore the entire apparatus for a 15-min session for three consecutive days before drug administration (habituation). The time spent in each compartment on the third day was used as the pre-conditioning data. The most preferred compartment was designated as the preferred compartment, and the other as the non-preference compartment. Each animal received individual CPP training.

2.2.3. Conditioning with drugs

Each rat was placed in the non-preference (drug-paired) and preference (drug-unpaired) compartments for a 40-min session/day each after the respective intervention. The floor and walls of each compartment were wiped everyday with 70% ethanol after each trial. Each rat underwent a conditioning trial for 30 days.

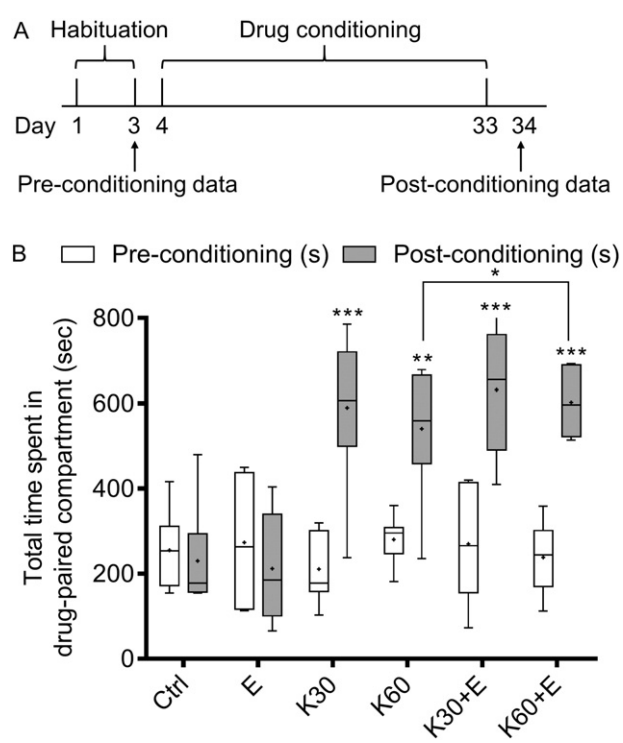

Fig. 1. CPP to the co-administration of ketamine and ethanol A) CPP experiment procedure; B) A grouped box and whisker plot showing the mean pre-conditioning and post-conditioning time (sec) spent in the drug-paired compartment treated with saline (ctrl), 20% ethanol (E), 30 mg/kg ketamine (K30), 60 mg/kg ketamine (K60), 30 mg/kg ketamine with 20% ethanol (K30 + E) and 60 mg/kg ketamine with 20% ethanol (K60 + E). *** indicates $p < 0.0005$, ** indicates $p < 0.005$, * indicates $p < 0.05$. '+' sign indicates the mean value of each treatment. The box extends from the 25th to 75th percentiles, the line in the middle of the box is plotted at the median, and the whiskers go down to the smallest value and up to the largest (Min to Max.). N = 6 per group.

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