Behavioural Brain Research 317 (2017) 494–501

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Research report

A novel synthetic cathinone, 2-(methylamino)-1-(naphthalen-2-yl) propan-1-one (BMAPN), produced rewarding effects and altered striatal dopamine-related gene expression in mice

Chrislean Jun Botanas[a,1], Seong Shoon Yoon[b,1], June Bryan de la Peña[a], Irene Joy dela Peña[a], Mikyung Kim[a], Taeseon Woo[a], Joung-Wook Seo[b], Choon-Gon Jang[c], Kyung-Tae Park[d], Young Hun Lee[d], Yong Sup Lee[d], Hee Jin Kim[a,*], Jae Hoon Cheong[a,*]

[a] Uimyung Research Institute for Neuroscience, School of Pharmacy, Sahmyook University, 815 Hwarangro, Nowon-gu, Seoul, 01795, Republic of Korea
[b] Center for Safety Pharmacology, Korea Institute of Toxicology, Daejeon 305-343, Republic of Korea
[c] Department of Pharmacology, School of Pharmacy, Sungkyunkwan University, Suwon, 440-746, Republic of Korea
[d] Department of Life and Nanopharmaceutical Sciences, Kyung Hee University, Seoul 02447, Republic of Korea

HIGHLIGHTS

- We designed and synthesized a new synthetic cathinone BMAPN.
- BMAPN is a synthetic cathinone with naphthalene substituent on the aromatic ring.
- BMAPN produced rewarding and reinforcing effects.
- BMPAN has the ability to alter dopamine-related gene expression.

ARTICLE INFO

Article history:
Received 2 September 2016
Received in revised form 7 October 2016
Accepted 9 October 2016
Available online 11 October 2016

Keywords:
Synthetic cathinones
Conditioned place preference
Self-administration
Locomotor sensitization
Abuse potential

ABSTRACT

The recreational use of synthetic cathinones has grown rapidly which prompted concerns from legal authorities and health care providers. However, in response to legislative regulations, synthesis of novel synthetic cathinones by introducing substituents in cathinone molecule has dramatically increased the diversity of these substances. Based on current trends, the aromatic ring is one of the popular sites in cathinone molecule being explored by designer-type modifications. In this study, we designed and synthesized a novel synthetic cathinone, 2-(methylamino)-1-(naphthalen-2-yl) propan-1-one (BMAPN), which has a naphthalene substituent on the aromatic ring. Thereafter, we determined whether BMAPN has rewarding and reinforcing effects through the conditioned place preference (CPP) test in mice and self-administration (SA) paradigm in rats. Locomotor sensitization was also assessed in mice during daily BMAPN treatment for 7 days and drug challenge. Furthermore, we investigated the effects on BMAPN on dopamine-related genes in the striatum of mice using quantitative real-time polymerase chain reaction (qRT-PCR). BMAPN induced CPP at 10 and 30 mg/kg and was modestly self-administered at 0.3 mg/kg/infusion. Repeated BMAPN (30 mg/kg) administration also produced locomotor sensitization. qRT-PCR analyses revealed decreased dopamine transporter and increased dopamine receptor D2 gene expression in the striatum of the BMAPN-treated mice. These data indicate that BMAPN has rewarding and reinforcing properties, which might be due to its effects on dopamine-related genes. The present study suggests that these findings may be useful in predicting abuse potential of future cathinone entities with aromatic ring substitutions.

1. Introduction

Synthetic derivatives of cathinone have become increasingly popular among recreational drug users [1,2]. Their dramatic increase has resulted in part from sensationalized media attention, online marketing, and widespread availability in convenience stores and head shops [3,4]. Synthetic cathinones are considered

* Corresponding authors.
E-mail addresses: msheejin@gmail.com (H.J. Kim), cheongjh@syu.ac.kr, wity_june@yahoo.com (J.H. Cheong).
[1] These authors have equal contribution in doing the experiments and writing this manuscript.

http://dx.doi.org/10.1016/j.bbr.2016.10.016
0166-4328/

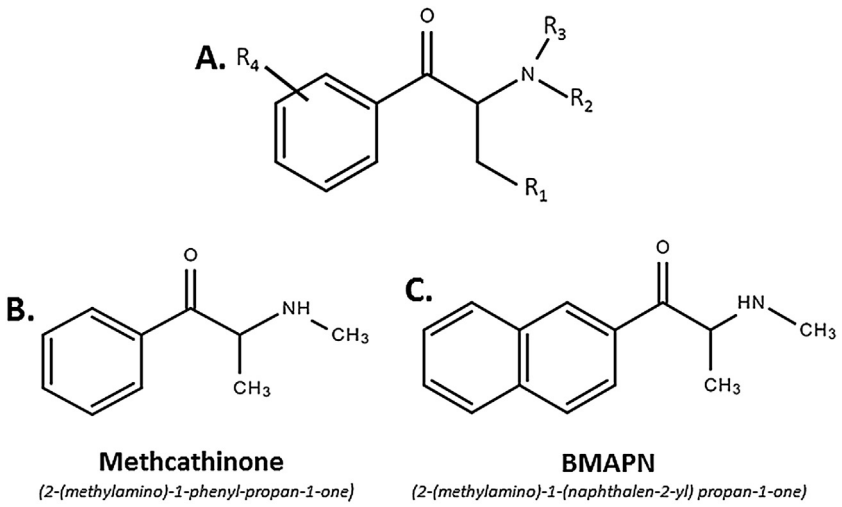

Fig. 1. The general chemical structure of synthetic cathinones (A) shows substitution patterns at four locations in the cathinone molecule: the carbon atom linked to the carbon in alpha position (R_1), on the nitrogen atom (R_2 and R_3) and on the aromatic ring (R_4) (A). Chemical structures of methcathinone (B), and BMAPN (2-(methylamino)-1-(naphthalen-2-yl) propan-1-one) (C).

"legal highs" or "designer drugs" and typically sold as "bath salts," "plant food", and "research chemicals," which are often labeled "not for human consumption" to circumvent drug abuse legislation [3,5]. The abuse of these psychoactive substances has become a widespread problem that it prompted concerns from the health providers and legal authorities. Moreover, in response to legislative regulation and market trends, novel synthetic cathinones are continuously synthesized, dramatically increasing the diversity of synthetic cathinones by introducing chemical modifications, which makes intervention measure mostly challenging [6].

Modifications to the chemical molecule of cathinone or its derivatives, such as methcathione, can create a broad range of designer drugs. Based on the structure of the unsubstituted cathinone molecule (Fig. 1A), there are distinct regions of the molecule where designer modifications are feasible: the carbon atom linked to the carbon in alpha position (R_1), on the nitrogen atom (R_2 and R_3), and on the aromatic ring (R_4) [6]. In recent trends, the aromatic ring is one of the regions popular of being explored by designer-type modifications. Synthetic cathinones with modifications on the aromatic ring have been reviewed by Loilier and colleagues [6]. Some of these synthetic cathinones have been shown to produce behavioral effects similar to other abuse cathinones and psychoactive drugs such as cocaine and methamphetamine [2,7–9]. Furthermore, these compounds can influence dopaminergic neurotransmissions in the brain reward system [2,6], the brain region implicated in drug addiction. In view of these observations, it seems that synthetic cathinones with modifications in the aromatic ring may have rewarding effects and could be abused by humans.

As part of the continuing effort of the Drug Abuse Research Institute of Korea (DARC) to hasten the regulation of new synthetic cathinones and to predict abuse potential of future synthetic cathinones entities with similar modifications, we designed and synthesized a novel synthetic cathinone with naphthalene substitution in the aromatic ring, 2-(methylamino)-1-(naphthalen-2-yl) propan-1-one (BMAPN) (Fig. 1C). Then, we examined the rewarding and reinforcing effects of this new synthetic cathinone through the two of the widely used animal models of drug addiction, the conditioned place preference (CPP) and self-administration (SA) test. In addition, we also investigated whether repeated exposure to BMAPN would induce locomotor sensitization during repeated treatment and drug challenge following 7 days of withdrawal. This was based on the findings that euphorigenic effects activate the same neural process as locomotor activation [10]. Furthermore, we evaluated the effects of BMAPN on dopaminergic activity by analyzing the expression of dopamine-related genes in the brain (striatum) of the mice through quantitative real-time polymerase chain reaction (qRT-PCR).

2. Materials and methods

2.1. Animals

All animals were purchased from Han Lym Animal Laboratory Co. (Hwasung, Korea). Male ICR (22–27 g) mice were used in the CPP, locomotor sensitization tests, and qRT-PCR and were housed 6–8 per cage. Sprague-Dawley rats (200–300 g) were used for the SA test and housed individually. All animals were kept in a temperature- (22 ± 2 °C) and humidity-controlled (55 ± 5%) animal room on a 12/12 H light/dark (07:00–19:00 H light) schedule. They were acclimatized first to the laboratory setting for five days before any experiments. They had *ad libitum* access to food and water during acclimatization and experiments, except for the rats during lever training and SA sessions. All tests were performed in accordance with the Principles of Laboratory Animal Care (NIH Publication No. 85-23, revised 1985) and the Animal Care and Use of Guidelines of Sahmyook University, Korea.

2.2. Drugs

BMAPN was synthesized as outlined in recent studies with some modifications [11–13]. Briefly, 2-naphthonitrile was treated with ethyl magnesium bromide and then brominated with bromine to give 2-bromo-1-(naphthalene-2-yl) propan-1-one. The resulting compound was reacted with N-benzylmethylamine and then further reacted with 1-chloroethyl chloroformate to afford BMAPN·HCl. Its structure was confirmed by the following spectroscopic analyses. 1H NMR (400 MHz, CD3OD) δ 8.72 (s, 1H), 8.13 (d, J = 8.1 Hz, 1H), 8.10–8.05 (m, 2H), 8.01 (d, J = 8.1 Hz, 1H), 7.76–7.65 (m, 2H), 5.31 (q, J = 7.2 Hz, 1H), 2.84 (s, 3H), 1.68 (d, J = 7.2 Hz, 3H); 13C NMR (100 MHz, CD3OD) δ 195.9, 136.6, 132.8, 131.5, 130.3, 129.8, 129.6, 129.1, 127.8, 127.3, 123.4, 59.5, 30.7, 15.4; HR-Mass calced for C14H16NO+ 214.1226, found 214.1181.

Methamphetamine hydrochloride (METH) was purchased from Sigma-Aldrich Corporation (St. Louis, Missouri, United States). All drugs were diluted with 0.9% sterile saline solution and administered intraperitoneally (i.p.) (CPP and locomotor sensitization) or