Biomedicine & Pharmacotherapy 100 (2018) 116–123

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

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

Psychotomimetic-like behavioral effects of memantine in the mouse

Nobue Kitanaka[a,1], Junichi Kitanaka[a,*,1], F. Scott Hall[b], Yoshiro Kubota[a,2], Yumi Mimura[a,2], Sayaka Ogura[a,2], Yukiya Okada[a,2], George R. Uhl[c], Motohiko Takemura[a]

[a] Department of Pharmacology, Hyogo College of Medicine, Hyogo 663-8501, Japan
[b] Department of Pharmacology and Experimental Therapeutics, College of Pharmacy and Pharmaceutical Sciences, University of Toledo, Toledo, OH 43614, USA
[c] New Mexico VA Healthcare System/BRINM, Albuquerque, NM 87108, USA

ARTICLE INFO

Keywords:
Memantine
Stereotyped behavior
Sniffing
Hyperlocomotion
Dopamine D_2 receptor
Histaminergic neurotransmission

ABSTRACT

A single administration of mice with memantine (1-amino-3,5-dimethyladamantane), a glutamatergic *N*-methyl-D-aspartate (NMDA) receptor antagonist, induced stereotyped behaviors in dose- and time-dependent manners. The predominant behavioral component of the stereotypy was a continuous, exaggerated sniffing which was accompanied by persistent locomotion. In contrast, a psychostimulant methamphetamine (METH) predominantly induced a stereotyped biting and other forms of intense stationary stereotypical behaviors. Memantine-induced stereotyped sniffing was attenuated by pretreatment with haloperidol, a dopamine D_2 receptor antagonist, in a dose-dependent manner. The memantine-induced stereotyped sniffing was also attenuated by pretreatment with betahistine (2-[2-(methylamino)ethyl]pyridine), an agent which increases histamine turnover and releases histamine in the brain. These observations suggest that memantine might induce stereotypies through neuronal mechanisms that are somewhat different from those of METH, but still overlap to a certain extent, since memantine-induced stereotypies can be attenuated by the mechanisms that also suppress METH-induced stereotypy. Importantly, these data suggests that the effects of memantine may be more limited to the ventral striatum including nucleus accumbens than those of METH, which is associated with dorsal striatal stimulation at high doses. In this respect memantine may also have pharmacological properties such as compartmentation (*i.e.* brain distribution) and neuronal mechanisms different from those of other NMDA receptor antagonists, such as ketamine, which may have important implications for therapeutic uses of these drugs.

1. Introduction

Memantine (1-amino-3,5-dimethyladamantane) is an amantadine derivative that functions a voltage-dependent non-competitive antagonist for glutamatergic *N*-methyl-D-aspartate (NMDA) receptors [1]. Memantine also blocks serotonin 5-HT_3 receptors [2,3] and α_7 nicotinic acetylcholine receptors [4] and activates dopamine D_2 receptors [5]. It is chronically used to treat the symptoms of Parkinson's disease (PD) [6–9] and Alzheimer's disease (AD) [10–13]. However, unlike other NMDA receptor-channel blockers such as phencyclidine (PCP), dizocilpine (MK-801) and ketamine, memantine at doses equivalent to those that purportedly produce therapeutic effects in PD and AD has been reported to possess no psychotomimetic effects [14,15]. Thus, it would appear that some actions of memantine, either related to the receptor actions mentioned or other effects, produce quite different actions from those of other NMDA antagonists.

In mice, memantine decreases the immobility time in the tail-suspension test in a dose-dependent manner, but the anti-depressant effect of memantine is not accompanied by locomotor stimulation while only a high dosage of memantine induces stereotypies [16], behaviors which are repetitive and compulsive without obvious purpose [17,18]. Although many psychopharmacological agents are currently available for the treatment of major depression, approximately 10–20% of patients treated with the common antidepressant medications do not achieve complete recovery and meet the criteria of treatment-resistance [19]. Under the current efficacy of ketamine in major depression, the antidepressant effects of memantine may be similar to the effects of ketamine [20,21], but perhaps with reduced psychotomimetic effects, although repetitive administration of high doses of memantine induces behavioral sensitization [22]. There are no reports regarding the characteristics of memantine-induced psychotomimetic effects, which will be important to determine. A comparison of types of stereotyped

* Corresponding author at: Department of Pharmacology, Hyogo College of Medicine, 1-1 Mukogawa-cho, Nishinomiya, Hyogo 663-8501, Japan.
E-mail address: kitanaka-hyg@umin.net (J. Kitanaka).
[1] These authors contributed equally to this study.
[2] These authors listed in alphabetical order contributed equally to this study as medical students participating in an orientation course for medical sciences (2013, 2014) held in the Department of Pharmacology, Hyogo College of Medicine.

https://doi.org/10.1016/j.biopha.2018.01.160
Received 25 October 2017; Received in revised form 23 January 2018; Accepted 29 January 2018

behavior induced by memantine and those induced by psychostimulants such as methamphetamine (METH) has not yet been made. In the present study, we first characterized behavioral components of stereotypies induced by memantine in order to compare them with those induced by METH. Secondly, we investigated effects of haloperidol, a dopamine D_2 receptor antagonist, on memantine-induced stereotyped behaviors, since haloperidol blocks METH-induced stereotypy [23]. Betahistine (2-[2-(methylamino)ethyl]pyridine) is an agent used in the treatment of vertigo associated with Ménière's disease [24], which is an analogue of histamine with weak agonist properties at histamine H_1 receptors and more potent antagonistic effects at histamine H_3 receptors [25], consequently increasing histamine turnover and releasing histamine in the brain [26]. The effect of betahistine on memantine-induced stereotypy was investigated as drugs with similar actions on histamine suppress METH-induced stereotypy since stereotypies induced by METH are alleviated by the brain histamine degrading enzyme (*i.e.* histamine *N*-methyltransferase) inhibitors, agents which increase histamine contents in the brain [27].

2. Materials and methods

2.1. Subjects

Male ICR mice (10–11 weeks old; Japan SLC, Shizuoka, Japan) were housed in groups of seven (cage size, 37 × 22 × 15 cm; with fresh wood chips) in a temperature- (22 ± 2 °C) and humidity- (50 ± 10%) controlled environment under a 12/12 h light/dark cycle (lights on at 07:00) with food and water available *ad libitum,* except during testing. Animal handling and care were conducted in accordance with the *Guide for the Care and Use of Laboratory Animals* (8th edition, Institute of Laboratory Animal Resources-National Research Council, National Academy Press, 2011), and all experiments were reviewed and approved by the Institutional Animal Research Committee of Hyogo College of Medicine. The mice were used once (n = 104, 11–12 weeks old, 33–49 g) after at least one-week habituation in the facility.

2.2. Reagents

Memantine hydrochloride and betahistine dihydrochloride were purchased from Sigma-Aldrich (St. Louis, MO, USA). Betahistine binds to histamine H_3 receptors and release histamine in the brain, increasing tissue histamine levels [25,26]. This reagent can apply systemically through an intraperitoneal route, since it is water-soluble, so that betahistine can manipulate brain histamine levels pharmacologically easier than histamine *N*-methyltransferase inhibitors metoprine (which is not soluble in water) or SKF 91488 (which is not permeable through the blood-brain barrier) [28]. METH hydrochloride and haloperidol (Serenace Injection®) were from Dainippon Sumitomo Pharma Co., Ltd. (Osaka, Japan). All reagents were dissolved in sterile saline. Drug solutions were prepared in such a way that the necessary dose could be injected in a volume of 0.1 ml/10 g of body weight by an i.p. route. The doses of the drugs were chosen based on the literature [16,23,29,30].

2.3. Treatment protocol

2.3.1. Memantine- and METH-induced stereotyped behavior and locomotion

Mice (n = 48) were weighed and randomly divided into six groups (n = 8 per group): saline, 10 mg/kg METH, 1 mg/kg memantine, 5 mg/kg memantine, 10 mg/kg memantine, and 20 mg/kg memantine. After injection all mice were immediately placed in the testing chamber to assess stereotypy and locomotion for 1 h as described below (see 2.4. Rating of stereotypy and 2.5. Measurement of locomotor activity).

2.3.2. Effects of haloperidol on memantine-induced stereotyped behavior and locomotion

Mice (n = 32) were weighed, randomly divided into four groups (n = 8 per group), and treated with 20 mg/kg of memantine (i.p.) 30 min after an injection of haloperidol (0.1, 0.5, and 1.0 mg/kg, i.p.) or vehicle (*i.e.* saline). After the memantine injection, all mice were placed in the testing chamber for measurements of stereotyped behavior and locomotion.

2.3.3. Effects of betahistine on memantine-induced stereotyped behavior and locomotion

Mice (n = 24) were weighed, randomly divided into four groups (n = 6 per group), and treated with 20 mg/kg of memantine (i.p.) or vehicle (*i.e.* saline) 30 min after an injection of 10 mg/kg betahistine (i.p.) or vehicle (*i.e.* saline). After the memantine (or saline vehicle) injection, all mice were placed in the testing chamber for measurements of stereotyped behavior and locomotion.

2.4. Rating of stereotypy

Test subjects were placed in a transparent acrylic box (29.5 × 29.5 × 34.5 cm) with approximately 25 g of fresh wood chips spread on the floor of the chamber and observed for stereotypy for 1 h following memantine or METH administration by observers unaware of the treatments. METH-induced stereotypy lasts for 170 min [31] while of the time-course of memantine-induced stereotypies have not been reported. The frequencies of each component of stereotyped behavior observed for 2 h are the same as the frequencies observed for 1 h (for instance, 2-h observations [32] *vs.* 1-h observations [33]). Therefore, we chose the period of 1 h for our observations. Behavior was assessed in 30-s intervals, and the predominant behavior observed during each interval was recorded. Quantification of the incidence of stereotyped behavior was made by trained observers blinded to the experimental conditions. Since individual stereotyped behaviors were unchanged for long periods (> 30 s) after drug treatment, it was possible to record the observations by hand. The behaviors scored were inactive (awake and inactive, or sleeping), ambulation, rearing, persistent locomotion, head bobbing (up-and-down movements of the head), continuous sniffing, circling, and continuous nail and/or wood chip biting or licking, according to a method described previously [34]. Head-bobbing is defined as rapid up-and-down movements of the head, while head-twitching is a side-to side movement of the head. These two categories of behavior occur in a completely different fashion so that observers can distinguish the two behaviors. As a result, the trained observers did observe a head-bobbing, but not head-twitching, as a predominant behavior throughout a set of these experiments. Ambulation, rearing, and persistent locomotion were considered locomotor and exploratory behaviors, and the last four categories were considered stereotypies. Persistent locomotion was not classified as stereotypy because the mice scored as having “persistent locomotion” showed horizontal locomotor activity less than or equal to that displayed by mice showing “hyperlocomotion” induced by 1 mg/kg METH (which is not generally defined as a stereotypy) measured by Animex Auto [35]. The cumulative number of intervals within each 5 min period in which stereotypies were observed is shown as a time-course (maximal value = 10). Stereotyped cage climbing [36] was not observed in our experimental system because of the use of an acrylic test chamber with an acrylic ceiling top with small air holes (*i.e.* no stainless steel grid top). Horizontal locomotor activity was simultaneously measured in the same box as described below, and two acrylic boxes were used in the same time in these experiments.

2.5. Measurement of locomotor activity

Locomotor activity was measured in a transparent acrylic test box (29.5 × 29.5 × 34.5 cm) mentioned above using an infrared