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Effects of memantine on hippocampal long-term potentiation, gamma activity, and sensorimotor gating in freely moving rats

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ABSTRACT

Memantine, an uncompetitive N-methyl-D-aspartate receptor antagonist, is used for treatment of patients with Alzheimer's disease. The mechanisms of memantine in relieving cognitive and behavioral symptoms are unclear, and this study attempts to elucidate its action on network and synaptic functions of the hippocampus. The effects of memantine on electrographic activity and hippocampal long-term potentiation (LTP) were investigated in freely moving rats. Basal dendritic excitation on hippocampal CA1 pyramidal cells showed a robust LTP after theta-frequency primed bursts, and the LTP was higher after 5–10 mg/kg intraperitoneal (ip) memantine pretreatment, as compared with saline pretreatment. Injection of scopolamine (5 mg/kg ip) before memantine failed to block the LTP-enhancing effect of memantine. Memantine as compared with saline pretreatment did not affect the LTP after an afterdischarge induced by high-frequency (200-Hz) train stimulation. Memantine (5 or 10 mg/kg ip) significantly enhanced gamma oscillations in the hippocampal local field potentials of 40–100 Hz during walking and awake immobility. Memantine at 10 mg/kg ip, but not at 5 mg/kg ip, increased prepulse inhibition of the acoustic startle response, while both 5 and 10 mg/kg ip memantine enhanced the acoustic startle response as compared with saline-injected rats. These electrophysiological and behavioral effects of memantine are unique among N-methyl-D-aspartate receptor antagonists but are consistent with memantine's effects in improving cognitive and sensorimotor functions of Alzheimer's patients.

1. Introduction

The uncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist memantine (1-amino-3,5-dimethyl-adamantane), with low-affinity but rapid blocking and unblocking ability at the NMDA receptor (Black et al., 1996; Chen et al., 1992; Parsons et al., 2007), is used as a therapeutic drug to improve cognitive functions and quality of life in Alzheimer's disease (Cummings, 2004; Parsons et al., 1999). However, its mechanisms of action on relieving cognitive and behavioral symptoms are unclear.

Animal research shows that memantine, at doses comparable to those given to patients, can improve cognitive functions in normal animals (Parsons et al., 1999, 2007; but see Creeley et al., 2006), animal models of Alzheimer's disease (Martinez-Coria et al., 2010; Minkeviciene et al., 2004), depression (Quan et al., 2011), ischemia (Chen et al., 1998), and neuroinflammation (Rosi et al., 2009). Acute treatment with memantine restored an experience-dependent expansion of place fields of hippocampal neurons in aged rats (Burke et al., 2008). The effect of memantine on NMDA-receptor dependent synaptic plasticity may help to explain its effect on cognitive improvements, and this effect appears to depend on dose and model. Memantine enhanced hippocampal long-term potentiation (LTP) when tonic NMDA-receptor currents were increased by low Mg^{2+} (Frankiewicz and Parsons, 1999) or NMDA (Zajaczkowski et al., 1997). Memantine also reversed the LTP suppression induced by stress (Quan et al., 2011), or by beta amyloid applied exogenously (Klyubin et al., 2011; Rammes et al., 2011) or produced by Alzheimer's model transgenic mice (Tozzi et al., 2015). However, a therapeutic dose of memantine (<10 μM) was shown to decrease or not change hippocampal LTP in brain slices perfused with a normal medium in vitro (Chen et al., 1998; Frankiewicz et al., 1996). In urethane-anesthetized rats, Klyubin et al. (2011) reported that 10 mg/kg intraperitoneal (ip) memantine did not affect the 200-Hz train-induced LTP in CA1. We are aware of only 1 study of memantine on LTP in behaving rats, in which Barnes et al. (1996) reported that chronic injection of memantine prolonged the duration of medial perforant-path LTP in the dentate gyrus of the hippocampus.

Memantine appears to be different from other uncompetitive NMDA-receptor antagonists, such as phencyclidine and ketamine,

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which induce both positive and negative symptoms of schizophrenia (Javitt and Zukin, 1991; Krystal et al., 1994). Instead, memantine was reported to improve agitation and/or aggression and delusions in Alzheimer's patients (Francis, 2009), which are part of the neuropsychiatric inventory commonly used in dementia patients (Cummings, 1997). Similarly, memantine apparently did not consistently induce schizophrenia-like behaviors in animals, unlike the high-affinity NMDA receptor antagonists phencyclidine and ketamine that induced hyperlocomotion, and decreased sensory gating and prepulse inhibition (PPI), a type of sensorimotor gating, in animals (Ma and Leung, 2000, 2007; Swerdlow et al., 2001). Memantine was reported to disrupt acoustic PPI in mice (Nakaya et al., 2011) and Sprague-Dawley rats (Wiley et al., 2003) at a conventional prepulse-startle interval (100 ms) but increased PPI at 10–20 ms prepulse-startle intervals in rats (Swerdlow et al., 2009). PPI was disrupted in Alzheimer's patients (Ueki et al., 2006; but see Hejl et al., 2004) and Alzheimer's animal models (Wang et al., 2012).

Behavioral alteration following an NMDA-receptor antagonist was accompanied by an increase in gamma (30–100 Hz) oscillations in the hippocampal local field potentials or neocortical electroencephalogram (EEG) (Kocsis, 2012; Lee et al., 2003; Ma and Leung, 2007). In urethane-anesthetized mice, 2.5 mg/kg ip memantine was reported to increase, while 10 mg/kg ip memantine decreased, the brainstem-stimulation induced hippocampal EEG at theta (5–7 Hz) and 20–40 Hz frequency bands (Guadagna et al., 2012). We are not aware of reports of memantine's effects on EEG in behaving animals. In Alzheimer's patients, memantine has been reported to increase vigilance accompanied by a decrease in alpha and delta EEG activity (Schulz et al., 1996), or a decrease in a pathological theta-frequency EEG (Sneddon et al., 2006) similar to the action of antiacetylcholinesterase (Babiloni et al., 2013). EEG, and in particular, theta and gamma oscillations, are proposed as possible biomarkers for Alzheimer's disease (Babiloni et al., 2013; Goutagny and Krantic, 2013).

The hippocampus is important for memory (Morris, 2007), and pathology and dysfunction of the hippocampus provide early signs of Alzheimer's disease (Braak and Braak, 1991). Alteration in synaptic plasticity is suggested to underlie memory impairments (Bliss et al., 2007; Rowan et al., 2003). A behavioral state-dependent LTP in animals provides a physiological relevant model for the study of cholinergic drugs on synaptic plasticity (Doralp and Leung, 2008; Leung et al., 2003), which is extended to memantine in the present study. Our previous studies showed that various uncompetitive and competitive NMDA-receptor antagonists attenuated hippocampal LTP induced by theta frequency-burst stimulation (TBS) in behaving rats but had mixed effects on hippocampal LTP induced by a high-frequency train stimulation (HFS) that evoked an afterdischarge (AD) (Leung and Shen, 1993, 1999). In accordance with its cognitive improvement effects, we hypothesized that memantine facilitates LTP induced by both TBS and HFS-AD trains.

To investigate whether memantine has effects on hippocampal activation and sensorimotor gating in behaving rats, we also studied memantine's effect on the spontaneous EEGs in the hippocampus and on PPI. Our hypothesis was that memantine enhances hippocampal gamma EEG activity without disruption of PPI performance.

2. Animals and methods

2.1. Surgery

Male Long-Evans hooded rats (Charles River Canada, St. Constance, Quebec, Canada) of 3–6 months old were housed in pairs in Plexiglas cages and kept on a 12-hour light-dark cycle (lights on at 7:00 hours), at a temperature of 22 ± 1°C. Rats were given food and water ad libitum. All experimental procedures were approved by the local Animal Use Committee and conducted according to the guidelines of the Canadian Council for Animal Care. Efforts were taken to minimize the pain and suffering of animals. All experiments were performed during the period of 9:00 to 18:00 hours, in conditions similar to previous LTP experiments using other NMDA-receptor antagonist (Doralp and Leung, 2008; Leung and Shen, 1993; Leung et al., 2003), EEG and PPI experiments (Ma and Leung, 2000, 2007) were also performed on young adult Long-Evan rats. This allows for comparison of the effects of different drugs, including NMDA-receptor antagonists, with the effect of memantine. Daytime corresponds to a behaviorally inactive period in rats, and is accompanied by relatively low cognitive and behavioral functions, similar to decreased arousal levels in Alzheimer's patients (Schulz et al., 1996).

Under pentobarbital anesthesia (60 mg/kg ip), rats were implanted with a pair of Teflon-coated stainless steel stimulating electrodes (127 μm) into the hippocampal CA1 region, straddling the pyramidal cell layer on both left and right sides (AP-3.5, L ± 2.8; V 3.3, and 2.3, units in mm), according to the atlas of Paxinos and Watson (1998). The dorsal electrode was located near CA1 stratum oriens, and the ventral electrode in CA1 stratum radiatum. During surgery, the evoked potentials were monitored to ensure reversed basal dendritic responses across the dorsal and ventral recording electrodes (Leung and Shen, 1993, 1999). Two jeweler's screws were fixed in the skull over the frontal cortex and cerebellum to serve as stimulus anode and recording ground, respectively. All electrodes and screws were finally anchored to the skull with dental cement. One week was allowed for the animals to recover from surgery.

2.2. Hippocampal LTP

The rat was habituated to a recording chamber (rectangular cage of 30″ × 12″ × 10″ high) for 3–5 days. Photo-isolated current stimulus pulses (0.1 ms in duration) were delivered cathodally to 1 stimulating electrode in CA1, using the screw over the cerebellum as the anode. Evoked responses were filtered at 0.1–3 kHz, sampled at 7 kHz, and averaged on-line by a microcomputer. The basal dendritic response after contralateral stratum oriens stimulation was recorded in CA1 stratum oriens (surface recording electrode) as negative-going field excitatory postsynaptic potentials (fEPSPs).

Two patterns of tetanic stimulation were used in this study: (1) 1 + 10 TBS: each burst consisted of a single priming pulse, at 1.5× threshold response intensity, followed 190 ms later by 10 pulses at 100 Hz; 8 primed bursts were delivered at a burst interval of 10 seconds (Leung and Shen, 1993). The first primed burst was delivered during waking immobility, but subsequent ones followed with a 10-second interval, irrespective of behavior (walking or immobility). Waking immobility was operationally defined as the state when the rat held its head up against gravity but with no gross movement of the body. EEG recordings were made during the whole period of TBS to ensure that a hippocampal AD was not evoked. (2) HFS-AD consisted of a high-frequency stimulus train that induced an AD. The stimulus train consisted of 200 pulses (1-second long) given at 200 Hz and 3× threshold response intensity. HFS was delivered during awake immobility. The threshold response intensity was defined as the lowest stimulus current (pulse duration 0.1 ms, cathodal to the stimulating electrode, typically 30–40 μA) that evoked a visually detectable average fEPSPs (4 sweeps were averaged). Average fEPSPs (4 sweeps) were recorded during awake immobility, operationally defined for time periods when a rat held its head up against gravity, with eyes open, and no gross body movements. During each recording session,