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Chronic memantine decreases nicotine self-administration in rats

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ABSTRACT

Neurobehavioral bases of tobacco addiction and nicotine reinforcement are complex, involving more than only nicotinic cholinergic or dopaminergic systems. Memantine is an NMDA glutamate antagonist used to improve cognitive function in people with Alzheimer's disease. Glutamate may be an important component of the reinforcing effects of nicotine, so memantine was evaluated as a potential smoking cessation aid. Two studies were conducted with adult female rats, one testing acute effects of memantine over a range of doses for changing nicotine self-administration and the other testing the chronic effects of memantine to reduce nicotine self-administration. Acute memantine injections slightly, but significantly, increased nicotine self-administration in a dose-related manner. In contrast, chronic memantine treatment significantly reduced nicotine self-administration. During the first day of memantine administration in the chronic study, nicotine self-administration was significantly elevated replicating the acute study. Starting in the second week of treatment there was a significant reduction of nicotine self-administration relative to controls. This was seen because memantine treatment prevented the increase in nicotine self-administration shown by controls. There even continued to be a memantine-induced lowered nicotine self-administration during the week after the cessation of memantine treatment. Memantine or other drugs affecting NMDA glutamate receptors may be useful aids to smoking cessation. Full efficacy for reducing nicotine self-administration was seen as the NMDA drug treatment is given chronically. Importantly, the effect persisted even after treatment is ended, indicating the high potential for NMDA glutamate receptors to impact nicotine addiction.

1. Introduction

Tobacco addiction is a complex syndrome primarily due to the pharmacological complexity of its active drug nicotine. Nicotine stimulates the release of a variety of neurotransmitters (Wonnacott et al., 1989). One transmitter dopamine has long been considered the most important transmitter system to tobacco addiction and addictions in general. However, the brain is a highly interconnected organ and there are undoubtedly many interacting brain systems beyond the dopamine system involved in addictions, especially tobacco addiction. Nicotine releases not only dopamine but also acetylcholine, serotonin, norepinephrine, GABA and glutamate (Wonnacott et al., 1989). In particular, glutamate, in particular, may play a key role in addiction.

Glutamate is the most common excitatory neurotransmitter in the brain. Glutamate systems are important for a wide variety of behavioral functions including reinforcement, and glutamatergic neurotransmission has been shown to be important in mediating nicotine-evoked dopamine release in the nucleus accumbens (Maex et al., 2014). NMDA glutamate receptor acting drugs have shown some efficacy in countering addictive drug self-administration in previous research, but the studies are not uniformly supportive (Tomek et al., 2013). Dextromethorphan, which among other actions inhibits NMDA glutamate receptors, was shown in our studies (Briggs et al., 2016) as well as in others (Glick et al., 2002) to significantly reduce nicotine self-administration. We have also found that the partial agonist of NMDA glutamate receptors D-cycloserine significantly decreases nicotine self-administration in rats with below the median rate of baseline nicotine self-administration (Levin et al., 2011). Recently we showed that the selective NMDA glutamate receptor antagonist ketamine significantly decreased nicotine self-administration in rats regardless of level of baseline rate of responding (Rezvani et al., 2018), although the efficacy of ketamine for reducing nicotine self-administration was attenuated when the ketamine treatment was given repeatedly. Although NMDA-antagonists may be effective in disrupting nicotine intake, compounds like ketamine are dissociative anesthetics and can have adverse side effects, such as sedation, psychedelic symptoms, and adverse effects on

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mood, cognition, and peripheral health (Niesters et al., 2014). Ketamine in particular also has significant abuse potential (Sassano-Higgins et al., 2016), so NMDA-antagonists with higher tolerability and lower risk should be identified and developed for nicotine cessation.

Memantine is an NMDA glutamate antagonist that significantly improves cognitive function in people with Alzheimer's disease (Doraiswamy, 2002). Its safety has been well established. Previous research has found that memantine blocks the acquisition of nicotine self-administration in mice (Blokhina et al., 2005). The current studies were conducted to determine what impact the glutamate NMDA antagonist memantine might have on nicotine self-administration in rats. First, the acute dose-effect function of memantine was characterized. Then, the chronic time-effect function of memantine on nicotine self-administration was determined.

2. Materials and methods

2.1. Design

Two studies were conducted with a rat model of nicotine self-administration. They were conducted with the approval of the Duke University Institutional Animal Care and Use Committee in compliance with federal and international animal welfare standards. The first study examined the acute dose-effect function of memantine on nicotine self-administration. In the acute study rats were trained on nicotine self-administration and then in a repeated measures design each rat was administered each dose of memantine and the saline vehicle in a counterbalanced order. Then the doses and the vehicle control injections were administered for a second time to confirm the findings. The second study with a separate set of rats examined the chronic time-effect function of memantine's impact on nicotine self-administration. In a between subjects design, rats were trained for nicotine self-administration and then assigned randomly to receive either repeated vehicle (saline) injections or repeated memantine injections. The repeated injections were given for two weeks of continued nicotine self-administration to determine the effects of chronic memantine on ongoing nicotine self-administration. The rats were not tested on the weekend. Then, there was a one-week period of enforced abstinence in which the rats were not given access to nicotine to model a cessation attempt in human smokers. The rats continued to receive IP injections of memantine. After this hiatus access to nicotine self-administration resumed and the rats resumed treatment with memantine or vehicle depending on their assigned group. Finally, there was an additional week of nicotine self-administration testing after the end of memantine treatment to determine the potential persistent effects of memantine.

2.2. Subjects

Young adult female Sprague-Dawley rats were used for these studies. They were kept in a temperature and light controlled room with automatically ventilated housing racks with ad lib availability of water and scheduled feeding to keep them at a lean healthy weight of approximately 85% of ad lib weight. The light was on from 7:00 a.m. till 7:00 p.m. All experiments were done during the dark cycle when the rats were active.

2.3. Operant training

All rats were trained to lever-press in a standard dual-lever experimental chamber. Each chamber was equipped with two levers (one active, the other inactive), two cue lights, one located above each lever, a house light, and a tone generator. A computer programmed with MED-PC software managed experimental events and data collection. Initially, rats were trained to respond to a lever to receive a 45 mg food pellet reward under a fixed ratio (FR) 1 schedule of reinforcement. Half the animals were trained to respond to the right lever, and the other half was trained to respond to the left lever. The cue light over the correct lever was illuminated, while the cue light over the inactive lever remained dark. Food restricted rats were put in operant box for 1 h/day for 3 consecutive days and number of lever presses were recorded for food pellet. Once rats met a criterion of ≥ 50 correct lever responses for food in three consecutive 1-h training sessions, they had jugular catheter surgeries to allow them to receive IV nicotine infusions and began nicotine self-administration trials.

2.4. Surgery

Following completion of training with food reinforcements, animals were anesthetized using 60 mg/kg of ketamine (Fort Dodge Animal Health, Fort Dodge, IA, USA) and 0.15 mg/kg of dexdomitor (Pfizer, New York, NY, USA) given via i.p. injections, and a catheter (Strategic Application Inc., Libertyville, IL, USA) was implanted into the jugular vein using aseptic techniques to facilitate nicotine infusions. After anesthetization, a small incision slightly lateral to the frontal midline was made, and the jugular vein was exposed via blunt dissection. The area of jugular vein distal to the desired region was tied off to prevent bleeding, and an incision was made in the vein for catheter insertion. The catheter was inserted until the tip was close to the heart. Once in place, the catheter was sutured to both the vein and deep muscle using silk thread. The remaining portion of catheter was routed subcutaneously around the back, through a skin pocket created by blunt instrument, and threaded through a small incision made between the scapulae. A plastic SoloPort was attached intraoperatively to a polyurethane catheter (Strategic Application Inc., Libertyville, IL, USA) The catheter was then attached to an infusion harness, which could be tethered to the infusion pump during experimental sessions. Surgical wounds were sutured using polypropylene thread. Harnesses were also tethered to each animal using polypropylene thread. All catheters were flushed daily prior to self-administration sessions with a 0.3 ml solution containing 100 U/mL heparinized saline (Baxter Health Corporation, Deerfield, IL, USA). Post-sessions, the nicotine solution remaining in each animal's harness was removed and replaced with a 0.3 ml sterile lock containing heparinized saline 500 U/ml with 8 mg/ml gentamicin (American Pharmaceutical Partners, Schaumberg, IL, USA). Upon completion of self-administration sessions, animals were tested for jugular-catheter patency using phenobarbital before sacrifice. Data was only included from animals with verified patent catheters.

2.5. Nicotine self-administration training

Nicotine self-administration sessions were conducted in the same dual-lever experimental chambers used for pellet training. Following catheterization, animals began self-administration sessions with nicotine (0.03 mg/kg/infusion) as a reinforcer. During each session, an illuminated light over the active lever indicated the correct lever to press. Responding to the active lever resulted in a 0.5 s tone generation, and a 50 µl infusion of nicotine (0.03 mg/kg/infusion) over less than 1 s on a fixed ratio-1 (FR1). Each infusion was followed by a 1-min timeout phase, where the cue light was exterminated and responses were recorded, but no reinforcement was given for responses. Inactive lever presses were recorded, but resulted in no infusion deliveries, serving as a control. All self-administration sessions lasted 1 h. Five baseline sessions were administered to each rat before memantine test sessions began.

2.6. Memantine testing

Two studies were conducted with separate sets of rats. In the acute dose-effect study doses of memantine (SC) were tested in a repeated measures counterbalanced design with each dose given twice. The doses were 0, 3, 10 and 30 mg/kg of memantine given in a volume of 1 ml/kg with saline (SC) as the vehicle of memantine 20 min before

testing.

In the chronic time-effect function study, separate sets of rats were given either 0 or 10 mg/kg/day (IP) of memantine. There were two groups of rats: one group was administered IP doses of memantine (10 mg/kg, IP) for two weeks of nicotine self-administration and the other group received saline. Rats were not treated during the weekend. Then, the rats had one week of enforced abstinence. After this hiatus the rats resumed access to nicotine self-administration treatment with memantine or vehicle depending on their assigned group. Finally, there was an additional week of nicotine self-administration after the end of treatment with memantine.

The same rats in the chronic study were also tested for memantine effects for memantine effects on food motivated responding in the operant apparatus and locomotor activity in the Figure-8 apparatus. To measure acute and chronic memantine effects on food-motivated responding, the rats were administered memantine (0 or 10 mg/kg, IP) and tested 20 min later in the operant test apparatus for 45 mg food rewards on an FR-1 schedule for 1 h. Test for food-motivated responding were conducted before the initial memantine treatment for effects on nicotine self-administration, after two weeks of treatment and after the week of resumed nicotine access and memantine treatment.

Acute and chronic memantine effects on locomotor activity were assessed in an enclosed maze in the shape of a figure-8. The Figure-8 apparatus consisted of a continuous alley that measured 10 cm × 10 cm, with the entire maze measuring 70 cm × 42 cm. Animals were allowed to freely explore the maze and locomotor activity was assessed by the crossing of eight photobeams located at equal points in the alley. Each locomotor test session lasted 1 h, and photobeam breaks were counted in 5 min blocks across the session. There was an initial test of locomotor activity before tests of memantine effects on nicotine self-administration began. The rats were tested for the effects of memantine (0 or 10 mg/kg, IP) and tested 20 min later on locomotor activity. Repeated tests were made after the first memantine test session, after two weeks of chronic memantine administration and finally after the week of resumed treatment and nicotine access.

2.7. Statistics

Analysis of variance as used to test the statistical significance of the results. In the acute dose-effect study of memantine dose and repetition of dose were within subjects factors. In the chronic time-effect study memantine dosing was a between subjects factor and week of administration was a repeated measure. Interactions with $P < 0.10$ were followed-up by tests of the simple main effects of drug treatment as recommended by Snedecor and Cochrane (Snedecor and Cochran, 1967). In all cases, an alpha cutoff of $P < 0.05$ was used as the threshold for statistical significance.

3. Results

3.1. Acute memantine dose-effect study

The main effect of acute memantine treatment (N = 13) showed a significant ($F(1,33) = 6.87$, $P < 0.025$) linear dose-effect function of increasing nicotine self-administration with increasing treatment dose (Fig. 1). Both the 10 mg/kg ($P < 0.05$) and 30 mg/kg ($P < 0.05$) doses caused a significant increase in nicotine self-administration compared with control. The effect of drug phase (giving the doses the first time vs. the second time) was significant ($P < 0.05$) with lower nicotine self-administration during the second phase. The interaction of memantine dose x repeated test phase was not significant.

3.2. Chronic memantine time-effect study

Different effects were seen with chronic memantine treatment. The main effect of memantine treatment was significant ($F(1,22) = 4.70$, $P < 0.05$) with the memantine-treated rats (11.4 ± 2.1, N = 13) having a significantly lower rate of nicotine self-administration than vehicle-treated controls (17.0 ± 2.1, N = 11). The weekly self-administration averages are shown in Fig. 2. Analysis of the more detailed session-by-session detected a significant memantine × session interaction was significant ($F(19,418) = 2.61$, $P < 0.0005$). As shown in Fig. 3, follow-up tests of the simple main effects of memantine during each of the sessions of testing showed that there was a significant memantine-induced increase in nicotine self-administration during the first session of treatment ($P < 0.05$). During sessions four through nine there were nearly significant ($P < 0.10$) decreases in nicotine self-administration relative to controls, as the controls continued to rise in nicotine self-administration with repeated sessions and the memantine-treated group showed a decreasing rate from the initial memantine treatment. During sessions nine ($P < 0.025$) and ten ($p < 0.01$), there were significant decreases in nicotine self-administration relative to controls. During the resumption period there was no significant difference between memantine treated and control rats. Interestingly,

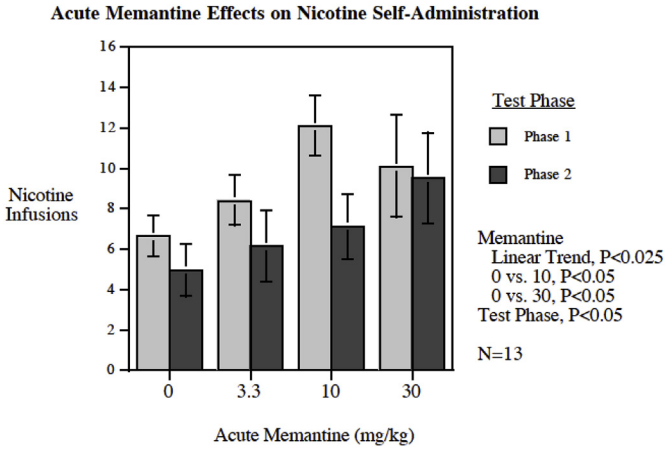

Fig. 1. Acute memantine acute dose-effect function for effects on nicotine self-administration (mean of infusions per session ± S.E.M.). Acute memantine caused a significant ($P < 0.05$) dose-related increase in nicotine self-administration.

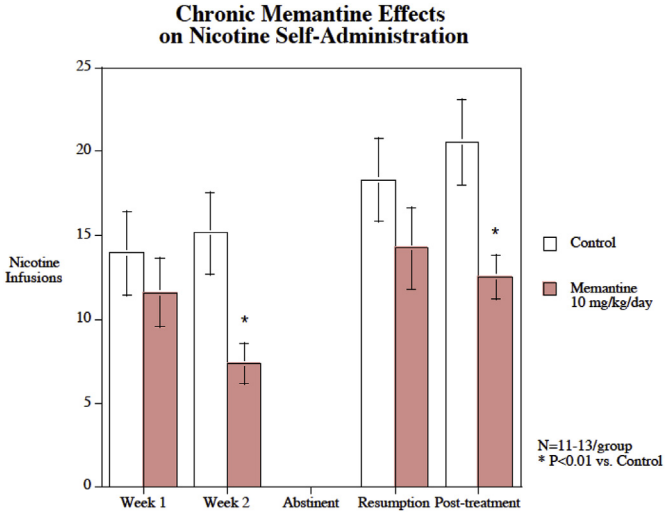

Fig. 2. Chronic memantine time-effect function for effects on nicotine self-administration, weekly averages (mean of nicotine infusions per session ± S.E.M.). Significant ($P < 0.05$) memantine-induced decreases in nicotine self-administration were seen during the second week of treatment and during the week after the end of treatment. No significant effects of memantine on nicotine self-administration were seen during the first week of treatment or during the resumed treatment after a week of enforced abstinence.

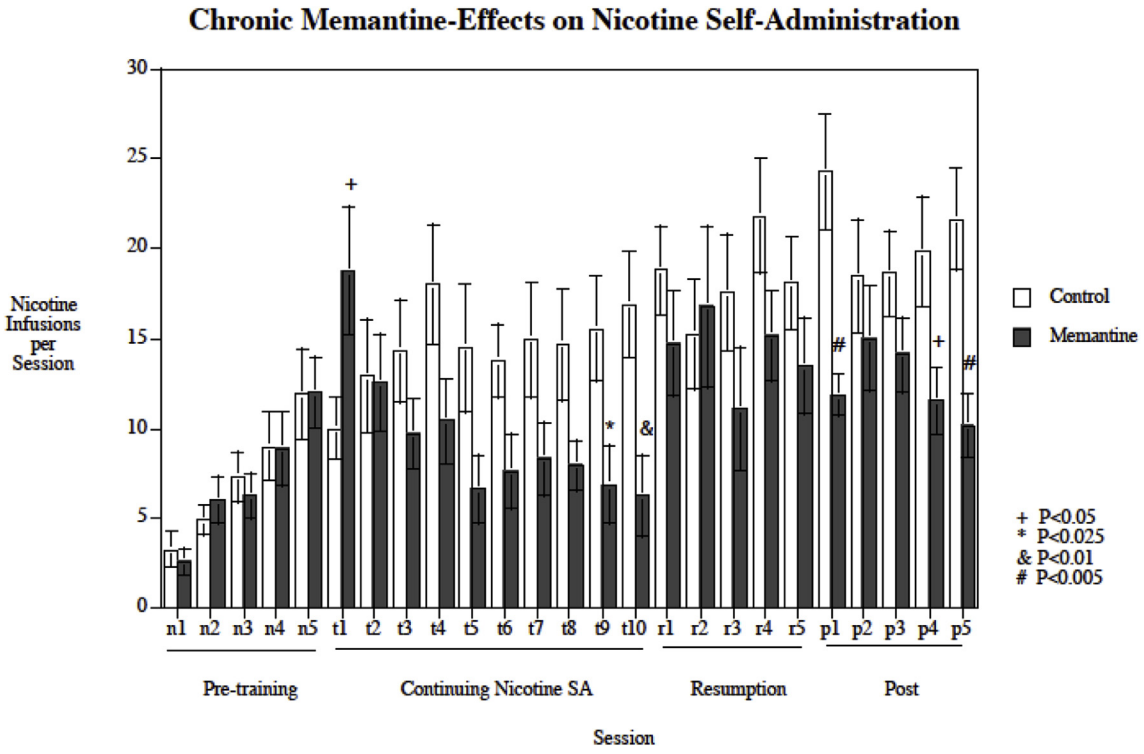

Fig. 3. Chronic memantine time-effect function for effects on nicotine self-administration, session-by-session data (mean of infusions per session ± S.E.M.).

during the post-treatment phase there were residual effects of memantine. During post-treatment sessions one ($P < 0.001$), four ($P < 0.05$) and five ($P < 0.01$) there were significantly lower rates of nicotine self-administration in the group of rats that had previously received memantine than controls.

Memantine effects on locomotor activity and food motivated responding were also tested. The main effect of memantine was not significant. Rather, there was a complex effect of memantine on locomotor activity as reflected in the significant two-way interactions of treatment x testing phase ($F(2,44) = 10.10$, $P < 0.0005$) and treatment x time block within session ($F(11,242) = 7.18$, $P < 0.0005$), as well as a three-way interaction of memantine treatment x testing phase x time block within session ($F(22,484) = 2.40$, $P < 0.0005$). As the highest order significant interaction, it was the three-way interaction that was followed up by tests of the simple main effects at each of the twelve 5-min time blocks with the 1-h tests during each phase of treatment (acute, chronic and resumption). As shown in Fig. 4, in general memantine caused significant locomotor hypoactivity during the early part of the test session with acute treatment. During the chronic phase of memantine treatment the hypoactivity was no longer seen, rather there were a couple of incidences of modest but significant hyperactivity. Then during the last phase of treatment during the resumption phase

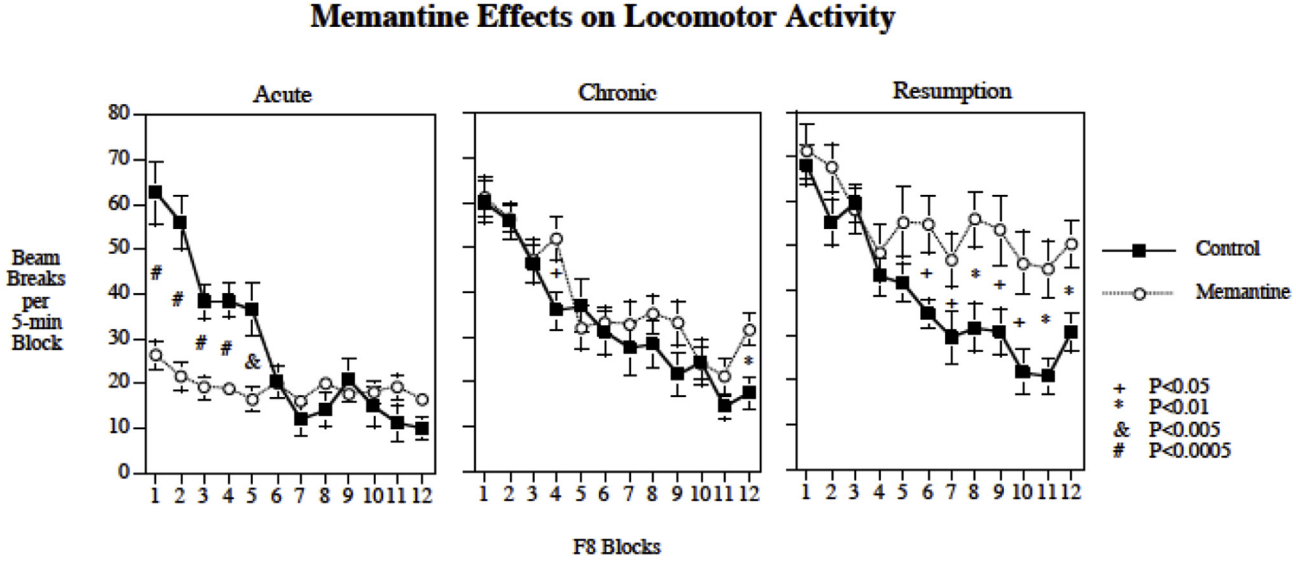

Fig. 4. Acute and chronic memantine effects on locomotor activity in the Figure-8 apparatus during the acute, chronic and resumption testing periods (mean of photobeam breaks per 5-min time block ± S.E.M.). Memantine caused hypoactivity during the first part of the 1-h session during the acute testing which disappeared by testing during the chronic phase of testing during which there were two instances of slight hyperactivity and finally with testing during the resumption phase memantine caused significant hyperactivity during the latter part of the 1-h test session.

Table 1
Acute and Chronic memantine and food motivated responding, (mean number of food pellets earned ± S.E.M.). No significant memantine effect on food motivated responding was seen.

Treatment		
Test Phase	Vehicle Control	Memantine (10 mg/kg)
Acute	117.8 ± 14.0	118.2 ± 13.7
Chronic	167.2 ± 10.3	160.7 ± 9.3
Resumption	173.3 ± 12.4	175.2 ± 22.4

memantine caused a significant degree of locomotor hyperactivity during the latter part of the test session. This constituted a blunted habituation in the memantine group. During the acute phase of memantine treatment, the significant memantine-induced hypoactivity were seen during testing time blocks: one ($P < 0.0005$), two ($P < 0.0005$), three ($P < 0.0005$), four ($P < 0.0005$) and five ($P < 0.005$). During the Chronic phase of memantine treatment significant memantine-induced hyperactivity was seen during time blocks: four ($P < 0.05$) and twelve ($P < 0.01$). During the Resumption phase of memantine treatment significant hyperactivity was seen during testing time blocks: six ($P < 0.05$), seven (pP < 0.05), eight ($P < 0.01$), nine ($P < 0.05$), ten ($P < 0.05$), eleven ($P < 0.01$) and twelve ($P < 0.01$). No significant effects of acute or chronic memantine were seen on food motivated responding (Table 1).

4. Discussion

Memantine treatment had opposite effects when given acutely and chronically. Acute administration memantine caused a dose-related increase in nicotine self-administration. In contrast, chronic memantine administration caused a time-related decrease in nicotine self-administration. The initial day of chronic administration, which was essentially a test of acute effects of memantine, replicated the acute dose-effect study. After this initial memantine-induced increase the level of nicotine self-administration decreased in the treated group while the level in the vehicle treated group continued to rise such that by the ninth session the memantine-treated group had significantly lower rates of nicotine self-administration than the control group.

There are several possible explanations for these divergent effects. It is possible that memantine diminished the reinforcing value of nicotine and acutely this caused a short-term extinction burst in which they briefly self-administered more nicotine. Then with further experience with memantine they decreased nicotine self-administration as nicotine self-administration behavior extinguished. This would explain the continued reduction in nicotine self-administration after the end of chronic memantine therapy.

This study builds on prior research that showed that memantine blocked the acquisition of nicotine self-administration in mice (Blokhina et al., 2005). This was a relatively specific effect inasmuch as memantine was not found to reduce cocaine self-administration. There has been pilot research testing memantine in smokers (Thuerauf et al., 2007). This study did not find memantine at a dose of 5 increasing to 10 mg/day to facilitate smoking reduction. It may be the case that increasing the memantine dose or duration could improve efficacy.

In addition to its effects on NMDA glutamate receptors, memantine has actions at other ligand gated ion channels as well, including nicotinic receptors. Memantine has been found to block α4β2 (Buisson and Bertrand, 1998) and α7 nicotinic receptors (Aracava et al., 2005). Chronic memantine increases the concentration of α7 nicotinic receptors (Unger et al., 2005), which may be important for the effect of chronic memantine reducing nicotine self-administration.

Sedative effects did not seem to explain memantine actions on nicotine self-administration. With acute memantine (10 mg/kg) administration there was a significant reduction in locomotor activity. Yet in both the first and second studies acute administration of 10 mg/kg of memantine caused a significant increase in nicotine self-administration. With chronic memantine treatment when there was a significant reduction in nicotine self-administration but there was no significant reduction in locomotor activity. In fact, there was some modest indication of memantine-induced elevated locomotor activity at this point. After the resumption period when there was no significant memantine effect on nicotine self-administration there was a significant degree of memantine-induced locomotor hyperactivity. Memantine did not seem to have generalized effects on motivated behavior. At no point during the acute, chronic or resumption periods were there any indications of an effect of memantine on food motivated responding.

Memantine could be an effective aid for smoking cessation. Previous studies with the nicotinic receptor antagonist mecamylamine have demonstrated initial increases in smoking behavior followed by decreased smoking over weeks (Rose et al., 1998). After an increase of nicotine self-administration with initial memantine administration, there was a persistent decrease in nicotine self-administration caused by memantine. Important for its possible use to help promote longer term cessation, there was a persistent decrease which lasted after the end of memantine therapy. Further human studies are warranted to explore the potential therapeutic efficacy of memantine in smoking cessation treatment.

Acknowledgement

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejphar.2019.172592.

Compliance with ethical standards

Conflict of interest

The authors declare that they have no conflict of interest.

Data access

Data are available to interested parties. Contact Dr. Edward D. Levin by email: (edlevin@duke.edu).

Author contributions and agreement

All of the authors substantively contributed to this project and agree to its publication, Edward D. Levin: Design of study, data analysis, writing, Corinne Wells: Conduct of study, data gathering, Leah Yao: Conduct of study, data gathering, Wendi Guo: Conduct of study, data gathering, Anica Nangia: Conduct of study, data gathering, Sarah Howard: Conduct of study, data gathering, Erica Pippen: Conduct of study, data gathering, Andrew B. Hawkey: Conduct of study, data gathering, Jed E. Rose: Design of study, Amir H. Rezvani: Data analysis, writing.

There are no conflicts of interest.

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