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Lamotrigine attenuates the motivation to self-administer ketamine and prevents cue- and prime-induced reinstatement of ketamine-seeking behavior in rats

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ABSTRACT

Background: Lamotrigine is an anticonvulsant drug used in the treatment of epilepsy and bipolar disorder. A case report has demonstrated that a ketamine addict experienced a significant reduction in craving and ketamine use after taking lamotrigine. The present study determined whether lamotrigine can reduce the motivation for ketamine and prevent the relapse to ketamine seeking behavior in rats.

Methods: Male Sprague-Dawley rats were trained to respond for intravenous ketamine (0.5 mg/kg/infusion) self-administration or food pellets. The effects of lamotrigine on the motivation for ketamine or food were assessed using breakpoint test under a progressive ratio (PR) paradigm. Furthermore, the effects of lamotrigine on reinstatement of ketamine-seeking and food-seeking behaviors were examined after extinction.

Results: Lamotrigine significantly decreased the breakpoint for ketamine and prevented cue- and ketamine priming-induced reinstatement of ketamine seeking behavior. However, lamotrigine did not affect the breakpoint for food reinforcement, cue-induced reinstatement of food-seeking behavior, or spontaneous locomotor activity.

Conclusions: Our data reveal that lamotrigine is capable of attenuating the reinforcing efficacy of ketamine and reducing ketamine craving and relapse risk, which lays the foundation for conducting clinical trials in patients with ketamine use disorder.

1. Introduction

Ketamine, an anesthetic with dissociative, analgesic and psychedelic properties, has been long used in humans and veterinary medicine. Recreational use is on the increase among young adults attending clubs and parties worldwide in the past a few decades (Gahlinger, 2004; Li et al., 2011).

Ketamine alters numerous functions in the brain including color perception, memory, attention, cognition, reaction time and sense of time (Bokor and Anderson, 2014; Wolff and Winstock, 2006). With euphoric effects, ketamine has been shown to serve as a reinforcing stimulus to induce self-administration (Collins et al., 1984; De Luca and Badiani, 2011; De Luca et al., 2012) and conditioned place preference (Li et al., 2008; Suzuki et al., 2000) in animals, supporting its human abuse potential. Long-term ketamine use causes damages to various organs, including the brain, heart, liver, gastrointestinal tract, and genitourinary system (Pappachan et al., 2014). Recent reports further showed that ketamine-dependent patients had impaired cognitive function (Cheng et al., 2018; Wang et al., 2018). Cessation of ketamine use is the only effective treatment for preventing deterioration of organ function. However, there is no effective pharmacotherapy to manage the compulsive drug use in patients with ketamine use disorder currently.

Lamotrigine, a mood-stabilizing anticonvulsant, is clinically used to treat epilepsy and bipolar disorder. One proposed mechanism of action of lamotrigine has been associated with inhibiting voltage-sensitive sodium channels and consequently decreasing presynaptic release of glutamate and aspartate (Leach et al., 1986). Based on the important role of glutamatergic transmission in drug addiction (D'Souza, 2015), lamotrigine has been proposed to reduce drug reward and tested for treatment of certain abused substances in human subjects. Lamotrigine has been shown to be effective in treating cocaine addiction, either reduction in craving (Pavlovic, 2011) or in amount of cocaine use (Brown et al., 2012; Margolin et al., 1998). However, it does not alter

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the variables related to reducing the reinforcing properties of cocaine (Winther et al., 2000). Furthermore, clinical case reports demonstrated that lamotrigine use could effectively resist the craving for alcohol and benzodiazepines (Pavlovic, 2010) and inhalants (Shen, 2007).

The interactions of lamotrigine with several abused substances on their reinforcing effects and relapse-like behaviors have been also revealed in animal studies. Acquisition and expression of morphine-induced conditioned place preference were reduced by lamotrigine (Tehrani et al., 2009). Lamotrigine elevated intracranial self-stimulation (ICSS) thresholds and also attenuated cocaine-induced reduction of ICSS thresholds (Beguin et al., 2012). In addition, lamotrigine reduced the relapse-like alcohol drinking behaviors, the cue-induced alcohol reinstatement and alcohol deprivation effect in rats (Vengeliene et al., 2007). Repeated treatment with lamotrigine significantly reduced the voluntary alcohol intake in alcohol preferring rats (Zalewska-Kaszubska et al., 2015).

Drug interactions between lamotrigine and ketamine have been demonstrated. Lamotrigine significantly decreased ketamine-induced perceptual abnormalities (Anand et al., 2000). A case report revealed a failure of ketamine anesthesia in a patient with lamotrigine overdose (Kornhall and Nielsen, 2014). It seems that lamotrigine could effectively counteract certain pharmacological effects of ketamine. Importantly, a recent report revealed that a case of ketamine use disorder experienced a great reduction in craving and ketamine use after taking lamotrigine (Huang et al., 2016), suggesting that lamotrigine might have the potential for ketamine relapse prevention and may necessitate a clinical study. Prior to clinical trials initiation, it is important to determine whether lamotrigine is capable of counteracting the reinforcing effects of ketamine and reducing the ketamine drug-seeking behavior in animal models.

Thus, we determined the effects of lamotrigine on reinforcing efficacy of ketamine using a progressive ratio (PR) schedule, where each successive reinforcer requires an increasing number of lever presses until the cessation of responding. In addition, the effects of lamotrigine on cue- and ketamine priming-induced reinstatement of ketamine seeking were examined. The effects of lamotrigine on food-motivated behavior, reinstatement of food seeking and locomotor activity were also monitored.

2. Materials and methods

2.1. Animals

Male Sprague-Dawley rats weighing 225–250 g were purchased from LASCO Charles River Technology (Taiwan) and used in this study. The animals were housed in an animal care facility on a 12-h light/dark cycle, with ad libitum access to water. Food restriction was maintained throughout the studies except after surgery. All procedures for animal care were proved by the Institutional Animal Care and Use Committee of the National Health Research Institutes.

2.2. Drugs

Ketamine HCl (Sigma, St. Louis, MO, USA) was dissolved in physiological saline. Lamotrigine (GlaxoSmithKline Pharmaceuticals, Brentford, United Kingdom) was dissolved in distilled water and administered by oral gavage (1 ml/kg).

2.3. Ketamine self-administration procedures

2.3.1. Food pre-training

Rats were food-restricted (5 g/day) for 48 h prior to starting food training. During the 1 h training session, the animals were trained to press the lever for a single food pellet (45 mg; Bioserve, MD, USA) under fixed ratio (FR) 1. Only one lever was extended into the operant testing chamber during the initial food training period. Animals took 3–4 days to meet the criteria (defined as earning 100 food pellets within the 1 h session for three consecutive days).

2.3.2. Surgery

Rats received intravenous catheterization surgery under isoflurane (2% v/v) anesthesia at least three days after completion of food pretraining. The external jugular vein was implanted with a silicone tubing, made from Dow Corning Silastic®, (ID = 0.51 mm; OD = 0.94 mm). The other end of the tubing was connected to an injection port in a harness (Instech). The catheters were flushed daily with a mixed solution of antibiotic baytril (2.5%; Bayer) and heparinized saline (50 IU/ml) to preserve catheter patency. Rats were fed ad libitum for seven days following surgery, after which rats were given 15 g of food immediately following each daily drug self-administration session.

2.4. Ketamine self-administration training

All self-administration sessions were conducted in the operant chambers (32 × 25 × 34 cm, Med associates, Inc) housed in sound attenuating cubicles with a ventilation fan and linked to a computerized data collection program. Each chamber was equipped with two retractable levers and a yellow stimulus light above each lever.

Rats were allowed to access 2 h daily sessions, whereby each press on the active lever resulted in activation of the syringe pump to deliver ketamine (0.5 mg/kg/infusion), from FR1 to FR2. Each ketamine infusion (4 s) was followed by a 20-s timeout period (TO20), during which additional active lever presses were recorded but produce no programmed consequences. Each ketamine infusion delivery was accompanied by concurrent illumination of the stimulus light for 20 s. Animals received a 0.1 ml infusion of heparinized saline (33.3 U/ml) after each self-administration session. Self-administration training sessions were conducted until response patterns stabilized (i.e., the number of active lever presses per 2 h session varied less than 15% across two consecutive sessions) (Supplementary Fig. 1).

2.4.1. Progressive ratio schedule of reinforcement

A progressive ratio (PR) schedule of reinforcement was introduced following FR training. Each daily PR session was 3 h in duration. The lever presses required to obtain an infusion were determined by: $5 \times e^{(\text{infusion number} \times 0.2)} - 5$ (i.e., 1, 2, 4, 6, 9, 12, 15, 20, 25, 32, etc.) (Richardson and Roberts, 1996). The PR schedule was terminated automatically if animals did not gain another infusion within an hour. Lever presses, infusions, and breakpoints were assessed for each test. The breakpoint was defined as the number of lever presses required for the delivery of the last ketamine infusion.

Two sets of experiments were conducted to examine the dose-effects of lamotrigine (10 and 30 mg/kg) on breakpoint using a within-subjects Latin square design. Lamotrigine or vehicle was administered by oral gavage 30 min prior to the initiation of self-administration sessions. Test days were separated by 2–3 days to reduce the residual effect of lamotrigine. On each day between test days, the animals were similarly operated under a PR schedule.

2.4.2. Cue- and drug-induced reinstatement of ketamine seeking

Another group of trained animals were used to examine the cue- and ketamine-induced reinstatement. Once responding on the FR2 schedule was stable, animals were subjected to the daily 2 h extinction session, whereby pressing on the active lever no longer produced any programmed reinforcement consequence, namely no cue light presentation, nor the activation of the syringe pump. Extinction criteria were set when the subjects performed with the number of active lever presses at a rate below 20% of the final FR2 sessions.

After extinction criteria were met, the effects of lamotrigine were determined by the cue- and ketamine-induced reinstatement tests (2 h each) using a within subject design. A re-extinction session was

conducted between reinstatement tests. In the cue-induced restatement, the cue lights were presented after the successful active lever-press responses and this illumination continued through the TO period; however, no ketamine infusions were presented. For the ketamine-primed reinstatement, a ketamine (10 mg/kg, i.p.) injection was given 30 min before the 2 h session. Responses on the active lever were recorded, but had no further presentations of the cue light or drug infusions. In order to determine if lamotrigine priming or vehicle could reinstate the responding, lamotrigine or vehicle was administered 30 min prior to the test session.

2.5. Food self-administration procedures

Rats that were tested for effects of lamotrigine on breakpoints for food and food seeking behavior did not undergo catheter implantation. After animals went through food pre-training, the responses were maintained in the two lever schedules shifted progressively in an order of FR1 TO20 s (2 days), FR2 TO20 s (3 days) and FR5 TO 20 s (5 days). Afterward, animals were subjected to a PR schedule similar to that of ketamine self-administration except that a single food pellet (45 mg; Bioserve) was delivered as the reinforcer.

Another set of well-trained rats were used to examine the cue- and food-induced reinstatement. Once responding on the FR5 schedule was stable, animals were subjected to the daily 2 h extinction session to meet the extinction criteria (< 20% of the final FR5 sessions). The effects of lamotrigine on cue- and food pellet priming-induced reinstatement of food seeking were assessed.

2.6. Open field locomotor activity

Administration of lamotrigine (5–20 mg/kg, ip) did not affect spontaneous locomotor activity in rats (Consoni et al., 2006). We determined whether the effective dose of lamotrigine (30 mg/kg) given orally could affect the locomotor activity. Rats were placed in the locomotor chamber (42 × 42 × 30 mm, Animal Activity Monitoring System, AccuScan Instruments, Inc.) for 30 min habituation prior to administration of lamotrigine (30 mg/kg) or vehicle. The effects of lamotrigine and vehicle on locomotor activity were measured for 120 min.

2.7. Data analysis

The number of lever responses, breakpoints, and infusions under the PR schedules were analyzed using the paired *t*-test A two-way repeated measures ANOVA was used in reinstatement experiments followed by *post hoc* Newman-Keuls comparisons. A two-way mixed design ANOVA was used to compare the travelled distances in locomotor activity test, with time as a within subject factor. All data are expressed as the mean ± SEM.

3. Results

3.1. Effects of lamotrigine on ketamine reinforcement under a progressive ratio schedule

A within-subjects design was used to examine the effects of lamotrigine on 0.5 mg/kg/infusion ketamine self-administration under a PR schedule. The effects of pretreatment of lamotrigine at 10 mg/kg was assessed first. There was no difference between lamotrigine (10 mg/kg) and vehicle control group (Fig. 1A). Fig. 1B shows that the higher dose of lamotrigine (30 mg/kg) significantly reduced the number of lever responses ($t = 3.39$, $P < 0.01$), breakpoints ($t = 3.56$, $P < 0.01$) and ketamine infusions ($t = 4.54$, $P < 0.01$).

3.2. Effects of lamotrigine on cue- and drug-induced reinstatement of ketamine seeking

After the stable FR2 training, an extinction procedure was applied until the criteria were reached. The number of days required to reach extinction criterion for each animal was not the same. However, there was no significant difference in lever responses during the last extinction session before each reinstatement.

Lamotrigine (30 mg/kg) was given 30 min prior to each test for cue- and ketamine priming-induced reinstatement. A two-way repeated measures ANOVA revealed the significant main effects of cue ($F_{1, 8} = 34.365$, $P < 0.001$), lamotrigine treatment ($F_{1, 8} = 23.903$, $P < 0.01$) and cue x lamotrigine treatment interaction ($F_{1, 8} = 28.311$, $P < 0.001$). Similar observations were made in ketamine priming-induced reinstatement (ketamine priming: $F_{1, 8} = 26.033$, $P < 0.001$; lamotrigine treatment: $F_{1, 8} = 20.146$, $P < 0.01$; and ketamine priming x lamotrigine treatment interaction: $F_{1, 8} = 24.794$, $P < 0.001$). *Post hoc* tests indicated that cue- and ketamine priming-induced lever pressing responses were significantly reduced by lamotrigine (30 mg/kg) (Fig. 2A).

After we found that lamotrigine (30 mg/kg) significantly reduced the ketamine seeking behavior induced by cue and ketamine priming, the effects of a lower dose of lamotrigine (10 mg/kg) were further assessed (Fig. 2B). A two-way repeated ANOVA revealed the significant main effects of cue ($F_{1, 5} = 8.206$, $P < 0.05$), lamotrigine treatment ($F_{1, 5} = 7.714$, $P < 0.05$) and cue x lamotrigine treatment interaction ($F_{1, 5} = 7.448$, $P < 0.05$). In case of ketamine priming-induced reinstatement, lamotrigine at 10 mg/kg also significantly decreased the lever responses (ketamine priming: $F_{1, 5} = 10.634$, $P < 0.05$; lamotrigine treatment: $F_{1, 5} = 10.354$, $P < 0.05$; and ketamine priming x lamotrigine treatment interaction: $F_{1, 5} = 10.563$, $P < 0.05$).

Moreover, lamotrigine (30 mg/kg) or vehicle could not trigger the reinstatement of lever pressing (< 10 active responses).

3.3. Effects of lamotrigine on food self-administration under a PR schedule and cue- and food pellet-induced reinstatement of food seeking

Lamotrigine at 30 mg/kg was used to test the responding for food under the PR schedule as ketamine. No significant effect of lamotrigine was observed on the lever responses, breakpoints and the number of food pellets received (Fig. 3A).

In case of cue- and food pellet-induced reinstatement of food seeking, a two-way repeated measures ANOVA revealed the significant main effects of cue ($F_{1, 7} = 32.41$, $P < 0.001$) and food pellet ($F_{1, 7} = 71.87$, $P < 0.001$). As shown in Fig. 3B, cue and food pellet priming could successfully induce lever pressing responses. Lamotrigine (30 mg/kg) did not affect cue-and food pellet-induced reinstatement of food seeking behavior.

3.4. Effects of lamotrigine on locomotor activity

A between-subjects design was used to compare the effect of lamotrigine on locomotor activity. As shown in Fig. 4, after 30 min adaptation in the test chambers, administration of lamotrigine (30 mg/kg) did not affect the locomotor activity of rats.

4. Discussion

The present study is the first to determine whether lamotrigine has the capacity to treat ketamine use disorder by the rat intravenous ketamine self-administration paradigm. The results showed that lamotrigine significantly decreased the breakpoints for ketamine under a PR schedule. Moreover, the cue- and prime-induced reinstatement of ketamine seeking behaviors were remarkably suppressed by lamotrigine. However, lamotrigine did not affect the reinforcing effect of food and reinstatement of food seeking. An effective method for pharmacological

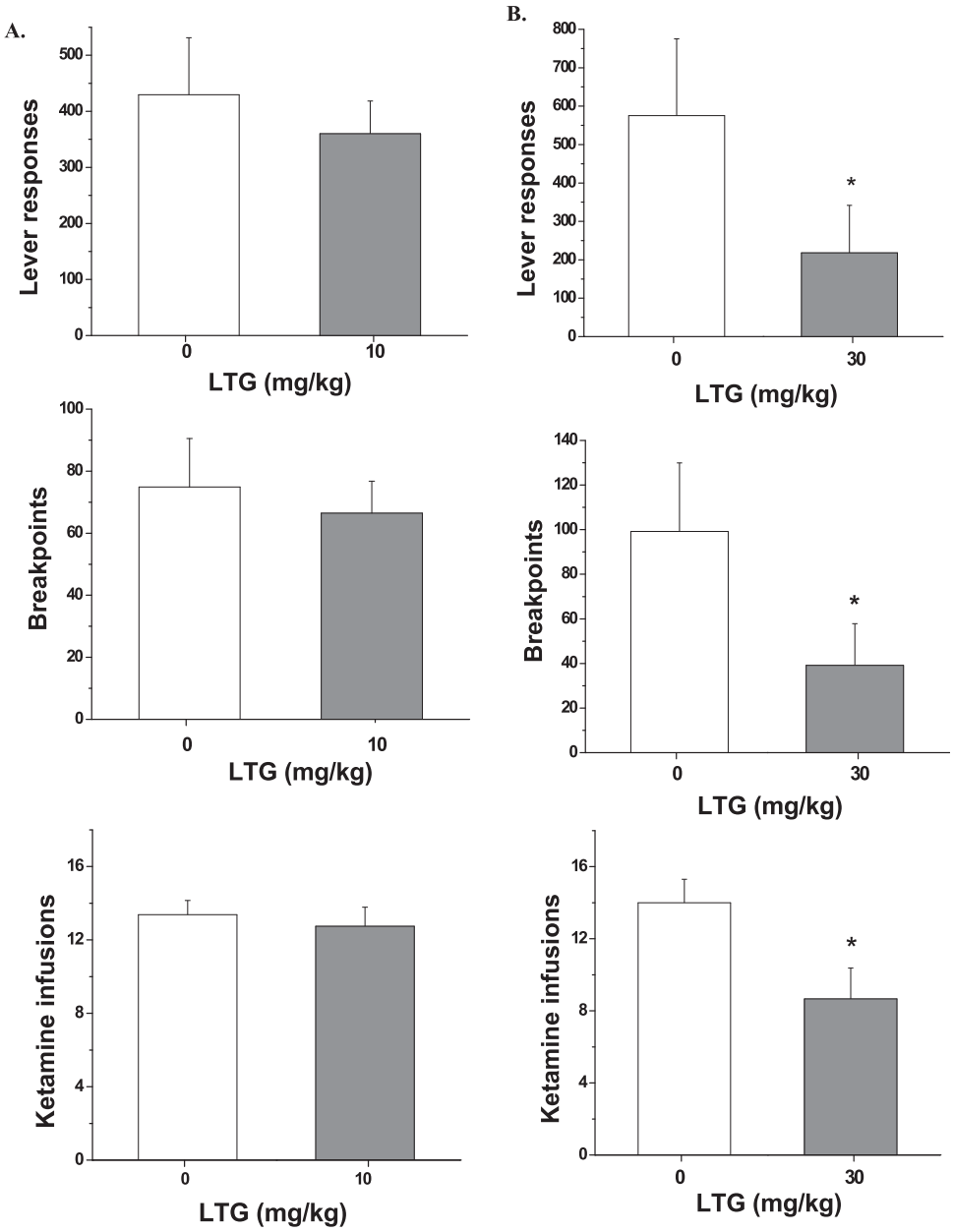


Fig. 1. Effects of lamotrigine on the motivation to self-administer ketamine under a PR schedule of reinforcement. Two sets of animals were administered with lamotrigine (10 mg/kg) or vehicle (n = 8) (A) and lamotrigine (30 mg/kg) or vehicle (n = 6) (B) by oral gavage 30 min prior to ketamine self-administration procedures. The numbers of lever responses, breakpoints and ketamine infusions were recorded. The data are presented as mean ± SEM. *p < 0.05 compared with vehicle controls. LTG: lamotrigine.

treatment of addiction should be able to reduce reinforcing effect and reinstatement of the abused drug, but not reduce reinforcing potency of natural rewards. These results revealed that lamotrigine counteracted the motivation to self-administer ketamine and attenuated the relapse-like ketamine seeking behavior, but did not apply to food reinforcement, providing the preclinical evidence to support the case showing that lamotrigine treatment was associated with significant improvement in drug craving and drug use in a patient with ketamine use disorder (Huang et al., 2016).

It has been reported that pretreatment with lamotrigine attenuated the perceptual abnormalities, positive and negative symptoms, learning and memory impairment (Anand et al., 2000) and the regional blood oxygen level-dependent signal (Deakin et al., 2008; Doyle et al., 2013) in response to ketamine infusion in healthy volunteers. These neuropsychiatric effects of ketamine have been associated with increased glutamate release in the frontal cortex (Stone et al., 2012). Thus, a reduction in glutamate release (Leach et al., 1986) was proposed to explain why lamotrigine can counteract ketamine's effects. In fact, ketamine increases the release of glutamate, not only occurred in the frontal cortex, but also in the nucleus accumbens (Razoux et al., 2007), a critical brain region for motivation and reward. The reduced glutamate release might be also associated with the attenuating effects of lamotrigine on the reinforcing efficacy of ketamine.

In addition to acting as a NMDA receptor channel blocker (Anis et al., 1983; Mendelsohn et al., 1984), ketamine has been reported to increase dopamine efflux and to block dopamine uptake (Hancock and Stamford, 1999) in the nucleus accumbens from brain slices. A microdialysis study further revealed that ketamine induced dopamine release in the rat nucleus accumbens (Masuzawa et al., 2003). Ketamine is also a partial agonist at D2 receptors (Kapur and Seeman, 2002). An acute

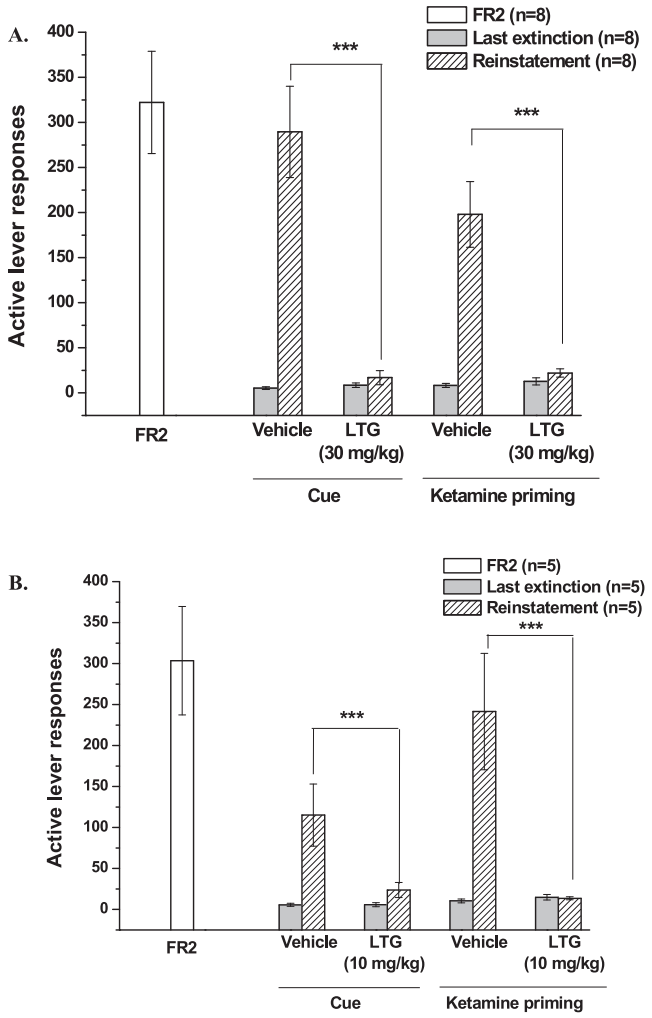
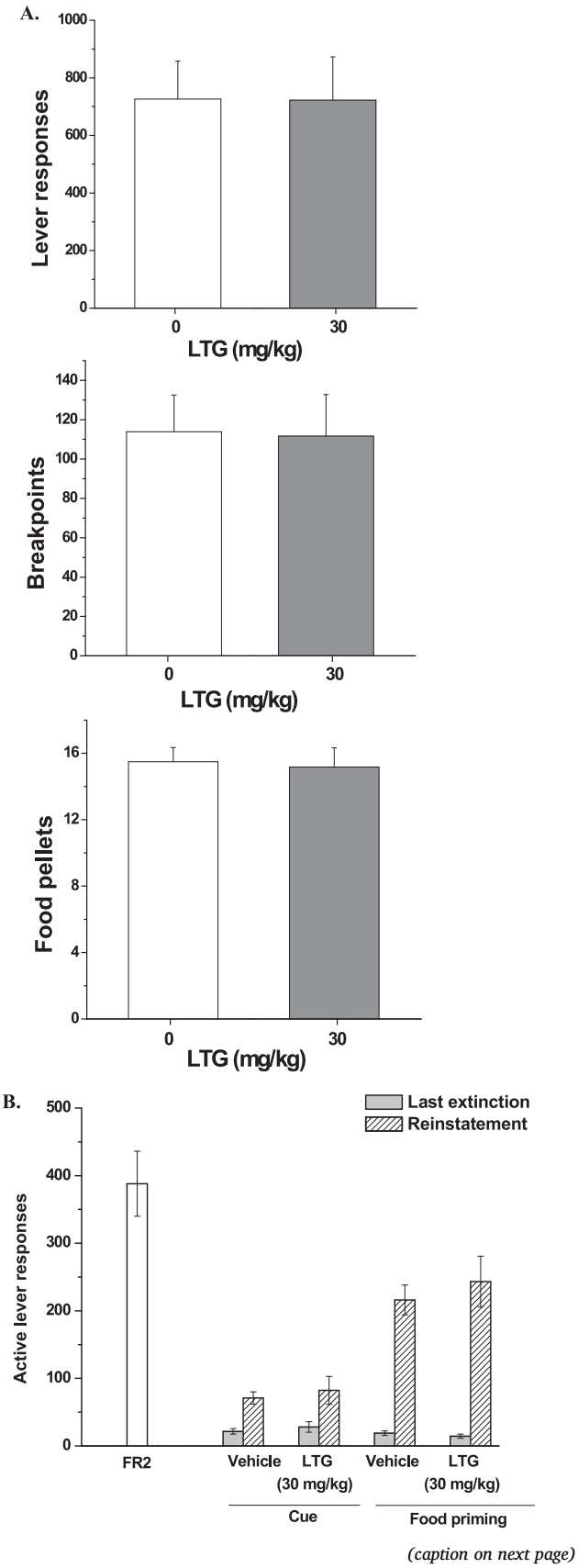


Fig. 2. Effects of lamotrigine on cue- and prime-induced reinstatement of ketamine seeking. The animals were trained to self-administer ketamine under a FR1 TO20 and FR2 TO20 two-lever schedule followed by the extinction procedures until criteria were reached. Two sets of animals were administered with lamotrigine (30 mg/kg) or vehicle (A) and lamotrigine (10 mg/kg) or vehicle (B) by oral gavage 30 min prior to cue- and ketamine (10 mg/kg, ip) priming-induced reinstatement. The numbers of active lever responses of last session of training (FR2), last session of extinction and reinstatement induced by cue or ketamine priming were demonstrated. The data are presented as mean ± SEM. ***$p < 0.001$ compared with vehicle controls.

decrease in extracellular DA and its metabolites by lamotrigine has been observed in the striatum (Vriend and Alexiuk, 1997). Lamotrigine and ketamine have opposing effects on dopamine transmission, which might, at least in part, explain why lamotrigine could counteract the reinforcing efficacy of ketamine.

Drug-seeking behaviors refer to the craving aspect of addiction. Glutamate release in the nucleus accumbens is necessary for reinstatement to drug-seeking, such as cocaine (McFarland et al., 2003) and heroin (LaLumiere and Kalivas, 2008). Likewise, the reinstatement of ketamine seeking might be attributed to increased glutamate levels in the nucleus accumbens. Suppression of glutamate release would, at least in part, explain why lamotrigine significantly reduced the cue- and drug-induced reinstatement of ketamine seeking.

It is of note that the higher dose (30 mg/kg) of lamotrigine was required to reduce the reinforcing efficacy of ketamine, whereas lamotrigine at 10 mg/kg and 30 mg/kg could effectively attenuate the ketamine seeking and relapse. Moreover, the higher dose of lamotrigine alone did not trigger the reinstatement of ketamine seeking. These



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results demonstrated that lamotrigine cannot produce ketamine-like effect to reduce the motivation to self-administer ketamine and implicated the mechanisms of action of lamotrigine in the reduction of

Fig. 3. Effects of lamotrigine on food reinforcement under a PR schedule and cue- and prime-induced reinstatement of food seeking. Lamotrigine (30 mg/kg) or vehicle was administered 30 min prior to food self-administration procedures under a PR schedule. The numbers of lever responses, breakpoints and the food pallets received were recorded (A). The animals were trained to self-administer food pellets followed by the extinction procedures. Lamotrigine (30 mg/kg) or vehicle were administered 30 min prior to cue- and food pellet priming-induced reinstatement. The numbers of active lever responses of last session of training (FR2), last session of extinction and reinstatement induced by cue or food pellet priming were demonstrated (B). The data are presented as mean ± SEM (n = 6). LTG: lamotrigine.

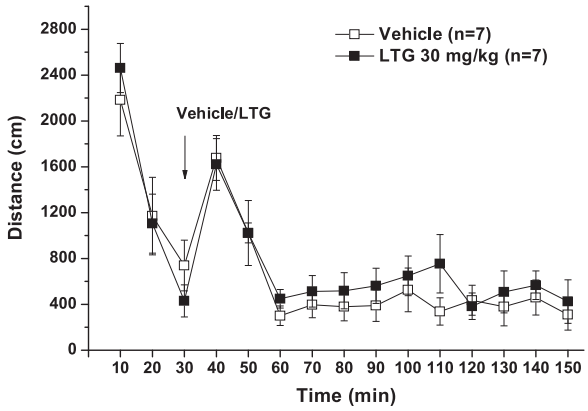

Fig. 4. Effects of lamotrigine on locomotor activity in the open field. The basal locomotor activity was measured for 30 min, followed by administration of lamotrigine (30 mg/kg) or vehicle and proceeded to measure for 120 min. The distance traveled for each 10 min are presented as mean ± SEM. LTG: lamotrigine.

reinforcement and reinstatement of ketamine-seeking behavior are not totally overlapped.

In fact, lamotrigine modulates various ion channels. It blocks the fast sodium inward currents (Kuo and Lu, 1997; Xie et al., 1995), calcium currents (Grunze et al., 1998b) and A-type potassium currents (Huang et al., 2004), yet positively modulates the transient potassium outward currents (Grunze et al., 1998a) and hyperpolarization-activated, cyclic nucleotide-gated (HCN) channel activity (Poolos et al., 2002). Recently, pharmacological stabilization of HCN channel activity in the prelimbic cortex has been reported to reduce cue-induced reinstatement of cocaine seeking (Parrilla-Carrero et al., 2018). Accordingly, modulation of HCN channels might possibly contribute to the reduction of reinstatement of ketamine seeking behaviors produced by lamotrigine.

Lamotrigine has been used in treating cocaine abuse in patients with comorbid depression or bipolar disorder, either reduction in craving (Pavlovic, 2011) or in the amount of cocaine use (Brown et al., 2012; Margolin et al., 1998). Similarly, lamotrigine use in patients with bipolar disorder and alcohol dependence revealed improvement in mood, alcohol craving and alcohol consumption (Rubio et al., 2006). Skin rash is a common adverse effect of lamotrigine. The most severe complications are potentially life-threatening dermatological disorders, Stevens-Johnson syndrome and toxic epidermal necrolysis. The incidence of rash and Stevens-Johnson syndrome/toxic epidermal necrolysis with lamotrigine was about 10% and 0.04%, respectively (Bloom and Amber, 2017; Wang et al., 2015). For those who can tolerate lamotrigine, lamotrigine appears to be potent and safe as a potential therapeutic agent for the treatment of ketamine use disorder.

In conclusion, the ability of lamotrigine to reduce motivation and relapse-like drug-seeking behavior of ketamine provides support for the involvement of the glutamatergic systems in these addiction-related effects of ketamine, suggesting a good rationale for pharmacological interventions that may reduce craving and relapse in ketamine dependent patients.

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Contributors

MYL and YCH contributed to the acquisition and analysis of the behavioral data. MYL drafted the manuscript. MHC and HHC provided the study concept and critical revision of the manuscript. All Authors have seen and approved the manuscript being submitted.

Conflict of interest

The authors declare that there are no conflicts of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drugalcdep.2018.10.028.

References

Anand, A., Charney, D.S., Oren, D.A., Berman, R.M., Hu, X.S., Cappiello, A., Krystal, J.H., 2000. Attenuation of the neuropsychiatric effects of ketamine with lamotrigine: Support for hyperglutamatergic effects of N-methyl-D-aspartate receptor antagonists. Arch. Gen. Psychiatry 57, 270–276.

Anis, N.A., Berry, S.C., Burton, N.R., Lodge, D., 1983. The dissociative anaesthetics, ketamine and phencyclidine, selectively reduce excitation of central mammalian neurones by N-methyl-aspartate. Br. J. Pharmacol. 79, 565–575.

Beguin, C., Potter, D.N., Carlezon Jr, W.A., Stohr, T., Cohen, B.M., 2012. Effects of the anticonvulsant lacosamide compared to valproate and lamotrigine on cocaine-enhanced reward in rats. Brain Res. 1479, 44–51.

Bloom, R., Amber, K.T., 2017. Identifying the incidence of rash, Stevens-Johnson syndrome and toxic epidermal necrolysis in patients taking lamotrigine: a systematic review of 122 randomized controlled trials. An. Bras. Derm. Sifilogr. 92, 139–141.

Bokor, G., Anderson, P.D., 2014. Ketamine: an update on its abuse. J. Pharm. Pract. 27, 582–586.

Brown, E.S., Sunderajan, P., Hu, L.T., Sowell, S.M., Carmody, T.J., 2012. A randomized, double-blind, placebo-controlled, trial of lamotrigine therapy in bipolar disorder, depressed or mixed phase and cocaine dependence. Neuropsychopharmacology 37, 2347–2354.

Cheng, W.J., Chen, C.H., Chen, C.K., Huang, M.C., Pietrzak, R.H., Krystal, J.H., Xu, K., 2018. Similar psychotic and cognitive profile between ketamine dependence with persistent psychosis and schizophrenia. Schizophr. Res. 199, 313–318.

Collins, R.J., Weeks, J.R., Cooper, M.M., Good, P.I., Russell, R.R., 1984. Prediction of abuse liability of drugs using IV self-administration by rats. Psychopharmacology (Berl.) 82, 6–13.

Consoni, F.T., Vital, M.A., Andreatini, R., 2006. Dual monoamine modulation for the antidepressant-like effect of lamotrigine in the modified forced swimming test. Eur. Neuropsychopharmacol. 16, 451–458.

D'Souza, M.S., 2015. Glutamatergic transmission in drug reward: implications for drug addiction. Front. Neurosci. 9, 404.

De Luca, M.T., Badiani, A., 2011. Ketamine self-administration in the rat: evidence for a critical role of setting. Psychopharmacology 214, 549–556.

De Luca, M.T., Meringolo, M., Spagnolo, P.A., Badiani, A., 2012. The role of setting for ketamine abuse: clinical and preclinical evidence. Rev. Neurosci. 23, 769–780.

Deakin, J.F., Lees, J., McKie, S., Hallak, J.E., Williams, S.R., Dursun, S.M., 2008. Glutamate and the neural basis of the subjective effects of ketamine: A pharmaco-magnetic resonance imaging study. Arch. Gen. Psychiatry 65, 154–164.

Doyle, O.M., De Simoni, S., Schwarz, A.J., Brittain, C., O'Daly, O.G., Williams, S.C., Mehta, M.A., 2013. Quantifying the attenuation of the ketamine pharmacological magnetic resonance imaging response in humans: a validation using antipsychotic and glutamatergic agents. J. Pharmacol. Exp. Ther. 345, 151–160.

Gahlinger, P.M., 2004. Club drugs: MDMA, gamma-hydroxybutyrate (GHB), Rohypnol, and ketamine. Am. Fam. Physician 69, 2619–2626.

Grunze, H., Greene, R.W., Moller, H.J., Meyer, T., Walden, J., 1998a. Lamotrigine may limit pathological excitation in the hippocampus by modulating a transient potassium outward current. Brain Res. 791, 330–334.

Grunze, H., von Wegerer, J., Greene, R.W., Walden, J., 1998b. Modulation of calcium and potassium currents by lamotrigine. Neuropsychobiology 38, 131–138.

Hancock, P.J., Stamford, J.A., 1999. Stereospecific effects of ketamine on dopamine efflux and uptake in the rat nucleus accumbens. Br. J. Anaesth. 82, 603–608.

Huang, C.W., Huang, C.C., Liu, Y.C., Wu, S.N., 2004. Inhibitory effect of lamotrigine on A-type potassium current in hippocampal neuron-derived H19-7 cells. Epilepsia 45, 729–736.
Huang, M.C., Chen, L.Y., Chen, C.K., Lin, S.K., 2016. Potential benefit of lamotrigine in managing ketamine use disorder. Med. Hypotheses 87, 97–100.
Kapur, S., Seeman, P., 2002. NMDA receptor antagonists ketamine and PCP have direct effects on the dopamine D(2) and serotonin 5-HT(2)receptors-implications for models of schizophrenia. Mol. Psychiatry 7, 837–844.
Kornhall, D., Nielsen, E.W., 2014. Failure of ketamine anesthesia in a patient with lamotrigine overdose. Case Rep. Crit. Care 2014, 916360.
Kuo, C.C., Lu, L., 1997. Characterization of lamotrigine inhibition of Na+ channels in rat hippocampal neurones. Br. J. Pharmacol. 121, 1231–1238.
LaLumiere, R.T., Kalivas, P.W., 2008. Glutamate release in the nucleus accumbens core is necessary for heroin seeking. J. Neurosci. 28, 3170–3177.
Leach, M.J., Marden, C.M., Miller, A.A., 1986. Pharmacological studies on lamotrigine, a novel potential antiepileptic drug: II. Neurochemical studies on the mechanism of action. Epilepsia 27, 490–497.
Li, F., Fang, Q., Liu, Y., Zhao, M., Li, D., Wang, J., Lu, L., 2008. Cannabinoid CB(1) receptor antagonist rimonabant attenuates reinstatement of ketamine conditioned place preference in rats. Eur. J. Pharmacol. 589, 122–126.
Li, J.H., Vicknasingam, B., Cheung, Y.W., Zhou, W., Nurhidayat, A.W., Jarlais, D.C., Schottenfeld, R., 2011. To use or not to use: an update on licit and illicit ketamine use. Subst. Abuse Rehabil. 2, 11–20.
Margolin, A., Avants, S.K., DePhilippis, D., Kosten, T.R., 1998. A preliminary investigation of lamotrigine for cocaine abuse in HIV-seropositive patients. Am. J. Drug Alcohol Abuse 24, 85–101.
Masuzawa, M., Nakao, S., Miyamoto, E., Yamada, M., Murao, K., Nishi, K., Shingu, K., 2003. Pentobarbital inhibits ketamine-induced dopamine release in the rat nucleus accumbens: a microdialysis study. Anesth. Analg. 96, 148–152 table of contents.
McFarland, K., Lapish, C.C., Kalivas, P.W., 2003. Prefrontal glutamate release into the core of the nucleus accumbens mediates cocaine-induced reinstatement of drug-seeking behavior. J. Neurosci. 23, 3531–3537.
Mendelsohn, L.G., Kerchner, G.A., Kalra, V., Zimmerman, D.M., Leander, J.D., 1984. Phencyclidine receptors in rat brain cortex. Biochem. Pharmacol. 33, 3529–3535.
Pappachan, J.M., Raj, B., Thomas, S., Hanna, F.W., 2014. Multiorgan dysfunction related to chronic ketamine abuse. Proc. (Bayl. Univ. Med. Cent.) 27, 223–225.
Parrilla-Carrero, J., Buchta, W.C., Goswamee, P., Culver, O., McKendrick, G., Harlan, B., Moutal, A., Penrod, R., Lauer, A., Ramakrishnan, V., Khanna, R., Kalivas, P., Riegel, A.C., 2018. Restoration of Kv7 channel-mediated inhibition reduces cued-reinstatement of cocaine seeking. J. Neurosci. 38, 4212–4229.
Pavlovic, Z., 2011. Lamotrigine reduces craving and depressive symptoms in cocaine dependence. J. Neuropsychiatry Clin. Neurosci. 23, E32.
Pavlovic, Z.M., 2010. Long-term treatment and relapse prevention of alcohol and benzodiazepine dependence with lamotrigine. J. Neuropsychiatry Clin. Neurosci. 22, E25–26.
Poolos, N.P., Migliore, M., Johnston, D., 2002. Pharmacological upregulation of h-channels reduces the excitability of pyramidal neuron dendrites. Nat. Neurosci. 5, 767–774.
Razoux, F., Garcia, R., Lena, I., 2007. Ketamine, at a dose that disrupts motor behavior and latent inhibition, enhances prefrontal cortex synaptic efficacy and glutamate release in the nucleus accumbens. Neuropsychopharmacology 32, 719–727.
Richardson, N.R., Roberts, D.C., 1996. Progressive ratio schedules in drug self-administration studies in rats: a method to evaluate reinforcing efficacy. J. Neurosci. Methods 66, 1–11.
Rubio, G., Lopez-Munoz, F., Alamo, C., 2006. Effects of lamotrigine in patients with bipolar disorder and alcohol dependence. Bipolar Disord. 8, 289–293.
Shen, Y.C., 2007. Treatment of inhalant dependence with lamotrigine. Prog. Neuropsychopharmacol. Biol. Psychiatry 31, 769–771.
Stone, J.M., Dietrich, C., Edden, R., Mehta, M.A., De Simoni, S., Reed, L.J., Krystal, J.H., Nutt, D., Barker, G.J., 2012. Ketamine effects on brain GABA and glutamate levels with 1H-MRS: relationship to ketamine-induced psychopathology. Mol. Psychiatry 17, 664–665.
Suzuki, T., Kato, H., Aoki, T., Tsuda, M., Narita, M., Misawa, M., 2000. Effects of the non-competitive NMDA receptor antagonist ketamine on morphine-induced place preference in mice. Life Sci. 67, 383–389.
Tehrani, S.P., Daryaafzoon, M., Bakhtiarian, A., Ejtemaeemehr, S., Sahraei, H., 2009. The effects of lamotrigine on the acquisition and expression of morphine-induced place preference in mice. Pak. J. Biol. Sci. 12, 33–39.
Vengeliene, V., Heidbreder, C.A., Spanagel, R., 2007. The effects of lamotrigine on alcohol seeking and relapse. Neuropharmacology 53, 951–957.
Vriend, J., Alexiuk, N.A., 1997. Lamotrigine inhibits the in situ activity of tyrosine hydroxylase in striatum of audiogenic seizure-prone and audiogenic seizure-resistant Balb/c mice. Life Sci. 61, 2467–2474.
Wang, L.J., Chen, C.K., Lin, S.K., Chen, Y.C., Xu, K., Huang, M.C., 2018. Cognitive profile of ketamine-dependent patients compared with methamphetamine-dependent patients and healthy controls. Psychopharmacology 235, 2113–2121.
Wang, X.Q., Xiong, J., Xu, W.H., Yu, S.Y., Huang, X.S., Zhang, J.T., Tian, C.L., Huang, D.H., Jia, W.Q., Lang, S.Y., 2015. Risk of a lamotrigine-related skin rash: Current meta-analysis and postmarketing cohort analysis. Seizure 25, 52–61.
Winther, L.C., Saleem, R., McCance-Katz, E.F., Rosen, M.I., Hameedi, F.A., Pearsall, H.R., Jatlow, P.I., Kosten, T.R., Woods, S.W., 2000. Effects of lamotrigine on behavioral and cardiovascular responses to cocaine in human subjects. Am. J. Drug Alcohol Abuse 26, 47–59.
Wolff, K., Winstock, A.R., 2006. Ketamine: from medicine to misuse. CNS Drugs 20, 199–218.
Xie, X., Lancaster, B., Peakman, T., Garthwaite, J., 1995. Interaction of the antiepileptic drug lamotrigine with recombinant rat brain type IIA Na+ channels and with native Na+ channels in rat hippocampal neurones. Pflugers Arch. 430, 437–446.
Zalewska-Kaszubska, J., Bajer, B., Gorska, D., Andrzejczak, D., Dyr, W., Bienkowski, P., 2015. Voluntary alcohol consumption and plasma beta-endorphin levels in alcohol preferring rats chronically treated with lamotrigine. Physiol. Behav. 139, 7–12.