Brain Research Bulletin 126 (2016) 68–73

Contents lists available at ScienceDirect

Brain Research Bulletin

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

Review

Ketamine abuse potential and use disorder

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ARTICLE INFO

Article history:
Received 6 March 2016
Received in revised form 26 May 2016
Accepted 30 May 2016
Available online 31 May 2016

Keywords:
Ketamine abuse
Neurobiology
Pharmacology
Anti-depressant
Toxic effect

ABSTRACT

Ketamine is a noncompetitive antagonist of *N*-methyl-D-asparate (NMDA) receptor and has been long used as an anesthetic agent in humans and veterinary medicine. The present article reviews the epidemiology, pharmacology, neurochemistry, and treatment of ketamine abuse. Ketamine has a unique mood controlling property and a number of studies have demonstrated a significant and rapid antidepressant effect of ketamine. However, the therapeutic value of ketamine to treat psychiatric disorders faces a major challenge that ketamine also owns significant reinforcing and toxic effects. Its abuse has posted severe harms on individuals and society. Disrupted learning and memory processing has long been related with ketamine use. It is hypothesized that ketamine blocks NMDA receptors on gamma-aminobutyric acid (GABA) neurons inside the thalamic reticular nucleus, which leads to disinhibition of dopaminergic neurons and increased release of dopamine. Currently, there is no specific treatment for treating every ketamine patient presenting peripheral toxicity. Interestingly, ketamine psychotherapy has been suggested to be a promising approach to treat addiction of other drugs. Future research can continue to develop creative ways to investigate potential mechanism and treatments related to ketamine abuse that have posted severe individual and social harms.

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Ketamine was firstly synthesized by Calvin Stevens of the Parke-Davis Pharmaceutical Company in 1962 (Copeland and Dillon, 2005). In chemical structure, Ketamine (2-chlorphenyl-2-methylamino-cyclohexanone) is a phencyclidine (PCP) derivative (Rowland, 2005). Ketamine is a noncompetitive antagonist of *N*-methyl-D-asparate (NMDA) receptor and has been long used as an anesthetic agent in humans and veterinary medicine (Kurdi et al., 2014). In addition, ketamine, as a dissociative anesthetic, has a unique psychological effect which displays both mood controlling and reinforcing properties (Coyle and Laws, 2015; Jansen and Darracot-Cankovic, 2001). Since the first placebo-controlled trial investigating the antidepressant effect of ketamine in 2000, a number of studies have demonstrated a significant and rapid antidepressant effect of ketamine (Berman et al., 2000; Costi et al., 2015). In line with the anti-depressant effect of ketamine, the use of subanethetic ketamine infusions has also been extended from treatment-resistant depression to bipolar disorder, anxiety and chronic pain (Romeo et al., 2015; Sheehy et al., 2015; Zgaia et al., 2015). However, ketamine and its derivative, methoxetamine, has also been shown to serve as a reinforcing stimulus to induce self-administration and conditioned place preference in rats, suggesting

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http://dx.doi.org/10.1016/j.brainresbull.2016.05.016
0361-9230/

its high potential of drug abuse (Botanas et al., 2015; De Luca and Badiani, 2011; Venniro et al., 2015; Winger et al., 2002; Young and Woods, 1981). Due to its reinforcing and rewarding properties, ketamine has become a recreational drug in the context of "raves" and the non-medical use of ketamine has grown steadily worldwide in the past a few decades (Bokor and Anderson, 2014; Chakraborty et al., 2011; Liu et al., 2006; Pavarin, 2006; Rome, 2001). In addition to its abuse potential, ketamine was proved to produce neurological and peripheral toxicity (Gable, 2004; Morgan et al., 2010). The present review focuses on the brain neurocircuitry that is engaged at the reinforcing effect of ketamine associated with its abuse.

1. Social harms of ketamine abuse

The recreational dose of ketamine is approximately 15–20% lower than its anesthetic dose. Due to its anesthetic and reinforcing properties, ketamine has become a commonly abused drugs in many parts of the world. The US survey in 2006 estimated that approximately 2.3 million teens and adults used ketamine in their lifetime (Administration, 2008). The number of ketamine-related death has increased 10 folds in UK from 1999 to 2008 (Morgan et al., 2012). According to an Australian survey, 40% of party drug users reported the use of ketamine (Breen et al., 2008). In the past decade, ketamine abuse has also been spread over the countries and regions in Asia. There was almost four-fold increase in ketamine users in Malaysia from 2006 to 2012 (Singh et al., 2013). Ketamine abuse started to emerge in China in 90s and Hong Kong has been one of the hardest hit regions in the country (Tang et al., 2015a,b). In Hong Kong along, over 2000 cases were reported for ketamine abuse in 2013 and 2014 (Tang et al., 2015a,b). The percentage of ketamine users among all registered drug users have also increased from 21.5% in 2001 to 40% in 2009 in mainland China (Jia et al., 2015). The rapidly deteriorating condition of ketamine abuse has resulted in the change of ketamine status from a class II to class I psychotropic drug in China.

Although ketamine is a relatively safe substance in medical settings, its abuse has posted severe harms on individuals and society (Morgan et al., 2012). One of the major concerns is driving under the influence of ketamine. The popularity of ketamine as a club drug has also led to an increased reports of driving under the influence of ketamine. For example, ketamine was the third most used illicit drugs among drivers tested positive for psychoactive drugs in Shanghai, China (Zhuo et al., 2010). In a survey conducted in Scotland, 36% of 122 partygoers confirmed driving after using ketamine. In Hong Kong, 9% of drivers involving fatal car crash were tested positive for ketamine (Cheng et al., 2005). The risks of ketamine associated traffic accident could be related to its impairing effect on executive cognitive functions, decreased attention, and impaired memory functioning (Giorgetti et al., 2015; Penning et al., 2010). In addition, ketamine has also been suggested to produce enhanced sex experience which could lead to drug-facilitated sexual assault (Bokor and Anderson, 2014). An increased incidence of unproductive sex among gay men with ketamine use has also caused concerns in many countries (Daskalopoulou et al., 2014; Lea et al., 2013; Pappas and Halkitis, 2011; Xu et al., 2014).

2. Psychological and physiological effects of ketamine

Ketamine has a plasma half-life of 2–4 h and a distribution half life of 7–11 min (Copeland and Dillon, 2005). Administration routes of ketamine commonly include intravenous, intramuscular, snorting, and smoking (Bokor and Anderson, 2014). The predominant route of ketamine administration for recreational use is intranasal and intravenous injection is rather rare (Reynaud-Maurupt et al., 2007). The primary psychological effect of ketamine is anesthesia and sedation. It should be noted that the use of ketamine for human anesthesia is often associated with hallucinations after waking up (Powers Iii et al., 2015). Reports of "out-of-body" experiences have been consistently associated with recreational use and abuse of ketamine (Muetzelfeldt et al., 2008; Wilkins et al., 2012). For unauthorized use of ketamine, low dose is associated with a feeling of relaxation, which is so called "K-land"; whereas high dose produces a dreamlike state called a "K-hole" (Britt and McCance-Katz, 2005). The dissociative anesthetic characteristics of ketamine greatly contribute to ketamine abuse. In addition to the psychoactive effects of ketamine, disrupted learning and memory processing has long been related with ketamine use (Morgan and Curran, 2006). An acute dose of ketamine has been demonstrated to induce cognitive impairments in healthy volunteers and cognitive deficits are also observed in frequent ketamine users (Curran and Morgan, 2000; Liang et al., 2013; Morgan et al., 2010). Particularly, verbal learning impairment and decreased performance on spatial memory was strongly correlated with estimated lifetime ketamine use (Chan et al., 2013; Morgan et al., 2010). Interestingly, ketamine-induced cognitive impairment has been suggested to have therapeutic value. Intravenous ketamine has rapid effects on explicit and inexplicit suicidal cognition, which makes it an attractive candidate for depressed patients at imminent risk of suicide (Price et al., 2014; Solé et al., 2015). Furthermore, chronic use of ketamine has been suggested to produce schizophrenia-like positive and negative symptoms, including hallucinations, detachment, delusions, amotivations etc. Auditory verbal hallucinations, a hallmark symptom of schizophrenia, have also been reported in healthy volunteers with high doses of ketamine (Powers Iii et al., 2015).

Ketamine also has systemic effects on a number of organs. Ketamine stimulates the cardiovascular system, due to decreased catecholamine reuptake. These changes lead to increased heart rate and blood pressure (Mayberg et al., 1995). As a matter of fact, the most complaints among ketamine abusers presenting at the Emergency Department were chest pains, palpitations, and tachycardia (Weiner et al., 2000). The symptoms were often transient and patients were often discharged within hours (Gable, 2004). Unlike first-time users of ketamine, patients with a history of chronic ketamine use commonly reported abdominal pain and urinary tract symptoms (Skeldon and Goldenberg, 2014). A number of cases reports suggest that ketamine abuse can cause suprapubic pain, dysurria and hematuria (Mason et al., 2010; Peng et al., 2014; Yek et al., 2015). Radiology results revealed decreased bladder volume, bladder wall thickening, musosal enhancement, dilation of ureter, and perivesical inflammation in ketamine abusers (Huang et al., 2014; Wu et al., 2012). Based on cytoscopy findings, erythema, edema, and epithelial inflammation are commonly associated with chronic ketamine use (Chu et al., 2008; Shahani et al., 2007). One possible mechanism underlying renal toxicity of ketamine is due to the direct toxic effects of ketamine and its metabolites (Bokor and Anderson, 2014; Gable, 2004). Marked alterations in epithelial cell-to-cell adhesion and cell coupling in the proximal kidney are also thought to be associated with renal toxicity of ketamine (Hills et al., 2013). Both clinical and animals studies confirm liver damage caused by chronic use of ketamine. For example bile duct dilatation, microscopic bile duct injury, and even significant liver fibrosis have been found among ketamine abusers (Wong et al., 2015).Fatty degeneration of liver cells, fibrosis and increase in liver glutamicoxaloacetic transaminase, proliferative cell nuclear antigen and lactate dehydrogenase were reported in rats with 16-week treatment with ketamine and alcohol (Wai et al., 2012). Mitochondrial dysfunction has been suggested to result in the underlying hepatotoxcity of ketamine (Chang et al., 2009; Kalkan et al., 2013; Lee et al., 2009; Venâncio et al., 2013).