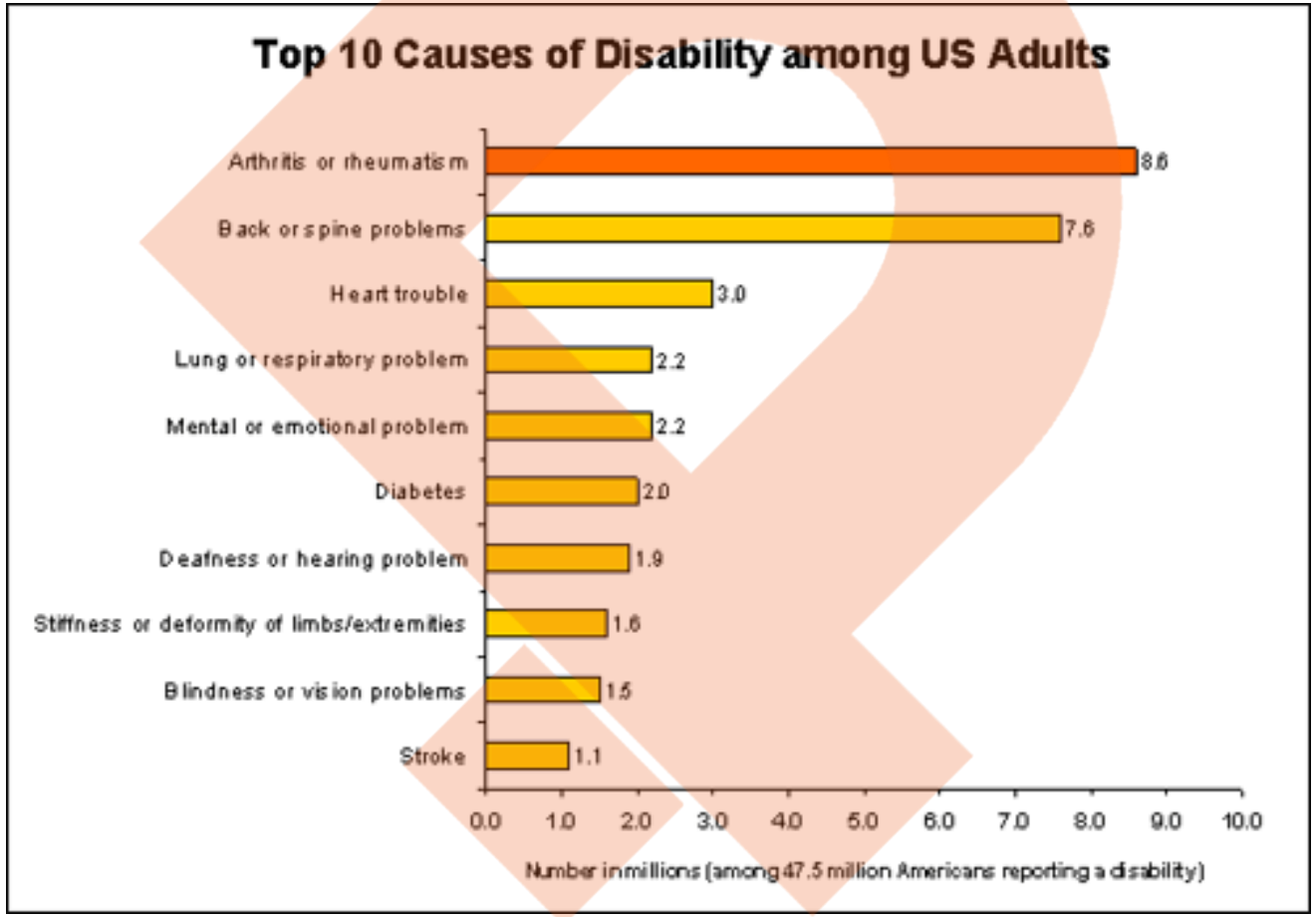
Introduction

- Neuropsychiatric disorders strike billions of people worldwide.
- 30% of all Americans have chronic physical pain (Institute of Medicine of the National Academies of Science).
- 10% of all Americans have chronic emotional pain according to: 1) Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study and also 2) National Institute of Mental Health.
- By extrapolation, **40% of the population experiences chronic pain when somatic and emotional sequelae are combined.**

Top 10 Causes of Disability according to CDC



One Drug, Many Benefits

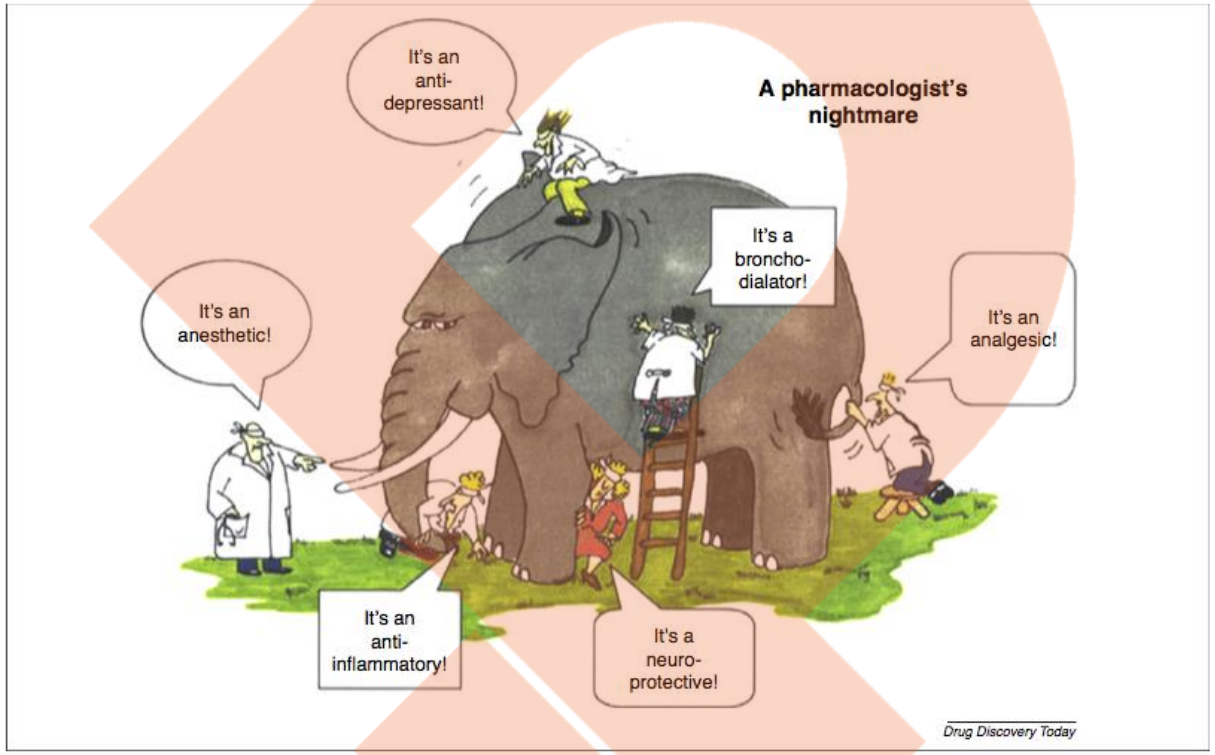


FIGURE 1

Pharmacologist's nightmare. Multifaceted activities of ketamine have suggested several potential therapeutic uses including those shown. This conundrum is reminiscent of the 'blind men and the elephant'. (Adopted from Original Artist - G. Renee Guzlas).

Use Magnetic Stimulation to Target Drug Delivery

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Article

Rhythmic TMS Causes Local Entrainment of Natural Oscillatory Signatures

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Summary

Background: Neuronal elements underlying perception, cognition, and action exhibit distinct oscillatory phenomena, measured in humans by electro- or magnetoencephalography (EEG/MEG). So far, the correlative or causal nature of the link between brain oscillations and functions has remained elusive. A compelling demonstration of causality would primarily generate oscillatory signatures that are known to correlate with particular cognitive functions and then assess the behavioral consequences. Here, we provide the first direct evidence for causal entrainment of brain oscillations by transcranial magnetic stimulation (TMS) using concurrent EEG.
Results: We used rhythmic TMS bursts to directly interact with an MEG-identified parietal α-oscillator, activated by attention and linked to perception. With TMS bursts tuned to its preferred α-frequency (α-TMS), we confirmed the three main predictions of entrainment of a natural oscillator: (1) that α-oscillations are induced during α-TMS (reproducing an oscillatory signature of the stimulated parietal cortex), (2) that there is progressive enhancement of this α-activity (synchronizing the targeted, α-generator to the α-TMS train), and (3) that this depends on the pre-TMS phase of the background α-rhythm (entrainment of natural, ongoing α-oscillations). Control conditions testing different TMS burst profiles and TMS-EEG in a phantom head confirmed specificity of α-boosting to the case of synchronization between TMS train and neural oscillator.
Conclusions: The periodic electromagnetic force that is generated during rhythmic TMS can cause local entrainment of natural brain oscillations, emulating oscillatory signatures activated by cognitive tasks. This reveals a new mechanism of online TMS action on brain activity and can account for frequency-specific behavioral TMS effects at the level of biologically relevant rhythms.

Introduction

As a method, transcranial magnetic stimulation (TMS) enables direct rhythmic stimulation of the human brain at frequencies that characterize electro- or magnetoencephalographic (EEG/MEG) signals [1, 2]. Likewise, the alternative method of transcranial alternating current stimulation (tACS) allows stimulation of the human brain at frequencies of biologically relevant brain rhythms [1, 2]. There is now accumulating experimental support that both rhythmic TMS and tACS interact with natural brain oscillations in a frequency-specific manner [3–8]. This is based on findings that rhythmic stimulation of occipital or parietal areas results in specific (and immediate) perceptual consequences, when the stimulation frequency is tuned to the preferred oscillation frequency of the target area [3–8]. (For analogous effects within the motor system, see [9].)

The above research provides new clues on two long-standing questions: (1) How does TMS (or tACS) interact with ongoing, here oscillatory brain activity to give rise to behavioral effects, and (2), what is the functional relevance of brain oscillations? It does so by pointing toward immediate and specific behavioral consequences depending on TMS (or tACS) frequency. However, these studies [3–8] have one main limitation: they manipulated stimulation frequency (TMS or tACS) and reported behavioral outcome, but they did not study changes in brain activity, i.e., the underlying mechanisms.

Here, we present the missing piece to the puzzle of how these immediate, frequency-dependent effects on perception could come about during rhythmic TMS. Our study builds from the evidence that the behavioral effects of rhythmic TMS (or tACS) are confined to stimulation frequencies that were identified as perceptually relevant in prior EEG/MEG research [3–8]. From this 1:1 frequency locking between the most effective TMS frequency and the perceptually relevant EEG/MEG frequency derives the hypothesis that rhythmic TMS pulses may have entrained the underlying rhythmic generator. This entrainment hypothesis therefore posits that frequency-tuned rhythmic TMS causes entrainment in direct interactions with the underlying brain oscillation. As a consequence, one of the mechanisms by which rhythmic TMS exerts its action on behavior could be the reproduction of a natural oscillatory signature of brain activity (that is also functionally relevant).

Entrainment supposes (1) the induction of a distinct entrainment signature, which emerges during rhythmic TMS and whose topography and frequency reproduce the natural oscillation of the targeted generator. Entrainment also supposes that there is (2) progressive enhancement of the target oscillation in the course of the TMS train as a result of progressive synchronization by each successive TMS pulse. Finally, entrainment should (3) depend on ongoing activity of the target generator, because it is supposedly driving existing brain oscillations, as opposed to generating new artificial rhythms.

We tested the entrainment hypothesis using neuronavigated rhythmic TMS of MEG-localized brain oscillators and concurrent multichannel EEG. We first identified a parietal α-oscillator (i.e., showing oscillatory activity at α-frequency, 8–14 Hz), whose EEG/MEG amplitude is regulated by visual attention [10–13] and correlates with visual perception [13–16]. We then tested in a passive condition whether rhythmic TMS of this parietal area at its preferred frequency entrains the underlying α-generator during TMS, explaining immediate and

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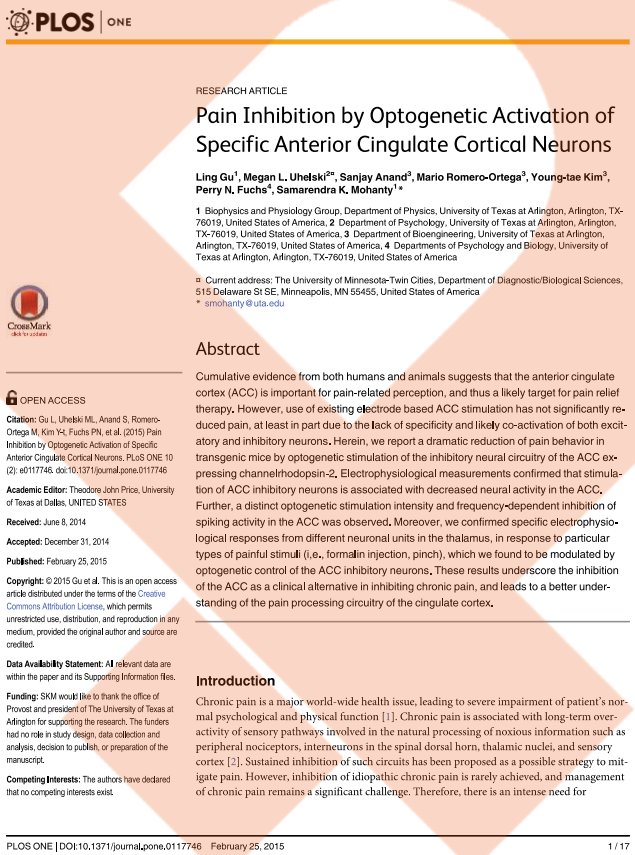
The same limbic circuit is involved in awareness of PAIN, and



PLOS | ONE

RESEARCH ARTICLE

Pain Inhibition by Optogenetic Activation of Specific Anterior Cingulate Cortical Neurons

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Abstract

Cumulative evidence from both humans and animals suggests that the anterior cingulate cortex (ACC) is important for pain-related perception, and thus a likely target for pain relief therapy. However, use of existing electrode based ACC stimulation has not significantly reduced pain, at least in part due to the lack of specificity and likely co-activation of both excitatory and inhibitory neurons. Herein, we report a dramatic reduction of pain behavior in transgenic mice by optogenetic stimulation of the inhibitory neural circuitry of the ACC expressing channelrhodopsin-2. Electrophysiological measurements confirmed that stimulation of ACC inhibitory neurons is associated with decreased neural activity in the ACC. Further, a distinct optogenetic stimulation intensity and frequency-dependent inhibition of spiking activity in the ACC was observed. Moreover, we confirmed specific electrophysiological responses from different neuronal units in the thalamus, in response to particular types of painful stimuli (i.e., formalin injection, pinch), which we found to be modulated by optogenetic control of the ACC inhibitory neurons. These results underscore the inhibition of the ACC as a clinical alternative in inhibiting chronic pain, and leads to a better understanding of the pain processing circuitry of the cingulate cortex.

OPEN ACCESS

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Introduction

Chronic pain is a major world-wide health issue, leading to severe impairment of patient's normal psychological and physical function [1]. Chronic pain is associated with long-term overactivity of sensory pathways involved in the natural processing of noxious information such as peripheral nociceptors, interneurons in the spinal dorsal horn, thalamic nuclei, and sensory cortex [2]. Sustained inhibition of such circuits has been proposed as a possible strategy to mitigate pain. However, inhibition of idiopathic chronic pain is rarely achieved, and management of chronic pain remains a significant challenge. Therefore, there is an intense need for

(and) in Depression.

PNAS

Optogenetic stimulation of infralimbic PFC reproduces ketamine's rapid and sustained antidepressant actions

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Ketamine produces rapid and sustained antidepressant actions in depressed patients, but the precise cellular mechanisms underlying these effects have not been identified. Here we determined if modulation of neuronal activity in the infralimbic prefrontal cortex (IL-PFC) underlies the antidepressant and anxiolytic actions of ketamine. We found that neuronal inactivation of the IL-PFC completely blocked the antidepressant and anxiolytic effects of systemic ketamine in rodent models and that ketamine microinfusion into IL-PFC reproduced these behavioral actions of systemic ketamine. We also found that optogenetic stimulation of the IL-PFC produced rapid and long-lasting antidepressant and anxiolytic effects and that these effects are associated with increased number and function of spine synapses of layer V pyramidal neurons. The results demonstrate that ketamine infusions or optogenetic stimulation of IL-PFC are sufficient to produce long-lasting antidepressant behavioral and synaptic responses similar to the effects of systemic ketamine administration.

prefrontal cortex | synapse | neural depolarization | antidepressant | glutamate

The NMDA receptor antagonist ketamine produces rapid and robust therapeutic responses in treatment-resistant (1, 2) as well as bipolar depressed patients (3). Preclinical studies report that ketamine also rapidly increases the number and function of spine synapses in the medial prefrontal cortex (mPFC) and that these effects are associated with rapid antidepressant behavioral responses in rodent models (4). These findings represent a major advance for the treatment of depression, although the widespread use of ketamine is limited by side effects (e.g., psychotomimetic and dissociative symptoms) and abuse potential. Further studies of the mechanisms underlying the actions of ketamine could lead to novel rapid antidepressant treatments with fewer side effects.

Neuroimaging studies in humans demonstrate that ketamine increases the activity of PFC (5–7), consistent with evidence of rapid increases of glutamate transmission in rodent PFC (8, 9). In addition, depressed patients are reported to have reduced activity in the PFC (10) that is normalized with treatment (11). Rodent studies also demonstrate that long-term stress causes neuronal atrophy of mPFC neurons (12, 13) that is rapidly reversed by ketamine (14). Subregions of the mPFC, including infralimbic (IL) and prelimbic (PrL), have been implicated in diverse cognitive and emotional processes, including fear learning, extinction, and anxiety (15–18). However, the role of PFC activity in the behavioral responses to ketamine has not been examined.

Here we examined the antidepressant behavioral effects of neuronal inactivation or direct infusions of ketamine into the IL-PFC and compared these effects with PrL-PFC. Using optogenetics, we also examined the antidepressant and anxiolytic effects of neuronal activation in IL-PFC and determined the impact on pyramidal cell spine number and function to assess long-term neuroplasticity.

Methods and Materials

Animals, Surgery Microinfusions, and Optical Stimulation. Adult male Sprague–Dawley rats (Charles River Laboratories) weighing 150–250 g were pair-housed on a 12-h light/dark cycle (lights on 07:00 h) with food and water available ad libitum. All procedures were done in accordance with the NIH guidelines for the care and use of laboratory animals and the Yale University Institutional Animal Care and Use Committee. Rats were anesthetized with pentobarbital (50 mg/kg, i.p.) and implanted with bilateral guide cannula positioned 1 mm above the site of infusion in either IL [+2.8 mm AP (anteroposterior); ±3.1 mm ML (mediolateral); 3.8 mm DV (dorsoventral); angled at 30°] or PrL (+3.0 mm AP; ±0.50 mm ML; 2.8 mm DV) (12). An angled placement was used for IL. Microinfusions were performed bilaterally into IL or PrL (0.2 μL, 0.1 μL/min) 7 d after surgery. The infusion sites and volumes were based on previous reports demonstrating restricted spread and subregion-specific inactivation following muscimol infusion in the IL or PrL (19, 20). Muscimol (1.25 μg/0.2 μL per hemisphere) or vehicle were microinfused 30 min before ketamine (10 mg/kg, i.p.), a dose that produces antidepressant responses (4). Microinfusion of ketamine included 3, 10, or 30 ng/0.2 μL per hemisphere.

For optogenetic stimulation, rAAV2/CaMKIIα-ChR2(H134R)-eYFP (University of North Carolina Viral Core) or a control vector expressing GFP (rAAV2-GFP, in-house) were infused. Rats were anesthetized with ketamine (80 mg/kg) and xylazine (6 mg/kg); this anesthetic dose of ketamine does not produce antidepressant actions (4). Virus was infused (0.5 μL, 0.1 μL/min) into the IL (+3.2 mm AP; ±0.8 mm ML; 5.5 mm DV) or PrL (+3.2 mm AP; ±0.8 mm ML; 3.0 mm DV) (12), and optical fibers were placed 0.2 mm above the virus injection site and attached to the skull. For optical stimulation, rats were lightly anesthetized (isoflurane) to attach the fiberoptic, and animals with both control and active virus received blue light pulses (pulse width, 15 ms; frequency, 10 Hz; intensity, 5 mW; 473-nm laser) for 60 min (1 min on and 1 min off for 30 cycles). Stimulation settings were based on firing patterns of mPFC pyramidal neurons induced by NMDA receptor antagonism (9) and optogenetic settings necessary to reproduce this firing pattern (21).

Brain Slice Preparation, Recordings, and Spine Analysis. Whole-cell recordings were obtained from layer V pyramidal cells in acute brain slices from rats that had been stereotaxically injected into the IL with rAAV2-ChR2-eYFP or rAAV2-GFP as previously described (14, 22). One day later, brains from stimulated rats were sectioned (400-μm-thick coronal mPFC sections). YFP+ or GFP+ pyramidal neurons in layer V were visualized by infrared differential

Significance

Clinical studies report that a single, low dose of ketamine produces a rapid antidepressant response in treatment-resistant depressed patients. Although rodent studies have begun to elucidate the molecular mechanisms underlying the behavioral actions of ketamine, the brain regions and cellular mechanisms have not been defined. Using a combination of pharmacological silencing and optogenetic stimulation approaches, the results of the current study demonstrate that ketamine infusion or optogenetic stimulation of the infralimbic prefrontal cortex produces antidepressant behavioral and synaptic responses similar to the actions of systemic ketamine. These findings further elucidate the mechanisms underlying the therapeutic actions of ketamine and will enhance the development of safer rapid-acting and efficacious agents.

Author contributions: M.F., G.K.A., and R.S.D. designed research; M.F., A.T., R.L., E.S.W., and B.B.L. performed research; M.F., R.L., R.J.D., and G.K.A. analyzed data; and M.F., G.K.A., and R.S.D. wrote the paper.

The authors declare no conflict of interest.

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This is the kind of drug that needs to be delivered for both pain and depression.

PERSPECTIVE Drug Discovery Today Volume 19, Number 12 December 2014

feature

Ketamine: repurposing and redefining a multifaceted drug

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This short review will highlight recent clinical and basic research that supports the therapeutic utility of ketamine as a rapid-acting, life-saving antidepressant and a versatile analgesic. After 50 years of use as a dissociative anesthetic and misuse as a street drug, ketamine has re-emerged as a useful off-label agent for ameliorating various types of pain and resistant depression. In addition to its ability to inhibit N-methyl-D-aspartate (NMDA) receptors, the diverse actions of ketamine might involve epigenetic mechanisms such as microRNA regulation. Thus, ketamine is transitioning from being the pharmacologist's nightmare to one of the most interesting developments in the pharmacology of depression and pain.

Introduction

With the reorganization of the biopharmaceutical research enterprise (academia, industry, government), repurposing of existing drugs has become a desirable mechanism for getting drugs into and out of the therapeutic pipeline expeditiously at a lower overall cost [1]. Ketamine is a prime example of repurposing a multifaceted drug because it has potential for multiple, dose-dependent uses for some challenging clinical situations that involve the need for safe, parenteral anesthesia as well as relief of pain [2] and depression [3]. The purpose of this short review is to highlight some of the pharmacological advances that suggest ketamine has utility as a (i) therapeutic agent in treating refractory pain and depression and (ii) pharmacological tool for discovering novel mechanisms that will lead to more efficacious therapies for diseases involving pain and depression.

Approximately 50 years ago, D.E. Potter worked with ketamine in discovery research at Parke-Davis, Ann Arbor, MI, USA. At the time, CI581 (ketamine) was identified as 'it' in a report to Duncan A. McCarthy, Jr; 'it' was the best candidate of all those phencyclidine derivatives that were tested as potential parenteral anesthetics in infrahuman primates and other species [4]. In the mid-1960s, ketamine was evaluated as an intravenous anesthetic agent in humans [5]; it was approved for clinical use in 1970. Subsequently, ketamine began its clinical life as a 'dissociative anesthetic' [6].

The parenterally administered drug was labeled clinically as a dissociative anesthetic because it induces a cataleptic state in which the eyes remain open and sensory input (perception) is suppressed at association areas (thalamic-limbic) below the level of the sensory cortex. Moreover, tone of the pharyngeal and laryngeal muscles is maintained, which lessens the possibility of aspiration should vomiting occur. Based on these properties, ketamine continues to be suitable as a parenterally administered anesthetic or sedative agent for uncooperative and/or compromised patients including: (i) children (e.g. burn injuries, fractures); (ii) battlefield emergencies (e.g. difficult airways, reactive airway disease) and (iii) veterinary subjects. Based on its utility in adults and children, under special circumstances, the World Health Organization has listed ketamine as a core medicine (a minimum medical need for a basic health system) [7]. For example, ketamine was designated the 'preferred agent' in a relatively common emergency room procedure, such as fracture reduction that requires conscious sedation of pediatric patients [8].

However, in addition to its ability to produce a combination of analgesia, amnesia, immobility and loss of consciousness at anesthetic doses, ketamine can produce significant dose- and duration-related adverse side-effects including psychotomimetic ideation, increases in blood and intracranial pressure (relative contraindications), and excessive secretions in the airway. However, appropriate premedications can attenuate the adverse psychotomimetic effects (e.g. lorazepam) and excessive secretions

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Here is your caveat – although it is a truly safe drug.

CNS Neuroscience & Therapeutics

REVIEW

Ketamine-An Update on Its Clinical Uses and Abuses

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Keywords
Abuse; Antidepressant; Asthmaticus; Ketamine.

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SUMMARY

This review highlights the recent clinical research that supports the therapeutic utility of ketamine as a multifaceted drug. After long-term use as a dissociative anesthetic, it has re-emerged as a useful agent for ameliorating pain, asthmaticus, and depression. In addition, it is also a substance of abuse. Chronic ketamine abuse over prolonged periods (weeks, months, and years) can produce toxicity to the genitourinary and urinary tract. In this review, we described the recent progression in clinical use and abuses.

Introduction

Ketamine, originally named "CI581," is a phencyclidine derivative. It has a molecular weight of 238 Da and a pKa of 7.5 [1]. There are two isomers: S (+) enantiomer ketamine and R (−) ketamine [2]. S enantiomer has several advantages over the R (−) isomer. The S (+) isomer, an active enantiomer [3], has a 4-fold greater affinity for the NMDA receptor, twice the analgesic potency, and fewer psychomimetic effects than the R (−) isomer. Commercially available ketamine is a chiral compound consisting of a mixture of both two isomers [4].

The most efficient route of administration is intravenous injection (bioavailability: 93%). While oral bioavailability of ketamine is only 16% [5]. The onset of action is rapid, and peak plasma concentrations are seen within 60 seconds of administration. The duration of action after a single bolus injection is 10–15 min and distribution half-life is 7–11 min [6]. Based on these properties, it is suitable as a parenterally administered anesthetic for children patients [7]. In addition to producing anesthesia in emergency department and operating theater settings [8], ketamine has shown significant effects on treating depression. The desired action represents an efficacious approach to amelioration of major depression, treatment-resistant depression, bipolar affective disorder, and suicidal ideation [9–13]. Furthermore, numerous studies prove that ketamine can be used alone and in combination with other drugs for pain relief in patients experiencing various surgeries and traumatic injuries [14–18]. More recently, the addition of ketamine to the standard treatment regimen of severe asthma has shown to improve outcome and alleviate the need for mechanical ventilation, suggesting ketamine might be a novel and rapid-acting drug in the treatment of patients with asthmaticus [17,18].

However, the dose- and duration-related side effects of ketamine are usually reported, such as psychotomimetic effects, increases in blood pressure and heart rate [19,20]. Being a strong psycho-stimulant, ketamine can also be the source of abuse, which could result in schizophrenia-like cognitive impairments and malfunction dysfunction [21–23].

This review will focus on two important aspects of ketamine: its clinical uses as a potential medication and the severe problems related to its abuses.

Major Depression

Successful treatment of depressive disorders remains as challenging today as it was nearly 100 years ago. Current approaches to major depression are highly unsatisfactory. In 2000, the first placebo-controlled, double-blinded trial demonstrated that ketamine has therapeutic effects in major depression [24]. After that, numerous RCT studies focusing on the effects of ketamine on major depressive disorder suggested a significant and rapid improvement in depressive symptoms after a single ketamine infusion [25,26]. The rapid-acting antidepressant could maintain its therapeutic effects for about 3–7 days [27]. Given that the effects of a single dose of ketamine were transient, another study