Subanesthetic Dose Ketamine in Posttraumatic Stress Disorder: A Role for Reconsolidation During Trauma-Focused Psychotherapy?

Cato Veen, Gabriel Jacobs, Ingrid Philippens, and Eric Vermetten

Abstract Despite efforts to develop more effective therapies, PTSD remains a difficult disorder to treat. Insight into the dynamic nature of memory formation and its required molecular machinery can provide an opportunity to target pathological memories for emotionally arousing events. As memories become labile upon retrieval, novel information can update the strength and course of these consolidated memories. Targeting the process of reconsolidation may offer a relevant approach to attenuate fearful and traumatic memories. Specific molecular mechanisms that are required for reconsolidation of arousing information include an intact functioning of the glutamatergic signaling pathways and, more specifically, the integrity of NMDA receptors. Ketamine, a noncompetitive NMDA-receptor antagonist, is receiving increasing interest for a variety of psychiatric indications. This compound can also be an interesting candidate for targeting emotional memories. We explore whether single intravenous infusion of a subanesthetic dose of ketamine can be considered as a viable augmentation strategy for trauma-focused psychotherapy in patients with PTSD. As a consequence, a systematic approach is needed to assess the pharmacodynamic effects of ketamine in relation to both psychotherapy and its pharmacokinetics prior to

C. Veen (✉)
Department of Psychiatry, Leiden University Medical Center, Leiden, The Netherlands
e-mail: c.veen@lumc.nl

G. Jacobs
Department of Psychiatry, Leiden University Medical Center, Leiden, The Netherlands

Centre for Human Drug Research, Leiden, The Netherlands

I. Philippens
Biomedical Primate Research Centre, Rijswijk, The Netherlands

E. Vermetten
Department of Psychiatry, Leiden University Medical Center, Leiden, The Netherlands

Arq Psychotrauma Research Group, Diemen, The Netherlands

Curr Topics Behav Neurosci (2018) 38: 137–162
DOI 10.1007/7854_2017_34
Published Online: 31 March 2018

its application in patient populations. By using a "question-based drug development plan," we can explore such aspects for novel drugs, and we formulated five additional topics that need to be addressed concerning the psychotherapeutic approach and phase orientation of pharmacological assisted psychotherapy.

Keywords Consolidation • Extinction learning • Ketamine • Memory • Pharmacological assisted psychotherapy • Posttraumatic stress disorder • Reconsolidation

Contents

1 Introduction

Posttraumatic stress disorder (PTSD) can be considered as a disorder in which emotional memory plays a key role (Yehuda and LeDoux 2007). Despite efforts to develop more effective therapies, it remains a difficult disorder to treat (Jonas et al. 2013). Targeting the strength of highly affective memories has shown to be a novel and promising approach to attenuate fearful and traumatic memories. Over the last decade, this has reflected in an abundance of research on memory resulting in the discovery that memories become labile upon retrieval. In this phase novel information can be integrated and can alter the nature and strength of consolidated fear memories (Quirk and Mueller 2008). This approach has opened opportunities for exploration of a new strategy with compounds that could lead to significant clinical improvements in treating PTSD.

In this review, we provide a rationale for targeting pathological memory formation with a pharmacological approach embedded in a psychological treatment. We will specifically highlight the role of *N*-methyl-D-aspartate (NMDA)-receptor functioning. We will argue that ketamine, a NMDA-receptor antagonist, potentially holds promise in treatment of PTSD when administered as a single intravenous (IV) infusion of a subanesthetic dose, especially as augmentation of trauma-focused

psychotherapy by attenuating reconsolidation of traumatic memories. Additionally, we will provide a framework to systematically address all relevant topics for drug-assisted psychotherapies, and we will apply this for ketamine-assisted psychotherapy in PTSD.

2 Memory Formation and Glutamatergic Signaling Through the NMDA Receptor

A well-studied translational model to understand formation of trauma-related memories is the Pavlovian fear-conditioning paradigm illustrated in Fig. 1 (Maren et al. 2013; Pavlov 1927; Pedreira and Maldonado 2003; Suzuki et al. 2004).

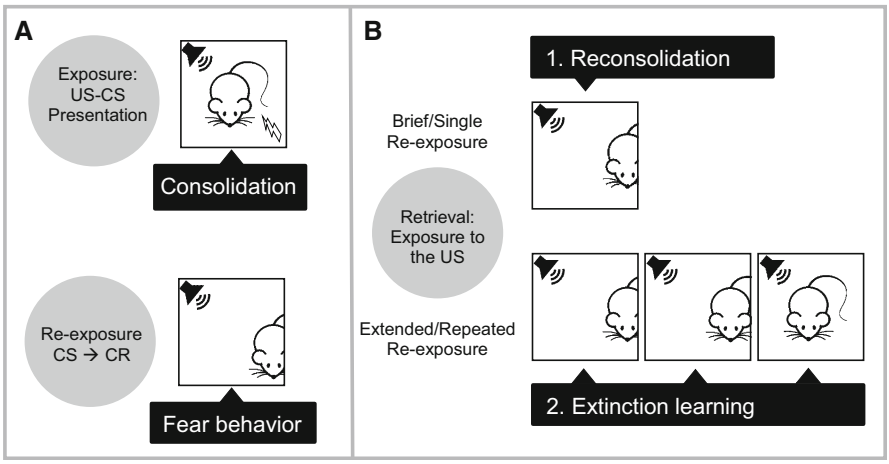


Fig. 1 A translational model to investigate trauma-related memories; a Pavlovian fear-conditioning paradigm. (**a**) An animal is exposed to a cue (tone), the conditioned stimulus (CS), followed by an aversive stimulus (shock), the unconditioned stimulus (US), several times. This US is an aversive stimulus and subsequently elicits fear behavior in the animals, the conditioned response (CR). This behavior represents a memory of the connection between the CS and the US, consolidation of the fear memory. During presentation of the CS without the US (re-exposure), the animal now exhibits fear behavior. A new (fear) memory is represented by a "memory trace" or "memory engram." (**b**) Depending on the frequency and duration of re-exposure, it can induce retrieval and reconsolidation of the primary memory trace or result in extinction learning. **1.** During brief re-exposure to the CS without US (re-exposure), the fear memory is retrieved and returned to its unstable state and subsequently restabilized (reconsolidation). When the memory is unstable, it is possible to integrate new information into the same memory trace. **2.** Extinction learning occurs if the duration or frequency of re-exposure is sufficient to induce extinction learning. Extinction learning does not affect the "old memory trace," but rather it creates a "new memory trace." Extinction learning results in decrease of fear behavior exposed by the animals by antagonizing the primary formed memory. Both reconsolidation and extinction learning can be involved in adaption of fear memory and behavior (CR) in animals after re-exposure

Consolidation, reconsolidation, and extinction learning have both common and distinct steps in their biological pathways (Miller and Sweatt 2006; Nader 2015; Suzuki et al. 2004). As consolidated memories become labile upon retrieval, novel information can update the strength and course of these consolidated memories; this process is reconsolidation (Miller and Sweatt 2006; Nader 2015). Extinction learning does not affect the "old memory trace" like in reconsolidation, but rather it creates a "new memory trace," and it is thought that the new memory antagonizes the previous formed fear memory (Berman and Dudai 2001; Quirk and Mueller 2008). The glutamatergic signaling pathway is important in synaptic plasticity and has a crucial role during several stages of learning such as consolidation, retrieval, reconsolidation, and extinction learning (Miller and Sweatt 2006; Quirk and Mueller 2008). More specifically, NMDA-receptor functioning has shown to be essential during all these phases of learning (Miller and Sweatt 2006; Quirk and Mueller 2008). Disruptions in NMDA signaling can lead to deficits, e.g., chronic stress exposure in rodents can disrupt NMDA-dependent hippocampal long-term potentiation (Shors et al. 1989). On the other hand, manipulating NMDA-receptor functioning after exposure to traumatic stress is a potential candidate mechanism to modify reconsolidation and extinction learning (Quirk and Mueller 2008). For example, the NMDA-receptor partial agonist D-cycloserine has shown to facilitate extinction learning and lead to an attenuated fear response (Quirk and Mueller 2008; Weber et al. 2007). On the other hand, NMDA-receptor antagonists can block reconsolidation but may also block extinction learning resulting in undesirable effects like prevention of extinction learning (Quirk and Mueller 2008). The duration of re-exposure (CS exposure see Fig. 1) to the fear cue determines whether the exposure will lead to reconsolidation or a shift to extinction. Suzuki et al. elegantly demonstrated in animals that the extent of re-exposure can lead to different learning mechanisms and opposite effects of NMDA-receptor antagonism. They showed that a 3-min re-exposure to a conditioned stimulus (CS) induced reconsolidation (Fig. 1), which could be blocked with an injection with a NMDA-receptor antagonist during the 3-min re-exposure (Suzuki et al. 2004). When mice were re-exposed to the CS for much longer, 30 min, the learning shifted to extinction. After a 30-min re-exposure, the animals would normally show reduced fear behavior, but injection of a NMDA-receptor antagonist prevented reduction of fear behavior and resulted in a blockade of extinction learning (Duclot et al. 2016; Suzuki et al. 2004). The potential dynamic of the NMDA receptor is complex since there are several binding sites for antagonistic compounds. Competitive antagonism at different bindings sites, like the glutamate or the glycine binding site, has been shown to block reconsolidation (Das et al. 2013; Nader 2015). Thus, pharmacological compounds that (temporarily) promote or inhibit the function of the NMDA receptor appear to be a promising strategy to attenuate fear memory either by facilitating extinction or blocking reconsolidation, respectively.

3 Treatment Opportunities of Combining Psychotherapy and Pharmacotherapy in PTSD

Evidence-based psychotherapies for PTSD are commonly divided as either trauma-focused or non-trauma-focused. A key element in trauma-focused psychotherapy is the exposure of the traumatic memory through speech, writing, or visualization. This is considered a common and essential intervention because it is responsible for the processing of traumatic memories (Schnyder et al. 2015). Targeting functional processes like extinction learning and desensitization are capable to reduce the fear response related to the traumatic memories (Garakani et al. 2006; Rauch et al. 2012). While both trauma-focused and non-trauma-focused psychotherapies are considered state-of-the-art treatments (Lancaster et al. 2016), almost all PTSD treatment guidelines recommend trauma-focused psychotherapies, and clinicians generally accept these as the most effective treatment strategy (Bisson et al. 2007; Rauch et al. 2012).

Several central nervous system (CNS)-penetrating agents, such as antidepressants and antipsychotics, are used as pharmacological treatments for patients with PTSD. Overall, the aforementioned drugs are hypothesized to exert their therapeutic effects by primarily modulating central monoaminergic neurocircuits (Casey 1997; Owens et al. 1997). Some of these drugs have additional effects on the autonomic nervous system (ANS) by either suppressing sympathetic activation or boosting parasympathetic activity (Casey 1997; Davidson 2015). These drugs influence clinical symptom clusters in PTSD such as anxiety, depressed mood and cognitive processes by modulating central monoaminergic circuits, and hyperarousal and sleep disruption via central and/or peripheral ANS effects in patients with PTSD (Davidson 2015). Yet these mechanisms are often insufficient for symptom relief in PTSD since these drugs alone or in different combinations have been shown to have only modest therapeutic effects when compared to psychotherapeutic interventions (Jonas et al. 2013; Lee et al. 2016). We argue that this might be partly due to the fact that these drugs do not target the key mechanism of the disorder, pathological memory formation (Yehuda and LeDoux 2007). Therefore, new strategies for pharmacotherapy that focus on pathological memory formation with pharmacological compounds, manipulating the excitatory glutamate system, seem to be very promising (Garakani et al. 2006; Rauch et al. 2012).

In everyday practice, it is common that patients are treated concurrently with psychotherapy and pharmacotherapy. However, it is not yet established on which of the treatments the efficacy is based (Hetrick et al. 2010). Moreover, therapeutic combinations involving both, therapy and current drugs (antidepressants and antipsychotics), have not been designed to target the etiopathophysiology of the disorder. Hence, new studies are needed to determine how psycho- and pharmacotherapy may have a synergistic effect. The possibility to manipulate consolidated traumatic memories (McGaugh 1966; Vermetten et al. 2014) may provide an opportunity to manipulate pathological memories even long after the incubation of PTSD. The addition of pharmacological compounds could target underlying memory mechanisms during psychotherapy and provide an opportunity to augment therapeutic

efficiency (see Fig. 3c, d) (Vermetten and Krugers 2016). Currently, patients undergo repeated exposure sessions to establish an improvement that is relying partly on extinction learning (Craske 2015). Pharmacological compounds could very well facilitate extinction learning that results in a faster reduction of the fear response (Quirk and Mueller 2008). Another intervention strategy in this respect is to block post-retrieval reconsolidation of a traumatic memory (Nader et al. 2013). Theoretically, blocking reconsolidation could lead to a faster reduction of symptoms in comparison with enhanced extinction learning (Nader 2015; Nader et al. 2013). It may be so that fear reduction could possibly be established just after one session, while several sessions are needed to achieve extinction learning.

The concept of enhancing or augmenting psychotherapy with pharmacotherapeutics is known as pharmacological or medication-assisted psychotherapy (Vermetten et al. 2014). Preclinical research has discovered several compounds with different receptor profiles (e.g., propranolol, cortisol, D-cycloserine, ketamine, oxytocin, and MDMA) that have been identified as potential candidates to enhance the effect of psychotherapy through several different mechanisms (Vermetten and Krugers 2016). This review focuses in particular on the possibility of ketamine to block reconsolidation of fear memories through NMDA-receptor antagonism. Furthermore, a background on ketamine as a CNS drug for augmenting psychotherapies in PTSD will be discussed.

4 Ketamine as a Central Nervous System Drug

4.1 Clinical Pharmacology of Ketamine

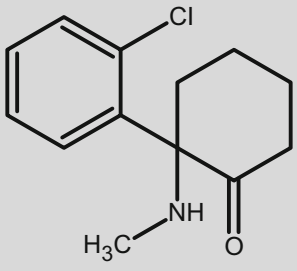
Ketamine is a pharmacological compound that was developed in the 1960s as an anesthetic agent (Domino et al. 1965). It easily crosses the blood-brain barrier (BBB) and affects a great variety of receptors. Ketamine often refers to a racemic mixture of two enantiomers, S(+)-ketamine and R(−)-ketamine, but is also available as S(+)-ketamine alone which is much more potent (Mion and Villevieille 2013). Demethylation of ketamine occurs within 2–3 min after IV infusion, and the metabolites (norketamine and hydroxynorketamine among others) have pharmacological properties as well. Relevant information about the chemical structure, pharmacokinetics, and pharmacodynamics is given in Box 1. Ketamine has a variety of dose-dependent pharmacodynamic effects on the human brain that are mediated through different receptors (Mion and Villevieille 2013; Oye et al. 1992). Its noncompetitive antagonism on the NMDA receptor is the most studied effect causing changes in opening time and opening frequency of the channel pore (Li and Vlisides 2016; Orser et al. 1997). When administered in subanesthetic dosages ($\leq$0.5 mg/kg), ketamine has an impact on mood, perception, and cognition (Bowdle et al. 1998; Krystal et al. 1994). Mood is first described to be flattened with some drowsiness, while with higher doses anxiety can occur (Li and Vlisides 2016). Ketamine can alter visual (heightened, dulled, and distorted), auditory, and tactile perception of the world and the self

(Bowdle et al. 1998; Pomarol-Clotet et al. 2006). Cognition can be affected by ketamine in a variety of ways, including vigilance and disrupted executive functioning (Krystal et al. 1994). Additionally, ketamine can induce referential thinking and delusions such as paranoia and subjective changes in thinking (Bowdle et al. 1998; Pomarol-Clotet et al. 2006). It was also shown that ketamine can induce amnesia (Oye et al. 1992) and disruption of recall (Krystal et al. 1994). Due to these effects, ketamine is used as a recreational drug especially among young people (Bearn and O'Brien 2015). Besides the central effects, ketamine has several systemic effects like increased heart rate and blood pressure through activation of the sympathetic ANS. All these effects are transitory and are dependent of time to peak concentration and elimination time (Kirby 2015; Li and Vlisides 2016).

Box 1: Pharmacological Structure, Pharmacokinetics, and Neuropharmacology of Ketamine

Chemical Structure

Ketamine is phencyclidine derivate (CI-581, 2-chlorophenyl-2-methylamino-cyclohexanone, $C_{13}H_{16}ClNO$) (Domino et al. 1965). Ketamine primarily existed of a racemic mixture of two enantiomers S(+)-ketamine and R(−)-ketamine. Where S(+)-ketamine has a CH3 group, R(−)-ketamine had H alone. Nowadays also S(+)-ketamine alone has become available. S(+)-ketamine is at least two times more potent compared to racemic ketamine (Mion and Villevieille 2013).



Chemical structure of S(+)ketamine

Pharmacokinetics

Ketamine is a lipid-soluble molecule with a large volume of distribution which rapidly crosses the blood-brain barrier (BBB). There is low binding of 10–40% to plasma proteins (Mion and Villevieille 2013). The bioavailability

(continued)

Box 1 (continued)

of ketamine is intramuscular 93%, oral 17–29%, and intranasal 8–45% (Li and Vlisides 2016). Via demethylation, approximately 80% of ketamine is metabolized into norketamine and 15% into 6-hydroxynorketamine (Woolf and Adams 1987). Subsequently, norketamine is metabolized by liver microsomal cytochrome P450. CYP3A4 is the major enzyme involved in ketamine's *N*-demethylation (Hijazi and Boulieu 2002). Demethylation of ketamine occurs within 2–3 min after injection of an intravenous (IV) bolus. Clearance of ketamine is high and it has an elimination halftime of 2–3 h (Domino et al. 1984). Norketamine is detectable after 2–3 min with a peak concentration after 30 min. The elimination of norketamine is slower than ketamine, and continuous IV administration of ketamine will result in an accumulation of norketamine (Mion and Villevieille 2013).

Pharmacodynamics

The primary central nervous system effects are thought to be mediated by binding on glutamate receptors (Mion and Villevieille 2013). The most known mechanism of action is the noncompetitive antagonism of the NMDA receptor through changes in opening time and opening frequency (Orser et al. 1997). The binding affinity for the NMDA receptor is high; Ki values are S(+)-ketamine 0.69 and for R(−)-ketamine 2.57 (Moaddel et al. 2013). Binding affinity for dopamine d2 receptor (Ki value =0.5 μM) and serotonin 5-HT2 receptor (Ki value = 15 μM) has been found within the pharmacological relevant range (Kapur and Seeman 2002). Ketamine also has the potential to bind to others (non-glutamate receptors) such as monoaminergic, cholinergic, opioid, muscarinic, and nicotinic receptors although with a much lower binding affinity (Mion and Villevieille 2013). Furthermore, metabolites of ketamine, such as norketamine and hydroxynorketamine, have pharmacological properties as well. For example, (S)-norketamine has a high affinity for the NMDA receptor, Ki value 2.25 (Moaddel et al. 2013).

Ketamine is used for anesthesia, for analgesia, and more recently for psychiatric disorders like depression. It is not yet completely clear which part of the effect is established by ketamine and which part by its metabolites. Norketamine is thought to be involved in nociception but has a three times smaller effect compared to ketamine (Li and Vlisides 2016). Recently hydroxynorketamine has been showed to be responsible for the antidepressant effect through binding on the AMPA receptors (Zanos et al. 2016).

Dosage depends strongly on the indication. Anesthesia is induced with dosages that range from 1 to 4.5 mg/kg IV, and a coma can be maintained with repeated dosages of 0.5–1 mg/kg IV. Because a coma is not induced by ketamine, 0.5 mg/kg IV is considered a subanesthetic dose (Li and Vlisides 2016).

4.2 Ketamine in Search of an Indication in Psychiatry

Because of its psychotropic effects (Krystal et al. 1994) and its ability to easily cross the BBB (Peltoniemi et al. 2016), research of ketamine has expanded to the field of psychiatry. Due to its effect on cognition and perception, ketamine can mimic psychosis-like symptoms and be used as a model of schizophrenia in healthy individuals without a prior or current history of psychotic disorder (Domino and Luby 2012). Increased interest in the use of ketamine as a potential treatment for psychiatric disorders emerged after the discovery of NMDA-receptor antagonism reversing depressive-like behaviors in animals (Papp and Moryl 1994; Przegalinski et al. 1997; Trullas and Skolnick 1990). Only two decades ago, Berman et al. published the first paper about the rapid effects of ketamine on patients with depressive episodes (Berman et al. 2000). They showed that a single IV infusion of 0.5 mg/kg ketamine resulted in greater reduction of depressive symptoms compared to placebo (Berman et al. 2000). This was replicated by Zarate et al. with a second randomized controlled trial who reported the antidepressant effect lasted for 1 week (Zarate et al. 2006). Since then, research on ketamine as a treatment strategy for depression has greatly expanded (Caddy et al. 2014). To extend the durability of the antidepressant effect, the protocol has been adjusted with repeated IV infusion of ketamine instead of a single IV infusion. A study using this protocol reported a prolonged effect of more than 2 weeks (18 days) (Murrough et al. 2013b). Although many studies (RCTs with passive and active placebo, open-label studies, case reports) published that ketamine exerts a rapid effect on symptom reduction (Caddy et al. 2014), the most recent meta-analysis concluded that this evidence is quite promising but limited due to risk of bias and small study samples (Caddy et al. 2015). In addition to the interest in ketamine as treatment for depression, studies have started to investigate the potential of ketamine as an acute treatment for suicidal ideation. The first reports are positive and these studies conclude a beneficial effect (Mallick and McCullumsmith 2016; Murrough et al. 2015; Price et al. 2009). Although a lot of research has already been performed, more research is needed to strengthen the evidence on ketamine as therapeutic drug in mood disorders and suicidal ideations. This research needs to address the question about optimal dosing and route of administration in order to establish a prolonged and sustained effect. Additionally, it should aim to unravel the underlying biological mechanism through which ketamine exerts its effect on mood symptoms. New insights have shown that the antidepressant effect of ketamine is partially mediated through its metabolite hydroxynorketamine, which appears to be NMDA receptor independent and accomplished through the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor (Zanos et al. 2016). Via this type of research, a more targeted treatment approach with fewer side effects could be developed.

4.3 Single IV Infusion of a Subanesthetic Dose Ketamine as Treatment in PTSD

In 2014 Feder et al. published the first randomized controlled trial using ketamine as treatment in patients with PTSD. In this proof of concept study, they compared a single IV infusion of racemic ketamine of 0.5 mg/kg for 40 min with IV midazolam as active comparator in 41 patients (Feder et al. 2014). The protocol used for this symptom-focused study is similar to the first studies that investigated the effect of ketamine on depression (R. M. Berman et al. 2000; Murrough et al. 2013a). Feder et al. reported a rapid and significantly increased improvement of PTSD symptoms in patients who received ketamine compared to midazolam. Reduction of subjective stress was measured 24 h after infusion with a self-report questionnaire (Impact of Event Scale – Revised). This questionnaire used subscales on symptoms of intrusion, avoidance, and hyperarousal. The reduction was significant for all three subscales. As patients with PTSD often suffer from comorbid depression, the study also discussed the effect of ketamine on depressive symptoms. They showed that ketamine infusion resulted in a significantly larger reduction in comorbid depressive symptoms when compared to midazolam. It is important to note that baseline depressive symptoms and the effects of treatment on depressive symptoms did not predict the effect of ketamine on PTSD symptoms. Therefore, Feder et al. argued that the improvement in symptoms of PTSD was not due to the effect on comorbid depressive symptoms (Feder et al. 2014). Supportive evidence exists from three case reports that demonstrated that ketamine decreases symptoms of PTSD in patients for a period up to 2 weeks (D'Andrea and Andrew Sewell 2013; Donoghue et al. 2015; Womble 2013). Another group highlighted the effect of ketamine on PTSD symptoms with a subanalysis of comorbid PTSD in patients with depression (Zeng et al. 2013).

An important contribution of the Feder study is that they were the first to show that ketamine is safe and well tolerated in the treatment of PTSD. They do report transient dissociative symptoms (Feder et al. 2014). This is specifically important because ketamine can induce (in a dose-dependent manner) dissociative symptoms and paranoid thoughts, which are symptoms reported by many patients with PTSD. However, it is not reported to what extent patients already experienced dissociative or cognitive symptoms at baseline. Furthermore, it should be noted that the Feder study is performed with racemic ketamine (mixture of both enantiomers S(+)-ketamine and R(−)-ketamine) and that side effects might be more prominent if only S(+)-ketamine would have been used (Peltoniemi et al. 2016). To strengthen these first promising results, a replication study is needed. The Feder study raises questions concerning the underlying mechanisms. Are these effects mediated solely through NMDA-receptor antagonism and how does it affect pathological memory formation? Additional studies need to answer these questions.

4.4 The Effects of Ketamine on Memory, Development of Memory, and Stress Disorders

The impact of ketamine on the different stages of memory formation in humans has not been systematically addressed. There is some circumstantial evidence on the relationship between ketamine and its effect on memory and stress in humans from retrospective observation studies in battlefield anesthetics (McGhee et al. 2008, 2014). They initially reported that perioperative use of ketamine would protect against the development of PTSD. However, in a larger study, this was not replicated, and they concluded that perioperative ketamine did not protect against acute and delayed stress symptoms (McGhee et al. 2008, 2014). On the other hand, another group reported that perioperative ketamine would even lead to a higher percentage of PTSD symptoms (Schonenberg et al. 2005). These studies could potentially give information whether ketamine can promote or inhibit memory consolidation. However, interpretation is difficult because the exact time window between the traumatic event (and thus the start of consolidation of the memory) and the administration of ketamine is not mentioned. Even though another study showed elevated symptoms of acute stress (dissociation, reexperiencing, hyperarousal, avoidance) 3 days after administration of perioperative ketamine, it is difficult to interpret this effect as an effect on traumatic memory due to the dissociative side effects (Schonenberg et al. 2008). Due to this conflicting evidence, the relation of perioperative ketamine administration after trauma and PTSD symptomology linked to pathological memories remains unclear. However, these studies did identify that something profound is going on with ketamine treatment after traumatic events, which is emphasized by a qualitative study that interviewed clinicians who used ketamine as an anesthetic (Wilson and Pokorny 2012). To obtain better knowledge about the effect of ketamine on human memory formation, dose-range studies during specific stages need to be performed.

5 Novel Use of Ketamine to Target Traumatic Memories in PTSD

5.1 Ketamine Targeting Pathological Memory Formation

The different stages of memory formation provide several treatment targets for PTSD and can be distinguished as the event-based "golden hours" and exposure-based "golden hours" (Fig. 2) (Vermetten and Krugers 2016). The event-based "golden hours" provide an opportunity to investigate the potential of ketamine as primary or secondary prevention of PTSD in high-risk groups. Thus, can ketamine

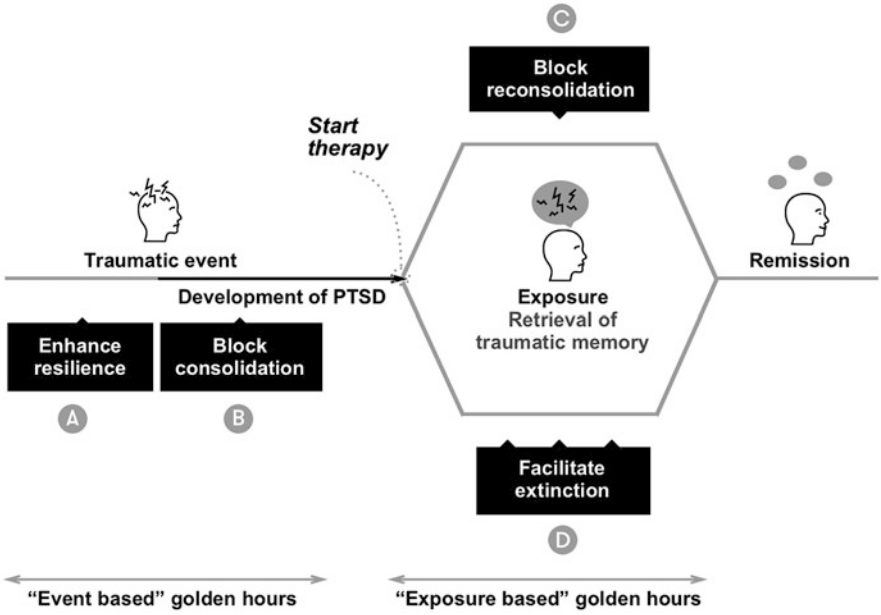


Fig. 2 This figure illustrates the development of traumatic memories over time. Four time points are identified for potential pharmacological interference with traumatic memory (formation). A. Prior to the exposure and formation of the traumatic memory, the compound could enhance resilience. B. Directly after exposure of a traumatic event, consolidation of the traumatic memory can be blocked. C. Blocking of reconsolidation directly after exposure within the time window of 0–6 h. D. Facilitation of extinction learning of traumatic memories

enhance resilience prior to a traumatic event or alter consolidation directly after a traumatic event?

A proof-of-mechanism study in mice showed the potential of ketamine to *enhance resilience* (Fig. 2A) to a stress exposure (Brachman et al. 2016; McGowan et al. 2017). They reported that injection of a subanesthetic dosage of ketamine prior to exposure of the CS + US in a fear-conditioning paradigm (Fig. 1) (in addition to the obvious effects on US perception) reduced fear behaviors in mice (McGowan et al. 2017). It was shown that this protective effect was only present within a specific time window. Injection of ketamine 1 week before CS + US exposure also enhanced resilience. However, injection of ketamine 1 h or 1 month before CS + US exposure did not result in this protective effect (McGowan et al. 2017). Furthermore, it is reported that the effect lasted beyond the half-life period of ketamine (Brachman et al. 2016; McGowan et al. 2017). Therefore the authors suggested that ketamine treatment might be implemented as a vaccine-like strategy in high-risk groups (Brachman et al. 2016; McGowan et al. 2017). The exact time window of this putative protective effect in humans would need to be more carefully investigated. For a successful translation of this approach to enhance resilience with ketamine, many other aspects, such as the dosage and dissociative side effects, need to be

carefully considered. Administration of ketamine directly after the traumatic event, within *the window of consolidation* (Fig. 2B), is another opportunity. However preclinical studies show inconsistent result of the effect that ketamine administration has on consolidation of fear memories (Groeber Travis et al. 2015; Ito et al. 2015; Juven-Wetzler et al. 2014; Suzuki et al. 2004). Due to this conflicting evidence, it is currently too early to implement ketamine as an effective prevention strategy for adverse memory formation after a traumatic event. Possible preclinical studies in healthy humans could help to determine the effect of ketamine on consolidation of fear-related and emotional memory.

Another novel and promising approach is to implement ketamine in trauma-focused psychotherapies for PTSD, during exposure-based "golden hours" (Fig. 2). During reconsolidation and extinction learning, NMDA-receptor functioning is essential. We argued in Sect. 3 that *blocking reconsolidation* (Fig. 2C) might have a more rapid effect compared to *facilitation of extinction learning* (Fig. 2D). There is convincing evidence that NMDA-receptor antagonism blocks reconsolidation in preclinical studies (Das et al. 2013; Duclot et al. 2016; Suzuki et al. 2004). Via antagonistic binding to the NMDA receptor, ketamine has the potential to adapt NMDA-receptor functioning (Orser et al. 1997). Therefore, we hypothesize that targeting reconsolidation of pathological memory formation with ketamine during the exposure-based "golden hours" is a potential treatment strategy for PTSD.

To our knowledge, only a few preclinical studies have investigated the effect of ketamine on reconsolidation in a fear-conditioning paradigm in rodents (Duclot et al. 2016; Honsberger et al. 2015). Honsberger et al. found that an injection of ketamine directly after re-exposure did not lead to reduction of fear behavior in an auditory fear memory paradigm (Honsberger et al. 2015). However, Duclot et al. showed that ketamine administration directly after re-exposure induced disruption of contextual fear memory and led to a reduction of fear behavior. This study also showed that the reduction of fear is dependent on the dosage of ketamine. A lower dose would lead to fear reduction, whereas a higher dose of ketamine would not. This study showed that ketamine is effective in blocking reconsolidation of fear memory in rodents in an inverted U-shaped dose-response manner (Duclot et al. 2016). Girgenti et al. also reported about their experiments with ketamine in a fear extinction paradigm. Results showed that ketamine administration before re-exposure of 30 s reduced fear behavior in animals (Girgenti et al. 2017). However, this study remains inconclusive whether this effect is due to blocking reconsolidation or facilitation of extinction. Most evidence reports that extinction learning requires NMDA-receptor functioning (Quirk and Mueller 2008), and Suzuki et al. reported that re-exposure paradigm of 3 min induces reconsolidation (Suzuki et al. 2004). Therefore, we argue that it seems more feasible that the effect that Girgenti et al. showed is the result of NMDA-receptor-dependent blockade of reconsolidation. Preliminary results in nonhuman primates also showed a reduction of fear behavior after ketamine was administered during the reconsolidation phase (Philippens et al. 2017). These studies trigger the demand to investigate the effect of ketamine on reconsolidation of fearful memories in humans and, more specifically, to answer the question if ketamine is

able to block reconsolidation of traumatic memories in patients with PTSD in relation to re-exposure during psychotherapy.

Ketamine is a promising candidate in the strategy of pharmacological assisted psychotherapy. Ketamine may indeed be able to reinforce the effect of psychotherapies. Patients might experience lower stress levels during therapy, and dropout rates could potentially be reduced. As far as we know, no studies have been performed with ketamine as additional treatment during trauma-focused psychotherapy. At the time of writing, two clinical trials are registered for the investigation of ketamine in combination with psychotherapy (The Cooper Health System n.d.).

In the next section, the steps that need to be taken to use ketamine as a method to specifically target pathological memory via reconsolidation are discussed.

5.2 *How to Investigate Ketamine-Assisted Psychotherapy for PTSD That Targets Reconsolidation*

Evidence that ketamine can modulate traumatic memory is predominantly circumstantial and originates mainly from preclinical animal data (Sect. 5.1) and retrospective observational studies in humans (Sect. 4.4). The implementation of ketamine as a viable pharmacological strategy to enhance psychotherapies in PTSD therefore requires further evaluation. To illustrate this point, the NMDA-receptor agonist D-cycloserine has recently been proposed as a promising candidate for pharmacologically augmented fear extinction during trauma-focused psychotherapy for PTSD (Rothbaum et al. 2014). Although numerous studies with D-cycloserine have been conducted, they lack methodological standardization such as dose selection, timing of administration relative to the psychotherapeutic invention, and primary outcome parameters; for review, see Mataix-Cols et al. (2017). Together, these issues contribute to wide range of compelling findings among research groups (for instance, post hoc classifications of good and bad therapy session response) and raise questions regarding its reliability, as a consequence, limited applicability in research and clinical practice. Thus the D-cycloserine case illustrates that designing a study to investigate pharmacologically augmented fear extinction during psychotherapy is not straightforward, since the compound's pharmacology, the psychotherapeutic intervention, and the functional CNS processes that underlie memory formation that are targeted all need to be considered.

In this context, ketamine can be conceived of as a novel pharmacological compound for the treatment of PTSD in general and the modulation of pathological traumatic memories in particular. As a consequence, a systematic approach is needed to assess its pharmacodynamic effects in relation to both psychotherapy and its pharmacokinetics prior to its application in patient populations. The "question-based drug development" approach has been proposed as a model to explore such aspects for novel drugs (Cohen et al. 2015). This approach consists of six questions that systematically address the most relevant aspects during drug development of a novel

pharmacological treatment (Cohen et al. 2015). In addition, we formulated five topics that need to be addressed concerning the psychotherapeutic approach and phase orientation of pharmacological assisted psychotherapy (see Box 2). We believe that addressing these questions and topics represents a crucial step in designing a study for drug-assisted psychotherapy, which systematically addresses below.

Box 2: Five Essential Topics for Designing Pharmacological Assisted Psychotherapy, in Addition to the "Question-Based Drug Development" Approach

Concerning the psychotherapeutic intervention

- Describe the therapeutic process that is targeted with the medication (*memory processing).
- Outline the psychotherapeutic approach for the combined approach (*trauma-focused psychotherapy).
- Define the essential therapy conditions in order to affect the target process (*prediction error, proper amount of emotional involvement).

Concerning phase orientation

- Define the timing of drug administration in relation to the psychotherapeutic intervention (*after retrieval of the traumatic memory within the reconsolidation window).
- Define the proper frequency of the combined intervention (*hypothesized one time, since repeated infusion might prevent extinction).

*Short answers for ketamine-assisted psychotherapy to block reconsolidation which is extensively explained in Sect. 5.4.

5.3 *"Question-Based Drug Development" Approach*

5.3.1 Does Ketamine Reach the Site of Action?

When administered intravenously in humans, ketamine has a high bioavailability, readily crosses the BBB, and dose-dependently induces transient psychomimetic effects in healthy humans (Krystal et al. 1994) and patients with mood disorders (Berman et al. 2000; Feder et al. 2014) around the maximal ketamine plasma concentration (Cmax) (Kleinloog et al. 2015). In addition, ketamine displays relatively high in vitro binding affinity for the NMDA receptor (see Box 1), with S(+)-ketamine having a higher affinity than R(−)-ketamine or the racemic mixture. Together, these findings provide confidence that ketamine reaches the NMDA receptors located within the CNS. It should be noted though that ketamine's active metabolites norketamine and hydroxynorketamine have also been demonstrated to have CNS effects. In fact, they have been implicated to contribute to both

the antidepressant and the nociceptive effects of ketamine (Box 1) (Mion and Villevieille 2013; Zanos et al. 2016). The exact extent to which the pharmacodynamic effects of ketamine in humans can be attributed to ketamine itself or to these metabolites still remains to be established and is subject to ongoing investigation.

5.3.2 Does Ketamine Exert an On-Target Pharmacological Effect?

For ketamine to effectively block reconsolidation of traumatic memories, it relies on its properties as central NMDA-receptor antagonist and possibly on some of its active metabolites, such as norketamine (Moaddel et al. 2013) (Box 1). Several potentially viable pharmacological biomarkers for NMDA-receptor antagonism have been suggested in literature. For example, gamma-band electroencephalography (EEG) has been proposed as a putative translational biomarker for antagonism of the NMDA receptor (Sanacora et al. 2014). In addition, in healthy volunteers ketamine demonstrates concentration-dependent decreases in saccadic peak velocity and smooth pursuit eye movements and increases of the total Positive and Negative Syndrome Scale (PANSS) (Kleinloog et al. 2015). Taken together, several candidate biomarkers for NMDA-receptor antagonism exist which may be applied to quantify ketamine's NMDA-receptor antagonistic properties in health and disease.

5.3.3 Does Ketamine Display Off-Target Pharmacological Effects?

Ketamine and its metabolites can bind to several non-glutamate receptors which may result in off-target pharmacological effects. Binding affinity for other receptors than the NMDA-receptor is generally much lower and can therefore be considered pharmacologically irrelevant (Hirota et al. 2002; Moaddel et al. 2013), with the exception of the dopamine 2 receptor (D2) and serotonin 5-HT2 receptor (Kapur and Seeman 2002). Ketamine is associated with concentration-dependent increases in peripheral serum prolactin (Kleinloog et al. 2015). Since prolactin release is modulated by dopamine in central tuberoinfindibular projections, these findings suggest that ketamine has potent D2 antagonistic properties. Ketamine is associated with the occurrence of transient increases in both systolic and diastolic blood pressure. The precise mechanism however is poorly understood and assumed to result from centrally mediated ANS activation.

5.3.4 Does Ketamine Display On-Target Pathophysiological Effects?

Central to this question is whether ketamine modulates memory reconsolidation by antagonizing the NMDA receptor and by doing that can enhance the effect of psychotherapy in PTSD. Preclinical research has shown that ketamine can block reconsolidation in rodents (Duclot et al. 2016) and nonhuman primates (Philippens et al. 2017). Investigators observed a reduction of fear behavior in a contextual fear

paradigm and concluded that reconsolidation of the fear memory was blocked. Whether ketamine can block reconsolidation of fear memory in humans is yet to be studied. No reliable biomarker that quantifies the disruption of memory reconsolidation by an intervention, whether psychotherapeutic or pharmacological, yet exists and will need to be developed. The on-target pathophysiological response in patients with PTSD to ketamine would be the reduction of fear related to the traumatic memory, which is most commonly measured with questionnaires. An elegant example of a stepped approach is the study by the group of Kindt investigating the effect that propranolol (noradrenergic β-blocker) has on reconsolidation (Kindt et al. 2009; Soeter and Kindt 2015). First a fear-conditioning model induced emotional (fear) memories in healthy human subjects, by applying painful shocks related to specific visual cues. They showed that after re-exposure to these specific cues, reconsolidation of the (fear) memories can be blocked by propranolol administration (Kindt et al. 2009; Schwabe et al. 2012). They measured fear reduction with the startle response, which is one of the most robust biological methods to measure fear in healthy humans (Kindt et al. 2009). For the next step, they successfully translated these results for patients with spider phobia. They showed if patients are treated with propranolol concurrent with exposure to real spiders, patients displayed a reduction of fear behavior toward real spiders. Thus this study elegantly showed that propranolol blocked reconsolidation of fear memories in patients with spider phobia (Soeter and Kindt 2015). An important next step now is to investigate if propranolol can block reconsolidation of traumatic memories in PTSD (Brunet et al. 2008; Kindt and van Emmerik 2016). Thus, a fear memory paradigm in healthy humans provides a more objective marker to determine if ketamine can indeed block reconsolidation of human memories and will help to determine the on-target pharmacological effect in patients with PTSD.

5.3.5 Does Ketamine Have Any Off-Target Pathophysiological Effects?

Ketamine has a high in vitro affinity for the central D2 receptor (see Box 1) and induces transient increases in systolic and diastolic blood pressure. D2-mediated sustained hyperprolactinemia with antipsychotic drugs is associated with the occurrence of untoward effects such as galactorrhea and sexual dysfunction (Bostwick et al. 2009). However, since the incidental administration of ketamine during psychotherapy in PTSD is not expected to result in sustained hyperprolactinemia, unwanted clinical symptoms are not anticipated. Also, transient blood pressure elevations are not expected to cause safety issues, provided that PTSD patients with hypertension are carefully selected and blood pressure is monitored during trials with ketamine. Both clinicians and patients should be aware that ketamine is an addictive drug that has a strong potential to be abused (Kirby 2015). This is specifically important since numbers of substance abuse are high in patients with PTSD (Kessler et al. 1995).

5.3.6 What Is Ketamine's "Therapeutic Window" for Pharmacologically Assisted Psychotherapy Targeting Reconsolidation?

The most frequently applied dosing regimen for both depression and PTSD currently is 0.5 mg/kg ketamine over 40 min (Feder et al. 2014; Zarate et al. 2006). Notably, these dosages are based on consensus derived from clinical experience with ketamine in depression research and dose-ranging studies with ketamine as anesthetic agent (Berman et al. 2000; Domino et al. 1984; Zarate et al. 2006). In addition a single study in depression demonstrated similar antidepressant effects for both the 0.2 and 0.5 mg/kg dose (Singh et al. 2016). Together, these findings raise the issue of dose selection for pharmacologically assisted psychotherapy that targets reconsolidation in PTSD. Moreover, an inadequate dose may be associated with no effect, while supratherapeutic doses may be associated with burdensome side effects or loss of effect due to a specific stimulatory effects and/or dissociative symptoms that might obscure desirable effects on memory. It is not yet known what the required dose is to block reconsolidation of a memory and more specifically of traumatic memory in PTSD.

The issues raised by this question-based approach might challenge researchers to think thoroughly about the design of studies with ketamine in PTSD. We emphasize the benefits of a stepped approach to first investigate the potential of ketamine to block reconsolidation in healthy humans with a fear memory paradigm. This provides an opportunity to determine if ketamine can indeed block reconsolidation of memories in humans in a controlled setting. During this experiment, it might be considered to add a dose-ranging element in order to determine the plasma concentration that is required to block reconsolidation of memories in healthy humans. Simultaneously the occurrence of side effects can be monitored for these plasma concentrations. A subsequent step is to examine if reconsolidation of traumatic memories can be blocked after re-exposure during psychotherapy in patients with PTSD. Notably, the sensitivity to ketamine and the robustness of the traumatic memories in patients with PTSD can differ greatly from trauma controls. An important step is to determine the sensitivity of patients with PTSD to ketamine, compared with the sensitivity of healthy controls. EEG or saccadic peak velocity and smooth pursuit eye movements combined with the PANSS might be considered as biomarkers for the on-target effects of NMDA-receptor antagonism (Kleinloog et al. 2015; Mion and Villevieille 2013; Sanacora et al. 2014). These biomarkers can be helpful to determine the differences in sensitivity by measuring NMDA-receptor antagonism of ketamine in patients with PTSD and compare the results with healthy controls. When done for various doses and plasma concentrations, this provides information on how to translate results from a fear-conditioning paradigm in healthy humans to a study design for patients with PTSD. The results from a healthy subject design can also be useful for other specific anxiety disorders, which are somewhat easier to investigate due to less generalization of fear and more straightforward retrieval of memories. Thus, a stepped approach to unravel the optimal dosing for

blockade of reconsolidation can be helpful before implementing ketamine as additional treatment during psychotherapy in patients with PTSD. Remaining topics that need to be addressed for pharmacological assisted psychotherapy concern the psychotherapeutic approach and phase orientation of both interventions, and these will be discussed in the next paragraph.

5.4 Ketamine Embedded in a Psychotherapeutic Process

To investigate if ketamine has an effect on reconsolidation of traumatic memories, it is important to expand the scope from the "question-based drug development" approach and consider also clinical aspects of pharmacological assisted psychotherapy. Researchers need to carefully think about how to best optimize the psychotherapeutic process and how medication and therapy may fit for optimal effect. A proper framework to carefully design studies that investigate medication-assisted psychotherapy is missing. We formulated five topics that need to be addressed in any study design of medication-assisted psychotherapy, also for ketamine-assisted psychotherapy. These issues need to be framed.

5.4.1 Describe the Therapeutic Process That Is Targeted with the Medication

For ketamine this is memory processing. With ketamine the goal is to change the memory engram of the consolidated traumatic memory by interfering with reconsolidation. It also may have an additional effect on affective processing, since the memories may be revisited in a slightly less fearful state, allowing more ease to revisit them. Perhaps we do not know enough yet to make a clear-cut distinction between manipulations of reconsolidation as opposed to extinction learning in current psychotherapies.

5.4.2 Outline the Psychotherapeutic Approach for the Combined Approach

For ketamine a trauma-focused psychotherapy is preferred. All specific techniques that are essential for re-exposure to the traumatic memory can be used, CPT, EMDR, or other exposure-based interventions. There are several protocols that describe these techniques (Schnyder et al. 2015).

5.4.3 Define the Essential Therapy Conditions in Order to Affect the Target Process

During re-exposure the aim is to retrieve and destabilize the traumatic memory. Only then it is possible to update the memory engram or interfere with subsequent

reconsolidation. Memory "de"stabilization can occur merely under the circumstances that there is something new to learn during retrieval (Sevenster et al. 2012). Based on prior experience and patterns of response, the brain expects (or predicts) what will happen with a certain stimulus or situation. A memory enters the unstable (labile) phase in the case that the outcome of "what is about to happen" is not fully predictable (Krawczyk et al. 2017). For that reason the time and the magnitude of the exposure should be planned in a proper way in order to be able to block reconsolidation of the memory. Yet, the intensity/quantity of emotional involvement of patients during exposure needs to be addressed in order for this strategy to be well evaluated; over-involvement could lead to dissociation and anxious flashbacks, while under-involvement may lead to avoidance. An experienced therapist is able to establish balanced and well-tolerated spot-on exposure and prevent avoidance, which would be preferred over a more standardized design, such as listening to a tape of the traumatic event when cognitive avoidance may be more likely to occur. To identify the right "hot spots" for retrieval and destabilization of traumatic memories in PTSD is quite a task, and to establish the right dose of exposure in such a study could perhaps prove to be one of the most challenging aspects. Since our therapeutic strategy targets reconsolidation of traumatic memories, a critical parameter is that a significant level of distress in patients should originate from these intrusive traumatic memories and flashbacks. Notably, this strategy may not necessarily need to affect all symptoms of PTSD, like feelings of distrust and guilt that are often reported in patients.

5.4.4 Define the Timing of Drug Administration in Relation to the Psychotherapeutic Intervention

In this strategy it concerns the relation between timing of ketamine administration and opportunity of proper reconsolidation of the memory. There is some evidence that NMDA-receptor antagonism by ketamine can interfere with (or even prevent) retrieval of the memory (Milton et al. 2013), and therefore ketamine should not be administered before retrieval, thus not before exposure. In addition, the time-specific nature of the reconsolidation window needs to be taken into account, which is generally considered 0–6 h after retrieval (Nader et al. 2000). These aspects together with the pharmacological knowledge of ketamine (Tmax, elimination time, effect of metabolites, etc.) determine the best timing of administration.

5.4.5 Define the Proper Frequency of the Combined Intervention

The frequency of administration relies on the clinical goals. Overall, this strategy aims to make psychotherapies for PTSD more effective, e.g., an increased symptom reduction or obtaining a more robust and sustainable effect. It can be argued that one exposure session and a single infusion of ketamine should be investigated first. In this way, the effect of ketamine on reconsolidation of memory after exposure can be

identified. However, reintegration sessions, independent of ketamine-assisted re-exposure session, are also important to integrate new learning into the patient's life. On another note, assuming that NMDA-receptor antagonism blocks extinction learning and if ketamine is integrated in multiple sessions, long-term studies can also induce undesirable effects. At this moment, there is no empirical evidence for the frequency in a psychotherapeutic approach.

6 Conclusion

To improve the treatment of PTSD, research should focus on targeting one of the core pathophysiological mechanisms, disrupted memory formation. Targeting NMDA receptors by using ketamine can be effective to change the retention of emotional and traumatic memories. There are promising first results for ketamine infusion without memory retrieval in PTSD. We argue that ketamine infusion after memory retrieval to block reconsolidation is another promising strategy for the treatment of PTSD. We propose the "question-based drug development plan" and the additional five topics as a framework for developing medication-assisted psychotherapy. By using this framework for ketamine-assisted psychotherapy to block reconsolidation in patients with PTSD, we showed that ketamine has potential but as well the gaps in the knowledge that need to be investigated. Additional preclinical research is needed to expand the understanding of the contribution of the NMDA receptor in the modulation, acquisition, and storage of memories for traumatic events before and after consolidation. This information will help to clarify whether targeting NMDA receptors with ketamine can indeed successfully contribute to the treatment of patients with PTSD.

Acknowledgments We are grateful to Dr. A. Feder and J. Boonstra for their insightful comments. We are grateful to Elien Phernambucq for her support in designing the illustrations.

References

Bearn J, O'Brien M (2015) "Addicted to euphoria": the history, clinical presentation, and management of party drug misuse. Int Rev Neurobiol 120:205–233. https://doi.org/10.1016/bs.irn.2015.02.005

Berman D, Dudai Y (2001) Memory extinction, learning anew, and learning the new: dissociations in the molecular machinery of learning in cortex. Science 291(5512):2417–2419. https://doi.org/10.1126/science.1058165

Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, Krystal JH (2000) Antidepressant effects of ketamine in depressed patients. Biol Psychiatry 47(4):351–354

Bisson JI, Ehlers A, Matthews R, Pilling S, Richards D, Turner S (2007) Psychological treatments for chronic post-traumatic stress disorder. Systematic review and meta-analysis. Br J Psychiatry 190:97–104. https://doi.org/10.1192/bjp.bp.106.021402

Bostwick JR, Guthrie SK, Ellingrod VL (2009) Antipsychotic-induced hyperprolactinemia. Pharmacotherapy 29(1):64–73. https://doi.org/10.1592/phco.29.1.64

Bowdle TA, Radant AD, Cowley DS, Kharasch ED, Strassman RJ, Roy-Byrne PP (1998) Psychedelic effects of ketamine in healthy volunteers: relationship to steady-state plasma concentrations. Anesthesiology 88(1):82–88

Brachman RA, McGowan JC, Perusini JN, Lim SC, Pham TH, Faye C et al (2016) Ketamine as a prophylactic against stress-induced depressive-like behavior. Biol Psychiatry 79(9):776–786. https://doi.org/10.1016/j.biopsych.2015.04.022

Brunet A et al (2008) Effect of post-retrieval propranolol on psychophysiologic responding during subsequent script-driven traumatic imagery in post-traumatic stress disorder. J Psychiatr Res 42 (6):503–506

Caddy C, Giaroli G, White TP, Shergill SS, Tracy DK (2014) Ketamine as the prototype glutamatergic antidepressant: pharmacodynamic actions, and a systematic review and meta-analysis of efficacy. Ther Adv Psychopharmacol 4(2):75–99. https://doi.org/10.1177/2045125313507739

Caddy C, Amit BH, McCloud TL, Rendell JM, Furukawa TA, McShane R et al (2015) Ketamine and other glutamate receptor modulators for depression in adults. Cochrane Database Syst Rev 9:CD011612. https://doi.org/10.1002/14651858.CD011612.pub2

Casey DE (1997) The relationship of pharmacology to side effects. J Clin Psychiatry 58 (Suppl 10):55–62

Cohen AF, Burggraaf J, van Gerven JMA, Moerland M, Groeneveld GJ (2015) The use of biomarkers in human pharmacology (phase I) studies. Annu Rev Pharmacol Toxicol 55:55–74. https://doi.org/10.1146/annurev-pharmtox-011613-135918

The Cooper Health System. TIMBER psychotherapy and ketamine single infusion in chronic PTSD. https://ClinicalTrials.gov/show/NCT02766192

Craske M (2015) Optimizing exposure therapy for anxiety disorders: an inhibitory learning and inhibitory regulation approach. Verhaltenstherapie 25(2):134–143

D'Andrea D, Andrew Sewell R (2013) Transient resolution of treatment-resistant posttraumatic stress disorder following ketamine infusion. Biol Psychiatry 74(9):e13–e14. https://doi.org/10.1016/j.biopsych.2013.04.019

Das RK, Freeman TP, Kamboj SK (2013) The effects of N-methyl D-aspartate and B-adrenergic receptor antagonists on the reconsolidation of reward memory: a meta-analysis. Neurosci Biobehav Rev 37(3):240–255. https://doi.org/10.1016/j.neubiorev.2012.11.018

Davidson J (2015) Vintage treatments for PTSD: a reconsideration of tricyclic drugs. J Psychopharmacol 29(3):264–269. https://doi.org/10.1177/0269881114565143

Domino EF, Luby ED (2012) Phencyclidine/schizophrenia: one view toward the past, the other to the future. Schizophr Bull 38(5):914–919. https://doi.org/10.1093/schbul/sbs011

Domino EF, Chodoff P, Corssen G (1965) Pharmacologic effects of Ci-581, a new dissociative anesthetic, in man. Clin Pharmacol Ther 6:279–291

Domino EF, Domino SE, Smith RE, Domino LE, Goulet JR, Domino KE, Zsigmond EK (1984) Ketamine kinetics in unmedicated and diazepam-premedicated subjects. Clin Pharmacol Ther 36(5):645–653

Donoghue AC, Roback MG, Cullen KR (2015) Remission from behavioral dysregulation in a child with PTSD after receiving procedural ketamine. Pediatrics 136(3):e694–e696. https://doi.org/10.1542/peds.2014-4152

Duclot F, Perez-Taboada I, Wright KN, Kabbaj M (2016) Prediction of individual differences in fear response by novelty seeking, and disruption of contextual fear memory reconsolidation by ketamine. Neuropharmacology 109:293–305. https://doi.org/10.1016/j.neuropharm.2016.06.022

Feder A, Parides MK, Murrough JW, Perez AM, Morgan JE, Saxena S et al (2014) Efficacy of intravenous ketamine for treatment of chronic posttraumatic stress disorder: a randomized clinical trial. JAMA Psychiat 71(6):681–688. https://doi.org/10.1001/jamapsychiatry.2014.62

Garakani A, Mathew SJ, Charney DS (2006) Neurobiology of anxiety disorders and implications for treatment. Mt Sinai J Med 73(7):941–949

Girgenti MJ, Ghosal S, LoPresto D, Taylor JR, Duman RS (2017) Ketamine accelerates fear extinction via mTORC1 signaling. Neurobiol Dis 100:1–8. https://doi.org/10.1016/j.nbd.2016.12.026

Groeber Travis CM, Altman DE, Genovese RF (2015) Ketamine administration diminishes operant responding but does not impair conditioned fear. Pharmacol Biochem Behav 139 (Part A):84–91. https://doi.org/10.1016/j.pbb.2015.10.013

Harps-Rotem I. Intensive 7-day treatment for PTSD combining ketamine with exposure therapy. https://ClinicalTrials.gov/show/NCT02727998

Hetrick SE, Purcell R, Garner B, Parslow R (2010) Combined pharmacotherapy and psychological therapies for post traumatic stress disorder (PTSD). Cochrane Database Syst Rev 7:CD007316. https://doi.org/10.1002/14651858.CD007316.pub2

Hijazi Y, Boulieu R (2002) Contribution of CYP3A4, CYP2B6, and CYP2C9 isoforms to N-demethylation of ketamine in human liver microsomes. Drug Metab Dispos 30(7):853–858

Hirota K, Hashimoto Y, Lambert DG (2002) Interaction of intravenous anesthetics with recombinant human M1-M3 muscarinic receptors expressed in chinese hamster ovary cells. Anesth Analg 95(6):1607–1610

Honsberger MJ, Taylor JR, Corlett PR (2015) Memories reactivated under ketamine are subsequently stronger: a potential pre-clinical behavioral model of psychosis. Schizophr Res 164 (1–3):227–233. https://doi.org/10.1016/j.schres.2015.02.009

Ito W, Erisir A, Morozov A (2015) Observation of distressed conspecific as a model of emotional trauma generates silent synapses in the prefrontal-amygdala pathway and enhances fear learning, but ketamine abolishes those effects. Neuropsychopharmacology 40(11):2536–2545. https://doi.org/10.1038/npp.2015.100

Jonas DE, Cusack K, Forneris CA, Wilkins TM, Sonis J, Middleton JC et al (2013) Psychological and pharmacological treatments for adults with posttraumatic stress disorder (PTSD). Agency for Healthcare Research and Quality, Rockville

Juven-Wetzler A, Cohen H, Kaplan Z, Kohen A, Porat O, Zohar J (2014) Immediate ketamine treatment does not prevent posttraumatic stress responses in an animal model for PTSD. Eur Neuropsychopharmacol 24(3):469–479. https://doi.org/10.1016/j.euroneuro.2013.08.007

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(8):837–844. https://doi.org/10.1038/sj.mp.4001093

Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CB (1995) Posttraumatic stress disorder in the National Comorbidity Survey. Arch Gen Psychiatry 52(12):1048–1060

Kindt M, van Emmerik A (2016) New avenues for treating emotional memory disorders: towards a reconsolidation intervention for posttraumatic stress disorder. Ther Adv Psychopharmacol 6(4):283–295

Kindt M et al (2009) Beyond extinction: erasing human fear responses and preventing the return of fear. Nat Neurosci 12(3):256–258

Kirby T (2015) Ketamine for depression: the highs and lows. Lancet Psychiatry 2(9):783–784. https://doi.org/10.1016/S2215-0366(15)00392-2

Kleinloog D, Uit den Boogaard A, Dahan A, Mooren R, Klaassen E, Stevens J et al (2015) Optimizing the glutamatergic challenge model for psychosis, using S+-ketamine to induce psychomimetic symptoms in healthy volunteers. J Psychopharmacol 29(4):401–413. https://doi.org/10.1177/0269881115570082

Krawczyk MC, Fernandez RS, Pedreira ME, Boccia MM (2017) Toward a better understanding on the role of prediction error on memory processes: from bench to clinic. Neurobiol Learn Mem 142(Pt A):13–20. https://doi.org/10.1016/j.nlm.2016.12.011

Krystal JH, Karper LP, Seibyl JP, Freeman GK, Delaney R, Bremner JD et al (1994) Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. Arch Gen Psychiatry 51(3):199–214

Lancaster C, Teeters J, Gros D, Back S (2016) Posttraumatic stress disorder: overview of evidence-based assessment and treatment. J Clin Med 5(11):105

Lee DJ, Schnitzlein CW, Wolf JP, Vythilingam M, Rasmusson AM, Hoge CW (2016) Psychotherapy versus pharmacotherapy for posttraumatic stress disorder: systemic review and meta-analyses to determine first-line treatments. Depress Anxiety 33(9):792–806

Li L, Vlisides PE (2016) Ketamine: 50 years of modulating the mind. Front Hum Neurosci 10:612. https://doi.org/10.3389/fnhum.2016.00612

Mallick F, McCullumsmith CB (2016) Ketamine for treatment of suicidal ideation and reduction of risk for suicidal behavior. Curr Psychiatry Rep 18(6):61. https://doi.org/10.1007/s11920-016-0680-7

Maren S, Phan KL, Liberzon I (2013) The contextual brain: implications for fear conditioning, extinction and psychopathology. Nat Rev Neurosci 14(6):417–428. https://doi.org/10.1038/nrn3492

Mataix-Cols D, Fernandez de la Cruz L, Monzani B, Rosenfield D, Andersson E, Perez-Vigil A et al (2017) D-Cycloserine augmentation of exposure-based cognitive behavior therapy for anxiety, obsessive-compulsive, and posttraumatic stress disorders: a systematic review and meta-analysis. JAMA Psychiat. https://doi.org/10.1001/jamapsychiatry.2016.3955

McGaugh JL (1966) Time-dependent processes in memory storage. Science 153(3742):1351–1358

McGhee LL, Maani CV, Garza TH, Gaylord KM, Black IH (2008) The correlation between ketamine and posttraumatic stress disorder in burned service members. J Trauma 64(2 Suppl): S195–S198.; Discussion S197–198. https://doi.org/10.1097/TA.0b013e318160ba1d

McGhee LL, Maani CV, Garza TH, Slater TM, Petz LN, Fowler M (2014) The intraoperative administration of ketamine to burned U.S. service members does not increase the incidence of post-traumatic stress disorder. Mil Med 179(8 Suppl):41–46. https://doi.org/10.7205/MILMED-D-13-00481

McGowan JC, LaGamma CT, Lim SC, Tsitsiklis M, Neria Y, Brachman RA, Denny CA (2017) Prophylactic ketamine attenuates learned fear. Neuropsychopharmacology. https://doi.org/10.1038/npp.2017.19

Miller CA, Sweatt JD (2006) Amnesia or retrieval deficit? Implications of a molecular approach to the question of reconsolidation. Learn Mem 13(5):498–505. https://doi.org/10.1101/lm.304606

Milton AL, Merlo E, Ratano P, Gregory BL, Dumbreck JK, Everitt BJ (2013) Double dissociation of the requirement for GluN2B- and GluN2A-containing NMDA receptors in the destabilization and restabilization of a reconsolidating memory. J Neurosci 33(3):1109–1115. https://doi.org/10.1523/JNEUROSCI.3273-12.2013

Mion G, Villevieille T (2013) Ketamine pharmacology: an update (pharmacodynamics and molecular aspects, recent findings). CNS Neurosci Ther 19(6):370–380. https://doi.org/10.1111/cns.12099

Moaddel R, Abdrakhmanova G, Kozak J, Jozwiak K, Toll L, Jimenez L et al (2013) Sub-anesthetic concentrations of (R,S)-ketamine metabolites inhibit acetylcholine-evoked currents in alpha7 nicotinic acetylcholine receptors. Eur J Pharmacol 698(1–3):228–234. https://doi.org/10.1016/j.ejphar.2012.11.023

Murrough JW, Iosifescu DV, Chang LC, Al Jurdi RK, Green CE, Perez AM et al (2013a) Antidepressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial. Am J Psychiatry 170(10):1134–1142. https://doi.org/10.1176/appi.ajp.2013.13030392

Murrough JW, Perez AM, Pillemer S, Stern J, Parides MK, aan het Rot M et al (2013b) Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. Biol Psychiatry 74(4):250–256. https://doi.org/10.1016/j.biopsych.2012.06.022

Murrough JW, Soleimani L, DeWilde KE, Collins KA, Lapidus KA, Iacoviello BM et al (2015) Ketamine for rapid reduction of suicidal ideation: a randomized controlled trial. Psychol Med 45(16):3571–3580. https://doi.org/10.1017/S0033291715001506

Nader K (2015) Reconsolidation and the dynamic nature of memory. Cold Spring Harb Perspect Biol 7(10):a021782. https://doi.org/10.1101/cshperspect.a021782

Nader K, Schafe GE, LeDoux JE (2000) Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval. Nature 406:722–726

Nader K, Hardt O, Lanius R (2013) Memory as a new therapeutic target. Dialogues Clin Neurosci 15(4):475–486

Orser BA, Pennefather PS, MacDonald JF (1997) Multiple mechanisms of ketamine blockade of N-methyl-D-aspartate receptors. Anesthesiology 86(4):903–917

Owens MJ, Morgan WN, Plott SJ, Nemeroff CB (1997) Neurotransmitter receptor and transporter binding profile of antidepressants and their metabolites. J Pharmacol Exp Ther 283(3):1305–1322

Oye I, Paulsen O, Maurset A (1992) Effects of ketamine on sensory perception: evidence for a role of N-methyl-D-aspartate receptors. J Pharmacol Exp Ther 260(3):1209–1213

Papp M, Moryl E (1994) Antidepressant activity of non-competitive and competitive NMDA receptor antagonists in a chronic mild stress model of depression. Eur J Pharmacol 263(1–2):1–7

Pavlov IP (1927) Conditioned reflexes: an investigation of the physiological activity of the cerebral cortex. Oxford University Press, Oxford

Pedreira ME, Maldonado H (2003) Protein synthesis subserves reconsolidation or extinction depending on reminder duration. Neuron 38(6):863–869

Peltoniemi MA, Hagelberg NM, Olkkola KT, Saari TI (2016) Ketamine: a review of clinical pharmacokinetics and pharmacodynamics in anesthesia and pain therapy. Clin Pharmacokinet 55(9):1059–1077. https://doi.org/10.1007/s40262-016-0383-6

Philippens I, Draaisma L, Krugers H, Vermetten E (2017) Ketamine treatment during reconsolidation of traumatic stress exposure: molecular biological validation of reduced avoidant behavior in marmoset monkeys. Poster presented at 56th meeting of the American College of Neuropsychopharmacology

Pomarol-Clotet E, Honey GD, Murray GK, Corlett PR, Absalom AR, Lee M et al (2006) Psychological effects of ketamine in healthy volunteers. Phenomenological study. Br J Psychiatry 189:173–179. https://doi.org/10.1192/bjp.bp.105.015263

Price RB, Nock MK, Charney DS, Mathew SJ (2009) Effects of intravenous ketamine on explicit and implicit measures of suicidality in treatment-resistant depression. Biol Psychiatry 66 (5):522–526. https://doi.org/10.1016/j.biopsych.2009.04.029

Przegalinski E, Tatarczynska E, Deren-Wesolek A, Chojnacka-Wojcik E (1997) Antidepressant-like effects of a partial agonist at strychnine-insensitive glycine receptors and a competitive NMDA receptor antagonist. Neuropharmacology 36(1):31–37

Quirk GJ, Mueller D (2008) Neural mechanisms of extinction learning and retrieval. Neuropsychopharmacology 33(1):56–72. https://doi.org/10.1038/sj.npp.1301555

Rauch SA, Eftekhari A, Ruzek JI (2012) Review of exposure therapy: a gold standard for PTSD treatment. J Rehabil Res Dev 49(5):679–687

Rothbaum BO, Price M, Jovanovic T, Norrholm SD, Gerardi M, Dunlop B et al (2014) A randomized, double-blind evaluation of D-cycloserine or alprazolam combined with virtual reality exposure therapy for posttraumatic stress disorder in Iraq and Afghanistan War veterans. Am J Psychiatry 171(6):640–648. https://doi.org/10.1176/appi.ajp.2014.13121625

Sanacora G, Smith MA, Pathak S, Su HL, Boeijinga PH, McCarthy DJ, Quirk MC (2014) Lanicemine: a low-trapping NMDA channel blocker produces sustained antidepressant efficacy with minimal psychotomimetic adverse effects. Mol Psychiatry 19(9):978–985. https://doi.org/10.1038/mp.2013.130

Schnyder U, Ehlers A, Elbert T, Foa EB, Gersons BP, Resick PA et al (2015) Psychotherapies for PTSD: what do they have in common? Eur J Psychotraumatol 6:28186. https://doi.org/10.3402/ejpt.v6.28186

Schonenberg M, Reichwald U, Domes G, Badke A, Hautzinger M (2005) Effects of peritraumatic ketamine medication on early and sustained posttraumatic stress symptoms in moderately injured accident victims. Psychopharmacology 182(3):420–425. https://doi.org/10.1007/s00213-005-0094-4

Schonenberg M, Reichwald U, Domes G, Badke A, Hautzinger M (2008) Ketamine aggravates symptoms of acute stress disorder in a naturalistic sample of accident victims. J Psychopharmacol 22(5):493–497. https://doi.org/10.1177/0269881107082481

Schwabe L, Nader K, Wolf OT, Beaudry T, Pruessner JC (2012) Neural signature of reconsolidation impairments by propranolol in humans. Biol Psychiatry 71(4):380–338

Sevenster D, Beckers T, Kindt M (2012) Retrieval per se is not sufficient to trigger reconsolidation of human fear memory. Neurobiol Learn Mem 97(3):338–345. https://doi.org/10.1016/j.nlm.2012.01.009

Shors TJ, Seib TB, Levine S, Thompson RF (1989) Inescapable versus escapable shock modulates long-term potentiation in the rat hippocampus. Science 244(4901):224–226

Singh JB, Fedgchin M, Daly E, Xi L, Melman C, De Bruecker G et al (2016) Intravenous esketamine in adult treatment-resistant depression: a double-blind, double-randomization, placebo-controlled study. Biol Psychiatry 80(6):424–431. https://doi.org/10.1016/j.biopsych.2015.10.018

Soeter M, Kindt M (2015) An abrupt transformation of phobic behavior after a post-retrieval amnesic agent. Biol Psychiatry 78(12):880–886

Suzuki A, Josselyn SA, Frankland PW, Masushige S, Silva AJ, Kida S (2004) Memory reconsolidation and extinction have distinct temporal and biochemical signatures. J Neurosci 24(20):4787–4795. https://doi.org/10.1523/JNEUROSCI.5491-03.2004

Trullas R, Skolnick P (1990) Functional antagonists at the NMDA receptor complex exhibit antidepressant actions. Eur J Pharmacol 185(1):1–10

Vermetten E, Krugers H (2016) A roadmap to golden hour intervention for posttraumatic stress disorder. Int J Neuropsychopharmacol 19:141–141

Vermetten E, Zhohar J, Krugers HJ (2014) Pharmacotherapy in the aftermath of trauma; opportunities in the 'golden hours'. Curr Psychiatry Rep 16(7):455. https://doi.org/10.1007/s11920-014-0455-y

Weber M, Hart J, Richardson R (2007) Effects of D-cycloserine on extinction of learned fear to an olfactory cue. Neurobiol Learn Mem 87(4):476–482. https://doi.org/10.1016/j.nlm.2006.12.010

Wilson JT, Pokorny ME (2012) Experiences of military CRNAs with service personnel who are emerging from general anesthesia. AANA J 80(4):260–265

Womble AL (2013) Effects of ketamine on major depressive disorder in a patient with posttraumatic stress disorder. AANA J 81(2):118–119

Woolf TF, Adams JD (1987) Biotransformation of ketamine, (Z)-6-hydroxyketamine, and (E)-6-hydroxyketamine by rat, rabbit, and human liver microsomal preparations. Xenobiotica 17(7):839–847. https://doi.org/10.3109/00498258709043993

Yehuda R, LeDoux J (2007) Response variation following trauma: a translational neuroscience approach to understanding PTSD. Neuron 56(1):19–32. https://doi.org/10.1016/j.neuron.2007.09.006

Zanos P, Moaddel R, Morris PJ, Georgiou P, Fischell J, Elmer GI et al (2016) NMDAR inhibition-independent antidepressant actions of ketamine metabolites. Nature 533(7604):481–486. https://doi.org/10.1038/nature17998

Zarate CA Jr, Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA et al (2006) A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch Gen Psychiatry 63(8):856–864. https://doi.org/10.1001/archpsyc.63.8.856

Zeng MC, Niciu MJ, Luckenbaugh DA, Ionescu DF, Mathews DC, Richards EM et al (2013) Acute stress symptoms do not worsen in posttraumatic stress disorder and abuse with a single subanesthetic dose of ketamine. Biol Psychiatry 73(12):e37–e38. https://doi.org/10.1016/j.biopsych.2012.10.017