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Memories reactivated under ketamine are subsequently stronger: A potential pre-clinical behavioral model of psychosis

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ABSTRACT

Background: Sub-anesthetic doses of the NMDA antagonist ketamine have been shown to model the formation and stability of delusion in human subjects. The latter has been predicted to be due to aberrant prediction error resulting in enhanced destabilization of beliefs. To extend the scope of this model, we investigated the effect of administration of low dose systemic ketamine on memory in a rodent model of memory reconsolidation.
Methods: Systemic ketamine was administered either prior to or immediately following auditory fear memory reactivation in rats. Memory strength was assessed by measuring freezing behavior 24 h later. Follow up experiments were designed to investigate an effect of pre-reactivation ketamine on short-term memory (STM), closely related memories, and basolateral amygdala (BLA) specific destabilization mechanisms.
Results: Rats given pre-reactivation, but not post-reactivation, ketamine showed larger freezing responses 24 h later compared to vehicle. This enhancement was not observed 3 h after the memory reactivation, nor was it seen in a closely related contextual memory. Prior inhibition of a known destabilization mechanism in the BLA blocked the effect of pre-reactivation ketamine.
Conclusions: Pre- but not post-reactivation ketamine enhances fear memory. These data together with recent data in human subjects supports a model of delusion fixity that proposes that aberrant prediction errors result in enhanced destabilization and strengthening of delusional belief.

1. Introduction

Delusions are fixed false beliefs. They are a characteristic of schizophrenia. Many delusions respond well to drugs that block dopamine D_2 receptors in striatum. However, up to 50% of patients experience residual delusions (Curson et al., 1985; Kane, 1996). This is devastating for patients and their families. The public health impact is significant (Lindenmayer, 2000); those for whom current medications are ineffective are more likely to be hospitalized long term, to have poor functional outcome and to engage in suicidal behavior (Meltzer and Okayli, 1995). Patients with treatment-refractory delusions do not show the typical pattern of striatal dopamine disruption (Demjaha et al., 2012), suggesting that other brain regions and neurotransmitters may be involved. There is a clear need for new treatments, inspired not by serendipity but by the development of a precise understanding of the neurocognitive mechanisms of delusion.

Delusions are, however, challenging to study empirically — the sufferer often denies any problem (Gibbs and David, 2003) and they don't present for clinical attention until their delusions are fully formed (Corlett et al., 2007). Experimental models provide a unique experimental window onto an otherwise inaccessible disease process (Corlett et al., 2007). Ketamine, the NMDA glutamate receptor antagonist compound, transiently and reversibly engenders delusion-like ideas in healthy human volunteers (Pomarol-Clotet et al., 2006). Likewise, ketamine administration in animal models can generate behavioral and neural disruptions that mimic human psychosis with face and construct validity (Corlett et al., 2007). In this report we used the ketamine model in a study of rodent learning and memory, to examine a phenomenon hitherto under explored in clinical and preclinical neuroscience, the fixity of delusions.

Setting aside philosophical questions regarding whether animals have beliefs (Dennett, 1995), pre-clinical behavioral neuroscience has furnished psychiatry with candidate processes that might contribute to the formation, updating and maintenance of beliefs in humans (Dickinson, 2001). One such process, prediction error, represents the mismatch between our expectancy in a given situation and what we experience (Rescorla and Wagner, 1972). It is signaled by dopamine and glutamate neural activity in the brain (Lavin et al., 2005). By reducing the mismatch between expectancy and experience we improve our ability to anticipate the causal structure of the environment and we form causal beliefs (Dickinson, 2001).

Using functional magnetic resonance imaging (fMRI) we established a neurobiological marker for prediction error in the right dorsolateral prefrontal cortex (Fletcher et al., 2001; Corlett et al., 2004; Turner et al., 2004). We used this marker to implicate aberrant prediction error in the genesis of endogenous delusions (Corlett et al., 2006) as

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well as those induced by ketamine in healthy volunteers (Corlett et al., 2006). We argue when prediction errors are signaled internally and inappropriately (Grace, 1991), individuals attend to and learn about irrelevant events. Delusions result as explanations for such aberrant experiences (Corlett et al., 2010).

We recently argued that the fixity of delusions might also be driven by prediction error, if we consider what happens to memories when they need to be updated (Corlett et al., 2009). The surprising (or prediction error driven) recall of a consolidated memory renders it labile and sensitive to disruption (Misanin et al., 1968; Nader et al., 2000). This process of memory reconsolidation is in competition with extinction learning (formation of a new competing memory that overrides the initial one) and the balance between the two may be mediated by prediction error (Pedreira et al., 2004; Eisenhardt and Menzel, 2007). Reconsolidation based memory strengthening (Lee, 2008) or reminder learning is mediated by positive prediction errors (Pedreira et al., 2004; Eisenhardt and Menzel, 2007; Lee, 2008).

Aberrant prediction error signaling should engender reminding of the initial memory and inappropriate strengthening — leading to exceptionally strong delusional memories (Corlett et al., 2009). Reactivating fear memories in human subjects under the influence of ketamine enhances subsequent expression of those memories (Corlett et al., 2013). Vulnerability to this enhancement is predicted by the neural prediction error signal and the severity of ketamine induced psychosis (Corlett et al., 2013), providing initial support for the model — delusions are formed and maintained due to aberrant prediction errors (Corlett et al., 2009). In the present study we sought to replicate and extend this finding in a preclinical setting.

Our understanding of reconsolidation in rodents is much greater and more nuanced than that in human subjects. From preclinical work, we know memory reconsolidation is composed of at least two separate processes, destabilization, and re-stabilization (Lee, 2008). The latter process depends on similar processes to consolidation [such as protein synthesis and gene transcription (Tronson and Taylor, 2007)], however, memory reconsolidation is molecularly distinct from consolidation (Lee et al., 2004). The former, destabilization, is a process dependent on prediction error (Winters et al., 2009; Sevenster et al., 2012, 2013) and GluN2B containing NMDA receptor activity (Ben Mamou et al., 2006; Milton et al., 2013). We examined the effect of ketamine on auditory fear reconsolidation in rodents, which is known to be critically dependent on the basolateral amygdala (BLA). We predicted an effect of ketamine on destabilization. Previous research has shown that while manipulations of re-stabilization are effective when administered prior to or immediately following memory reactivation (i.e. Nader et al., 2000; Lee, 2008), manipulations of memory destabilization are effective when administered prior to, but not immediately following memory retrieval (Ben Mamou et al., 2006). Following our model predictions (Corlett et al., 2009) and human data (Corlett et al., 2013), we hypothesized that ketamine would enhance fear memory when administered prior to, but not immediately following fear memory reconsolidation.

2. Methods

2.1. Subjects

Adult Sprague–Dawley male rats weighing about 300 g (Charles River) were pair-housed and maintained on a 12-h light–dark cycle, with food and water provided ad libitum. All procedures were in accordance with the Yale Animal Resources Center, and were approved by the Yale Institutional Animal Care and Use Committee.

2.2. Apparatus

Context A: Med-Associates' chambers were lit by near-infrared light with inserted white plastic floors and rounded walls, and wiped down with 1% ascetic acid

Context B: The apparatus was changed by lighting it with diffuse white light, removing the plastic inserts rectangular plexiglass, acrylic and stainless steel aluminum walls, metal grid floors and wiped down with 70% ethanol

2.3. Fear conditioning (training)

Twenty-four hours following two days of exposure to Context A animals were trained in Context B. Following 180 s of acclimatization three 30 s tones (5000 Hz 75 dB) co-terminated with a mild foot shock (1″ 0.7 mA); the intertrial intervals were 60 s and 30 s following the final shock they were removed from the chamber. To avoid ceiling effects following surgery in Experiment #4 the shock intensity was reduced to 0.5 mA.

2.4. Fear conditioning (reactivation)

Twenty-four hours after training animals were placed in Context A. After 180 s of acclimatization a 30 second tone was presented. Animals were removed from the context 30 s after the tone. All drug manipulations were performed either prior to, or immediately following this reactivation session.

2.5. Fear conditioning (testing)

Twenty-four hours after reactivation animals were returned to Context A and exposed to three 30 second tone presentations (ITI 60 s) following 180 s of acclimatization (post-reactivation long-term memory test [PR-LTM]). Tests of contextual fear were performed in the same context as training, Context B. For this test animals were placed in the chamber for 5 min.

2.6. Measurement of freezing behavior

The default settings for the Med-Associates' automated freezing software have been calibrated for detecting mice (Anagnostaras et al., 2010). Using a similar approach we determined that to detect freezing behavior in rats, optimal freezing was defined as the Motion Index being less than 75 for at least 15 frames (0.5 s). Auditory evoked freezing behavior was scored continuously for each of the three tones and analyzed as average percent. Context evoked freezing behavior was scored continuously for the duration of the test and analyzed as percent of total time.

2.7. Surgery

Rats were anesthetized with a combination of 87.5 mg/kg ketamine and 5 mg/kg xylazine. Rats were administered 5 ml of lactated Ringer's solution and 5 mg/kg of the analgesic Rimadyl before implantation with bilateral intracranial cannulae (3.0 mm posterior, 5.2 mm lateral and 8.0 mm ventral of bregma. 22 gauge; Plastics One) and given seven days to recover.

2.8. Drugs

Ketamine (dissolved in sterile saline, 10 mg/kg: Henry Schein, Melville, NY) was administered intraperitoneally (i.p.). In Experiment #4 ifenprodil (2 μg/μl for two minutes at 0.25 μl/min: Sigma-Aldrich, St. Louis, MO) or vehicle (sterile saline) was infused into the BLA.

2.9. Histological assessment

At the termination of the experiment, rats anesthetized (90 mg/kg sodium pentobarbital, i.p.) and stored in 10% formalin/20% sucrose. Their brains were sectioned at 50 μm thickness and examined with light microscopy for cannula placement. After histological verification,