Neuropsychopharmacology (2015) 40, 1278–1288
© 2015 American College of Neuropsychopharmacology. All rights reserved 0893-133X/15
www.neuropsychopharmacology.org

A Diet Enriched with Curcumin Impairs Newly Acquired and Reactivated Fear Memories

Melissa S Monsey[1,4], Danielle M Gerhard[1,4], Lara M Boyle[1], Miguel A Briones[2], Ma'ayan Seligsohn[3] and Glenn E Schafe*[,2,3]

[1]Department of Psychology, Yale University, New Haven, CT, USA; [2]The Graduate Center, The City University of New York, New York, NY, USA; [3]Department of Psychology, Hunter College, The City University of New York, New York, NY, USA

Curcumin, a yellow-pigment compound found in the popular Indian spice turmeric (*Curcuma longa*), has been extensively investigated for its anti-inflammatory, chemopreventative, and antidepressant properties. Here, we examined the efficacy of dietary curcumin at impairing the consolidation and reconsolidation of a Pavlovian fear memory, a widely studied animal model of traumatic memory formation in posttraumatic stress disorder (PTSD). We show that a diet enriched with 1.5% curcumin prevents the training-related elevation in the expression of the immediate early genes (IEGs) Arc/Arg3.1 and Egr-1 in the lateral amygdala (LA) and impairs the 'consolidation' of an auditory Pavlovian fear memory; short-term memory (STM) is intact, whereas long-term memory (LTM) is significantly impaired. Next, we show that dietary curcumin impairs the 'reconsolidation' of a recently formed auditory Pavlovian fear memory; fear memory retrieval (reactivation) and postreactivation (PR)-STM are intact, whereas PR-LTM is significantly impaired. Additional experiments revealed that dietary curcumin is also effective at impairing the reconsolidation of an older, well-consolidated fear memory. Furthermore, we observed that fear memories that fail to reconsolidate under the influence of dietary curcumin are impaired in an enduring manner; unlike extinguished fear memories, they are not subject to reinstatement or renewal. Collectively, our findings indicate that a diet enriched with curcumin is capable of impairing fear memory consolidation and reconsolidation processes, findings that may have important clinical implications for the treatment of disorders such as PTSD that are characterized by unusually strong and persistently reactivated fear memories.
Neuropsychopharmacology (2015) **40,** 1278–1288; doi:10.1038/npp.2014.315; published online 7 January 2015

INTRODUCTION

Posttraumatic stress disorder (PTSD), a trauma- and stress-related disorder that is estimated to affect as much as 8% of the adult US population (Kessler *et al*, 2012), is characterized by intense fear and avoidance, hyperarousal, and the maladaptive and frequent reexperiencing of a traumatic event (Yehuda, 2002; Yehuda and LeDoux, 2007). Given that fearful, traumatic memories are a core feature of this disorder, a major focus of PTSD research at the preclinical level has been to understand how associative fear memories are formed and stored in the brain (Schafe *et al*, 2001; Rodrigues *et al*, 2004; Sears *et al*, 2014), and how they might be erased (Quirk *et al*, 2010; Maren, 2011; Sandkuhler and Lee, 2013). Although this work has progressed rapidly in recent years, few pharmacological compounds have emerged that are readily applicable for use in a clinical setting. Antidepressant medications, including selective serotonin-reuptake inhibitors (SSRIs), remain the only currently approved pharmacological treatments for PTSD. Although this approach has shown promise (Brady *et al*, 2000; Davidson *et al*, 2001a, b), there are many well-documented side effects associated with the use of SSRIs, and as many as 50% of patients fail to respond to treatment altogether (Berger *et al*, 2009). It is thus of considerable interest to investigate the efficacy of alternative compounds that may be used either alone or in combination with existing approaches.

In recent years, interest has grown in the medicinal applications of naturally occurring compounds. Among these so-called 'nutraceuticals', curcumin is perhaps the best characterized. A yellow-pigment polyphenol compound found in the popular Indian spice turmeric (*Curcuma longa*), curcumin has been extensively investigated for its anti-inflammatory, chemopreventative, and neuroprotective properties (Aggarwal and Shishodia, 2006; Aggarwal *et al*, 2007; Jagetia and Aggarwal, 2007; Aggarwal and Harikumar, 2009). More recently, evidence has accumulated indicating that curcumin may also be useful for the treatment of psychological disorders (Kulkarni *et al*, 2009). In rodent models of depression, for example, orally administered curcumin has been observed to significantly elevate brain monoamines and to reduce depressive-like behaviors (Xu *et al*, 2005a; Bhutani *et al*, 2009). Furthermore, daily oral administration of curcumin during a period of chronic unpredictable stress has been observed to reverse the effects

*Correspondence: Professor GE Schafe, Department of Psychology, Hunter College, The City University of New York, 695 Park Avenue, HN611, New York, NY 10065, USA, Tel: +1 212 396 6802, Fax: +1 212 772 5620, E-mail: glenn.schafe@hunter.cuny.edu
[4]These authors contributed equally to this work.
Received 20 June 2014; revised 11 September 2014; accepted 20 November 2014; accepted article preview online 28 November 2014

of stress on serum CORT levels, hippocampal morphology, hippocampal neurogenesis, and hippocampal-dependent cognitive tasks (Xu *et al*, 2006, 2009). Finally, a recent study has suggested that treatment with curcumin is comparable to that of the SSRI fluoxetine in alleviating depression in human clinical populations (Sanmukhani *et al*, 2013).

Although interest has grown in the use of curcumin as a potential adjunct treatment for depression, few studies have examined its efficacy in the treatment of other stress-related disorders, including PTSD. Accordingly, in the present study we examined the effects of a dietary source of curcumin on Pavlovian fear conditioning, a widely studied preclinical model of traumatic memory formation in PTSD (Milad *et al*, 2006; Yehuda and LeDoux, 2007; Mahan and Ressler, 2012; Zovkic and Sweatt, 2013). We show that rats freely fed a diet enriched with curcumin around the time of fear conditioning or fear memory retrieval exhibit impairments in the consolidation and reconsolidation of a Pavlovian fear memory, respectively. Our findings suggest that curcumin may be useful as an adjunct in the treatment of psychological disorders such as PTSD that are characterized by unusually strong and persistently reactivated traumatic memories.

MATERIALS AND METHODS

Subjects

Adult male Sprague-Dawley rats (Harlan), weighing 300–350 g and aged 2–3 months, were housed individually in plastic cages and maintained on a 12 h light/dark cycle. Food and water were provided *ad libitum* throughout each experiment.

Curcumin Diet

Rats were given either a global 18% protein chow diet (Control chow; Harlan Teklad) or a global 18% protein chow diet commercially made with 1.5% curcumin (Curcumin chow; Fisher Scientific, 95% curcumin (diferuloylmethane)). This relatively high concentration of curcumin was chosen because of the well-documented low bioavailability of the compound (Anand *et al*, 2007; Prasad *et al*, 2014). Both diets were provided in pellet form and stored at 4 °C until use. Rats were observed to eat, on average, 18 g of each diet per day over a 5-day period ($\sim$270 mg curcumin/day, on average) that did not differ significantly between groups (Control chow: 18 ± 0.6 g; Curcumin chow: 18.6 ± 0.5 g, $p > 0.05$; not shown). Rats were observed to tolerate the curcumin-enriched diet well, with no observable signs of distress and comparable weight gain on day 5 of the diet relative to a group eating control chow (Control chow: 5.9 ± 0.3% gain from day 1; Curcumin chow: 5.6 ± 0.2% gain from day 1, $p > 0.05$; not shown).

Western Blotting Experiments

For western blotting experiments examining Arc/Arg3.1and Egr-1 expression, rats were placed on either a control chow or a 1.5% curcumin-enriched chow diet (day 1) 5 days before fear conditioning. Rats were habituated to handling and to the conditioning chamber (chamber A) for 15 min on the day before training (day 5). On the conditioning day (day 6), rats received 2 tone-shock pairings consisting of a 20 s, 5 kHz, 75 dB tone conditioned stimulus (CS) that coterminated with a 1 s, 0.5 mA footshock unconditioned stimulus (US). At 2 h after fear conditioning, rats were rapidly and deeply anesthetized using isoflurane and brains were removed, frozen on dry ice, and stored at -80 °C until processing. 'Naive' rats fed either a diet of control chow or curcumin-enriched chow were handled and killed on the same day as fear conditioned rats, but did not receive fear conditioning.

Punches containing the lateral amygdala (LA) were obtained with a 1 mm punch tool (Fine Science Tools) from 400-μm-thick sections taken on a sliding freezing microtome. Punched slices were examined using low-power light microscopy to verify the accuracy of the LA punch. Only those rats with punches confined to the borders of the LA were included in the analysis. Punches were manually dounced in 100 μl of ice-cold hypotonic lysis buffer (10 mM Tris-HCl, pH 7.5, 1 mM EDTA, 2.5 mM EDTA, 2.5 mM sodium pyrophosphate, 1 mM phenylmethylsulfonyl fluoride, 1 mM β-glycerophosphate, 1% Igepal CA-630, 1% protease inhibitor cocktail (Sigma), and 1 mM sodium orthovanadate). Sample buffer was immediately added to the homogenates, and the samples were boiled for 4 min. Homogenates were electrophoresed on 10% Tris-HCl gels and blotted to Immobilon-P (Millipore). Western blots were blocked in TTBS buffer (50 mM Tris-HCl, pH 7.5, 150 mM NaCl, and 0.05% Tween-20) with 5% dry milk. Blots were incubated with either anti-Arc antibody (1 : 1000; cat. no. SC17839; Santa Cruz Biotechnology) or anti-Egr-1 antibody (1 : 1000; cat. no. SC110; Santa Cruz Biotechnology). Blots were then incubated with either anti-mouse (for Arc/Arg3.1) or anti-rabbit (for Egr-1) antibody conjugated to horseradish peroxidase (Cell Signaling) and developed using West Dura chemiluminescent substrate (Pierce Laboratories). Western blots were developed in the linear range used for densitometry. Densitometry was conducted using NIH ImageJ software. To control for inconsistencies in loading, optical densities were normalized to glyceraldehyde-2-phosphate dehydrogenase (GAPDH) protein (1 : 20,000; cat. no. ab9484; Abcam). Data were normalized to the average value of naive controls fed a diet of control chow and analyzed using ANOVA.

Fear Conditioning Experiments

To examine the effects of dietary curcumin on fear memory consolidation, rats were placed on either control chow or a 1.5% curcumin-enriched chow diet (day 1) for 5 days before auditory fear conditioning. On the day before conditioning (day 5), rats were habituated to the conditioning chamber (chamber A) for 15 min that consisted of a lit rodent conditioning chamber with a grid floor (Coulbourn Instruments). The following day (day 6), rats were placed in chamber A and exposed to 2 tone-shock pairings consisting of 20 s, 5 kHz, 75 dB tone CS that co-terminated with a 1 s, 0.5 mA footshock US. Testing for short-term memory (STM) and long-term memory (LTM) occurred 2 and 24 h (days 6 and 7) following training, respectively. The testing chamber (chamber B) was dark (no light) with a black

plastic floor that had been washed with a peppermint-scented soap. Rats were exposed to 3 CS tones for the STM test and 10 CS tones for the LTM test. Rats in the curcumin group remained on curcumin-enriched chow throughout the STM and LTM tests.

To examine the effects of dietary curcumin on fear memory reconsolidation, rats were habituated to chamber A on the day before conditioning (day 1). The following day (day 2), rats were fear conditioned in chamber A with 2 tone-shock pairings as described above. On day 3, rats were placed on either a control chow or 1.5% curcumin-enriched chow diet. After 5 days on the diet (day 8), rats were given a memory reactivation trial in chamber B in which they received a single presentation of a CS tone (20 s, 5 kHz, 75 dB). At 2 h after reactivation, rats were returned to chamber B and tested for postreactivation STM (PR-STM) consisting of presentation of three CS tones (20 s, 5 kHz, 75 dB). After 24 h (day 9), rats were returned to chamber B where they received a postreactivation LTM (PR-LTM) test consisting of 10 CS tone presentations (20 s, 5 kHz, 75 dB). In a separate experiment, 'non-reactivated' controls were habituated and trained (days 1 and 2) and placed on a control chow or 1.5% curcumin-enriched chow diet (day 3) for 5 days. On day 8, rats were placed in chamber B for the same duration as the reactivated group but were not exposed to a tone CS. Rats then received tests of 'PR'-STM and 'PR'-LTM in chamber B in an identical manner to the reactivated groups. Rats in the curcumin groups in each experiment (reactivated and nonreactivated) remained on curcumin-enriched chow throughout the reactivation, PR-STM, and PR-LTM tests.

To examine the effects of dietary curcumin on the reconsolidation of an older fear memory, rats were habituated (day 1) and trained (day 2) as above. After 9 days, rats were placed on either a control chow or 1.5% curcumin-enriched chow diet. At 5 days after starting the diet (day 16; 2 weeks after training), rats were given a memory reactivation trial in chamber B where they received a single presentation of a CS tone (20 s, 5 kHz, 75 dB). At 2 and 24 h following the reactivation trial, rats received testing for PR-STM (day 16) and PR-LTM (day 17) in chamber B as described above. Rats in the curcumin group remained on curcumin-enriched chow throughout the reactivation, PR-STM, and PR-LTM tests.

To test whether fear memories that fail to reconsolidate under the influence of dietary curcumin are susceptible to reinstatement or renewal, rats were habituated (day 1) and fear conditioned (day 2) as above. The following day (day 3), rats were placed on either a control chow or 1.5% curcumin-enriched chow diet. On day 5 of the diet (day 8), two groups of rats fed a diet of control chow received extinction training with 40 CS presentations (20 s, 5 kHz, 75 dB) in chamber B, whereas another two groups fed a diet of either control chow or curcumin-enriched chow received a memory reactivation trial consisting of a single tone CS presentation in chamber B. The following day (day 9), all rats received an initial retention test consisting of 5 CS tone presentations (20 s, 5 kHz, 75 dB) in chamber B as test for fear extinction retention or reconsolidation impairment. Following this first tone test, all rats were returned to a control chow diet. After 1 day (day 10), all rats received a reinstatement session consisting of a single exposure to a shock US (0.5 mA) in chamber C. The reinstatement chamber (chamber C) was a distinct, brightly lit chamber with a grid floor and cedar wood chips. The following day (day 11), all rats were given a second tone test consisting of 5 CS presentations (20 s, 5 kHz, 75 dB) in chamber B to test for reinstatement of the fear memory. The next day (day 12), all rats were given a final tone test consisting of 5 CS presentations (20 s, 5 kHz, 75 dB) in a new context (chamber D) to examine renewal of the fear memory. Chamber D was a lit chamber with grid floors wrapped in blue pads with scented fabric softener.

All behavioral testing was videotaped for subsequent scoring of freezing behavior by an experimenter blind to dietary conditions. Freezing was defined as a lack of all movement with the exception of that which is required for respiration and was quantified as the percent of time the rat spent engaged in freezing behavior during each of the CS presentations. All data were analyzed using ANOVA and Duncan's *post hoc* *t*-tests. Differences were considered significant if $p < 0.05$.

RESULTS

Dietary Curcumin Impairs the Consolidation of a Pavlovian Fear Memory

In our first series of experiments, we asked whether dietary curcumin is capable of impairing the consolidation of a Pavlovian fear memory. Rats were provided with either a control diet or a 1.5% curcumin-enriched diet before fear conditioning. A portion of the rats was killed 2 h after conditioning to examine the effect of dietary curcumin on training-related expression of Arc/Arg3.1 and Egr-1 in the LA, two immediate early genes (IEGs) that we and others have shown to be necessary for fear memory consolidation in the LA (Malkani *et al*, 2004; Ploski *et al*, 2008; Maddox *et al*, 2011). The remaining rats were tested for STM and LTM at 2 and 24 h following training, respectively (Figure 1a).

Consistent with previous findings (Malkani and Rosen, 2000; Ploski *et al*, 2008; Maddox *et al*, 2011), we observed a significant elevation in both Arc/Arg3.1 and Egr-1 expression in the LA in fear conditioned rats fed control chow (Chow/FC) relative to naive control rats fed control chow (Chow/Naive). The ANOVA for each IEG revealed a significant effect for group (Arc/Arg3.1: $F_{(3,36)} = 3.41$, $p < 0.05$; Egr-1: $F_{(3,36)} = 3.29$, $p < 0.05$), with the Chow/FC group differing significantly from all other groups ($p < 0.05$; Duncan's test; Figure 1b). Importantly, this training-related expression of Arc/Arg3.1 and Egr-1 in the LA was observed to be completely blocked in fear conditioned rats fed curcumin-enriched chow (Chow/Naive *vs* Curc/FC; $p > 0.05$; Duncan's test; Figure 1b). Furthermore, curcumin alone had no effect on the expression of Arc/Arg3.1 and Egr-1 in the LA (Chow/Naive *vs* Curc/Naive; $p > 0.05$; Duncan's test; Figure 1b).

In our behavioral experiments, we observed intact freezing during training ('postshock freezing' (PSF)) for each group. The ANOVA for postshock freezing revealed a significant effect of trial ($F_{(2,20)} = 121.54$, $p < 0.001$), but no significant effects of group ($F_{(1,10)} = 0.63$, $p > 0.05$) or the group by trial interaction ($F_{(2,10)} = 0.12$, $p > 0.05$), suggesting that dietary curcumin has no effect on shock sensitivity

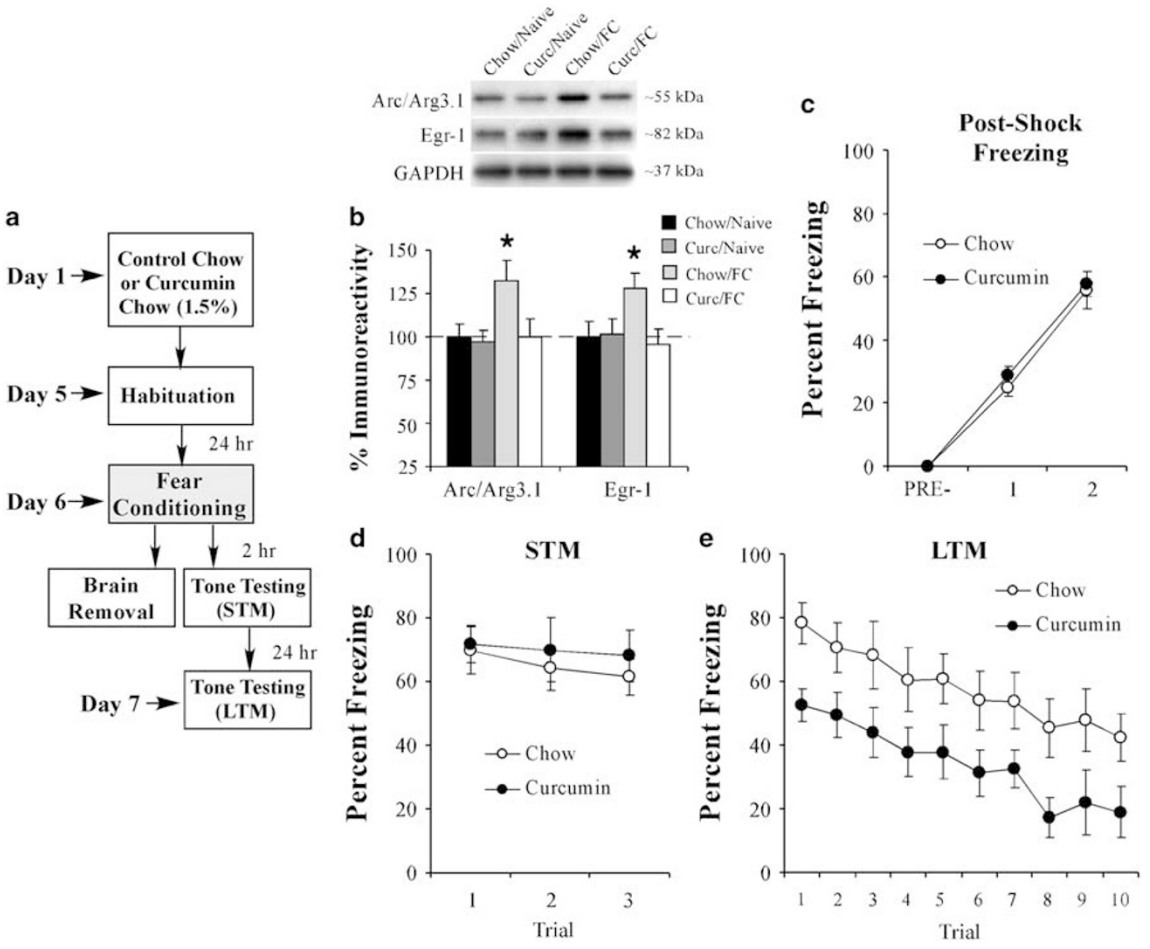

Figure 1 Dietary curcumin impairs the consolidation of an auditory fear memory. (a) Schematic of the behavioral protocol. (b) Mean (±SEM) immunoreactivity for Arc/Arg3.1 and Egr-1 proteins in the LA of Chow/Naive ($n=10$), Curcumin/Naive ($n=10$), Chow/Fear Conditioned (FC; $n=10$), and Curcumin/FC ($n=10$) groups 120 min after training. Representative blots can be seen in the inset. Here, IEG protein levels have been normalized to GAPDH levels for each sample. Each protein is expressed as a percentage of the Chow/Naive group. *$P<0.05$, relative to the Chow/Naive group. (c) Mean (±SEM) postshock freezing in Chow ($n=6$) and Curcumin ($n=6$) groups immediately after the conditioning trials. (d) Mean (±SEM) STM assessed at 2 h after conditioning in each group. (e) Mean (±SEM) LTM assessed 24 h after conditioning in each group (Chow *vs* Curcumin; $p<0.05$).

(Figure 1c). Furthermore, we observed no effect of dietary curcumin on STM (Figure 1d). The ANOVA for STM revealed no significant main effects of group ($F_{(1,10)}=0.28$, $p>0.05$), trial ($F_{(2,20)}=0.78$, $p>0.05$), or the group by trial interaction ($F_{(2,20)}=0.13$, $p>0.05$). Dietary curcumin was, however, observed to significantly impair LTM (Figure 1e). The ANOVA for LTM revealed a significant effect of group ($F_{(1,10)}=7.04$, $p<0.05$) and trial ($F_{(9,90)}=9.91$, $p<0.001$), but no significant group by trial interaction ($F_{(9,90)}=0.09$, $p>0.05$). Additional experiments showed that 5 days of dietary curcumin exposure has no effect on baseline levels of plasma corticosterone (CORT) or training (eg, shock)-related elevation in plasma CORT (Supplementary Figure S1b). Furthermore, dietary curcumin was observed to have no significant effect on performance in the elevated plus maze (Supplementary Figure S1c and d) or the open field test (Supplementary Figure S1e), two unlearned measures of fear and/or anxiety. Collectively, these findings indicate that a diet enriched with curcumin impairs both the training-related regulation of memory-related IEGs in the LA and the consolidation of a Pavlovian fear memory; acquisition and STM are intact, whereas LTM is impaired.

Dietary Curcumin Impairs the Reconsolidation of a Pavlovian Fear Memory

In our second series of experiments, we asked whether dietary curcumin is effective at impairing the reconsolidation of a Pavlovian fear memory. Rats were habituated and fear conditioned as above, and then provided with either a control diet or a 1.5% curcumin-enriched diet. Rats were then given a reactivation (retrieval) trial consisting of a single presentation of the tone CS followed by PR-STM and PR-LTM tests 2 and 24 h later, respectively (Figure 2a). Both groups exhibited intact PSF during the initial training session (Figure 2b). The ANOVA for PSF scores revealed a significant effect of trial ($F_{(2,20)}=45.42$, $p<0.001$), but nonsignificant effects of group ($F_{(1,10)}=0.03$, $p>0.05$) and the group by trial interaction ($F_{(2,20)}=0.02$, $p>0.05$). Furthermore, both groups exhibited intact and equivalent memory recall during the reactivation session (Figure 2c). The ANOVA for the reactivation session revealed a significant effect for trial (pre-CS *vs* CS; $F_{(1,10)}=44.92$, $p<0.001$), and nonsignificant effects of group ($F_{(1,10)}=0.01$, $p>0.05$) and the group by trial interaction ($F_{(1,10)}=0.01$, $p>0.05$). Similarly, curcumin was

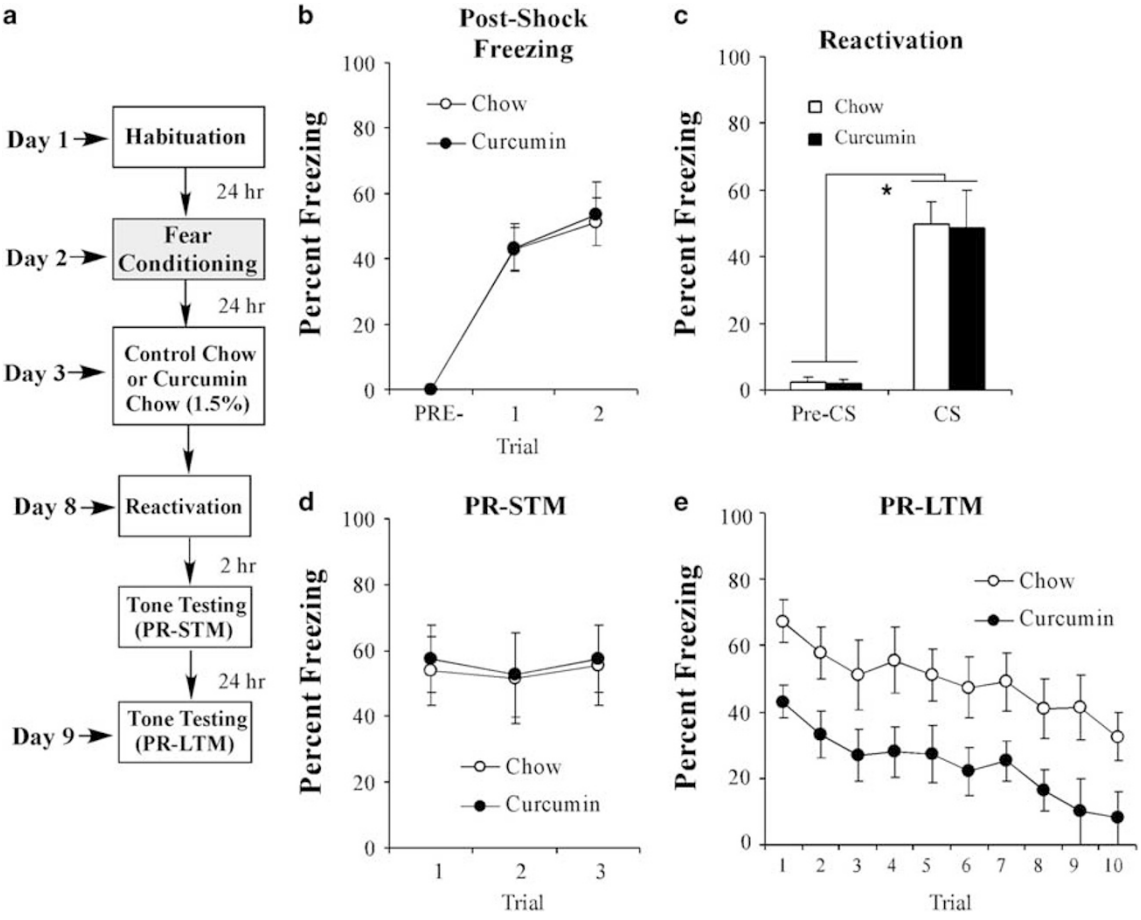

Figure 2 Dietary curcumin impairs the reconsolidation of an auditory fear memory. (a) Schematic of the behavioral protocol. (b) Mean (±SEM) postshock freezing in Chow ($n=6$) and Curcumin ($n=6$) groups immediately after the conditioning trials. (c) Mean (±SEM) percent freezing in each group during the reactivation trial. *$P<0.05$ relative to the pre-CS period. (d) Mean (±SEM) PR-STM assessed 2 h after the reactivation trial in each group. (e) Mean (±SEM) PR-LTM assessed 24 h after the reactivation trial in each group (Chow *vs* Curcumin; $p<0.05$).

found to have no effect on PR-STM tested 2 h after the reactivation session (Figure 2d). The ANOVA for PR-STM showed nonsignificant effects of group ($F_{(1,10)}=0.01$, $p>0.05$), trial ($F_{(2,20)}=0.85$, $p>0.05$), and the group by trial interaction ($F_{(2,20)}=0.07$, $p>0.05$). Dietary curcumin was, however, observed to significantly impair PR-LTM (Figure 2e). The ANOVA for PR-LTM revealed a significant effect of group ($F_{(1,10)}=21.56$, $p<0.001$) and trial ($F_{(9,90)}=5.18$, $p<0.001$), but a nonsignificant group by trial interaction ($F_{(9,90)}=0.07$, $p>0.05$). These findings indicate that a diet enriched with curcumin effectively impairs the reconsolidation of a Pavlovian fear memory; reactivation and PR-STM are intact, whereas PR-LTM is impaired.

The Effect of Dietary Curcumin on Fear Memory Reconsolidation Is Specific to Reactivated Memories

As a control for our reconsolidation experiments, we next examined the effect of a curcumin-enriched diet on a 'nonreactivated' fear memory. Rats were habituated, trained, and provided a diet of either control chow or 1.5% curcumin-enriched chow as above. On the reactivation day, rats were placed in the testing chamber for the same duration as the reactivated groups, but they were not exposed to the CS (Figure 3a). Similar to our reactivation experiments, both groups exhibited intact PSF during the initial training session (Figure 3b). The ANOVA for PSF scores revealed a significant effect of trial ($F_{(2,28)}=194.14$, $p<0.001$), but nonsignificant effects of group ($F_{(1,14)}=0.02$, $p>0.05$) and the group by trial interaction ($F_{(2,28)}=0.03$, $p>0.05$). The ANOVA for the 'no-reactivation' session predictably showed no main effects of trial (pre-'CS' *vs* 'CS'; $F_{(1,14)}=0.01$, $p>0.05$), group ($F_{(1,14)}=0.01$, $p>0.05$), or the group by trial interaction ($F_{(1,14)}=0.01$, $p>0.05$; Figure 3c). Furthermore, dietary curcumin was observed to have no effect on either 'PR'-STM or 'PR'-LTM (Figures 3d and e). The ANOVA for 'PR'-STM revealed no main effects of group ($F_{(1,14)}=0.01$, $p>0.05$), trial ($F_{(2,28)}=2.09$, $p>0.05$), or the group by trial interaction ($F_{(2,28)}=0.14$, $p>0.05$). The ANOVA for 'PR'-LTM revealed a significant effect for trial ($F_{(9,126)}=6.57$, $p<0.001$), but no significant effects of group ($F_{(1,14)}=0.01$, $p>0.05$) or a group by trial interaction ($F_{(9,126)}=0.11$, $p>0.05$). These findings suggest that the ability of dietary curcumin to effectively impair the reconsolidation of a fear memory is predicated on active memory recall during the reactivation session; in the absence of memory reactivation, curcumin has no effect on the retention of the fear memory.

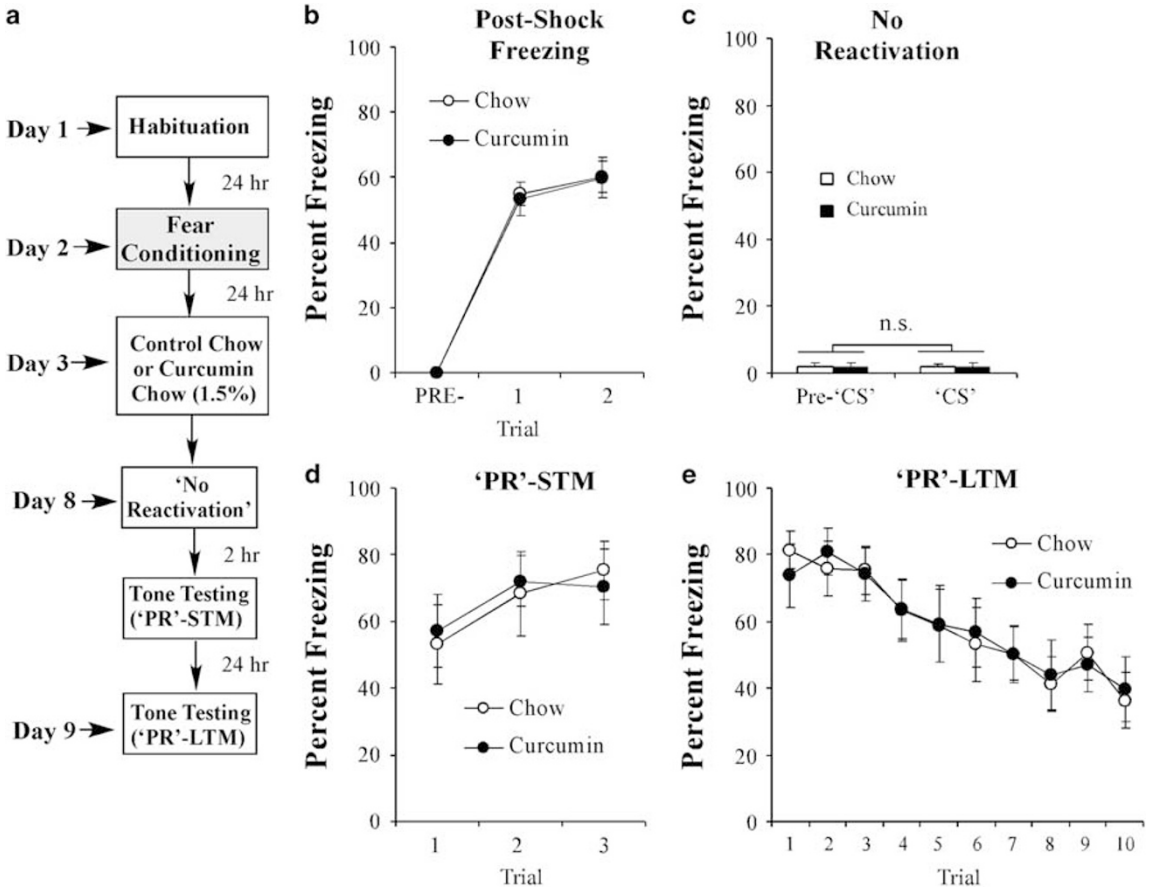

Figure 3 Dietary curcumin has no effect on a nonreactivated fear memory. (a) Schematic of the behavioral protocol. (b) Mean (±SEM) postshock freezing in Chow ($n=8$) and Curcumin ($n=8$) groups immediately after the conditioning trials. (c) Mean (±SEM) freezing in each group during the 'no-reactivation' trial. (d) Mean (±SEM) 'PR'-STM assessed 2 h after the no-reactivation trial in each group. (e) Mean (±SEM) 'PR'-LTM assessed 24 h after the no-reactivation trial in each group.

Dietary Curcumin Impairs the Reconsolidation of an Older Fear Memory

In our initial reconsolidation experiment, we reactivated the fear memory within 24 h following training. Here, we asked whether dietary curcumin can impair the reconsolidation of an older, well-consolidated fear memory. Rats were habituated, trained, and provided with a diet of control chow or 1.5% curcumin-enriched chow as in our previous reconsolidation experiment, with the exception that the memory reactivation session occurred 14 days after fear conditioning. After reactivation of the older fear memory, rats were then tested for PR-STM and PR-LTM at 2 and 24 h following the reactivation session (Figure 4a). Both groups exhibited intact PSF during the initial training session (Figure 4b). The ANOVA for PSF revealed a significant effect for trial ($F_{(2,124)}=52.92$, $p<0.001$), and nonsignificant effects for group ($F_{(1,12)}=0.01$, $p>0.05$) and the group by trial interaction ($F_{(2,24)}=0.01$, $p>0.005$). We observed that dietary curcumin had no effect on retrieval of the older fear memory (Figure 4c). The ANOVA revealed a significant effect of trial (pre-CS *vs* CS; $F_{(1,11)}=61.92$, $p<0.001$), but a nonsignificant effect of group ($F_{(1,11)}=0.04$, $p>0.05$) and the group by trial interaction ($F_{(1,11)}=0.01$, $p>0.05$). Furthermore, we observed that dietary curcumin effectively impairs the reconsolidation of the older fear memory; PR-STM was intact, whereas PR-LTM was significantly impaired (Figures 4d and e). The ANOVA for PR-STM revealed no significant effects of group ($F_{(1,12)}=0.15$, $p>0.05$), trial ($F_{(2,24)}=0.06$, $p>0.05$), or the group by trial interaction ($F_{(2,24)}=0.07$, $p>0.05$). The ANOVA for PR-LTM test revealed significant main effects of group ($F_{(1,12)}=7.74$, $p<0.05$) and trial ($F_{(2,24)}=4.74$, $p<0.05$), but no significant interaction ($F_{(2,24)}=0.04$, $p>0.05$).

Fear Memories That Fail to Reconsolidate Under the Influence of Dietary Curcumin Are Impaired in an Enduring Manner

Our experiments thus far collectively suggest that dietary curcumin impairs the reconsolidation of a Pavlovian fear memory in a retrieval-specific manner. Previous studies have shown that amygdala-dependent fear memories that are lost because of interference with the reconsolidation process are lost in an enduring manner; unlike fear memories that are impaired following fear extinction procedures, memories that fail to reconsolidate are not typically sensitive to spontaneous recovery, reinstatement following a series of reminder shocks, or renewal in a new

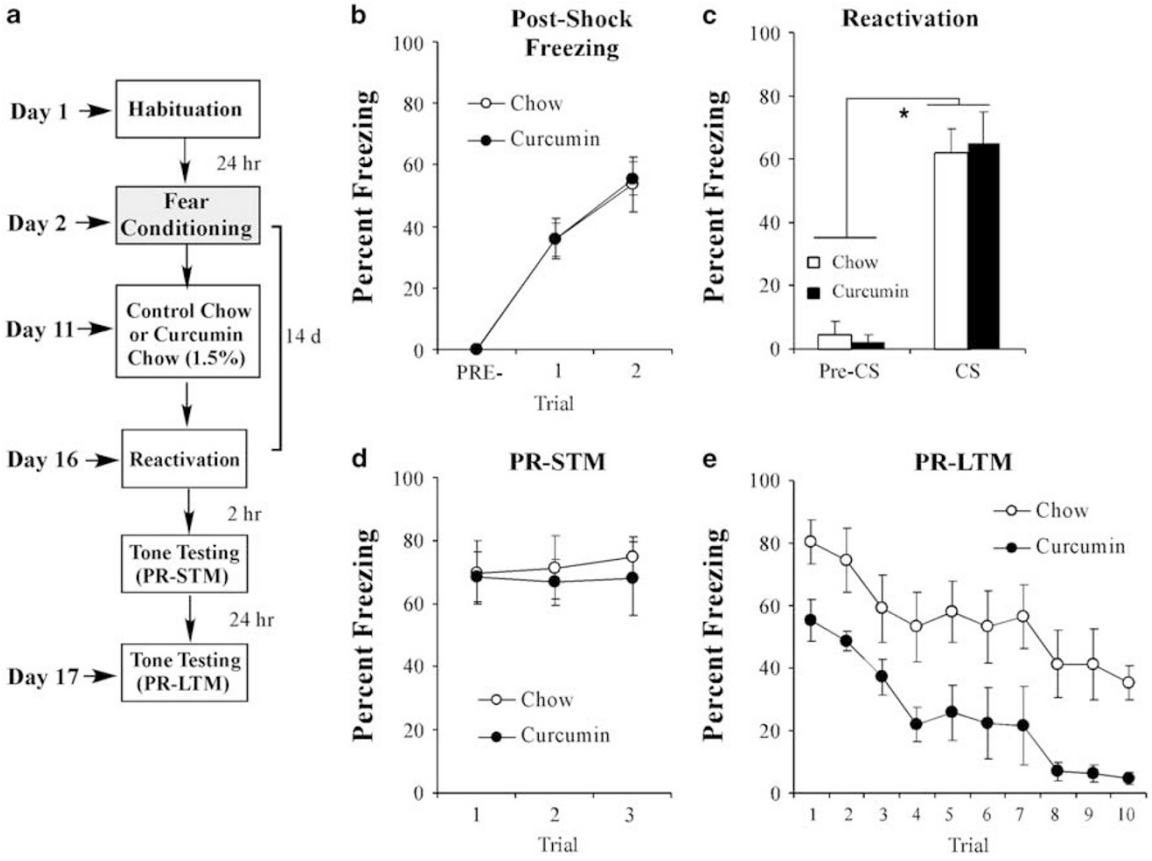

Figure 4 Dietary curcumin impairs the reconsolidation of an older auditory fear memory. (a) Schematic of the behavioral protocol. (b) Mean (±SEM) postshock freezing in Chow ($n=8$) and Curcumin ($n=8$) groups immediately after the conditioning trials. (c) Mean (±SEM) freezing in each group during the reactivation trial. *$P<0.05$ relative to the pre-CS period. (d) Mean (±SEM) PR-STM assessed 2 h after the reactivation trial in each group. (e) Mean (±SEM) PR-LTM assessed 24 h after the reactivation trial in each group (Chow *vs* Curcumin; $p<0.05$).

testing context (Debiec and LeDoux, 2004; Duvarci and Nader, 2004; Kindt *et al*, 2009; Maddox and Schafe, 2011a, b). In this final series of experiments, we asked whether fear memories that fail to reconsolidate under the influence of dietary curcumin are similarly resistant to reinstatement and renewal. Rats were habituated, trained, and placed on a diet of either control chow or 1.5% cucurmin-enriched chow. Rats in each diet condition then received a memory reactivation trial consisting of a single tone CS as in our previous experiments. To compare the effects of reconsolidation impairment with that of fear extinction, two additional groups of rats fed a diet of control chow underwent extinction training consisting of 40 CS presentations. One of these extinction groups (Chow/Ext/Reinst) would later undergo reinstatement, whereas the other (Chow/Ext/No Reinst) would not. The following day, rats in each of the four groups (Chow/React, Curcumin/React, Chow/Ext/Reinst, and Chow/Ext/No Reinst) received a tone test consisting of 5 CS presentations as an initial test for extinction retention and reconsolidation impairment. To test for reinstatement of fear, rats in the reactivated groups (Chow/React; Curcumin/React) and those in one of the extinguished groups (Chow/Ext/Reinst) received a reinstatement session consisting of exposure to the US in a distinct context. After 24 h, rats in each group were given a second tone test consisting of 5 CS presentations as a test of reinstatement. The following day, all rats received a final tone test in a distinct, novel context to test for fear memory renewal (Figure 5a).

All groups exhibited intact PSF during the initial training session (Figure 5b). The ANOVA for PSF scores revealed a significant effect of trial ($F_{(2,68)}=207.14$, $p<0.001$), and nonsignificant effects of group ($F_{(3,34)}=0.11$, $p>0.05$) and the group by trial interaction ($F_{(6,68)}=0.12$, $p>0.05$). The ANOVA for the reactivation session (Figure 5c) revealed a significant effect of trial (pre-CS *vs* CS; $F_{(1,68)}=29.25$, $p<0.001$), but nonsignificant effects of group ($F_{(2,17)}=3.13$, $p>0.05$) and the group by trial interaction ($F_{(2,17)}=4.91$, $p>0.05$), indicating that each of the groups exhibited intact and equivalent memory reactivation. The ANOVA for the extinction session (Figure 5d) revealed a significant effect of trial ($F_{(39,663)}=11.53$, $p<0.001$) and nonsignificant effects of group ($F_{(1,17)}=0.01$, $p>0.05$) and the group by trial interaction ($F_{(39,663)}=0.16$, $p>0.05$), indicating that each of the groups exhibited equivalent memory extinction across trials.

During the initial retention test, the Curcumin/React group and the two extinguished groups exhibited impaired reconsolidation of the fear memory and intact fear extinction, respectively (Figure 5e). The ANOVA revealed a significant effect for group ($F_{(3,35)}=20.86$, $p<0.001$) and trial ($F_{(4,140)}=18.02$, $p<0.001$), but no significant interaction ($F_{(12,140)}=1.00$, $p>0.05$). Duncan's *post hoc* analysis re-

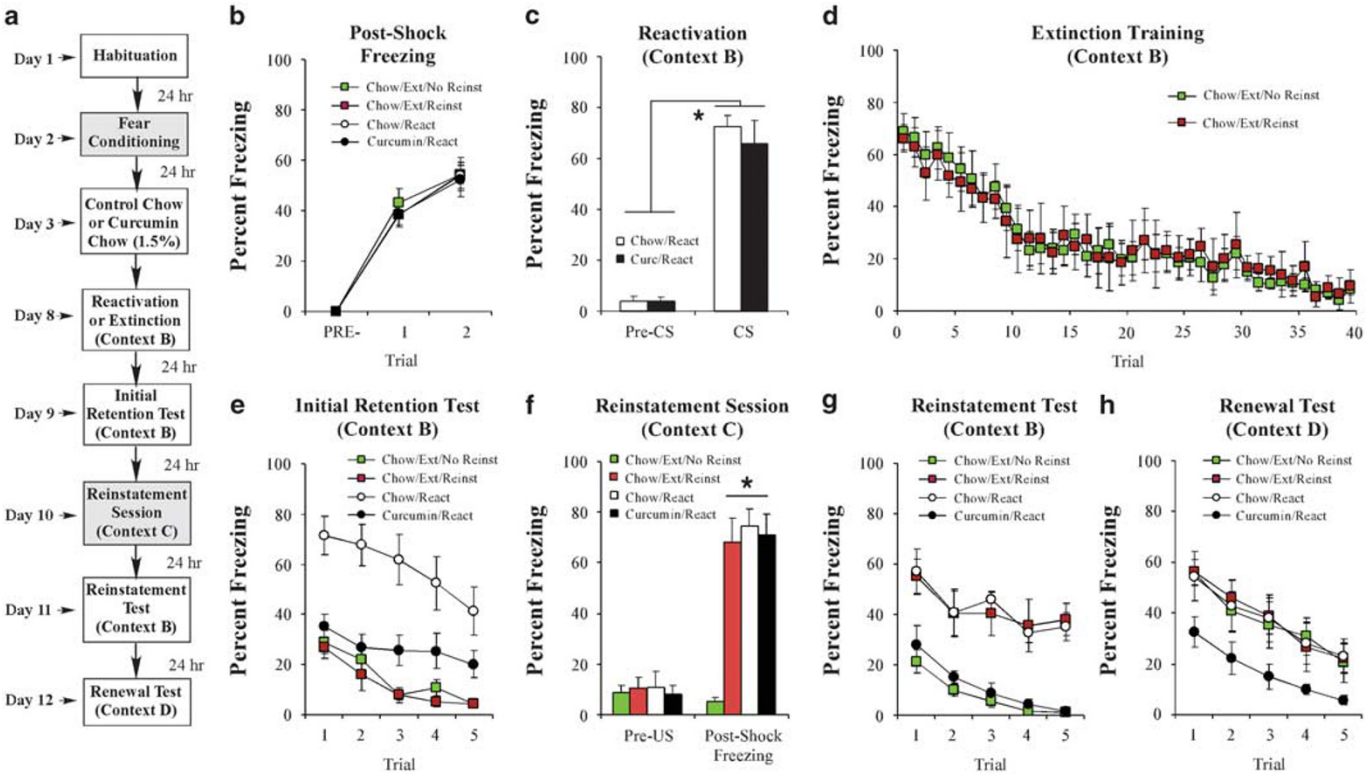

Figure 5 Curcumin-induced reconsolidation impairments are not subject to reinstatement or renewal. (a) Schematic of the behavioral protocol. (b) Mean (±SEM) postshock freezing in Chow/Ext/No Reinst ($n=10$), Chow/Ext/Reinst ($n=9$), Chow/React ($n=9$), and Curcumin/React ($n=10$) groups immediately after the conditioning trials in context A. (c) Mean (±SEM) freezing in the reactivated groups during the reactivation trial in context B. *$P<0.05$ relative to the pre-CS period. (d) Mean (±SEM) freezing during extinction training in context B in the two groups fed a diet of regular chow. Note that one of these groups (Chow/Ext/Reinst) would later be exposed to an unsignaled shock US to reinstate the fear memory, whereas the other group (Chow/Ext/No Reinst) would not (f). (e) Mean (±SEM) freezing in each group in context B during the initial retention test 24 h after reactivation or extinction trials. (f) Mean (±SEM) PSF in each group during the reinstatement session in context C. (g) Mean (±SEM) freezing during the second tone test (Reinstatement Test) given in context B 24 h after the reinstatement session. Note that the fear memory has returned in the Chow/Ext/Reinst group, but not in the Curcumin/React group. (h) Mean (±SEM) freezing during the third tone test (renewal test) given in context D 24 h after the Reinstatement Test. Note that the fear memory has returned in the both of the extinction groups, but not in the Curcumin/React group.

vealed that the Chow/React group differed significantly from all other groups ($p<0.05$). Thus, rats fed curcumin during the reactivation trial (Curcumin/React) exhibited impaired PR-LTM as we have observed previously, whereas rats in the two extinction groups exhibited intact long-term extinction memory. During the reinstatement session, each of the three groups receiving the US exhibited intact PSF (Figure 5f). The ANOVA for the reinstatement session revealed significant main effects of group ($F_{(3,35)}=8.13$, $p<0.001$), trial ($F_{(1,35)}=137.47$, $p<0.001$), and the group by trial interaction ($F_{(3,35)}=19.44$, $p<0.001$), with the Chow/Ext/No Reinst group differing significantly from all other groups ($p<0.01$; Duncan's test). During the second tone test (Reinstatement Test), the Chow/Ext/Reinst group exhibited reinstatement of fear whereas the Curcumin/React group did not (Figure 5g). The ANOVA revealed significant main effects of group ($F_{(3,35)}=23.25$, $p<0.001$) and trial ($F_{(4,140)}=13.51$, $p<0.001$), and a nonsignificant group by trial interaction ($F_{(12,140)}=0.29$, $p>0.05$), with the Chow/React and Chow/Ext/Reinst groups differing significantly from the other groups ($p<0.05$, Duncan's test). Thus, curcumin-fed rats that exhibit impaired PR-LTM because of interference with the reconsolidation process (Curcumin/React) fail to recover their fear memory following presentation of an aversive US, whereas rats that exhibit impaired fear memory following extinction (Chow/Ext/Reinst) do recover their fear memory. Finally, during the third tone test (Renewal Test), each of the two extinguished groups exhibited renewal of the fear memory, whereas the Curcumin/React group did not (Figure 5h). The ANOVA revealed significant main effects of group ($F_{(3,35)}=3.54$, $p<0.05$) and trial ($F_{(4,140)}=27.73$, $p<0.001$), but a nonsignificant group by trial interaction ($F_{(12,140)}=0.20$, $p>0.05$), with the Curcumin/React group differing significantly from the other groups ($p<0.05$, Duncan's test). Thus, curcumin-fed rats that exhibit impaired PR-LTM because of interference with the reconsolidation process do not recover their memory when tested in a new context, whereas rats that exhibit impaired fear memory following extinction do.

Collectively, these findings suggest that memory loss following interference with the reconsolidation process in rats fed a diet enriched with curcumin is enduring; unlike fear memories that are impaired because of extinction, memories that fail to reconsolidate under the influence of curcumin are not susceptible to reinstatement or renewal.

DISCUSSION

The study of the cellular and molecular mechanisms underlying the consolidation and reconsolidation of Pavlovian fear memories has progressed rapidly in recent years (Schafe *et al*, 2001; Dudai and Eisenberg, 2004; Maren and Quirk, 2004; Rodrigues *et al*, 2004; Alberini, 2005; Tronson and Taylor, 2007), due in part to the promise of discovering novel pharmacological compounds for the treatment of psychological disorders, such as PTSD, that are characterized by unusually strong and persistently reactivated traumatic memories. Few compounds, however, have emerged from these efforts that are readily useful in a clinical setting. In the present study, we systematically investigated the efficacy of a dietary source of curcumin at impairing the consolidation and reconsolidation of a Pavlovian fear memory. We show that rats fed a diet enriched with curcumin before fear conditioning exhibit impaired expression of memory-related IEGs in the LA and impaired consolidation of a fear memory. Furthermore, rats fed curcumin before retrieval of either recently formed or older fear memories exhibit impaired reconsolidation of a fear memory. Finally, we show that fear memories that fail to reconsolidate under the influence of dietary curcumin are impaired in an enduring manner; unlike extinguished fear memories, they do not reinstate following reminder shocks or renew in a new context. Our findings collectively provide the first preclinical evidence that curcumin may be a beneficial pharmacological tool, either alone or in combination with existing approaches, for the treatment of psychological disorders that involve the formation and frequent reexperiencing of fearful or traumatic memories.

Curcumin is a naturally occurring lipophilic polyphenol compound derived from the rhizome of the turmeric plant (*C. longa)*, a species within the ginger family. Turmeric is a commonly used yellow-pigmented spice in Indian and East Asian cuisines and consists of several distinct curcuminoids, curcumin (diferuloylmethane) being the most widely studied. In preclinical studies, curcumin has been shown to possess a wide variety of biological actions, including anti-inflammatory, antioxidant, chemopreventative, and neuroprotective properties (Aggarwal and Shishodia, 2006; Aggarwal *et al*, 2007; Jagetia and Aggarwal, 2007; Aggarwal and Harikumar, 2009). Orally administered curcumin has been shown to be well tolerated by human subjects with relatively few side effects (Anand *et al*, 2007), and is currently the focus of clinical trials for a wide range of human diseases, including various types of cancer, heart disease, arthritis, and asthma. Furthermore, given that curcumin readily enters the brain (Anand *et al*, 2007), interest has recently grown in its use for the potential treatment of neuropsychiatric disorders ranging from dementia to schizophrenia to depression (Kulkarni and Dhir, 2010). Curcumin, for example, has shown considerable promise in rodent models of depression (Xu *et al*, 2005a, b, 2006, 2009; Bhutani *et al*, 2009; Kulkarni *et al*, 2009; Hurley *et al*, 2013) and in a recent clinical trial in patient populations with clinical depression (Sanmukhani *et al*, 2013). However, no studies, of which we are aware, have systemically examined the effects of curcumin at the preclinical level on measures of fear and anxiety or at the clinical level in the treatment of anxiety-related disorders, including PTSD.

In our experiments, we show that 5 days of dietary curcumin exposure is sufficient to impair training-related increases in the expression of Arc/Arg3.1 and Egr-1 in the LA, two IEGs that we and others have previously implicated in the consolidation of Pavlovian fear memories (Malkani *et al*, 2004; Ploski *et al*, 2008; Maddox *et al*, 2011). This finding suggests that orally administered curcumin is reaching the brain in sufficient concentrations to impair intracellular processes in LA neurons related to fear memory consolidation. Consistent with this finding, in behavioral experiments we show that curcumin effectively impairs the consolidation of an auditory Pavlovian fear memory; PSF and STM are intact, whereas LTM is significantly impaired. Importantly, the observation of intact PSF and STM rules out the possibility that the observed LTM deficits in curcumin-fed rats may be because of altered sensory (eg, tone or shock) processing at the time of fear acquisition or to motivational or performance factors at the time of testing. This finding is further reinforced in our reconsolidation experiments, where we observed no effect of dietary curcumin on reactivation (or retrieval) of a Pavlovian fear memory or on PR-STM. Curcumin was, however, observed to impair PR-LTM, but only in rats in which the fear memory had been reactivated. Importantly, the curcumin-enriched diet was observed to effectively impair the reconsolidation of both a recently formed (within 24 h) as well as an older, 'well-consolidated' (2-week-old) fear memory, suggesting that even older fear memories are susceptible to reconsolidation impairment using this compound. This latter finding adds to a growing body of evidence that amygdala-dependent memories are susceptible to reconsolidation interference regardless of their age (Nader *et al*, 2000; Debiec and LeDoux, 2004; Maddox and Schafe, 2011a), and has important implications for the use of reconsolidation-based approaches in a clinical setting given that many patients may not seek help immediately following a traumatic experience. Finally, and perhaps most important from a clinical perspective, we show that fear memories that fail to reconsolidate under the influence of dietary curcumin are impaired in an enduring manner; we found no evidence that they are subject to reinstatement following an unsignaled footshock or to renewal following a shift in the testing context, both of which are trademark characteristics of fear memories that are lost because of fear extinction procedures (Pavlov, 1927; Bouton and Bolles, 1979; Bouton and Ricker, 1994). Thus, the present study provides additional evidence in support of the use of 'reconsolidation'-based approaches for the treatment and long-term maintenance of traumatic memories.

The exact molecular mechanism by which curcumin impairs fear memory consolidation and reconsolidation processes remains to be explored. Curcumin has been shown to exhibit a remarkably wide range of pharmacological effects that may account for its diverse medicinal properties, including effects on neurotransmitters, trophic factors, protein kinases, and transcription factors (Aggarwal and Harikumar, 2009). One attractive hypothesis is that curcumin may be regulating fear memory consolidation processes via modulating the IKK-NF-κB signaling pathway and resultant modification of chromatin structure on memory-related IEGs in the LA. The NF-κB pathway, of which curcumin is known to be a potent inhibitor (Jobin *et al*, 1999; Bremner and Heinrich, 2002), has traditionally

been studied in the context of cellular inflammatory processes and activation of the immune response (Baeuerle and Henkel, 1994). Within the past decade, however, it has become increasingly clear that NF-κB signaling is also involved in memory formation, including the consolidation (Yeh *et al*, 2004) and reconsolidation (Si *et al*, 2012) of Pavlovian fear memories. At a mechanistic level, recent findings have suggested that IKK–NF-κB may regulate memory by promoting alterations in chromatin structure on memory-related genes (Lubin and Sweatt, 2007). Retrieval of a contextual fear memory, for example, has been observed to lead to an increase in histone H3 acetylation on the Zif-268 (Egr-1) gene in the hippocampus, an effect that is blocked by intrahippocampal infusions of an IKK inhibitor (Lubin and Sweatt, 2007). Once in the nucleus, it has been suggested that NF-κB may promote altered patterns of acetylation on memory-related genes by recruiting coactivators such as p300/CBP (Chen *et al*, 2001), a histone acetyltransferase (HAT) that is also potently inhibited by curcumin (Balasubramanyam *et al*, 2004). Fear conditioning has been reported to increase the association of NF-κB with CBP in the amygdala, an effect that can be further enhanced through the use of a histone deacetylase (HDAC) inhibitor (Yeh *et al*, 2004). Furthermore, our lab has shown that pharmacological inhibition of HAT or HDAC activity in the LA can impair or further enhance the consolidation and reconsolidation of Pavlovian fear memories, respectively (Maddox and Schafe, 2011b; Monsey *et al*, 2011; Maddox *et al*, 2013). Given these findings, it is plausible to hypothesize that curcumin may be regulating fear memory consolidation processes via the inhibition of IKK–NF-κB signaling, the inhibition of p300/CBP HAT activity, or a combination of both mechanisms. Additional studies will be required to evaluate this hypothesis further.

In summary, our findings provide compelling evidence that a naturally occurring compound derived from the diet can significantly impair either newly formed or reactivated fear memories in a widely studied animal model of traumatic memory formation in PTSD. Our findings suggest that curcumin, or a derivative thereof, may hold great promise as a therapeutic agent in alleviating fear and anxiety disorders characterized by persistent, unwanted memories when administered either during traumatic memory formation or in conjunction with 'reconsolidation'-based forms of psychotherapy. In this paper, we clearly focus on only one aspect of PTSD—fear memory formation. Clinical PTSD, of course, is thought to involve long-term stress-related changes in the brain (Yehuda and LeDoux, 2007; Heim and Nemeroff, 2009; Pitman *et al*, 2012) in addition to the formation of traumatic memories. Curcumin, however, may prove an ideal avenue of treatment for PTSD given its increasingly well-documented antidepressant properties (Kulkarni *et al*, 2009; Kulkarni and Dhir, 2010) in addition to its ability to impair newly formed and reactivated fear memories. Future studies employing human clinical populations will be critical for evaluating this hypothesis.

FUNDING AND DISCLOSURE

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

We thank Dr Kristie T Ota for help with the corticosterone assay. Glenn E Schafe has been funded by the National Institute of Mental Health (MH 073949), the Center for Translational and Basic Research (CTBR) at Hunter College (National Institute of Minority Health and Health Disparities Grant MD 007599), and by Yale University. Melissa S Monsey was supported by an American Psychological Association Dissertation Award during this project.

REFERENCES

Aggarwal BB, Shishodia S (2006). Molecular targets of dietary agents for prevention and therapy of cancer. *Biochem Pharmacol* **71**: 1397–1421.

Aggarwal BB, Harikumar KB (2009). Potential therapeutic effects of curcumin, the anti-inflammatory agent, against neurodegenerative, cardiovascular, pulmonary, metabolic, autoimmune and neoplastic diseases. *Int J Biochem Cell Biol* **41**: 40–59.

Aggarwal BB, Sundaram C, Malani N, Ichikawa H (2007). Curcumin: the Indian solid gold. *Adv Exp Med Biol* **595**: 1–75.

Alberini CM (2005). Mechanisms of memory stabilization: are consolidation and reconsolidation similar or distinct processes? *Trends Neurosci* **28**: 51–56.

Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB (2007). Bioavailability of curcumin: problems and promises. *Mol Pharm* **4**: 807–818.

Baeuerle PA, Henkel T (1994). Function and activation of NF-kappa B in the immune system. *Annu Rev Immunol* **12**: 141–179.

Balasubramanyam K, Varier RA, Altaf M, Swaminathan V, Siddappa NB, Ranga U *et al* (2004). Curcumin, a novel p300/CREB-binding protein-specific inhibitor of acetyltransferase, represses the acetylation of histone/nonhistone proteins and histone acetyltransferase-dependent chromatin transcription. *J Biol Chem* **279**: 51163–51171.

Berger W, Mendlowicz MV, Marques-Portella C, Kinrys G, Fontenelle LF, Marmar CR *et al* (2009). Pharmacologic alternatives to antidepressants in posttraumatic stress disorder: a systematic review. *Prog Neuropsychopharmacol Biol Psychiatry* **33**: 169–180.

Bhutani MK, Bishnoi M, Kulkarni SK (2009). Anti-depressant like effect of curcumin and its combination with piperine in unpredictable chronic stress-induced behavioral, biochemical and neurochemical changes. *Pharmacol Biochem Behav* **92**: 39–43.

Bouton ME, Bolles RC (1979). Contextual control of the extinction of conditioned fear. *Learn Motiv* **10**: 445–466.

Bouton ME, Ricker ST (1994). Renewal of extinguished responding in a second context. *Animal Learn Behav* **22**: 317–324.

Brady K, Pearlstein T, Asnis GM, Baker D, Rothbaum B, Sikes CR *et al* (2000). Efficacy and safety of sertraline treatment of posttraumatic stress disorder: a randomized controlled trial. *JAMA* **283**: 1837–1844.

Bremner P, Heinrich M (2002). Natural products as targeted modulators of the nuclear factor-kappaB pathway. *J Pharm Pharmacol* **54**: 453–472.

Chen L, Fischle W, Verdin E, Greene WC (2001). Duration of nuclear NF-kappaB action regulated by reversible acetylation. *Science* **293**: 1653–1657.

Davidson J, Pearlstein T, Londborg P, Brady KT, Rothbaum B, Bell J *et al* (2001a). Efficacy of sertraline in preventing relapse of posttraumatic stress disorder: results of a 28-week double-blind, placebo-controlled study. *Am J Psychiatry* **158**: 1974–1981.

Davidson JR, Rothbaum BO, van der Kolk BA, Sikes CR, Farfel GM (2001b). Multicenter, double-blind comparison of sertraline and placebo in the treatment of posttraumatic stress disorder. *Arch Gen Psychiatry* **58**: 485–492.

Debiec J, LeDoux JE (2004). Disruption of reconsolidation but not consolidation of auditory fear conditioning by noradrenergic blockade in the amygdala. *Neuroscience* **129**: 267–272.

Dudai Y, Eisenberg M (2004). Rites of passage of the engram: reconsolidation and the lingering consolidation hypothesis. *Neuron* **44**: 93–100.

Duvarci S, Nader K (2004). Characterization of fear memory reconsolidation. *J Neurosci* **24**: 9269–9275.

Heim C, Nemeroff CB (2009). Neurobiology of posttraumatic stress disorder. *CNS Spectr* **14**: 13–24.

Hurley LL, Akinfiresoye L, Nwulia E, Kamiya A, Kulkarni AA, Tizabi Y (2013). Antidepressant-like effects of curcumin in WKY rat model of depression is associated with an increase in hippocampal BDNF. *Behav Brain Res* **239**: 27–30.

Jagetia GC, Aggarwal BB (2007). "Spicing up" of the immune system by curcumin. *J Clin Immunol* **27**: 19–35.

Jobin C, Bradham CA, Russo MP, Juma B, Narula AS, Brenner DA *et al* (1999). Curcumin blocks cytokine-mediated NF-kappa B activation and proinflammatory gene expression by inhibiting inhibitory factor I-kappa B kinase activity. *J Immunol* **163**: 3474–3483.

Kessler RC, Petukhova M, Sampson NA, Zaslavsky AM, Wittchen HU (2012). Twelve-month and lifetime prevalence and lifetime morbid risk of anxiety and mood disorders in the United States. *Int J Methods Psychiatr Res* **21**: 169–184.

Kindt M, Soeter M, Vervliet B (2009). Beyond extinction: erasing human fear responses and preventing the return of fear. *Nat Neurosci* **12**: 256–258.

Kulkarni S, Dhir A, Akula KK (2009). Potentials of curcumin as an antidepressant. *ScientificWorld Journal* **9**: 1233–1241.

Kulkarni SK, Dhir A (2010). An overview of curcumin in neurological disorders. *Indian J Pharm Sci* **72**: 149–154.

Lubin FD, Sweatt JD (2007). The IkappaB kinase regulates chromatin structure during reconsolidation of conditioned fear memories. *Neuron* **55**: 942–957.

Maddox SA, Schafe GE (2011a). The activity-regulated cytoskeletal-associated protein (Arc/Arg3.1) is required for reconsolidation of a Pavlovian fear memory. *J Neurosci* **31**: 7073–7082.

Maddox SA, Schafe GE (2011b). Epigenetic alterations in the lateral amygdala are required for reconsolidation of a Pavlovian fear memory. *Learn Mem* **18**: 579–593.

Maddox SA, Monsey MS, Schafe GE (2011). Early growth response gene 1 (Egr-1) is required for new and reactivated fear memories in the lateral amygdala. *Learn Mem* **18**: 24–38.

Maddox SA, Watts CS, Schafe GE (2013). p300/CBP histone acetyltransferase activity is required for newly acquired and reactivated fear memories in the lateral amygdala. *Learn Mem* **20**: 109–119.

Mahan AL, Ressler KJ (2012). Fear conditioning, synaptic plasticity and the amygdala: implications for posttraumatic stress disorder. *Trends Neurosci* **35**: 24–35.

Malkani S, Rosen JB (2000). Specific induction of early growth response gene 1 in the lateral nucleus of the amygdala following contextual fear conditioning in rats. *Neuroscience* **97**: 693–702.

Malkani S, Wallace KJ, Donley MP, Rosen JB (2004). An egr-1 (zif268) antisense oligodeoxynucleotide infused into the amygdala disrupts fear conditioning. *Learn Mem* **11**: 617–624.

Maren S (2011). Seeking a spotless mind: extinction, deconsolidation, and erasure of fear memory. *Neuron* **70**: 830–845.

Maren S, Quirk GJ (2004). Neuronal signalling of fear memory. *Nat Rev Neurosci* **5**: 844–852.

Milad MR, Rauch SL, Pitman RK, Quirk GJ (2006). Fear extinction in rats: implications for human brain imaging and anxiety disorders. *Biol Psychol* **73**: 61–71.

Monsey MS, Ota KT, Akingbade IF, Hong ES, Schafe GE (2011). Epigenetic alterations are critical for fear memory consolidation and synaptic plasticity in the lateral amygdala. *PLoS One* **6**: e19958.

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

Pavlov IP (1927). *Conditioned Reflexes*. Oxford University Press: London.

Pitman RK, Rasmusson AM, Koenen KC, Shin LM, Orr SP, Gilbertson MW *et al* (2012). Biological studies of post-traumatic stress disorder. *Nat Rev Neurosci* **13**: 769–787.

Ploski JE, Pierre VJ, Smucny J, Park K, Monsey MS, Overeem KA *et al* (2008). The activity-regulated cytoskeletal-associated protein (Arc/Arg3.1) is required for memory consolidation of pavlovian fear conditioning in the lateral amygdala. *J Neurosci* **28**: 12383–12395.

Prasad S, Tyagi AK, Aggarwal BB (2014). Recent developments in delivery, bioavailability, absorption and metabolism of curcumin: the golden pigment from golden spice. *Cancer Res Treat* **46**: 2–18.

Quirk GJ, Pare D, Richardson R, Herry C, Monfils MH, Schiller D *et al* (2010). Erasing fear memories with extinction training. *J Neurosci* **30**: 14993–14997.

Rodrigues SM, Schafe GE, LeDoux JE (2004). Molecular mechanisms underlying emotional learning and memory in the lateral amygdala. *Neuron* **44**: 75–91.

Sandkuhler J, Lee J (2013). How to erase memory traces of pain and fear. *Trends Neurosci* **36**: 343–352.

Sanmukhani J, Satodia V, Trivedi J, Patel T, Tiwari D, Panchal B *et al* (2013). Efficacy and safety of curcumin in major depressive disorder: a randomized controlled trial. *Phytother Res* **28**: 579–585.

Schafe GE, Nader K, Blair HT, LeDoux JE (2001). Memory consolidation of Pavlovian fear conditioning: a cellular and molecular perspective. *Trends Neurosci* **24**: 540–546.

Sears RM, Schiff HC, LeDoux JE (2014). Molecular mechanisms of threat learning in the lateral nucleus of the amygdala. *Prog Mol Biol Transl Sci* **122**: 263–304.

Si J, Yang J, Xue L, Yang C, Luo Y, Shi H *et al* (2012). Activation of NF-kappaB in basolateral amygdala is required for memory reconsolidation in auditory fear conditioning. *PLoS One* **7**: e43973.

Tronson NC, Taylor JR (2007). Molecular mechanisms of memory reconsolidation. *Nat Rev Neurosci* **8**: 262–275.

Xu Y, Ku BS, Yao HY, Lin YH, Ma X, Zhang YH *et al* (2005a). The effects of curcumin on depressive-like behaviors in mice. *Eur J Pharmacol* **518**: 40–46.

Xu Y, Ku BS, Yao HY, Lin YH, Ma X, Zhang YH *et al* (2005b). Antidepressant effects of curcumin in the forced swim test and olfactory bulbectomy models of depression in rats. *Pharmacol Biochem Behav* **82**: 200–206.

Xu Y, Ku B, Tie L, Yao H, Jiang W, Ma X *et al* (2006). Curcumin reverses the effects of chronic stress on behavior, the HPA axis, BDNF expression and phosphorylation of CREB. *Brain Res* **1122**: 56–64.

Xu Y, Lin D, Li S, Li G, Shyamala SG, Barish PA *et al* (2009). Curcumin reverses impaired cognition and neuronal plasticity induced by chronic stress. *Neuropharmacology* **57**: 463–471.

Yeh SH, Lin CH, Gean PW (2004). Acetylation of nuclear factor-kappaB in rat amygdala improves long-term but not short-term retention of fear memory. *Mol Pharmacol* **65**: 1286–1292.

Yehuda R (2002). Post-traumatic stress disorder. *N Engl J Med* **346**: 108–114.

Yehuda R, LeDoux J (2007). Response variation following trauma: a translational neuroscience approach to understanding PTSD. *Neuron* **56**: 19–32.

Zovkic IB, Sweatt JD (2013). Epigenetic mechanisms in learned fear: implications for PTSD. *Neuropsychopharmacology* **38**: 77–93.

Supplementary Information accompanies the paper on the Neuropsychopharmacology website (http://www.nature.com/npp)