Neuropsychopharmacology (2017) 42, 581–583

www.neuropsychopharmacology.org

Commentary

Garcinol: A Magic Bullet of Amnesia for Maladaptive Memories?

Rita A Fuchs*[,1] and Ryan J McLaughlin[1]

[1]*Department of Integrative Physiology and Neuroscience, Washington State University, College of Veterinary Medicine, Pullman, WA, USA*

Neuropsychopharmacology (2017) **42,** 581–583; doi:10.1038/npp.2016.165; published online 14 September 2016

According to the most recent US statistics, ~ 15% of individuals aged 12 and older report having used cocaine at least once in their lifetime (National Survey on Drug Use and Health, 2015), and cocaine continues to be the most frequently cited drug of abuse during drug-related emergency room visits (Drug Abuse Warning Network, 2014). Relapse, frequently precipitated by exposure to drug-associated environmental cues (Rohsenow *et al*, 1990), is the most significant impediment in the treatment of cocaine addiction, and pharmacological interventions that disrupt the acute motivational effects of cocaine-paired cues or facilitate the establishment of inhibitory cue-no drug associations have been largely unsuccessful due to unfavorable off-target effects and temporary/context-dependent therapeutic effects, respectively (for review, see Torregrossa and Taylor, 2016). Thus, FDA-approved medications for cocaine addiction remain unavailable. However, reports of novel therapeutic targets, compounds, and methodological advances suggest that progress is being made toward the development of effective therapies for cocaine addiction. One such report is offered by Monsey *et al* (2016) in the current issue of *Neuropsychopharmacology*.

On the basis of research conducted in rats, the authors propose a novel experimental treatment that impairs cocaine-cue memories and subsequent cue-induced goal-directed behavior. The idea that the long-term memories of maladaptive associations can be weakened is a corollary of the memory reconsolidation hypothesis proposed by Nader *et al* (2000). They postulated that fear memories destabilize upon retrieval and must undergo a protein synthesis-dependent reconsolidation process in order to be maintained over time. Furthermore, according to more recent literature, drug memories undergo a similar reconsolidation process, and reconsolidation inhibitor manipulations applied following drug memory destabilization disrupt subsequent Pavlovian cocaine-conditioned responses and instrumental goal-directed behaviors in animal models of drug relapse (for review, see Hernandez and Kelley, 2005; Sorg, 2012; García-Pardo *et al*, 2016).

*Correspondence: Dr RA Fuchs, Department of Integrative Physiology and Neuroscience, Washington State University, College of Veterinary Medicine, P.O. Box 647620, Pullman, WA 99164-7620, USA, Tel: +1 202 5093356164, Fax: +1 202 5093354650, E-mail: ritafuchs@vetmed.wsu.edu

Received 12 August 2016; accepted 16 August 2016; accepted article preview online 23 August 2016

The study by Monsey *et al* (2016) indicates that garcinol, a polyisoprenylated benzophenone derivative, disrupts cocaine memory reconsolidation. In the study, garcinol was systemically administered to rats at the putative time of cocaine memory reconsolidation, 30 min after exposure to the previously cocaine-paired conditioned stimuli (CS). Remarkably, garcinol completely inhibited subsequent CS-induced cocaine-seeking behavior and the acquisition of a new CS-reinforced response in the absence of cocaine reinforcement. The effects of garcinol were dependent on explicit CS memory reactivation and specific to the reactivated CS-drug associative memory. Garcinol failed to inhibit cocaine-primed reinstatement of cocaine-seeking behavior, and thus it may not be of much benefit once cocaine is on board. This was to be expected, given that cocaine priming and cocaine-associated cues can trigger relapse through different mechanisms that need to be addressed individually. Importantly, the inhibitory effects of garcinol on cue-induced reinstatement endured following more extensive CS-cocaine training in the form of a 24-day cocaine self-administration regimen and persisted after a 2-week forced abstinence period.

Monsey *et al* (2016) findings are significant because, disappointingly, research examining the effects of systemic manipulations on cocaine memory reconsolidation has not yet led to feasible and efficacious treatments for cocaine addiction for a number of reasons. Most studies involved site-specific brain manipulations and aimed to increase our mechanistic understanding of cocaine memory reconsolidation. Findings from such studies may provide rationale for the development of nuanced, site-directed treatments for cocaine addiction in the future; however, their translational potential is limited in the short term. Several other studies focused on compounds that are systemically bioavailable but unsuitable for administration in clinical populations. Finally, encouraging preclinical findings with compounds that are approved for human use, such as mTOR inhibitors, have not been followed up in clinical studies (for review, see Torregrossa and Taylor, 2016). One exception to this has been the beta adrenergic receptor antagonist propranolol. In substance abusers, acute or repeated propranolol administration following cue exposure or guided addiction-related memory reactivation reduced self-reports of craving (Saladin *et al*, 2013; Longergan *et al*, 2016). However, the effects of propranolol were modest and transient in humans (Saladin *et al*, 2013) and inconsistent across animal models (Milton *et al*, 2008; Dunbar and Taylor, 2016). Thus,

Table 1 Schematic of the 'Two Cue Procedure'

Self-administration		Memory reactivation	Treatment	Test of cocaine seeking	Actual/predicted results
Cocaine + CS1 (50%) CS2 (50%)	Forced abstinence	CS1 exposure in a novel context No CS2 exposure	Garcinol DMSO None	Response-contingent CS1 then CS2 presentation (30 min each)	Garcinol CS1 < DMSO CS1
		CS2 exposure in a novel context	*6-h delay Garcinol DMSO*		*Garcinol CS1 < (garcinol CS2 = DMSO CS1/CS2)*

Conditioned stimuli (CS), a light, and a tone are independently paired with cocaine infusions during drug self-administration training. In the study by Monsey *et al* (2016), CS1 (ie, light or tone, CS type counterbalanced) was presented intermittently in a novel context to reactivate CS1 cocaine memories. Treatment (ie, 10 mg/kg garcinol or DMSO vehicle, i.p.) was administered 30 min after the memory reactivation session. CS2 was not manipulated. Twenty-four hours later, cocaine-seeking behavior was assessed in the response contingent presence of CS1 and CS2 (order of tests counterbalanced). Italicized font: suggested alternative to No CS2 exposure. Here, CS2 cocaine memories are reactivated in the same subject on a different day. However, treatment following CS2 presentation is administered with a 6-h time delay, outside the time window of memory reconsolidation. Treatment remains a between-subjects factor.

safe and effective inhibitors of drug memory reconsolidation have been elusive.

Monsey *et al* (2016) findings have great translational potential and will probably instigate mechanistic studies that further increase our understanding of memory reconsolidation. Garcinol is a naturally occurring compound isolated from the rind of the fruit, *Garcinia indica*, which has been used in traditional medicine for centuries for its antioxidant, anti-inflammatory, and anticancer properties (Liu *et al*, 2015; Padhye *et al*, 2009). This may expedite the transition from basic research in laboratory animals to studies in human subjects. The mechanisms of action for the amnesic effects of garcinol have not been determined, but garcinol may interfere with epigenetic mechanisms involved in cocaine memory reconsolidation (Liu *et al*, 2015; Padhye *et al*, 2009). Consistent with this possibility, intralateral amygdala infusion of garcinol or c646, a selective p300/CBP histone acetyltransferase inhibitor, impairs histone H3 acetylation and fear memory reconsolidation (Maddox *et al*, 2013a; Maddox *et al*, 2013b). However, garcinol also has anticholinesterase activity (Padhye *et al*, 2009). Therefore, the dominant mechanism of action and resulting effect of garcinol on memory function may vary dose dependently, as well as across experimental paradigms, which will be important to determine. Hence, the findings reported by Monsey *et al* (2016) will likely stimulate much crucial basic research in the future.

Finally, the study is significant from a methodological perspective. An attractive feature of all memory reconsolidation studies from Jane Taylor's laboratory is that cues are reactivated outside of the cocaine-paired environmental context. This permits the selective experimental manipulation of cue-cocaine, *vs* context-cocaine, memories and is similar to memory reconsolidation procedures utilized in clinical settings. However, the most novel and elegant methodological feature of the study by Monsey *et al* (2016) is that, in one of the experiments, two CS were paired with cocaine (Table 1) and were manipulated independently to demonstrate that the effects of garcinol on reconsolidation are cue memory-specific. A full between-subjects design was employed in this experiment, which resulted in differential exposure to the CS1 and CS2 without cocaine prior to testing. A partial within-subjects design (see italicized font in Table 1), in which reactivation and no-reactivation conditions (ie, treatment outside the time window of memory reconsolidation) are conducted in the same subject, would equalize CS1 and CS2 exposure history and conserve research subjects. Nevertheless, the 'two cue procedure' as employed by Monsey *et al* (2016) represents a significant advancement in modeling memory reconsolidation.

In conclusion, the findings by Monsey *et al* (2016) suggest that garcinol disrupts memory reconsolidation processes that underlie enduring cue control over goal-directed behaviors in animal models of drug relapse and conditioned reinforcement. Future studies will need to evaluate whether garcinol has significant therapeutic effects in substance abusers exposed to multiple relapse triggers including psychosocial stress and small amounts of drug. Independent of whether garcinol turns out to be the magic bullet (if one exists), the sophisticated methodology developed by Monsey *et al* (2016) will continue to have a significant impact on modeling appetitive memory reconsolidation and on research into effective pharmacotherapies for cocaine addiction.

FUNDING AND DISCLOSURE

RAF research is supported by extramural funds from NIDA and research funds from the state of Washington administered through the Alcohol and Drug Abuse Research Program. RJM research is supported by the Washington State University College of Veterinary Medicine and the Alcohol and Drug Abuse Research Program. The authors declare no conflict of interest.

ACKNOWLEDGMENTS

We thank Dr Yavin Shaham for insightful comments on a draft of this manuscript.

REFERENCES

Dunbar AB, Taylor JR (2016). Inhibition of protein synthesis but not beta-adrenergic receptors blocks reconsolidation of a cocaine-associated cue memory. *Learn Mem* **23**: 391–398.

García-Pardo MP, Roger-Sanchez C, Rodríguez-Arias M, Miñarro J (2016). Pharmacological manipulation of protein kinases as a new approach to treat addiction to cocaine and opiates. *Eur J Pharmacol* **781**: 10–24.

Hernandez PJ, Kelley AE (2005). Cracking addiction the second time around: reconsolidation of drug-related memories. *Neuron* **47**: 772–775.

Liu C, Ho PC, Wong FC, Sethi G, Wang LZ, Goh BC (2015). Garcinol: current status of its anti-oxidative, anti-inflammatory and anti-cancer effects. *Cancer Lett* **362**: 8–14.

Longergan M, Saumier D, Tremblay J, Kieffer B, Brown TG, Brunet A (2016). Reactivating addiction-related memories under propranolol to reduce craving: a pilot randomized controlled trial. *J Behav Ther Exp Psychiatry* **50**: 245–249.

Maddox SA, Watts CS, Doyere V, Schafe GE (2013a). A naturally-occurring histone acetyltransferase inhibitor derived from *Garcinia indica* impairs newly acquired and reactivated fear memories. *PLoS One* **8**: e54463.

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

Milton AL, Lee JL, Everitt BJ (2008). Reconsolidation of appetitive memories for both natural and drug reinforcement is dependent on {beta}-adrenergic receptors. *Learn Mem* **15**: 88–92.

Monsey MS, Sanchez H, Taylor JR (2016). The naturally-occurring compound *Garcinia Indica* selectively impairs the reconsolidation of a cocaine-associated memory. *Neuropsychopharmacology*10.1038/npp.2016.117 [Epub ahead of print].

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

Padhye S, Ahmad A, Oswal N, Sarkar FH (2009). Emerging role of Garcinol, the antioxidant chalcone from *Garcinia indica* Choisy and its synthetic analogs. *J Hematol Oncol* **2**: 38.

Rohsenow DJ, Niaura RS, Childress AR, Abrams DB, Monti PM (1990). Cue reactivity in addictive behaviors: theoretical and treatment implications. *Int J Addict* **25**: 957–993.

Saladin ME, Gray KM, McRae-Clark AL, Larowe SD, Yeatts SD, Baker NL *et al* (2013). A double blind, placebo-controlled study of the effects of post-retrieval propranolol on reconsolidation of memory for craving and cue reactivity in cocaine dependent humans. *Psychopharmacology* **226**: 721–737.

Sorg BA (2012). Reconsolidation of drug memories. *Neurosci Biobehav Rev* **36**: 1400–1417.

Torregrossa MM, Taylor JR (2016). Neuroscience of learning and memory for addiction medicine: from habit formation to memory reconsolidation. *Prog Brain Res* **223**: 91–113.