Neurobiology of Learning and Memory 142 (2017) 118–125

Contents lists available at ScienceDirect

Neurobiology of Learning and Memory

journal homepage: www.elsevier.com/locate/ynlme

Consolidation and reconsolidation are impaired by oral propranolol administered before but not after memory (re)activation in humans

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ARTICLE INFO

Article history:
Received 24 August 2016
Revised 10 December 2016
Accepted 14 December 2016
Available online 18 December 2016

Keywords:
Emotional memory
Propranolol
Reconsolidation

ABSTRACT

Propranolol administered immediately after learning or after recall has been found to impair memory consolidation or reconsolidation (respectively) in animals, but less reliably so in humans. Since reconsolidation impairment has been proposed as a treatment for mental disorders that have at their core an emotional memory, it is desirable to understand how to reliably reduce the strength of pathogenic memories in humans. We postulated that since humans (unlike experimental animals) typically receive propranolol orally, this introduces a delay before this drug can exert its memory impairment effects, which may render it less effective. As a means to test this, in two double-blind placebo-controlled experiments, we examined the capacity of propranolol to impair consolidation and reconsolidation as a function of timing of ingestion in healthy subjects. In Experiment 1, (n = 36), propranolol administered immediately after learning or recall failed to impair the consolidation or reconsolidation of the memory of a standardized slideshow with an accompanying emotional story. In Experiment 2 (n = 50), propranolol given 60–75 min before learning or recall successfully impaired memory consolidation and reconsolidation. These results suggest that it is possible to achieve reliable memory impairment in humans if propranolol is given before learning or before recall, but not after.

1. Introduction

Emotional events can lead to long-lasting and vivid memories. This evolutionary asset may allow us better to recognize features of our environment that may be important to our subsequent survival (Tully & Bolshakov, 2010). However, emotional memories may also underlie psychiatric conditions such as posttraumatic stress disorder (PTSD) (Pitman, 1989). Therefore, understanding how emotional memories may be reduced may provide new insight for the treatment of mental disorders that have at their core a strong emotional memory (Brunet, Poundja, et al., 2011).

It is well-established that newly formed memories remain in a labile state after encoding, as they progress from short- to long-term memory storage through a process termed consolidation (McGaugh, 2000). Similarly, consolidated memories that are reactivated may undergo a process that recapitulates, at least in part, the process of consolidation, hence the term *re*consolidation (Nader, Schafe, & LeDoux, 2000; Przybyslawski & Sara, 1997; Sara, 2000a). Consolidation and reconsolidation both involve a time-dependent cascade of molecular events (Alberini, 2005; Cheval et al., 2012; Dudai & Eisenberg, 2004), which can be disrupted pharmacologically or behaviourally to induce memory impairment (Besnard, Caboche, & Laroche, 2012). One way of reliably impairing memory in animals involves administering an 'amnestic agent,' such as the beta-adrenergic blocker propranolol, systemically or centrally (a) after new learning, in order to impair consolidation (e.g. Liang, Juler, & McGaugh, 1986; Roozendaal, Castello, Vedana, Barsegyan, & McGaugh, 2008), or (b) after memory retrieval (reactivation) in order to impair reconsolidation (Przybyslawski, Roullet, & Sara, 1999). Propranolol is a β-blocker that has an affinity for both β_1 and β_2 adrenoceptors, which are G protein couple receptors (Hoffman, 2001). Propranolol's amnestic activity is ascribed to its antagonist effect on the β adrenoceptors, which prevents norepinephrine from exerting its full effect. Specifically, by binding to the β adrenoceptor, propranolol prevents adenylyl cyclase from inducing the molecular cascade of second messengers (cyclic adenosine monophosphate (cAMP), protein kinase A (PKA), cAMP response element binding protein (CREB))

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http://dx.doi.org/10.1016/j.nlm.2016.12.010
1074-7427/

which ultimately lead to the synthesis of new proteins (Ferry & McGaugh, 1999; Izquierdo & Medina, 1997; Przybyslawski et al., 1999; Tully & Bolshakov, 2010) that are thought to underlie the formation and strengthening of memory traces. Indeed, the molecular events occurring during consolidation, comprising those linked to the cAMP/PKA/CREB pathway, are thought to reiterate (or partly reiterate) at the time of reconsolidation (Dudai & Eisenberg, 2004; Nader, 2003; Sara, 2000b). The β adrenoceptors are distributed in a number of different regions of the human brain, including hippocampus and amygdala (Joyce et al., 1992; Klimek et al., 1999; van Waarde, Vaalburg, Doze, Bosker, & Elsinga, 2004). Several studies have suggested a specific role for amygdala in emotional memory and this role appears to be partly mediated by norepinephrine (for a review, Davis & Whalen, 2001; LeDoux, 2000; Maren & Quirk, 2004; McGaugh, 2004). Because of its effect on the noradrenergic system, propranolol decreases amygdala activity, and thus interferes more effectively with emotional than non-emotional memory (McGaugh, 2004; Strange & Dolan, 2004; van Stegeren et al., 2005). Congruently, many studies have found that, in humans, propranolol reduces more readily the consolidation and reconsolidation of emotional than of non-emotional memory (Cahill, Prins, Weber, & McGaugh, 1994; Kroes, Strange, & Dolan, 2010; Maheu, Joober, Beaulieu, & Lupien, 2004; Schwabe, Nader, Wolf, Beaudry, & Pruessner, 2012; van Stegeren, Everaerd, Cahill, McGaugh, & Gooren, 1998). Post-learning and post-retrieval administration of the amnestic agent may be regarded as the optimal approach to the scientific study of memory impairment, since it allows both learning and retrieval to remain uninfluenced by the drug itself, which can only act upon the subsequent consolidation or reconsolidation phases (Nader et al., 2000; Rodrigues, Schafe, & LeDoux, 2004). In humans, some authors have successfully demonstrated that *post-retrieval* propranolol can alter reconsolidation of a fear memory (Brunet et al., 2008; Soeter & Kindt, 2012a, 2012b, 2015). However, in other experimental designs involving humans, post-retrieval oral propranolol administration has not reliably led to memory impairment (Miller, Altemus, Debiec, LeDoux, & Phelps, Unpublished in Schiller & Phelps, 2011). These conflicting findings are problematic and require an explanation (Brunet, Ashbaugh, et al., 2011), especially considering the potential for pharmacological reconsolidation impairment to serve as a novel treatment for trauma-related mental disorders, phobias, as well as addictions (Brunet et al., 2008; Lonergan et al., 2016; Soeter & Kindt, 2015).

In contrast, numerous studies have demonstrated that in humans *pre-retrieval* propranolol reliably impairs the reconsolidation of emotional episodic memory (Kroes et al., 2010; Schwabe et al., 2012) and of implicit emotional memory (Brunet, Poundja, et al., 2011; Kindt, Soeter, & Vervliet, 2009; Sevenster, Beckers, & Kindt, 2012; Soeter & Kindt, 2010; Soeter & Kindt, 2011) (for a review see Lonergan, Olivera-Figueroa, Pitman, & Brunet, 2013). Despite its clinical potential, this approach is often dismissed by basic scientists because of its inability to rule out potentially confounding anterograde effects of propranolol on memory in humans (e.g. Schiller & Phelps, 2011) which is not a problem in a post-learning or post-retrieval propranolol design. However, some authors disagree (Finnie & Nader, 2012) and argue that in humans, as long as the pre-retrieval amnestic agent does not affect the retrieval of the memory trace, it can be used as a valid way to study reconsolidation.

In order to explore the effects of the pre- vs. post-learning/retrieval approaches in humans, we conducted a first experiment using the memory paradigm developed by Cahill et al. (1994). Post-learning and post-retrieval propranolol (or placebo) were administered double-blind to healthy subjects in an attempt to impair the memory consolidation and reconsolidation, respectively, of an emotional story in the form of a slide show accompanied by an audio narrative. Based upon previously published results (McGaugh, 2000; Nader et al., 2000; Sara, 2000a) we hypothesized that post-learning and post-retrieval propranolol would impair memory for the story's emotional components but not its neutral components. However, when we failed to support this hypothesis, we then performed this experiment again, but this time we gave the propranolol prior to –instead of immediately after- learning or retrieval. Each experiment involved three groups of participants seen once a week over three consecutive weeks: the consolidation impairment visit (week 1), the reconsolidation impairment visit (week 2), and a test visit (week 3). The first group, a control group, received a placebo (PL) during both the memory consolidation and reconsolidation visits (henceforth referred to as the PL_1-PL_2 group). The second group, henceforth called *the consolidation impairment group*, received propranolol (PR) during the memory consolidation visit and a PL during the reconsolidation visit (PR_1-PL_2). The third group, henceforth called *the reconsolidation impairment group* received a PL during the memory consolidation visit and PR during the reconsolidation visit (PL_1-PR_2).

2. Material and methods

2.1. Ethics approval, recruitment, and consent

The experiments were approved by the Douglas Mental Health University Institute Research Ethics Board and a no objection letter was obtained from Health Canada. Participants were recruited through advertisements in Montréal universities. After a full explanation of the procedures, participants provided written informed consent and received a modest financial compensation of 80$ CAD upon study completion.

2.2. Participants

All participants were fluent in either French or English. Each underwent a medical evaluation (by Jacques Tremblay, M.D.) to ensure that they were in good physical and mental health, and could safely take propranolol.

Experiment 1 participants included 24 men and 17 women (of whom 8 were taking hormonal contraception). Average age was 32.6 years (SD = 11.7; range 18–59 years). Average completed years of education was 16.0 (SD = 3.3). Three participants from the PR_1-PL_2 group (3 men) and 1 participant from the PL_1-PL_2 group (1 woman) dropped out between week 1 and 2. One participant from the PL_1-PL_2 group (1 man) was excluded after week 1 upon reporting mild medication-related side effects.

Experiment 2 participants included 17 men and 37 women (of whom 15 were taking hormonal contraception) who did not participate in Experiment 1. Average age was 25.4 years (SD = 7.8; range 18–55 years). Average completed years of education was 15.8 (SD = 2.3). Three participants from the PR_1-PL_2 group (2 women and 1 man) and one participant from the PL_1-PR_2 group (1 woman) dropped out between week 1 and 2.

2.3. Exclusion criteria

Exclusion criteria included: (a) resting systolic blood pressure < 100 mmHg; (b) asthma, bronchitis, or emphysema; heart failure, heart block, or cardiac arrhythmia; insulin-requiring diabetes; or hyperthyroidism; (c) previous adverse reaction to a β-blocker; (d) current use of a β-blocker; (e) use of a medication that could adversely interact with propranolol; (f) pregnancy or breast feeding; (g) current use of any psychotropic medication or psychoactive substances; (h) current or past mental disorder accord-