Archival Report

An Abrupt Transformation of Phobic Behavior After a Post-Retrieval Amnesic Agent

Marieke Soeter and Merel Kindt

ABSTRACT

BACKGROUND: Although disrupting the process of memory reconsolidation has a great potential for clinical practice, the fear-amnesic effects are typically demonstrated through Pavlovian conditioning. Given that older and stronger memories are generally more resistant to change, we tested whether disrupting reconsolidation would also diminish fear in individuals who had developed a persistent spider fear outside the laboratory.

METHODS: Spider-fearful participants received a single dose of 40 mg of the noradrenergic β-blocker propranolol (*n* = 15), double-blind and placebo-controlled (*n* = 15), after a short 2-min exposure to a tarantula. To test whether memory reactivation was necessary to observe a fear-reducing effect, one additional group of spider-fearful participants (*n* = 15) received a single dose of 40 mg propranolol without memory reactivation.

RESULTS: Disrupting reconsolidation of fear memory transformed avoidance behavior into approach behavior in a virtual binary fashion—an effect that persisted at least 1 year after treatment. Interestingly the β-adrenergic drug did initially not affect the self-declared fear of spiders but instead these reports followed the instant behavioral transformation several months later.

CONCLUSIONS: Our findings are in sharp contrast with the currently pharmacological and cognitive behavioral treatments for anxiety and related disorders. The β-adrenergic blocker was only effective when the drug was administered upon memory reactivation, and a modification in cognitive representations was not necessary to observe a change in fear behavior. A new wave of treatments that pharmacologically target the synaptic plasticity underlying learning and memory seems to be within reach.

Keywords: Anxiety disorders, Fear memory, Propranolol, Reconsolidation, Spider phobia, Treatment

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Fear memories are no longer considered as indelible entities. During past years, it was rediscovered that retrieval of a consolidated fear memory may instigate a protein synthesis–dependent restabilization process called reconsolidation (1). Pharmacological disruption of this process enables the modification of a previously acquired fear memory. In the laboratory, specific fear memories can be established through Pavlovian fear conditioning, which involves the repeated pairing of an initially neutral cue (e.g., a tone or picture; conditioned stimulus, CS) with an inherently noxious stimulus (e.g., an electric stimulus; unconditioned stimulus, US). As a result, an associative memory trace is being formed and the later presentation of the CS will retrieve the US representation, thereby eliciting a conditioned fear response. An important asset of the fear-conditioning paradigm is that it is well-suited to investigate the neurobiological mechanisms underlying associative fear learning and memory across species (e.g., crabs, rats, and humans). Fear conditioning is also an excellent translational model to develop, and advance treatment given that anxiety disorders are by definition irrational (2) and refer to learned fears as opposed to innate fears. Although associative fear memory lies at the core of fear and anxiety disorders (3), it bears mentioning that anxiety disorders do not necessarily result from direct conditioning experiences such as traumatic events. Fear memory may also result from indirect or vicarious fear learning experiences (4). However, irrespective of the learning history, people with anxiety disorders act as if the feared stimulus (e.g., heart palpitations) predicts the later occurrence of a negative outcome (e.g., panic attack or heart failure). Insofar as associative fear memory is regarded as the core of anxiety disorders (5), it not only entails predictive learning in which the originally neutral or ambiguous stimulus (CS) becomes a valid predictor for a negative experience (US) but also that this feared stimulus is endowed with a negative valence through its association with the negative consequence (US) (6,7).

Insights on disrupting reconsolidation of fear memories may point to an efficient strategy for the treatment of anxiety disorders and posttraumatic stress disorder (8). By now, the fear-erasing effect has been replicated in a variety of species and paradigms (9). A series of human fear-conditioning studies showed that disrupting reconsolidation by the noradrenergic β-blocker propranolol HCl neutralized the fear memory (10–13) while leaving the expectancy learning unaffected. Propranolol HCl passes the blood-brain barrier and is supposed to block the β-adrenergic receptors in the amygdala, thereby interfering with the PKA-CREB pathway involved in the neuroplasticity of memory (14,15). However, experimental models of human fear conditioning are an oversimplification of the emotional memory characteristic for pathological fear and its related

disorders (5,16–18). It may therefore be questioned whether the current procedure of disrupting memory reconsolidation can be effectively applied to people with fear and anxiety disorders (2). First, the fear-erasing effects in humans have most convincingly been demonstrated for relative young (1 day old) and weak fear memories, because human fear conditioning involves only a mild noxious experience. From the animal literature, it is known that the activation of the reconsolidation process appears to be dependent on both the age and strength of memories, in which older and stronger memories become increasingly resistant to disruption (19). On the other hand, preliminary evidence in patients with posttraumatic stress disorder revealed a reduction in trauma-relevant physiological responding after a β-adrenergic interference with reconsolidation (8), but this effect could not be replicated (20). A second potential boundary condition relates to the fact that fear memories in people with anxiety disorders are generally broader and less well-defined than the simple fear association between a specific stimulus (e.g., picture) and a single aversive event (e.g., electric stimulus) installed by a Pavlovian fear-conditioning procedure. In previous fear-conditioning studies, we demonstrated that the fear-reducing effect was not restricted to the reactivated stimulus but also generalized to other stimuli from the same semantic category, not previously associated with the originally conditioned stimulus (11,12). However, strengthening fear memory by either variation in training intensity (21) or pharmacologically induced CREB phosphorylation (12,22,23) triggers a broader fear generalization. Therefore, it remains unclear whether older, stronger, and broader fear memories acquired outside the laboratory are also sensitive to a memory reconsolidation intervention. Another challenge for clinical applications is that the anticipated threat event does not necessarily involve a circumscribed threat event such as in a Pavlovian fear-conditioning procedure. In many cases, people tend to fear objects and situations that they have never really experienced (4). Although we have shown that disrupting reconsolidation also erased fear for a noxious event (i.e., electrical stimulus) that was anticipated but never actually experienced (24), the anticipated catastrophe in people with anxiety disorders does not necessarily refer to external events but may also refer to aversive feelings such as the fear of losing control (25,26).

In sum, a key question is whether targeting fear memory by amnesic agents will be of value for clinical practice. For addressing this question, we tested whether disrupting reconsolidation by a noradrenergic β-blocker also diminishes fear responding in individuals who have spider phobia. In fear-conditioning studies, it was demonstrated that reconsolidation occurs when a retrieval session involves an event that 1) generates an expectation of threat (27) and 2) initiates new learning—meaning that the magnitude of the outcome or the outcome itself is not being fully predicted (i.e., a prediction error) (13,28). However, a retrieval session that engages "too much" learning might not trigger destabilization of an original fear memory but forms a boundary condition even before fear extinction can be observed (29,30). Bearing these points in mind the spider-fearful participants were very briefly exposed to a tarantula while they were in the supposition that they had to touch the spider, but, in reality, this never happened, to prevent possible extinction learning. After the participants

were exposed to the tarantula for only 2 minutes, the therapist closed the terrarium. We assumed that this short exposure session would trigger destabilization of the associative fear memory (i.e., spider ≥ aversive consequence) and prevent the risk of inducing fear extinction (29,30). After this brief exposure, the participants received (double-blind and placebo-controlled) a single oral dose of 40 mg of propranolol HCl, a β-adrenergic receptor antagonist known to disrupt memory reconsolidation (10–13). For discarding any nonspecific dampening effects of propranolol HCl on the degree of spider fear, the drug was administered (single-blind) to a third group of spider-fearful participants without the memory reactivation (MR) session. For assessing the degree of spider fear, we used self-report assessments as well as two behavioral approach tasks. The experimental design is shown in Figure 1.

METHODS AND MATERIALS

Participants

A total of 45 healthy individuals,[1] 41 women scoring >17 on the Spider Phobia Questionnaire (31) and ranging in age from 18–32 years (mean ± SD age, 21.6 ± 3.2 years), were referred for the study. Participants were randomly assigned to either the propranolol HCl (n = 15, 13 women) or the pill placebo group (n = 15, 14 women). An additional propranolol no-reactivation group was also included (n = 15, 14 women) for discarding any nonspecific dampening effects of the propranolol drug (Table S1 and Supplement).

Assessments

Questionnaires. For obtaining an assessment of the self-reported spider fear, the Spider Phobia Questionnaire was administered, consisting of 31 items to be rated true or false (31). Participants rated on 0- to 8-point scales the credibility of the standard behavioral therapy for spider phobia (i.e., exposure) as well as the experimental treatment with propranolol.

Behavioral Tests. Behavioral approach tests (i.e., BATs) were used to assess the degree of fear while being exposed to a spider as well as overt approach behavior toward spiders. See the Supplement for details on the phobic stimuli.

Pre- and Posttreatment Assessments with Baby Tarantula (t0, t3, t4, t5). A baby tarantula was placed in a closed jar on a table in the far end of a 3.5 × 5-m room. Participants were instructed to enter the room and to accomplish each step of the standardized baby-tarantula BAT within 3 minutes, but they were free to stop the test at any point (Table 1). Behavioral approach ratings ranged from 0 to 8, corresponding to the last accomplished step. Participants were further required to rate their level of fear or anxiety by using 0- to 100-point scales (32) at each completed step: 0 = no fear,

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[1] A sample size of 15 participants per group was considered to be adequate based on a power analysis of our previous fear conditioning studies (10–13).