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Enhancing exposure therapy for anxiety disorders with glucocorticoids: From basic mechanisms of emotional learning to clinical applications

Dorothée Bentz [a,b], Tanja Michael [a,1], Dominique J.-F. de Quervain [b], Frank H. Wilhelm [a,*]

[a] Department of Clinical Psychology & Psychotherapy, Faculty of Psychology, University of Basel, Switzerland
[b] Division of Cognitive Neuroscience, Faculty of Psychology and Faculty of Medicine, University of Basel, Switzerland

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ABSTRACT

Current neurophysiological and psychological accounts view exposure therapy as the clinical analog of extinction learning that results in persistent modifications of the fear memory involved in the pathogenesis, symptomatology, and maintenance of anxiety disorders. Evidence from studies in animals and humans indicate that glucocorticoids have the potential to facilitate the processes that underlie extinction learning during exposure therapy. Particularly, glucocorticoids can restrict retrieval of previous aversive learning episodes and enhance consolidation of memory traces relating to non-fearful responding in feared situations. Thus, glucocorticoid treatment especially in combination with exposure therapy might be a promising approach to optimize treatment of anxiety disorders. This review examines the processes involved in aversive conditioning, fear learning and fear extinction, and how glucocorticoids might enhance restructuring of fear memories during therapy.

1. Introduction

The most effective psychotherapy for anxiety disorders, such as specific phobia, social phobia, and posttraumatic stress disorder (PTSD), is exposure therapy (Chambless & Ollendick, 2001). Its core element is to expose patients to fear-provoking stimuli in a repeated and systematic manner in order for them to acquire a sense of safety in the presence of the formerly feared stimuli (e.g., Öst, 1997). Besides this cognitive-behavioral treatment (CBT) strategy, pharmacotherapy with anxiolytic agents such as monoamine oxidase inhibitors, tricyclic antidepressants, and benzodiazepines has been proven to be an effective treatment for anxiety disorders (Gould, Buckminster, Pollack, Otto, & Yap, 1997; Gould, Otto, & Pollack, 1995). Meta-analyses comparing CBT and psychopharmacological therapy for anxiety disorders indicate that both treatments have similar efficacy in treating acute fear symptoms, but that CBT shows better stability of treatment gains after the end of treatment (e.g., Gould et al., 1995, 1997). The stand-alone success of both exposure therapy and psychopharmacotherapy has led to the idea of combining these interventions to boost the effectiveness of either treatment method. Although it seems reasonable to assume that the combination of two effective interventions would maximize treatment gains, this approach has not been very successful, in particular with respect to long-term outcome. Studies of combined treatment regimes indicate that a combination of the two methods can be advantageous in the short and intermediate term, but that the effect typically reverses in the long term (e.g., Coldwell et al., 2007; Foa, Franklin, & Moser, 2002; Otto, Smits, & Reese, 2005; Wilhelm & Roth, 1997).

It is generally assumed that the high rate of relapse after medication discontinuation both with monotherapy and combined therapy may be explained by the mechanism by which anxiolytic psychotropics unfold their activity. Common to all anxiolytic psychotropics is that they attenuate fear symptoms elicited by the fear-provoking stimulus, albeit via different brain pathways. Such attenuation of the anxiety response seems to work only as long as psychotropics are given (e.g., Noyes, Garvey, Cook, & Samuelson, 1989; Noyes, Garvey, Cook, & Suelzer, 1991). In contrast, CBT regimes for anxiety disorders are not just aimed at attenuating fear symptoms but are aimed at emotional learning processes that are believed to lead to persistent modifications of neuronal networks in specific brain areas associated with the pathogenesis and maintenance of anxiety disorders. For example, LeDoux (2002) believes that "Psychotherapy is fundamentally a learning process for its patients, and as such is a way to rewire the brain. In this

* Corresponding author at: Clinical Psychophysiology Laboratory, University of Basel, Faculty of Psychology, CH-4055 Basel, Switzerland. Tel.: +41 61 2670593; fax: +41 61 2670659.
E-mail addresses: dorothee.bentz@unibas.ch (D. Bentz), t.michael@mx.uni-saarland.de (T. Michael), dominique.dequervain@unibas.ch (Dominique J.-F. de Quervain), frank.wilhelm@unibas.ch (F.H. Wilhelm).
[1] Present address: Department of Clinical Psychology & Psychotherapy, University of Saarbrücken, Germany.

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sense, psychotherapy ultimately uses biological mechanisms to treat mental illness." This perspective on psychotherapy has important implications for the combination of psychopharmacologic and psychotherapeutic treatment methods.

If psychotherapy changes central nervous system structures and subsequently central nervous system processes associated with fear responding it is logical to ask the following questions: What is the underlying central nervous system mechanism of successful psychotherapy for anxiety disorders?, and, Is there any medication that can directly enhance this mechanism?

Procedurally, exposure therapy parallels extinction training within a model of learning and unlearning of conditioned responses. In this model, the patient's decline of fear within an exposure session is the result of continuous decrements in the conditioned response seen over successive extinction trials. Thus, extinction of fear responses is generally assumed to be the most important underlying mechanisms of exposure therapy. This implies that pharmacological enhancers of psychological treatments for anxiety disorders should focus on facilitation of extinction and on stabilization of treatment gains after extinction.

It has been argued that extinction of conditioned responses and consolidation processes that stabilize extinction are both amenable to pharmacologic manipulations (Myers & Davis, 2002). Thus, deeper knowledge about behavioral and molecular mechanisms leading to extinction and consolidation will present opportunities for creating new effective treatment approaches that combine psychopharmacologic and psychotherapeutic treatments. The aim of this review is to present administration of glucocorticoids as a promising approach that intends to enhance extinction learning and facilitate consolidation of extinction memory into long-term memory. We begin by elucidating the underlying mechanisms of acquisition and extinction of fear and then translate basic knowledge from the field of neuroscience into a novel clinical application.

2. Acquisition of fear and the role of the fear memory

Both from a learning theory and neuroscience perspective, anxiety disorders can be characterized as disorders involving disturbed emotional learning and memory processes resulting in enhanced fear response acquisition and maintenance. It has been convincingly argued that these alterations are key components of anxiety disorders and not just secondary symptoms (e.g., Centonze, Siracusano, Calabresi, & Bernardi, 2005). A central mechanism in the pathogenesis of anxiety disorders is associative learning or conditioning. For example, aversive memories play a pivotal role in the pathogenesis of PTSD. Re-experiencing of the traumatic event (e.g., traumatic nightmares or flashbacks) is a hallmark of PTSD and results from an easy triggering of traumatic memories (Michael, Ehlers, & Halligan, 2005; Michael, Ehlers, Halligan, & Clark, 2005).

Pavlovian fear conditioning, besides having served as an important animal model for the molecular mechanisms underlying learning and memory for many decades, is also the experimental model for the pathogenesis of human anxiety disorders (e.g., Myers & Davis, 2002). Via classical conditioning a formerly neutral stimulus can acquire emotional impact. The classical behaviorist view is that phobias are manifestations of intense conditioned fears, at which an association of an originally neutral conditioned stimulus (CS) with a traumatic or aversive experience (unconditioned stimulus, US) has been formed. Such associations manifest themselves in form of memory traces that connect the CS with the US. After fear acquisition, a conditioned (fear) response (CR) to the originally neutral stimulus alone can be observed, because the CS has become a valid predictor of the US.

Consolidation is the process responsible for the stabilization of the newly formed associations. During the process of consolidation information from short-term memory gets transferred into long-term memory. This leads to persistent alterations in brain networks associated with the learning processes (Kandel, 2001). A large body of evidence from experimental animal studies implicates that the amygdala is the brain region that plays a key role in the acquisition, consolidation and expression of conditioned fear. Recent studies have shown that these findings also apply to the human brain (LeDoux, 2000).

It has been argued that fear conditioning mechanisms are not sufficient to explain the etiology of all fears and phobias. For example, outside the laboratory specific circumstances of fear acquisition in patients are often unknown, and patients often cannot remember a specific traumatic conditioning situation. Thus, important questions like the following are often unanswered: When exactly did acquisition happen? Was it a one-trial learning or repeated experience? What were the physical, internal, and emotional contexts?

Rachman (1978) proposed two further associative pathways for developing anxiety disorders next to direct traumatic conditioning: transmission of verbal information (e.g., threatening information about specific objects or situations) and vicarious learning (e.g., a model responding fearfully or being traumatized in the presence of a specific stimuli).

Only at superficial glance are these other pathways at odds with the Pavlovian fear conditioning account, since on the process level, transmission of verbal information and vicarious learning are also considered forms of conditioning. The associative structure of a vicarious learning episode can be conceptualized in the same way as a direct conditioning episode. Mineka and Cook (1993) suggest that in a vicarious learning episode the observed reaction of another person to the CS acts as a US, because seeing the distress of the model is an anxiety-provoking event for the observer. Thus, the observer experiences the CS in the presence of an anxiety-provoking event. Similar associative processes can be postulated for transmission of verbal information (for a detailed discussion of conditioning processes in phobias; Field, 2006). Thus, contemporary thinking subsumes these three conditioning pathways of fear acquisition under fear learning, or more general, emotional learning, which refers to the creation of a stimulus-associated fear memory consisting of past phobic experiences and negative believes about the phobic stimulus. Subsequent encounters with the former neutral event will automatically activate the stimulus-associated memory trace in the fear memory.

The fear memory can be seen as a network that contains information about (a) the feared stimuli, (b) verbal, physiological, and behavioral reactions to the stimuli, and (c) appraisal of the stimuli and associated connections (Foa, Huppert, & Cahill, 2006; Foa & Kozak, 1986). The CS is the retention cue that leads to the reactivation of the memory trace prompting the CR. Every confrontation to the CS (phobic situation or object) almost invariably triggers retrieval of the stimulus-associated fear memory. Retrieval fosters the CR during anticipation and confrontation and influences the post-event processing of the confrontation with the phobic stimulus (Cuthbert et al., 2003; Foa & Kozak, 1986; Lang, 1985). Furthermore, retrieval by reactivation of a memory trace leads to the reconsolidation of fearful memories, which further strengthens the aversive memory trace (Sara, 2000). In PTSD, traumatic re-experiencing phenomena are triggered by a trauma cue. After each re-experiencing episode the traumatic memory trace gets further strengthened through reconsolidation (Michael & Ehlers, 2007). Thus, reconsolidation processes of fearful memories contribute strongly to the maintenance of anxiety disorders.

Additionally, it is assumed that during an episode of conditioning not only associations between the CS and the US are formed,