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High cortisol awakening response and cortisol levels moderate exposure-based psychotherapy success

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Summary
Background: Research suggests that elevated stress hormones during exposure can facilitate fear extinction in laboratory settings. However, prospective studies on the clinical benefits of endogenous cortisol on clinical improvements in naturalistic exposures are lacking.
Methods: Twenty-six patients with panic disorder and agoraphobia completed three weekly in-vivo exposure sessions and a fourth session 2 months following therapy completion, resulting in a total of 94 in-vivo exposure sessions. Salivary cortisol was collected at multiple times during the first exposure day (cortisol morning response, prior, -during, -after exposure) and at subsequent exposure sessions (prior, -during, -after exposure). Cortisol collection on a non-exposure comparison day followed the same time schedule as session 1.
Results: Exposure day anxiety and cortisol levels were significantly higher than control day levels. Higher absolute cortisol levels during exposures moderated clinical improvement (avoidance behavior, threat appraisal, perceived control). Therapeutic gains were not just related to exposure day cortisol levels, but were also linked to non-exposure day levels. Greater morning rises in cortisol on exposure day predicted greater treatment gains, but greater rises on the control day were associated with poorer outcomes.
Conclusions: The study provides first evidence for a moderating effect of cortisol awakening response and absolute cortisol levels on fear extinction processes during naturalistic,

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prospective exposure-therapy. Additionally, we replicated and extended prior findings on the therapeutic benefits of high exposure cortisol levels. Together, the findings suggest that cortisol may act as a general moderator of facilitated learning during exposure therapy.

1. Introduction

Patients with panic disorder experience paroxysmal panic attacks with intense physical symptoms and associated expectations of catastrophic outcomes (American Psychiatric Association, 1994; Meuret et al., 2011). Consequently, sufferers fear future attacks and adopt maladaptive coping strategies dominated by avoidance. Confrontation with feared situations or sensations leads to retrieval of conditioned, cue-associated fear memories (Cuthbert et al., 2003; Mineka and Ohman, 2002). Post-event processing can further strengthen irrational beliefs and avoidance behaviors. Exposure therapy — the systematic confrontation with feared situations or sensations — facilitates fear extinction through acquisition of new, fear-discordant information (Bouton, 2002). However, a significant number of patients experience limited recovery or a return of fear following exposure, so detection of internal mediators and external agents that can facilitate corrective learning is extremely important (Craske et al., 2008; Meuret et al., 2012a).

Pharmacological enhancement of extinction processes has been attempted using drugs such as D-cycloserine (DCS) (e.g., Hofmann et al., 2006) and glucocorticoids (GCs) (Soravia et al., 2006; de Quervain et al., 2011). GCs may facilitate fear extinction by impairing retrieval of aversive phobia-related memories while simultaneously enhancing learning of new information (Roozendaal, 2006; de Quervain et al., 2009). Oral administration of GC prior to phobic-cue exposure enhances fear reductions in spider phobics when confronted with photographs of spiders (Soravia et al., 2006) and real spiders (Soravia et al., 2014), and height phobics exposed to a virtual-height environment (de Quervain et al., 2011). Reduced fear expression was also observed in social phobia patients receiving exogenous cortisol prior to undergoing a socio-evaluative task; in those who received placebo, greater release of endogenous cortisol was also related to lower fear ratings (Soravia et al., 2006). Additionally, Lass-Hennemann and Michael (2014) showed that spider phobics who were treated in the morning (when average endogenous cortisol levels were higher than in the evening) showed greater avoidance reductions on a behavior approach test compared to patients that were treated in the evening.

The suggested benefits of exogenous and endogenous GC on fear extinction are promising, but have been demonstrated only in laboratory settings, with fixed cues of varying relevance to sufferers. Naturalistic exposures purposefully vary in settings, durations, and intensities, to maximally evoke and challenge a patient's individual fear network. Consequently, clinically common situational phobias cannot be easily reproduced in the laboratory, perhaps limiting the generalizability of these initial findings. These studies also used fear or anxiety intensity during exposure as markers of GC-related improvement, but these are only weak indicators of more global, long-term, therapeutic benefits (Craske et al., 2008; Meuret et al., 2012b). Furthermore, none assessed cortisol as moderator of outcome, with the exception of one small, naturalistic study that examined endogenous cortisol as a predictor of treatment outcome using in-vivo exposure therapy (Siegmund et al., 2011). Findings indicated a trend toward greater clinical improvements in panic patients with higher cortisol levels during exposure. There was no overall cortisol response to exposure itself, suggesting that cortisol's therapeutic impact was a result of its absolute levels rather than the system's acute reactivity.

Prior studies have also largely focused on the function of cortisol mobilization during stress provocation, but pre-stress or pre-exposure levels may also impact outcomes. Whereas laboratory stress induction has situational characteristics known to affect HPA activity (novelty, unpredictability, uncontrollability, personal scrutiny), excessive and prolonged anticipatory anxiety is more highly characteristic of in-vivo exposure, as individuals anticipate confronting highly distressing and avoided stimuli and situations. There is in fact evidence that phobia-related cortisol elevations are already present an hour before driving phobia patients report to the clinic for an exposure therapy session (Alpers et al., 2003). Impact of pre-session cortisol levels on treatment outcomes, however, has not been examined.

Cortisol awakening response (CAR) provides another measure of stress system activity prior to exposure with potential relevance to treatment outcomes. CAR reflects an acute rise in cortisol triggered by morning awakening and has attracted considerable attention as a biomarker of stress system activity that is distinct from diurnal variation (Wilhelm et al., 2007). Whereas the function of this awakening response remains undetermined, it may facilitate orientation to the day's upcoming demands (Fries et al., 2009; Chida and Steptoe, 2009). Alterations in CAR have been associated with chronic stress, but the link between CAR and responses to acute stressors has only been investigated with single, temporary stressors. Rohleder et al. (2007) observed increases in CAR in dancers on the morning of a ballroom tournament, but not on a non-competitive day, which was interpreted as an (adaptive) preparatory response.

This study was designed to provide an in-depth analysis of the predictive value of CAR, cortisol levels prior to exposure, and cortisol levels during exposure on fear extinction in 26 panic disorder patients undergoing three weekly in-vivo exposure sessions and a fourth session 2 months following therapy completion, resulting in a total of 94 in-vivo exposure sessions. Exposures were individually tailored (different settings and durations) to achieve maximal potency across sessions. We examined both absolute levels of cortisol and the change in exposure day cortisol levels from time-matched, non-exposure day levels (cortisol change). Based on prior findings, we hypothesized that greater cortisol levels would be predictive of greater clinical improvements.