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CHAPTER 17

Glucocorticoid-induced reduction of traumatic memories: implications for the treatment of PTSD

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Abstract: Post-traumatic stress disorder (PTSD) is an anxiety disorder that can occur after a traumatic event such as military combat, terrorist attacks, or accidents. The disorder is characterized by traumatic memories that manifest as reexperiencing symptoms including daytime recollections, traumatic nightmares, or flashbacks in which components of the event are relived. These symptoms result from excessive retrieval of traumatic memories that often retain their vividness and power to evoke distress for decades or even a lifetime. We have reported previously that elevated glucocorticoid levels inhibit memory retrieval in animals and healthy human subjects. We therefore hypothesized that the administration of cortisol might also inhibit the retrieval of traumatic memories in patients with PTSD. In a recent pilot study we found the first evidence to support this hypothesis. During a 3-month observation period, low-dose cortisol (10 mg per day) was administered orally for 1 month to three patients with chronic PTSD using a double-blind, placebo-controlled, crossover design. In each patient investigated, there was a significant treatment effect with cortisol-related reductions in one of the daily-rated symptoms of traumatic memories without causing adverse side effects. Furthermore, we have reported evidence for a prolonged effect of the cortisol treatment. Persistent retrieval and reconsolidation of traumatic memories is a process that keeps these memories vivid and thereby the disorder alive. By inhibiting memory retrieval, cortisol may weaken the traumatic memory trace and thus reduce symptoms even beyond the treatment period. Future studies with more patients and longer treatment periods are required to evaluate the efficacy of cortisol treatment for PTSD.

Keywords: PTSD; glucocorticoids; cortisol; memory; retrieval; traumatic memory; treatment

Traumatic memories in post-traumatic stress disorder

Post-traumatic stress disorder (PTSD) is a response to a traumatic event and characterized by the following features: reexperiencing the traumatic event, avoidance of stimuli associated with the trauma, and hyperarousal. Reexperiencing symptoms include daytime recollections, traumatic nightmares, and flashbacks in which components of the event are relived (American Psychiatric Association, 1994; Yehuda, 2002b). These reexperiencing symptoms result from excessive retrieval of traumatic memories that often retain their vividness and power to evoke distress for decades or even a lifetime. Importantly, traumatic reexperiencing phenomena are again consolidated (reconsolidated) into memory that cements the traumatic memory trace. In fact, persistent retrieval, reexperiencing, and reconsolidation of traumatic memories is a process that keeps these memories vivid

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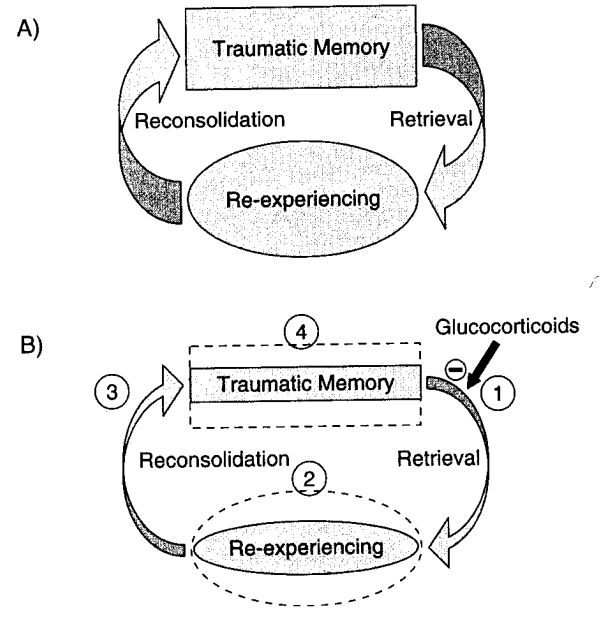

Fig. 1. Model on the role of glucocorticoids in the reduction of traumatic memory. (A) Persistent retrieval, reexperiencing, and reconsolidation of traumatic memories is a process that keeps these memories vivid and thereby the disorder alive. (B) Glucocorticoid-induced reduction of traumatic memory. By inhibiting memory retrieval, glucocorticoids partly interrupt the vicious cycle of retrieving (1), reexperiencing (2), and reconsolidating (3) traumatic memories and, thereby, promote forgetting and extinction processes (4) (see text for details).

and thereby the disorder alive (Fig. 1A). Therefore, it would be desirable to have a drug that reduces excessive retrieval of traumatic memories, as this would result in less reexperiencing phenomena and, consequently, in a weakening of the traumatic memory trace.

Glucocorticoids and memory retrieval

Glucocorticoids, stress hormones released from the adrenal cortex, are known to influence memory processes and growing evidence suggests that glucocorticoids have differential effects on discrete memory phases. In animal and human subjects, single administration of glucocorticoids enhances the consolidation of new memories (Kovacs et al., 1977; Flood et al., 1978; Roozendaal, 2000; Buchanan and Lovallo, 2001; Kuhlmann and Wolf, 2006). In contrast, we found that glucocorticoids impair memory retrieval processes (de Quervain et al., 1998). Specifically, we reported that 30 min after an electric footshock, rats have impaired retrieval of spatial memory acquired 24 h earlier. Interestingly, memory retrieval was not impaired 2 min or 4 h after the footshock. These time-dependent effects on retrieval performance corresponded to the circulating corticosterone levels at the time of testing, which suggested that the retrieval impairment is directly related to increased adrenocortical function. In support of this idea, we found that suppression of corticosterone synthesis with metyrapone blocks the stress-induced retention impairment. In addition, systemic corticosterone administered to non-stressed rats 30 min before retention testing induced dose-dependent retention impairment. Because corticosterone did not affect acquisition or immediate recall, the corticosterone-induced impairment in retention performance is attributable to a selective influence on long-term memory retrieval. In a next step we have translated these findings to healthy humans and found that a single administration of 25 mg cortisone impairs the recall of words learned 24 h earlier (de Quervain et al., 2000). Several further studies from different laboratories have indicated that impaired memory retrieval after the administration of glucocorticoids is a consistent finding in both animals and humans (Wolf et al., 2001; de Quervain et al., 2003; Roozendaal et al., 2003, 2004a; Buss et al., 2004; Het et al., 2005; Kuhlmann et al., 2005a; Sajadi et al., 2007). Moreover, there is recent evidence that emotionally arousing information is especially sensitive to the retrieval-impairing effects of glucocorticoids (Kuhlmann et al., 2005a, b; de Quervain et al., 2007).

Whereas elevated glucocorticoid levels are certainly detrimental when information should be retrieved (e.g., during exams), they may actually be beneficial in conditions when memory retrieval is distressing. As detailed above, PTSD is such a condition. We therefore hypothesized that by inhibiting the retrieval of traumatic memories, the administration of cortisol may be beneficial in patients with PTSD.

Glucocorticoids reduce traumatic memories in PTSD

Recently, we investigated the effects of cortisol treatment on the retrieval of traumatic memories in a small number of patients with chronic PTSD (Aerni et al., 2004). During a 3-month observation period, low-dose cortisol (10 mg per day) was administered orally for 1 month using a double-blind, placebo-controlled, crossover design. The administration of this low dose of cortisol for 1 month does not cause major side effects and does not suppress endogenous cortisol production (Cleare et al., 1999). To assess possible treatment effects on retrieval of traumatic memories, the patients daily rated the intensity and frequency of the feeling of reliving the traumatic event and the physiological distress felt in response to traumatic memories and nightmares (self-administered rating scales from the Clinician Administered PTSD Scale questions). Patient 1 was a 50-year-old man who survived a terrorist attack 4.5 years before inclusion into the study. There was a significant treatment effect for the intensity of the feeling of reliving the traumatic event (Fig. 2). Of interest, the intensity ratings during the last study month (with no medication) were significantly lower compared to those during the first month (placebo), suggesting a carryover effect of cortisol. There was also a significant treatment effect for the intensity of physiological distress. Patient 2 was a 40-year-old woman who experienced a life-threatening physical assault 1 year before inclusion in the study. There was a significant treatment effect for the frequency of nightmares (Fig. 2). Patient 3 was a 55-year-old man who had a severe car accident 8 years before inclusion in the study. To control for possible treatment order effects, this patient

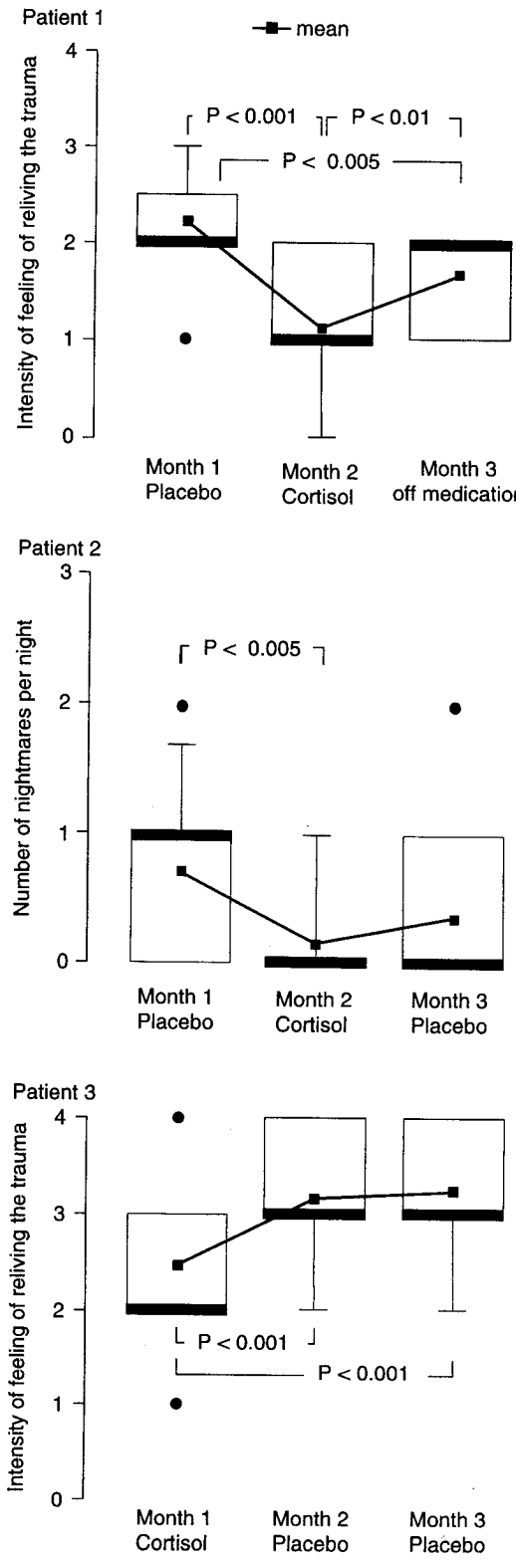

Fig. 2. Effects of cortisol on traumatic memories in PTSD. Most significant treatment-related change in frequency or intensity among the daily-rated symptoms of traumatic memories in each patient. The thick black line indicates the median. Black dots indicate outliers, whiskers which start from the boxes indicate the 10th and the 90th percentiles of the distribution, respectively; top and bottom of each box indicate the 75th and 25th percentiles, respectively. For further details, see Aerni et al. (2004).

received cortisol in the first month, followed by 2 months of placebo medication. Significant treatment effects were detected for the intensity of the feeling of reliving the traumatic event (Fig. 2), the physiological distress, and the frequency of nightmares. None of the patients complained about treatment-related disturbances of everyday memory upon questioning. Taken together, in all patients investigated, low-dose cortisol treatment had beneficial effects with significant reductions of at least 38% in one of the daily-rated symptoms of traumatic memories.

In recent experiments in patients with phobia we additionally found evidence that glucocorticoids may not only reduce retrieval of traumatic memory in patients with PTSD but also retrieval of fear memory in patients with phobia (Soravia et al., 2006). Phobic disorders are characterized by marked and persistent fear that is excessive or unreasonable, cued by the presence or anticipation of a specific object or situation (American Psychiatric Association, 1994; Barlow and Liebowitz, 1995). Exposure to a phobic stimulus almost invariably provokes retrieval of stimulus-associated fear memory (Cuthbert et al., 2003). In addition, phobic individuals tend to construct highly negative images of a phobic situation that substantially contributes to anticipatory anxiety as well as negative post-event processing. Such images are usually associated with explicit fearful memories of past phobic experiences that reinforce negative beliefss that are difficult to suppress and may strengthen the phobic response (Rapee and Heimberg, 1997; Fehm and Margraf, 2002). We hypothesized that glucocorticoids might inhibit retrieval of fear memory in phobia and thereby reduce stimulus-induced fear. We tested this hypothesis by administering glucocorticoids to 40 subjects with social phobia and 20 subjects with spider phobia in two double-blind, placebo-controlled studies (Soravia et al., 2006). In the social phobia study, cortisone (25 mg) administered orally 1 h before a socio-evaluative stressor significantly reduced self-reported fear during the anticipation-, exposure-, and recovery phase of the stressor. Moreover, the stress-induced release of cortisol in placebo-treated subjects correlated negatively with fear ratings, suggesting that endogenously released cortisol in the context of a phobic situation buffers fear symptoms. In the spider phobia study, repeated oral administration of cortisol (10 mg), but not placebo, 1 h before exposure to a spider photograph induced a progressive reduction of stimulus-induced fear. This effect was maintained when subjects were exposed to the stimulus again 2 days after the last cortisol administration, suggesting that cortisol may also have facilitated the extinction of phobic fear. Importantly, cortisol treatment did not reduce general, phobia-unrelated anxiety. These experiments indicate that by a common mechanism of reducing memory retrieval, glucocorticoids may be suited for the treatment of PTSD as well as phobias.

Possible mode of action of glucocorticoids in the reduction of traumatic memories

In the PTSD-study detailed above (Aerni et al., 2004) we found that the administration of cortisol reduces reexperiencing symptoms, which is a direct measure of traumatic memory retrieval. Extensive evidence from studies in amnesic patients, human-imaging studies, and lesion studies in animals indicates that the medial temporal lobe (MTL) is crucially involved in memory retrieval and that activation of the MTL is associated with successful memory retrieval (Squire, 1992; Moser and Moser, 1998; Cabeza and Nyberg, 2000). Moreover, a functional magnetic resonance imaging (fMRI) study in patients with PTSD showed that the MTL becomes activated by viewing masked traumatic images (Sakamoto et al., 2005). Using positron emission tomography (PET) imaging in healthy humans, we found that acutely administered cortisone reduces blood flow in the MTL during memory retrieval, an effect that correlated with the degree of memory retrieval impairment (de Quervain et al., 2003). Furthermore, systemic administration of glucocorticoids to rats shortly before retention testing induced memory retrieval impairments for contextual memory (Roozendaal et al., 2004b), a task that depends on the MTL (Squire, 1992), and local infusions of a glucocorticoid receptor agonist into the hippocampus of rats induced retrieval impairments comparable to those seen after systemic administration

(Roozendaal et al., 2003). Together, these findings suggest that elevated cortisol levels may have reduced the retrieval of traumatic memories by inhibiting MTL activity.

In the PTSD-study (Aerni et al., 2004), we additionally found evidence for a prolonged effect of the cortisol treatment. Persistent retrieval, reexperiencing, and reconsolidation of traumatic memories is a process that keeps these memories vivid and thereby the disorder alive (Fig. 1A). By inhibiting memory retrieval, cortisol may weaken the traumatic memory trace and thus reduce symptoms even beyond the treatment period. Specifically, by inhibiting memory retrieval, cortisol may partly interrupt the vicious cycle of spontaneous retrieving, reexperiencing, and reconsolidating traumatic memories and, thereby, promote forgetting (Fig. 1B), a spontaneous process that occurs when memory is not reactivated. Furthermore, and in line with findings in animals (Bohus and Lissak, 1968), cortisol may facilitate the extinction of conditioned responses to traumatic memory cues. Accordingly, because of the cortisol-induced reduction of memory retrieval, a traumatic memory cue would not be followed by the usual traumatic memory retrieval and reexperiencing but, instead, may become associated with a non-traumatic experience that would be stored as extinction memory.

In addition to the inhibitory effect on memory retrieval, elevated glucocorticoid levels are known to enhance the long-term consolidation of memories (Kovacs et al., 1977; Flood et al., 1978; Roozendaal, 2000; Buchanan and Lovallo, 2001; Kuhlmann and Wolf, 2006). It is therefore possible that glucocorticoids may have further promoted extinction of the traumatic memory by facilitating the storage of corrective experiences, as evidenced by recent findings indicating that glucocorticoids enhance the consolidation of fear extinction memory (Barrett and Gonzalez-Lima, 2004; Cai et al., 2006).

Role of endogenous cortisol in PTSD

Patients with PTSD often show low endogenous cortisol levels (Mason et al., 1986; Yehuda et al., 1995; Yehuda, 2002a). However, some studies also found normal (Young and Breslau, 2004) or higher (Pitman and Orr, 1990) cortisol levels. Furthermore, evidence indicates that a reduced cortisol excretion in response to a traumatic event may be associated with a higher risk of developing subsequent PTSD (McFarlane et al., 1997; Yehuda et al., 1998; Delahanty et al., 2000). The idea that higher cortisol levels may be protective with regard to the development of PTSD is strongly supported by the work of Schelling et al. (2001, 2004) who showed that the prolonged administration of stress doses of cortisol during intensive care treatment in critically ill patients reduces the risk for later PTSD. We propose that cortisol may influence both risk and symptoms of PTSD by controlling the amount of retrieved traumatic memories. Elevated cortisol levels may decrease risk and symptoms of PTSD by inhibiting excessive retrieval of traumatic memories, whereas low endogenous cortisol levels may promote development and symptomatology of PTSD by a disinhibition of traumatic memory retrieval. This notion is in line with the broader view that glucocorticoid release during acute stress represents an adaptive response that helps the organism to deal with a wide spectrum of internal and external demands (McEwen, 1998; de Kloet et al., 1999).

Conclusions

In a first small study we found evidence that the administration of low-dose cortisol reduces reexperiencing symptoms in patients with PTSD. This finding indicates that the inhibiting effect of glucocorticoids on memory retrieval is not restricted to episodic memory in healthy humans but also applies to traumatic memories in patients with PTSD. Furthermore, by inhibiting memory retrieval, glucocorticoids may weaken the traumatic memory trace and thus reduce symptoms even beyond the treatment period. Additional studies with more patients and longer treatment periods are needed to further evaluate the therapeutic efficacy and safety of low-dose cortisol for the treatment of PTSD.

Abbreviations

fMRI	functional magnetic resonance imaging
MTL	medial temporal lobe
PET	positron emission tomography
PTSD	post-traumatic stress disorder

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Discussion: Chapter 17

QUESTION: Do you know anything about HPA-axis reactivity of those patients?

DE QUERVAIN: No, we did not assess HPA-axis reactivity in this study but we now plan a larger study in PTSD patients where we will perform a corticotropin stimulation test and dexamethasone suppression test before and after cortisol treatment.

PITMAN: I wonder how memory would be involved in this in spite of the situation without seeing a picture of the stimulus at the time of the testing. So they might have to remember the focal stimulus right in front of them.

DE QUERVAIN: There might be a fear network that is stored in the brain, perhaps based on fearful experiences earlier in life, which is activated by fearful cues. Such a process involves memory retrieval.

JOËLS: I was wondering about the test where you expose these social phobia patients to a social stress test. I do have a hard time seeing that as a memory situation. Also, assuming in this case cortisol levels are high during retrieval, what could happen is that by giving extra cortisol you are just blunting the patient's own HPA-axis.

DE QUERVAIN: What we found is less fear both after cortisol administration and after endogenous HPA-axis activation. Memory comes into play after the written introduction to the stress test, when the fear network is activated by this cue and when patients also may start to think about past failures in such situations, which would additionally trigger the fear response.

SANDI: My question is related to the test applied in the experiment in which you find a correlation between cortisol and subsequent fear. To what is this fear? Is it fear to the Trier test?

DE QUERVAIN: It is subjective fear related to the Trier test measured at different time points.

GUNNAR: It is interesting, because in the Trier test usually you don't find any association with fear and, thus, whatever is going on perhaps is specific to those phobic patients. Also, Pruessner found that when he subjected individuals to the Trier test repeatedly most individuals habituated. Those who didn't habituate were the ones who had more fearful, anxious personalities. It isn't clear how your results fit with his. His seem to show that fear is associated with continued glucocorticoid respondings, yours that elevated glucocorticoids reduce fear. Perhaps there is something specific to phobic patients.

DE QUERVAIN: Yes, fear memory — and we assume that glucocorticoids reduce phobic fear by reducing fear memory retrieval in these patients.

LIBERZON: From our data, we have actually used traumatic memory in Roger Pitman's paradigm of autobiographic scripts in PTSD and normal controls. We did get significant response in PTSD both in cortisol and in ACTH but it was very small. Interestingly the ACTH response was present in combat controls as well. We also have activation in the brain associated with these responses. But it is very difficult to show a robust response in PTSD to any psychological stimuli other than TSST.

BREMNER: You can show that in women with abuse-related PTSD. One of the slides that I presented was from Bernet Elzinga, who is first author on this, was reading a script of childhood sexual abuse the patients had a threefold higher increase of cortisol during the reading of the traumatic script. In that study you can measure intrusive memory at the time of the slides or sounds or traumatic scripts and patients report an increase in traumatic memory, so we sort of — the point that I wanted to make — for saying that for saying that increase relates in glucocorticoids is a good thing and I am not necessarily going to argue that specifically but then you are — increase glucocorticoids release enhances the encoding of the, or the consolidation of emotional memory, you are saying that the patients were administered glucocorticoids right after the trauma, how could that be good to enhance the consolidation of the traumatic memory? And another thing I wanted to ask if you can tell me what exactly is the citation for the humans that glucocorticoids enhance consolidation. From our data it actually impairs consolidation of emotional memory based on a negative correlation on the emotional words remembered a couple of hours.

DE QUERVAIN: There are a couple of studies I can give you the references of, especially for emotional memory consolidation. To go back to your first point, we have looked at the effects of glucocorticoids in established, chronic PTSD. Here, glucocorticoids reduce the retrieval of traumatic memories.