Review

Glucocorticoids for the treatment of post-traumatic stress disorder and phobias: A novel therapeutic approach

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Abstract

Post-traumatic stress disorder (PTSD) and phobias belong to the most common anxiety disorders and to the most common psychiatric illnesses in general. In both disorders, aversive memories are thought to play an important role in the pathogenesis and symptomatology. Previously, we have reported that elevated glucocorticoid levels inhibit memory retrieval in animals and healthy humans. We therefore hypothesized that the administration of glucocorticoids might also inhibit the retrieval of aversive memory, thereby reducing symptoms in patients with PTSD and phobias. In recent clinical studies, we found first evidence to support this hypothesis. In patients with PTSD, low-dose cortisol treatment for one month reduced symptoms of traumatic memories without causing adverse side effects. Furthermore, we found 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. In patients with social phobia, we found that a single oral administration of cortisone 1 h before a socio-evaluative stressor significantly reduced self-reported fear during the anticipation-, exposure-, and recovery phase of the stressor. In subjects with spider phobia, repeated oral administration of cortisol 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 two days after the last cortisol administration, indicating that cortisol facilitated the extinction of phobic fear. In conclusion, by a common mechanism of reducing the retrieval of aversive memories, glucocorticoids may be suited for the treatment of PTSD as well as phobias. More studies are needed to further evaluate the therapeutic efficacy of glucocorticoids in the treatment of anxiety disorders and to explore the potential of combining glucocorticoid treatment with psychotherapy.

Keywords: PTSD; Phobia; Glucocorticoids; Cortisol; Memory; Retrieval

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1. Introduction

Post-traumatic stress disorder (PTSD) and phobias belong to the most common anxiety disorders and to the most common psychiatric illnesses in general (Becker et al., 2007; Furmark, 2002; Kessler et al., 1995; Magee et al., 1996; Michael et al., 2007; Yehuda, 2002). These anxiety disorders have a dramatic impact on patients’ well-being and social functioning and have major public health significance in terms of high prevalence, chronicity, and disability (Cuthbert, 2002; Yehuda, 2002). Exposure-based and cognitive–behavioral psychotherapy have been shown to be effective in the treatment of phobias (Choy et al., 2007; Heimberg, 2002; Margraf, 2000; Norton and Price, 2007). For social phobia, pharmacotherapy with selective serotonin reuptake inhibitors (SSRIs) in the first line is an additional treatment option. However, the combined treatment of psychotherapy and SSRIs does not yield any further advantage (Blanco et al., 2003; Davidson et al., 2004a). Although the effectiveness of these treatments has been demonstrated, many patients, especially in social phobia, do not respond to treatment, achieve only partial remission of symptoms or show a high incidence of relapse after discontinuation of the treatment (Blanco et al., 2003; Cottraux, 2005; Cuthbert, 2002; Davidson et al., 2004a; Heimberg, 2002). Behavioral psychotherapy and SSRIs have also been shown to be effective in the treatment of PTSD, but they are far from satisfactory (Bisson and Andrew, 2007; Bisson et al., 2007; Brunello et al., 2001; Davidson et al., 2004b; Ipser et al., 2006).

Consequently, the development of novel psychobiological approaches combining effective psychotherapy methods with synergizing pharmacotherapy is a primary challenge in research on treatment of anxiety disorders (Black, 2006; Mitte, 2005). Recently, using an innovative treatment approach, it has been shown that D-cycloserine may be useful in facilitating the extinction of fear during psychotherapy of phobias (Davis et al., 2006). In the present paper, we describe another approach, which is aimed at reducing the retrieval of aversive memories in PTSD and phobias by administering glucocorticoids.

2. The role of aversive memories in PTSD and phobias

Post-traumatic stress disorder (PTSD) is a response to a traumatic event and characterized by the following features: re-experiencing the traumatic event, avoidance of stimuli associated with the trauma, and hyper-arousal. Re-experiencing symptoms include intrusive daytime recollections, traumatic nightmares and flashbacks in which components of the event are relived (American Psychiatric Association, 1994; Yehuda, 2002). These re-experiencing symptoms result from excessive retrieval of traumatic memories, which often retain their vividness and power to evoke distress for decades or even a lifetime. Importantly, traumatic re-experiencing phenomena are again consolidated (re-consolidated) into memory, which cements the traumatic memory trace (see the discussion of the concept of intrusions in the PTSD research literature, e.g. Brewin, 2001; Michael et al., 2005a,b). Persistent retrieval, re-experiencing and reconsolidation of traumatic memories is a process that keeps these memories vivid and thereby the disorder alive.

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; Marks, 1987). Exposure to a phobic stimulus almost invariably provokes retrieval of stimulus-associated fear memory that leads to the fear response (Cuthbert et al., 2003; Foa and Kozak, 1986; Lang, 1985). In addition, phobic individuals tend to construct highly negative images of a phobic situation, which substantially contribute to anticipatory anxiety as well as negative post-event processing. Such images are usually associated with explicit fearful memories of past phobic experiences, which reinforce negative beliefs that are difficult to suppress and may strengthen the phobic response (Fehm and Margraf, 2002; Rapee and Heimberg, 1997).

Thus, retrieval of aversive memories (traumatic memory in PTSD and fear memory in phobias) plays an important role in the symptomatology of these anxiety disorders. It would therefore be desirable to have a drug that reduces excessive retrieval of aversive memories, as this would result in less re-experiencing phenomena in PTSD and in a reduced fear response in phobia.

3. 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 (Buchanan and Lovallo, 2001; Flood et al., 1978; Kovacs et al., 1977; Kuhlmann and Wolf, 2006; Roozendaal, 2000). 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 cortisol 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 (Buss et al., 2004; De Quervain et al., 2003; Het et al., 2005; Kuhlmann et al., 2005a; Roozendaal et al., 2003; Roozendaal et al., 2004b; Sajadi et al., 2007; Wolf...
et al., 2001). Moreover, there is recent evidence that emotionally arousing information is especially sensitive to the retrieval-impairing effects of glucocorticoids (De Quervain et al., 2007; Kuhlmann et al., 2005a; Kuhlmann et al., 2005b).

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 and phobias are such conditions. We therefore hypothesized that by inhibiting the retrieval of aversive memories, the administration of cortisol may be beneficial in these conditions.

4. 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 one month using a double-blind, placebo-controlled, crossover design. The administration of this low dose of cortisol for one 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. 1). 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. 1). 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 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. 1), 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 three patients investigated, low-dose cortisol treatment had beneficial effects with significant reductions in one of the daily rated symptoms of traumatic memories.

5. Glucocorticoids reduce fear in phobia

In recent clinical studies we 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 and thereby reduce stimulus-induced fear (Soravia et al., 2006). We administered glucocorticoids to 40 subjects with social phobia and 20 subjects with spider phobia in two
In 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 (Fig. 2A). 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 (Fig. 2B). This effect was maintained when subjects were exposed to the stimulus again two days after the last cortisol administration, suggesting that cortisol has also facilitated the extinction of phobic fear (Fig. 2B). As in phobias retrieval processes cannot be measured directly, it cannot be ruled out that cortisol, perhaps in addition to influencing memory retrieval, may have reduced fear by exerting a direct anxiolytic effect or by modulating other systems involved in the expression of fear. However, in favor of the view that glucocorticoids had reduced fear by inhibiting the retrieval of aversive memories we found, as detailed before, that cortisol administration to patients with PTSD reduced re-experiencing of the trauma, which is a direct measure of memory retrieval (Aerni et al., 2004). In addition, in the phobia study glucocorticoid administration did not affect phobia-unrelated anxiety, mood, wakefulness, or calmness, suggesting that this hormone reduced phobic fear specifically. Moreover, recent findings indicating that acute cortisol elevations cause heightened arousal ratings of neutral stimuli (Abercrombie et al., 2005) make a general or direct anxiolytic effect of glucocorticoids unlikely.

6. Possible mode of action of glucocorticoids in the reduction of aversive memory

Extensive evidence from studies in amnesic patients, human imaging studies, and lesion studies in animals indicates that the medial temporal lobe is crucially involved in memory retrieval and that activation of the medial temporal lobe is associated with successful memory retrieval (Cabeza and Nyberg, 2000; Moser and Moser, 1998; Squire, 1992). Moreover, a functional magnetic resonance study in patients with PTSD showed that the medial temporal lobe becomes activated by viewing masked traumatic images (Sakamoto et al., 2005) and a positron emission tomography study in patients with social phobia reported that after successful psycho- or pharmacotherapy the medial temporal lobe becomes less activated by public speaking (Furmark et al., 2002). Using positron emission tomography in healthy humans, we found that acutely administered cortisone reduces blood flow in the medial temporal lobe during memory retrieval. 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 (Fig. 2B). This effect was maintained when subjects were exposed to the stimulus again two days after the last cortisol administration, suggesting that cortisol has also facilitated the extinction of phobic fear (Fig. 2B). As in phobias retrieval processes cannot be measured directly, it cannot be ruled out that cortisol, perhaps in addition to influencing memory retrieval, may have reduced fear by exerting a direct anxiolytic effect or by modulating other systems involved in the expression of fear. However, in favor of the view that glucocorticoids had reduced fear by inhibiting the retrieval of aversive memories we found, as detailed before, that cortisol administration to patients with PTSD reduced re-experiencing of the trauma, which is a direct measure of memory retrieval (Aerni et al., 2004). In addition, in the phobia study glucocorticoid administration did not affect phobia-unrelated anxiety, mood, wakefulness, or calmness, suggesting that this hormone reduced phobic fear specifically. Moreover, recent findings indicating that acute cortisol elevations cause heightened arousal ratings of neutral stimuli (Abercrombie et al., 2005) make a general or direct anxiolytic effect of glucocorticoids unlikely.

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retrieval, an effect that correlated with the degree of memory retrieval impairment (De Quervain et al., 2003). Moreover, a recent functional magnetic resonance imaging study found that glucocorticoids decrease hippocampal and prefrontal activation during declarative memory retrieval (Oei et al., 2007). Furthermore, systemic administration of glucocorticoids to rats shortly before retention testing induced memory retrieval impairments for contextual memory (Roozendaal et al., 2004a), which depends on the medial temporal lobe (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 indicate that the medial temporal lobe (possibly among other brain regions) is involved in mediating the inhibitory effects of glucocorticoids on the retrieval of aversive memories.

7. Glucocorticoids may weaken the aversive memory trace

In both the PTSD study (Aerni et al., 2004) and the phobia study (Soravia et al., 2006) we additionally found evidence for a prolonged effect of the glucocorticoid treatment. What might be the underlying mechanism? Let’s first have a look at the processes that contribute to the persistence of these disorders: In PTSD, excessive retrieval of traumatic memory, which may be spontaneous or triggered by a trauma cue, leads to re-experiencing the traumatic event (Michael and Ehlers, 2007). In phobia, retrieval of fear memory triggered by a fear cue (phobic situation or object) leads to a fear response. Reconsolidation of such aversive experiences further cements the aversive memory trace and thereby contributes to the persistence of these disorders (Fig. 3A). By inhibiting memory retrieval, cortisol may weaken the aversive memory trace, and thus reduce symptoms even beyond the treatment period (Fig. 3B). Specifically, by inhibiting memory retrieval, cortisol may partly interrupt the vicious cycle of spontaneous retrieving, re-experiencing and reconsolidating traumatic memories in PTSD and, thereby, promote forgetting, 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 aversive cues. Accordingly, because of the cortisol-induced reduction of memory retrieval, an aversive cue is no longer followed by the usual aversive memory retrieval and re-experiencing but, instead, becomes associated with a non-aversive experience that is 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 (Buchanan and Lovallo, 2001; Flood et al., 1978; Kovacs et al., 1977; Kuhlmann and Wolf, 2006; Roozendaal, 2000). It is therefore possible that glucocorticoids may have further promoted extinction of the aversive 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).

8. Conclusions

In two first clinical studies we found evidence that the administration of glucocorticoids may be beneficial for patients with PTSD and phobias by reducing excessive retrieval of aversive memories. Furthermore, we found evidence for a prolonged effect of glucocorticoid treatment. This may have resulted from a facilitated extinction of aversive memories, as subjects learn that the aversive stimulus becomes less fearful under elevated glucocorticoid levels. Therefore, glucocorticoid treatment, especially in combination with exposure techniques in cognitive–behavioral therapy, may be a promising approach to facilitate the extinction of aversive memories. More studies are needed to further evaluate the therapeutic efficacy of glucocorticoids in the treatment of anxiety disorders and to explore the potential of combining glucocorticoid treatment with psychotherapy.

Acknowledgment

Supported by a grant from the Swiss National Science Foundation to D.Q. (PP00B-106708).
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