Healing anxiety disorders with glucocorticoids

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Around 6% of the adult population experiences strong anxiety and dizziness when exposed, or in anticipation of exposure, to a wide range of height-related situations (e.g., stairs, elevators, terraces, high floors in tall buildings, plane trips), devoting big efforts to avoid them. Severe fear of heights is known as acrophobia, an anxiety disorder that belongs to the category of specific phobias (e.g., fear of spiders or blood). Specific phobias in general and acrophobia in particular respond quite well to behavioral therapy (1). Behavioral therapies aim at achieving habituation and eventual extinction of the phobic reaction by confronting the patient, either directly or through imagination, with the phobic object or situation, generally in a graduated way. There are many patients who fail to respond effectively to treatment, however, or show reduced symptoms only partially or temporarily (2). In PNAS, a promising combination of behavioral therapy with pharmacotherapy is presented as a successful attempt to improve the efficacy of therapeutical approaches addressed to extinguish fear responses (3). The administration of cortisol (a glucocorticoid hormone whose levels increase under stress) to patients treated with virtual reality exposure to heights is shown to facilitate the efficacy of the exposure therapy, an effect that was evident both in a test performed a few days after discontinuation of the treatment and in a follow-up assessment performed 1 mo afterward.

Therapeutic Actions

One of the prevailing views about the etiology of phobias is that associative learning processes are at their core. Accordingly, phobic anxiety is a conditioned response triggered by an original aversive experience with the phobic stimulus. The subsequent avoidance of that stimulus is then instrumental for the maintenance of the phobia because of the reinforcing properties of reducing anxiety (4). Behavioral therapies tackle both processes by forcing individuals to face the feared stimulus and by aiming at reducing the magnitude of the fear responses elicited by the feared situation, and thus breaking (i.e., extinguishing) the association between them. Previous attempts to facilitate extinction of phobic processes by administration of anxiolytic drugs during behavioral therapy were disappointing. On the contrary, the effectiveness of a recent pharmacotherapeutical approach (i.e., D-cycloserine, a partial agonist of the glutamate receptor NMDA) aimed at improving the learning processes that occur during exposure therapy (5) suggested that targeting extinction learning could be the way to improve treatment outcome. The approach developed by de Quervain et al. (3) brings a unique dimension to this therapeutical scheme by attempting to affect two key processes of extinction learning simultaneously: the retrieval of aversive memories and the storage or consolidation of the extinction process itself.

The relevance of this study relies on the clear facilitating effect of virtual reality therapy's efficacy by cortisol treatment.

A wide body of animal and human data indicates that glucocorticoids are potent modulators of brain function and cognition (6–8). Importantly, glucocorticoids exert opposite effects in different memory phases and processes, typically facilitating memory consolidation while impairing memory retrieval (8, 9). In addition, there are several examples showing that glucocorticoids facilitate extinction processes (8).

In the report by de Quervain et al. (3) in PNAS, 40 patients with specific phobia to heights received either cortisol (20 mg/kg) or placebo orally 1 h before each of the three sessions of virtual reality exposure to heights. The exposure to the virtual reality height environment was done via physiological sensors and a headset with integrated video display glasses. During the exposure sessions, patients were guided through a height environment, simulated by a computer program, with different platforms connected by bridges and elevators, passing through different predefined stations with increasing difficulty. The beginning of the session included the use of an elevator at a rather low building, whereas the end of the session required the crossing of a long and small bridge connecting two very high platforms. Anxiety levels were assessed at particular stations, and patients were only guided toward the next station once anxiety levels were below a preestablished threshold. Changes in fear of heights with treatment were measured through (*i*) self-report questionnaires assessing subjects' anxiety, attitudes, expectancy, and cognitions with respect to heights; (*ii*) the direct rating of their anxiety levels by means of a verbal Subjective Units of Discomfort scale during virtual reality exposure; (*iii*) and a Behavioral Avoidance Test that assesses behaviors of subjects when exposed to a relevant real-life height situation. Physiological anxiety was evaluated by measuring changes in skin conductance.

De Quervain et al. (3) show that, on its own, virtual reality exposure led to a reduction of fear to heights, as measured with self-reported questionnaires and the Behavioral Avoidance Test. These observations support the popularity, since its outset in 1995, of virtual reality exposure over other behavioral therapies for the treatment of height phobia (10). However, the relevance of this study relies on the clear facilitating effect of virtual reality therapy's efficacy by cortisol treatment, however. Patients who received cortisol before each virtual reality session showed a greater reduction in acute anxiety during virtual exposure to a phobic situation at posttreatment and a significantly smaller exposure-induced increase in a physiological index of anxiety at follow-up assessment after 1 mo. Notably, cortisol treatment did not reduce general phobia-unrelated anxiety.

Underlying Mechanisms

The efficacy of glucocorticoids to interfere with the retrieval of aversive memories in anxiety disorders was previously shown in posttraumatic stress disorder (PTSD) (11) and in social and spider phobias (12). In the PTSD study, patients received glucocorticoids chronically for 1 mo without any associated psychotherapy (11). In the phobia study, the efficacy of acute corticosterone treatment to reduce fear responses was circumscribed to a particular stimulus (12). The report in PNAS (3) thus combines glucocorticoid and virtual reality therapies and shows that the efficacy of the

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treatment generalizes to other stimulus-related situations and is maintained for at least 1 mo after treatment discontinuation.

What are the mechanisms whereby glucocorticoids affect the efficacy of exposure treatment in reducing fear responses to a specific stimulus? Because cortisol was given before each virtual reality session in the study by de Quervain et al. (3), it is not possible to ascertain whether cortisol acted by impairing the retrieval of fearful memories during the exposure session or by facilitating the consolidation of the extinction processes elicited by exposure therapy. There is evidence in the literature supporting both types of effects for glucocorticoids; therefore, it is highly possible that a combined action on both memory processes accounts for the therapeutical efficacy of cortisol in this study. Glucocorticoids can get access to the brain, where, through binding to specific receptors, they can affect different memory processes. Classic genomic actions of glucocorticoids have been implicated in their effects on memory consolidation, a process that normally requires de novo protein synthesis. More recently, rapid nongenomic effects have been implicated in the processing of ongoing information, and thereby as a potential mechanism to affect the processes of acquisition and retrieval of information (13). Strikingly, both genomic and nongenomic actions of glucocorticoids can have an impact on glutamatergic mechanisms in the context of memory processing, including actions through NMDA receptors (13). There may thus be some convergence between the mechanisms involved in the therapeutical efficacy of D-cycloserine and those of glucocorticoids in their facilitating effects on extinction learning. In addition, glucocorticoid actions may be reinforced through their effects on other pathways (e.g., activation of extrasynaptic NMDA receptors in their impairing effects on retrieval or their regulation of gene transcription in their facilitating effects on consolidation) (13). This suggests that the therapeutical efficacy of glucocorticoids in the extinction of fear memories during psychotherapy might be particularly long lasting. Future studies are warranted to compare the effectiveness of different pharmacotherapeutical approaches, including follow-up evaluations at longer time intervals.

A key open question regarding the beneficial effects of glucocorticoids in extinction processes is whether they also protect against reinstatement (i.e., the return of the fear response to the phobic stimulus that generally occurs when stress is experienced after extinction training). The phenomenon of reinstatement occurs because extinction does not represent deletion of the original fear memory but, instead, involves different learning that inhibits the expression of the original fear association. This is an important question with enormous clinical implications that needs to be addressed as well in future studies. The outcome of such studies will depend on both the magnitude at which glucocorticoids reinforce the strength of the inhibitory association between the phobic cues and the fear memory acquired during exposure therapy as well as on the capability of glucocorticoids to render the newly acquired learning context-independent. Glucocorticoids might be particularly suitable to exert these actions (14, 15). In addition, it might be worth exploring the therapeutical efficacy of glucocorticoid manipulations in reconsolidation paradigms. In these paradigms, a brief exposure to the reminder cue turns the associated memory labile and susceptible to being "erased" by pharmacological or behavioral manipulations given during a time window after cue presentation (16). In rodents, a traumatic memory was persistently disrupted if glucocorticoid receptors were inactivated in the amygdala immediately after its retrieval (17). A plausible experimental approach would be to use the same virtual reality setup as in the extinction study by de Quervain et al. (3) with shorter exposures to the phobic stimulus (to a particular height in this case) followed by the administration of a glucocorticoid receptor antagonist.

The approach of de Quervain et al. (3) to facilitate extinction therapy by applying glucocorticoids is not only very promising for the treatment of phobias and other anxiety disorders but points toward the possibility of treating other psychiatric conditions in which aversive memories are at the core of the problem, such as depression, in similar ways (18). Importantly, this study, with main hypotheses based on mechanistic data collected in rodents, exemplifies the relevance of basic research in animals for the advancement of the development of unique treatments for human clinical conditions.

1. Choy Y, Fyer AJ, Lipsitz JD (2007) Treatment of specific phobia in adults. *Clin Psychol Rev* 27:266–286.
2. de Quervain DJ, Margraf J (2008) Glucocorticoids for the treatment of post-traumatic stress disorder and phobias: A novel therapeutic approach. *Eur J Pharmacol* 583:365–371.
3. de Quervain DJ-F, et al. (2011) Glucocorticoids enhance extinction-based psychotherapy. *Proc Natl Acad Sci USA* 108:6621–6625.
4. Mowrer OH (1939) A stimulus-response analysis of anxiety and its role as a reinforcing agent. *Psychol Rev* 46: 553–565.
5. Ressler KJ, et al. (2004) Cognitive enhancers as adjuncts to psychotherapy: Use of D-cycloserine in phobic individuals to facilitate extinction of fear. *Arch Gen Psychiatry* 61:1136–1144.
6. de Kloet ER, Oitzl MS, Joëls M (1999) Stress and cognition: Are corticosteroids good or bad guys? *Trends Neurosci* 22:422–426.
7. McGaugh JL, Roozendaal B (2002) Role of adrenal stress hormones in forming lasting memories in the brain. *Curr Opin Neurobiol* 12:205–210.
8. de Quervain DJ, Aerni A, Schelling G, Roozendaal B (2009) Glucocorticoids and the regulation of memory in health and disease. *Front Neuroendocrinol* 30:358–370.
9. Sandi C, Pinelo-Nava MT Stress and memory: Behavioral effects and neurobiological mechanisms. *Neural Plast*, 10.1155/2007/78970.
10. Coelho CM, Waters AM, Hine TJ, Wallis G (2009) The use of virtual reality in acrophobia research and treatment. *J Anxiety Disord* 23:563–574.
11. Aerni A, et al. (2004) Low-dose cortisol for symptoms of posttraumatic stress disorder. *Am J Psychiatry* 161: 1488–1490.
12. Soravia LM, et al. (2006) Glucocorticoids reduce phobic fear in humans. *Proc Natl Acad Sci USA* 103:5585–5590.
13. Sandi C (2011) Glucocorticoids act on glutamatergic pathways to affect memory processes. *Trends Neurosci* 34:165–176.
14. Brinks V, de Kloet ER, Oitzl MS (2009) Corticosterone facilitates extinction of fear memory in BALB/c mice but strengthens cue related fear in C57BL/6 mice. *Exp Neurol* 216:375–382.
15. Conboy L, Sandi C (2010) Stress at learning facilitates memory formation by regulating AMPA receptor trafficking through a glucocorticoid action. *Neuropsychopharmacology* 35:674–685.
16. Schiller D, et al. (2010) Preventing the return of fear in humans using reconsolidation update mechanisms. *Nature* 463:49–53.
17. Tronel S, Alberini CM (2007) Persistent disruption of a traumatic memory by postretrieval inactivation of glucocorticoid receptors in the amygdala. *Biol Psychiatry* 62:33–39.
18. Sandi C, Richter-Levin G (2009) From high anxiety trait to depression: A neurocognitive hypothesis. *Trends Neurosci* 32:312–320.