In this column, the authors first present a composite of several cases of psychiatrically healthy individuals who developed manic-depressive symptoms after receiving a course of prednisone to treat symptoms of inflammatory processes, such as Crohn’s disease. The next section summarizes key points from 50 years of clinical experience with such cases. The authors then present an overview of the effects of exogenous administration of glucocorticoids on cognitive performance and emotional processing via effects on medial temporal lobe and prefrontal structures, including the amygdala, hippocampus, and dorsolateral prefrontal cortex. These effects include glucocorticoid-induced deficits in declarative and autobiographical memory, altered activation of medial temporal lobe structures, and delayed habituation of hemodynamic responses to emotional faces. Finally, these findings are connected in a discussion of how glucocorticoid exposure can result in mood disturbances and what light that may shed on the neurobiology underlying spontaneous bipolar and unipolar affective illnesses. (Journal of Psychiatric Practice 2013;19:309–315)

KEY WORDS: manic-depressive symptoms, prednisone, corticosteroids, cognition, memory, bipolar disorder, unipolar depression, affective illness

This column extends the discussion of our continuously expanding knowledge of the neurobiological basis of psychiatric illness, begun in an earlier column on affective illness. This column will focus on how knowledge of the effects of corticosteroids on human cognitive and emotional processing is advancing the goal of understanding the neurobiology of affective illnesses.

Corticosteroids can cause a diverse range of impairment in cognitive and emotional processing, which can present as major depression, mania, and mixed states. The second author of this column recently encountered several examples of such cases, principally in professional individuals from various backgrounds. To increase the applicability of this column for clinical practice, we present here a composite case based on these presentations, with quotations taken from the patients involved included to illustrate how closely corticosteroid-induced symptoms mimic those of de novo affective illnesses.

Case presentation

A 55-year-old professional with a history of Crohn’s disease developed a bout of diarrhea and was treated with high-dose prednisone with a tapering schedule. After 1 day of treatment with 40 mg, the patient noticed increased distractibility. After 3 days on a dose of 40 mg/day, the patient felt “really good” with “lots of energy and creativity.” Two days later, he no
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longer needed to sleep “so much—if at all” and had “inspiration for books that would generate more than a million dollars in revenue.” After 2 more days, the patient requested that his credit card limits be increased and began giving his possessions away because he “did not need the clutter.” The next day, the patient began to suspect the intentions of his family and friends and to experience “rushing, uncontrollable flights of ideas” including “fleeting and intense visual and auditory imagery” and “considerable difficulty in maintaining attention.” He “felt the impulse to be extremely active, proceeding from one task to the next in rapid sequence, and an intense drive to communicate my thoughts to others.” Notwithstanding the “intense nature of these experiences,” the patient was not aware that anything abnormal was happening. He “felt highly energetic which was not unpleasant and seemed only an extension of my usual personality.” He then made several uncharacteristic errors at work and had minor but again uncharacteristic confrontations with co-workers. The patient then became “despondent,” “tearful,” and psychomotor retarded. At this point, the patient’s family and friends had to force the individual to see the physician who was treating him, who immediately sought psychiatric consultation. A decision to stop the prednisone was made on the basis that its risks outweighed its benefits in this patient. Medications were used to aid in counteracting the effects of the prednisone. (A discussion of which medications might be considered in such cases is beyond the scope of this column but may be a topic for a subsequent column.) Within 2 weeks, this individual had returned to his premorbid condition.

Clinical literature on corticosteroid-induced psychiatric complications

The composite case presented above illustrates many of the classic features of corticosteroid-induced psychiatric symptoms. To put this case in perspective, a PubMed literature search was conducted on the following topics (the number of papers identified appears in parentheses): steroids and psychiatric symptoms (4,448 articles), dexamethasone and psychiatric symptoms (1,099 articles), steroids and mania (982 articles), steroid-induced psychiatric symptoms solely involving humans (650 articles), steroid and judgment restricted to humans only (129 articles), dexamethasone and cognition restricted to humans (113 articles), and steroids and hypomania (25 articles).

Corticosteroid-induced adverse psychiatric effects were first reported in the medical literature soon after the introduction of these medications in the 1950s. It has been recognized for over 35 years that treatment with corticosteroids can cause a plethora of cognitive and emotional effects, including agitation, anxiety, apathy, auditory and visual hallucinations, delusions, depression, distractibility, disturbances of body image, emotional lability, hypomania, insomnia, intermittent memory impairment, mutism, perplexity, pressured speech, and sensory flooding, depending on the dose and duration of the treatment as well as the biology of the person involved.

During corticosteroid therapy, 75% of patients experience mood disturbance, and such disturbances are severe in 5% of patients. Severe psychiatric reactions frequently occur early in the course of such therapy, suggesting a predisposition in the affected individual. Corticosteroid-induced symptoms are consistent with psychiatric symptoms that occur in patients with primary Cushing’s disorder. Both patients with primary Cushing’s disorder and those who develop psychiatric symptoms as a result of treatment with exogenous corticosteroids frequently minimize or conceal their psychiatric disturbances, perhaps as a result of being unable to understand and identify the nature of their cognitive/emotional disturbance or as a result of denial.

In addition to these clinically evident disturbances, recent research has found that administration of exogenous steroids can produce transient impairment in working memory and can also impair cognitive flexibility in healthy volunteers. In addition to functional measures, corticosteroid administration has been reported to impair temporal lobe functioning as measured by structural, functional, and spectroscopic imaging.

In summary, the psychiatric complications of corticosteroid treatment are neither rare nor consequential, ranging from clinically significant anxiety and insomnia, to severe mood and psychotic disorders, and at the extreme, delirium and dementia. While these complications are indisputable, they are also unpredictable, so that clinicians cannot prospectively determine which patients are at risk, but instead they must deal with the phenomenon after the problem has arisen. Perhaps due to the fact that corticosteroid treatment most often lasts no
more than a few weeks, the cognitive and emotional disturbances associated with treatment are almost always fully reversible within a few days to a week or two after the steroid is discontinued. This is true both when the exposure occurs in clinical practice to treat a condition or in a research setting where exposure is even shorter term (e.g., one or a few doses) and is done to study the neurobiology of corticosteroid effects on brain functioning.

**Neurobiology underlying the effects of corticosteroids on cognitive and emotional processing**

In this section, we move from clinical data to the emerging understanding of the neurobiology underlying cognitive and emotional processing and how corticosteroids can produce the disturbances seen in the composite case presented above. Glucocorticoid receptors are abundantly expressed in the temporal and prefrontal regions important for memory and emotional processing. Dysfunction of emotional evaluation, expression, and modulation are dominant characteristics of many psychiatric disorders, including the transient states caused by corticosteroid exposure. Knowledge of the neurophysiological correlates of emotion regulation and of how these correlates are influenced by the glucocorticoid system has increased our understanding of how these processes are altered in specific psychiatric illnesses and in response to exposure to specific substances, including corticosteroids.

Cortisol is a glucocorticoid hormone secreted by the adrenal gland that serves major homeostatic roles, both in energy mobilization and as a crucial component of the body’s response to stress. Cortisol contributes to a wide range of regulatory functions, including glucose metabolism and various behavioral and cognitive functions (see Erickson et al. 2003 for a review). In some regions of the brain, glucocorticoids have inhibitory effects, such as the suppression of glucose metabolism in the hippocampus, anterior cingulate cortex, dorsolateral prefrontal cortex, and precuneus, and inhibition of the hypothalamic-pituitary-adrenal axis. In other regions of the brain, glucocorticoids have facilitatory effects, such as increased activation of the amygdala.

Cortisol binds to mineralocorticoid (MR) and glucocorticoid (GR) receptors in the brain, which are also referred to as Type I and Type II glucocorticoid receptors, respectively. These receptors are located in mesiotemporal and prefrontal cortical structures involved in learning, memory, and emotional processing, including the amygdala, prefrontal cortex, and hippocampus. The affinity of cortisol for MR receptors is 6–10 times higher than its affinity for GR receptors. However, during the peak phase in the circadian cycle or during periods of stress, the MR receptors become saturated, and cortisol increasingly binds to GR receptors. The effects of cortisol on cognitive functioning appear to be determined by the ratio of MR/GR activation. Treatment with corticosteroids can result in persistently elevated occupancy of these receptors in contrast to the usual daily circadian cycle seen under normal physiological conditions, in which levels of cortisol are high in the mornings and decrease as the day progresses.

Although chronically elevated levels of cortisol (and hence occupancy of these receptors) have been found to impair performance on a wide variety of cognitive tasks, including tests of spatial memory, arousal, attention, and executive function, the effects of acute alterations in cortisol levels are hypothesized to follow an inverted U shape function on cognitive performance. Extremely high or low cortisol levels impair memory performance, and moderate levels enhance it. It is hypothesized that these effects are mediated via the ratio of MR/GR occupation. When most of the MRs and only part of the GRs are activated, cognitive function can be enhanced. This rep-
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resists the top of the inverted U shape function with the optimal MR/GR ratio. On the other hand, when circulating levels of glucocorticoids are significantly decreased (respectively low MR occupancy; high MR/GR occupation ratio) or increased (relatively high GR occupancy; low MR/GR occupation ratio), cognitive impairment can result. These are the extremes of the inverted-U shape function. 23 Figure 1 is a pictorial representation of the inverted U function and its relationship to MR/GR occupation. 26

The inverted U-shape association has also been described with glucocorticoids and long-term potentiation (LTP) in hippocampal neurons. Extremely low or high levels of cortisol inhibit LTP, while moderate levels enhance this process. 27 LTP is believed to be a critical component in the formation of memories; therefore, memory enhancements seen following cortisol administration may be due to increases in LTP in the hippocampus. In healthy humans, dose-dependent effects of hydrocortisone administration have been reported, with low doses facilitating and high doses impairing memory performance when administered after learning. 28 These effects appear to be specific to the episodic memory system, since cortisol administration does not impair performance on non-episodic memory tasks. 29,30 Thus, cortisol exerts dose-dependent effects on the consolidation of episodic information when administered prior to learning.

In contrast, studies in which corticosteroids were administered after learning but before retrieval suggest that cortisol only impairs memory retrieval, and that cortisol’s effect on retrieval of previously learned information does not follow the inverted U function. 31–33 However, these studies have not adequately addressed whether glucocorticoid hormone administration results in differential effects on retrieval of episodic information from long-term memory at distinct doses (for a review, see de Quervain et al. 2009 34). Studies typically test memory for items learned within the 24 hours prior to administration of a single dose of cortisol. Testing memory for episodic information encoded longer than 24 hours prior to the alteration of cortisol levels would provide information regarding whether cortisol’s effects on memory retrieval extend beyond information learned the previous day.

Autobiographical memory is a subsystem of episodic memory in which remembered events are specific to one’s own past experiences with their temporal and historical context intact. 35 This memory system is unique because it involves self-referential episodic memory and because it shows marked enhancement by the emotional salience or arousal associated with the remembered event. Based on several studies, high doses of hydrocortisone result in a decrease in the number of specific memories and an increase in the number of categorical memories recalled in response to emotionally valenced cue words. 36–38 Reduced access to specific memories of past events can lead to ineffective problem solving. As responses to current situations depend on past experiences, the ability to successfully recall autobiographical experiences may enable adaptive responses in novel circumstances. Corticosteroid exposure may therefore impair appropriate responding and planning via reduced access to specific autobiographical memories.

The amygdala is a brain region that has a significant role in mediating effects of cortisol on brain function. The amygdala is a key component of two distinct, distributed neural networks by which humans are able to evaluate the emotional salience of sensory stimuli: 1) a network involving cortical regions that allows conscious or explicit stimulus perception, and 2) a network involving subcortical structures that allow rapid, non-conscious (i.e., below the level of conscious or prefrontal awareness) assessment of stimulus features. 39,40 There is considerable evidence that the amygdala is involved in acquisition and expression of emotional/arousing memories. 39,41,42

Based on several functional imaging studies in healthy participants, greater amygdala activity occurs in response to negatively valenced fearful and sad faces than in response to neutral or happy faces. 43–46 This response to negative faces is even greater in patients with depression and reverts toward normative levels during remission. 47 The involvement of the amygdala in responses to subliminally presented faces and the fact that cortisol has acute effects on the amygdala suggest that altering cortisol levels would also affect habituation to faces presented below conscious awareness via effects on cerebral blood flow in the amygdala.

Functional neuroimaging studies have revealed differences in hemodynamic responses in the amygdala when emotionally valenced stimuli, including those involving recognition of facial expressions, are presented. 43,48,49 The magnitude of blood flow in the amygdala is positively correlated with the degree of fear expressed in fearful faces, and negatively with
the degree of happiness expressed in happy faces.\textsuperscript{43} Subliminal presentations of “masked” faces lead to stronger activations of the amygdala than do overt presentations, providing support for the detection of emotionally valenced faces presented below the level of conscious awareness at the subcortical level.\textsuperscript{46} Notably, healthy subjects show greater amygdala responses to happy versus sad faces when stimuli are presented below conscious awareness. This finding suggests the existence of a normal positive processing bias that is supported by subcortical networks that mediate rapid, automatic emotional evaluations.\textsuperscript{50} That processing bias appears to be reversibly flipped by exposure to high and persistent levels of corticosteroids during the period of exposure. Interestingly, this processing bias is also flipped in the presence of clinical depression (with increased amygdala responses to masked sad versus happy faces) and reverses toward normal with effective antidepressant treatment.\textsuperscript{51}

Glucocorticoid receptor stimulation can also alter emotional processing by affecting the rate of habituation to stimuli, resulting in changes in brain activity. High doses of hydrocortisone delay habituation to conditioned stimuli\textsuperscript{52,53} and emotional stimuli, including fearful\textsuperscript{54} and angry\textsuperscript{55} faces. Hydrocortisone can also delay habituation to sad faces (a validated experimental paradigm frequently used in work in this area). Neurophysiologically, cortisol administration in men prior to conditioning tasks results in reduced activation in the anterior cingulate cortex, orbitofrontal cortex and medial prefrontal cortex in response to the conditioned stimuli.\textsuperscript{52} When subjects were prevented from becoming aware of the contingency relationship between the conditioned stimuli and the unconditioned stimuli, men showed decreased activation in the insula, hippocampus, and thalamus following hydrocortisone administration.\textsuperscript{53}

Functional studies have shown that the amygdala is activated during the initial period of exposure to fear-conditioned stimuli, but that it then becomes deactivated (or habituated) during repeated exposures to the same stimulus.\textsuperscript{56–58} In addition to paradigms with phobia-related components, evidence of amygdala habituation as measured by functional imaging has been found with multiple presentations of affective facial expressions in healthy controls.\textsuperscript{49,59,60}

It is relevant that activity in these neural circuits is heightened by a prior experience with an environment insult such as a traumatic life event. Such exposure could neurobiologically prime an individual for a more pronounced reaction when he or she encounters this same stimulus or a closely related stimulus while taking corticosteroids.

Conclusion:

For more than 50 years, the exogenous administration of corticosteroids has been known to cause a range of disturbances in emotional regulation and cognitive processing in humans. Through both basic and clinical research, a better understanding of the neurobiology underlying these disturbances has been and is continuing to be developed. Given the similarity between the signs and symptoms induced by corticosteroids and those of primary affective illnesses, both bipolar and unipolar mood disorders, this work is now being extended to the understanding of the neurobiology underlying these primary psychiatric illnesses. From that knowledge, new treatments—potentially preventive—will undoubtedly come.

References


