The Stress Axis Gone Awry: A Possible Neuroendocrine Explanation for Increased Risk of Completed Suicide

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Abstract

While the dexamethasone suppression test (DST) has not proven useful as a diagnostic test for “true” depression, it shows increasing promise as a potential indicator of psychiatric patients at increased risk for suicide. An indicator of the activity level of the hypothalamic-pituitary-adrenal (HPA) axis, the DST is an endocrine test that has caught the interest of psychiatric researchers throughout the last century because of the role of the HPA axis in managing an organism’s homeostasis and stress response. This article will present a brief literature review of the role of the DST in psychiatry. It will propose a hypothesis, supported by data from two recent small studies, that suggests that chronic overdrive in the HPA axis, as manifested in a nonsuppressing DST, may result in an increased likelihood of suicide when the individual is acutely stressed.

Introduction

Could depression and even suicide be construed as neuroendocrine problems? Since the 1960s, abnormalities in the hypothalamic-pituitary-adrenal (HPA) axis have been associated with severe depressive states, and neuroendocrine interactions have been a logical place to look for evidence of biology’s hegemony over psychology. As biological psychiatry began to assert its authority over the psychodynamic school during the 1970s and the 1980s, its “holy grail” became an objective test to prove depression’s presence or absence. Proponents proposed the dexamethasone suppression test (DST), a measure of HPA axis activity, as a clinical diagnostic test to distinguish definitively between biologically driven melancholic depression and psychologically dominated depressive neurotic states. According to the dogma, when given a dexamethasone challenge, neurotic depressives should suppress the HPA axis, while “real” melancholic depressives should not.

The HPA Axis and Mental Status

The HPA axis is crucial to survival. At baseline, it maintains homeostasis and circadian rhythms through a fine-tuned feedback loop, consisting of the paraventricular nucleus (PVN) of the hypothalamus, the anterior pituitary, and the adrenal cortex. The PVN is the HPA axis master controller, receiving modifying input from the hippocampus, the prefrontal cortex, and other brain regions, as well as the axis itself (Figure).

In humans, cortisol is the hormone messenger that feeds back to the PVN via two receptors. High-potency, type-I mineralocorticoid receptors that preferentially bind cortisol in low-concentration environments give predominantly positive feedback at baseline, fine tuning homeostasis in cardiovascular, metabolic, and immune systems. Under stressful conditions, however, massive amounts of cortisol are produced. Mineralocorticoid receptors are saturated, and low-potency glucocorticoid receptors located on the PVN and anterior pituitary dominate. They offer negative feedback to contain the all-out stress response. At these times, hyperarousal trumps homeostasis. The individual demonstrates heightened alertness, decreased libido, insomnia, and cognitive changes in the throes of a “fight-or-flight” mode.

The HPA axis, the so-called “stress axis,” has long been linked to effects on mental status. Cannon observed as early as 1939 that the adrenal glands...
respond to stress with increased production, and Cushing noticed a link between endocrine overproduction and "psychic disturbances" in 1913. This stress response is a normal and necessary protective response in the arsenal of survival weapons. When hyperarousal and consequent cortisol excess become chronic, however, the brain is altered permanently, as has been shown in diverse experiments with rats, macaque monkeys, and humans. The force behind these permanent changes, both experimentally and naturalistically, is neglect or abuse early in development. The hippocampus, an inhibitory influence on the hypothalamus, loses volume and efficacy, and the hypothalamus itself undergoes receptor changes associated with nonsuppression status and HPA axis hyperarousal.

Many features of the stress response are identical to neurovegetative symptoms of depression when chronic. In the 1960s and 1970s, Sachar, Sachar and colleagues, Bunney and colleagues, and Gibbons explored the relationship between depressive pathology and elevated urine and plasma corticosteroids. They found particularly strong correlations between corticosteroid abnormalities and more severe forms of depressive illness, particularly psychotic depression. The DST, already used to diagnose Cushing's disease, opened a window on disturbed HPA axis feedback in severe depression.

The DST and Depression

The DST works in the following way: control subjects who are given a 1 mg dose of the synthetic steroid dexamethasone at 11pm will typically show subnormal cortisol levels in blood drawn the next day, indicating appropriate suppression of the HPA axis at the level of the hypothalamus. HPA axes in a significant proportion of depressed subjects, however, "escape," and fail to demonstrate a suppressed cortisol level. Thus, the DST was heralded as a specific laboratory test for the diagnosis of melancholia, a form of depression with prominent neurovegetative signs. Carroll and colleagues asserted in 1981 that "extensive evidence validates this practical test for the diagnosis of melancholia."

Writing about the controversy of articulating between the differential diagnoses of depressive disorders, Carroll and colleagues distinguished between the "classical condition, melancholia," also known as endogenous depression, and the related condition of nonendogenous depression, a term synonymous with "neurotic, reactive, or characterological" depression. Some authorities, they wrote, "insist that there is no demonstrated difference," but they asserted that they had proven wrong with "a test of neuroendocrine function that is highly specific for melancholia." Another article, typical of the many produced in the 1980s, purported to show that the DST was a valid marker for endogenous depression by describing all the things that nonsuppressors were not. In a 1986 study of 187 unipolar depressed inpatients by Zimmerman and colleagues, nonsuppressors were shown to be older, not as personality disordered, not as socially or maritally compromised, and not as assailed with recent stressful events as suppressors. Moreover, nonsuppressors had made fewer nonserious suicide attempts and were less likely to have alcoholic or antisocial first-degree relatives. This demonstrated that not only was melancholia innate to the organism, but that its sufferers also experienced to a lesser degree all the comorbidities affecting reactive depressives and presumably driving their nonendogenous disorder.

However, despite the excitement over the DST, which led to thousands of subjects being studied and countless patients undergoing the test in conjunction with their psychiatric treatment, there were harsh critics of the descriptive-biological approach. In a scathing editorial in Biological Psychiatry, Ros lambasted the theory behind the test for its "reductionism." "The depressed patient emits various signals indicating his depressed state," he wrote. "Some of these are physiological, but not all. The assumption that the DST, which is a highly transduced signal, is more real than the clinical signals is nonscientific and ideologically based."

Ros’ skepticism proved prophetic. Patients who looked melancholic frequently suppressed and neurotic appearing patients frequently did not suppress, although both types had symptoms meeting criteria for major depressive disorder (MDD). In 1985, Arana and colleagues showed that while the DST had a sensitivity of 78% in psychotic depressives, sensitivity dropped to only 44% if psycho-

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**Figure**

The Hypothalamic-Pituitary-Adrenal Axis

- **Hypothalamus PVN**: MR, CRF/AVP
- **Anterior pituitary**: GR, ACTH
- **Adrenal cortex**: Glucocorticoids (cortisol)

* The PVN of the hypothalamus is the master controller for the HPA axis. In stressful situations, in response to modulatory input from the hippocampus, the amygdala, the ventral prefrontal cortex, and other brain regions, the PVN releases CRF, which causes the anterior pituitary to release ACTH, which in turn stimulates the adrenal cortex to produce cortisol. In high concentrations during stress, cortisol gives negative feedback to the PVN and anterior pituitary through GRs to terminate the axis’ stress response. In low concentrations, cortisol gives the PVN primarily positive feedback through MRs to maintain homeostatic balance.

CNS=central nervous system; MR=mineralocorticoid receptor; PVN=paraventricular nucleus; GR=gluocorticoid receptors; CRF=corticotropin-releasing factor; AVP=vasopressin; ACTH=adrenocorticotropic hormone; HPA=hypothalamic-pituitary-adrenal.

sis was not present. Two years later, the American Psychiatric Association\(^4\) repudiated the DST on the basis of its lacking both sensitivity and specificity as a diagnostic test for MDD. Like insulin-shock therapy and prefrontal leukotomy, the DST seemed destined to become a historical anomaly.

The DST and Risk of Suicide

Its lack of validity as a diagnostic test notwithstanding, something significant appears to be happening in the stress axis of depressed patients, which has continued to attract research attention. While specific details still remain vague, the interplay between the HPA axis and prefrontal serotonin systems—components of larger brain modulatory networks—have come to be understood to modulate mood and levels of impulsivity. The DST, therefore, has shown new promise in a different psychiatric arena: identifying subjects at elevated suicide risk.

Coryell and Schlesser,\(^11\) for example, reported findings on the mortality in the ensuing years of 78 affectively ill subjects they had originally studied between 1979 and 1981. Thirty-two had been DST nonsuppressors and 46 had been suppressors. During an average of 10 years of follow-up, 8 of the 78 had committed suicide. Seven of these eight were nonsuppressors, for a nonsuppressor suicide prevalence of 27%, an order of magnitude greater than the prevalence of 3% in the suppressor group.\(^15\)

With a sample of 114 depressed patients almost evenly split between suppressor and nonsuppressors, Bostwick and Warzecha\(^16\) replicated these findings. Of the seven suicides in their sample during an average 14-year follow-up, all but one occurred in nonsuppressors.

Clues to understanding these findings are found in the functioning of the HPA axis in health and disease. Under normal conditions, the HPA axis serves to maintain organism homeostasis. The PVN of the hypothalamus releases corticotropin-releasing factor (CRF), which stimulates the anterior pituitary to secrete adrenocorticotropic hormone (ACTH), which in turn causes the adrenal cortex to release cortisol. Through a negative feedback loop, the cortisol binds to hypothalamic receptors in a two-level recognition system.\(^10\)

The first level involves mineralocorticoid receptors, high-potency receptors that respond to low concentrations of cortisol to maintain optimal cellular functioning in immune, metabolic, and autonomic nervous systems, among others. This exquisitely tuned regulatory mechanism assures appropriate basal cortisol levels through a typical day's circadian fluctuations. When cortisol levels are high, as occurs during acute physical or psychological threat perceived by the cortex and funneled through the hypothalamus, the latter emits a burst of CRF. The resultant cortisol outpouring from the adrenals saturates mineralocorticoid receptors, and second-level glucocorticoid receptors are activated. Ineffective and quiescent when cortisol is at baseline levels, these low-potency receptors, when engaged in a cortisol-rich environment, have the capacity to trump the organism's homeostatic processes in favor of mobilizing energy reserves for the fight-or-flight response. Heightened alertness and increased fuel supply to muscles occur at the temporary expense of sleep, appetite, and libido. When cortical input to the hypothalamus indicates the threat has passed, glucocorticoid receptor-mediated negative feedback brings the HPA axis back to baseline function.\(^17\)

Both basal regulatory activities of mineralocorticoid receptors and stress-management functions of glucocorticoid receptors are essential to negotiating internal requirements and external threats. When glucocorticoid receptor hyperactivity becomes chronic, however, as it does in such conditions as Cushing's syndrome and severe depression, continuous high levels of cortisol exert a potent influence on hormone and neurotransmitter receptor function, causing dramatic affective and cognitive changes. Those familiar with behavioral side effects prominent during exogenous high-dose corticosteroid administration for multifarious medical and surgical conditions will appreciate similar findings in the context of endogenous HPA axis disruption. These may include mood extremes ranging from euphoria to depression, anxious and obsessive behavior, insomnia, irritable and labile mood states, and cognitive disturbances in perception, attention, concentration, and memory. All of these features can complicate depressive states that result from either endogenous or iatrogenic elevated corticosteroid levels. At their most extreme, these signs and symptoms constitute the psychosis of certain depressive conditions. Indeed, while the DST proved inadequately sensitive for general depressive states, it is more reliably positive in psychotic depression,\(^1\) a fact which makes intuitive sense given the potential role of elevated corticosteroids in producing conditions in which agitation and psychosis may emerge. As early as 1982, Reus\(^18\) observed the clinical distinctiveness of patients with hypercortisolemia:

Regardless of the diagnosis appended, the failure to suppress cortisol following the DST appears to identify subjects who are more symptomatic both objectively and subjectively at admission. The most significant differences were an increased incidence of sleep disorder, feelings of anxiety, and thoughts of suicide.

Chronically elevated corticosteroids can result in permanent brain changes,\(^8,19\) a fact that has important implications for stress responsiveness up to and including susceptibility to suicidal states. Such hypercortisolemic baselines can have developmental roots. Studies in neonatal rats removed from their mothers; monkeys raised by stressed, neglectful mothers; and mammals raised under stressful conditions have demonstrated HPA axis overdrive, as manifested in increased CRF receptors throughout the axis, increased corticotropin-releasing hormone, and ACTH levels with stress, increased cortisol at baseline, increased susceptibility to stress, and alterations in brain function.\(^20,24\)

Brain damage in the form of corticosteroid-induced hippocampal atrophy yields reduced inhibitory capacity characterized by a baseline trait of mild hyperarousal. Under stress, this hyperarousal balloons into more severe arousal states than found in subjects with normal hippocampal volume.\(^25\) This implies that abuse or neglect may produce permanent changes in the developing brain, according to Nemeroff.\(^25\) These changes chronically boost the input of and responsiveness to CRF, and therefore increase the lifetime vulnerability of subjects to depression.\(^25\) Certainly, histories of childhood abuse and failures in nurturance figure prominently in clinical histories of patients with dysthymia or many personality disorders. In patients with chaotic or neglectful developmental histories, genetic predispositions to depression, or both, superimposed acute stress can throw them into depressed or suicidal states.\(^26,27\)
A further correlate of the HPA axis gone awry is a reduction in ventral prefrontal cortex (PFC) serotonin levels when cortisol levels are high.\(^2^8\) Associated with damping impulsive and angry behavior, as well as regulating mood, the ventral PFC has been the brain region most closely linked to the monoamine hypothesis of depression in vogue since the 1960s, even as this theory grows increasingly simplistic as knowledge of neural networks and the complexity of reciprocal neurotransmitter interactions swells.

In 1994, Dinan\(^2^9\) proposed that reduced ventral PFC serotonin was actually a downstream effect of HPA axis overdrive. Mann,\(^2^8\) a prominent investigator of ventral PFC activity in suicidal states, also proposed a “stress-diathesis” model of suicide in which developmental failures and genetic predisposition correlates of HPA axis abnormalities are the substrates against which a stressor invokes the low-serotonin state driving impulsive acts against others or the self.\(^2^9\)

While the exact mechanisms by which the HPA axis modulates ventral PFC activity have not yet been elucidated, additional correlations continue to emerge. Van Praag,\(^3^0\) for example, noted how prefrontal regions are critical in damping acute stress reactors via negative feedback, how low serotonin in these regions is linked to disturbed anxiety and aggression regulation, and how stress—presumably HPA-axis induced—can trigger increased anxiety extending all the way up to the self-directed aggression of suicidal behavior. Westrin and Nimeus\(^3^1\) also showed that nonsuppressors with low levels of cerebrospinal fluid 5-HIAA, a serotonin metabolite, had higher scores on the Suicide Assessment Scale than either nonsuppressors with normal 5-HIAA or suppressors with either low or normal 5-HIAA.

**Conclusion**

The DST may prove to be a neuroendocrine window to suicidal propensity. Studies by Coryell and Schlesser\(^1^5\) and Bostwick and Warzecha\(^1^6\) support HPA axis dysregulation not as a psychiatric diagnostic tool but rather as an indicator of propensity toward lethal behavior. While DST nonsuppressor status will not pinpoint specific patients who will kill themselves and does not yet have clinical relevance in primary care settings, it does hold the promise of identifying a subgroup of patients at greatly elevated risk. Studies with larger numbers of subjects are needed to confirm the findings of these two small efforts. When depressive episodes in such patients assume the agitated or psychotic proportions suggestive of HPA-axis overdrive, they should be closely monitored for suicidality. In medical inpatients whose treatment includes high-dose corticosteroids, the emergence of affective or behavioral instability should be taken seriously, since impulsivity and disinhibition are closely linked to completed suicide while in the hospital. Psychiatric and nonpsychiatric providers alike should respond to anxiety or agitation, particularly in patients with this HPA axis abnormality, to avert suicidal crises.

**References**