Minireview: Stress-Related Psychiatric Disorders with Low Cortisol Levels: A Metabolic Hypothesis

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Several stress-associated neuropsychiatric disorders, notably posttraumatic stress disorder and chronic pain and fatigue syndromes, paradoxically exhibit somewhat low plasma levels of the stress hormone cortisol. The effects appear greatest in those initially traumatized in early life, implying a degree of developmental programming, perhaps of both lower cortisol and vulnerability to psychopathology. In these conditions, lowered cortisol is not due to any adrenal or pituitary insufficiency. Instead, two processes appear involved. First, there is increased target cell sensitivity to glucocorticoid action, notably negative feedback upon the hypothalamic-pituitary-adrenal (stress) axis. Altered density of the glucocorticoid receptor is inferred, squaring with much preclinical data showing early life challenges can permanently program glucocorticoid receptors in a tissue-specific manner. These effects involve epigenetic mechanisms. Second, early life trauma/starvation induces long-lasting lowering of glucocorticoid catabolism, specifically by 5α-reductase type 1 (predominantly a liver enzyme) and 11β-hydroxysteroid dehydrogenase type 2 (in kidney), an effect also seen in model systems. These changes reflect a plausible early-life adaptation to increase the persistence of active cortisol in liver (to maximize fuel output) and kidney (to increase salt retention) without elevation of circulating levels, thus avoiding their deleterious effects on brain and muscle. Modestly lowered circulating cortisol and increased vulnerability to stress-associated disorders may be the outcome. This notion implies a vulnerable early-life phenotype may be discernable and indicates potential therapy by modest glucocorticoid replacement. Indeed, early clinical trials with cortisol have shown a modicum of promise. **(*Endocrinology* 152: 4496–4503, 2011)**

In a well-documented triumph of neuroendocrinology, severe stress-related psychiatric disorders, notably severe melancholic and bipolar depression, have been consistently associated with elevated levels of cortisol and insensitivity to glucocorticoid feedback as assessed by the low-dose dexamethasone suppression test (1), a relationship that survives the rigors of meta-analysis (2). However, it has subsequently emerged that ostensibly similar stress-associated neuropsychiatric conditions are marked by paradoxically low cortisol levels. This unexpected story begins with Mason's observations (3) of low urinary free cortisol levels in patients with posttraumatic stress disorder (PTSD), data extended by Yehuda and others (4, 5). PTSD is a psychiatric condition that is precipitated by extremely traumatic experiences, but occurs in only a proportion of those exposed to such events; some individuals are vulnerable, others resilient. The condition itself is thought to represent a specific phenotype associated with a failure to recover from the normal effects of trauma (6). Interestingly, some 50–70% of patients with PTSD also meet diagnostic criteria for major depression or another mood or anxiety disorder (7). Nonetheless, the endocrine profile associated with PTSD *per se* is distinct from that observed in major depression. Low cortisol levels are not mere artifacts of measurement or sampling methods, a variety of different technologies have shown low cortisol

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Abbreviations: CNS, Central nervous system; GR, glucocorticoid receptor; HPA, hypothalamic-pituitary-adrenal; 11β-HSD, 11β-hydroxysteroid dehydrogenases; MR, mineralocorticoid receptor; PTSD, posttraumatic stress disorder.

levels in saliva, urine, and blood in many, but not all, populations with PTSD (8).

Although *a priori* prejudice suggests chronic fatigue, chronic pain syndromes, fibromyalgia, and other functional somatic disorders are distressing, these too associate with low cortisol (8, 9). Although the modest reductions of cortisol observed are, for an endocrinologist, not sufficient to engender thoughts of Addisonian insufficiency, nonetheless, allowing for the difficulties in detecting relatively slight changes in a labile stress hormone, some consistency has emerged. Intriguingly, in PTSD, low cortisol occurs particularly in the context of early-life physical or sexual abuse (10). Moreover, lower cortisol predicted later fatigue in a large prospective cohort, suggesting it is a trait rather than a state marker (11). So the questions then become what the mechanism of hypocortisolism in these syndromes is, whether the link with early-life events can be understood, and whether this is of pathological importance.

Mechanisms Producing Lower Cortisol

Low(ish) cortisol levels could be due to partial primary adrenal insufficiency, hypothalamic-pituitary-adrenal (HPA) axis underactivity, increased negative feedback sensitivity and/or changes in glucocorticoid metabolism. Most work has been conducted in PTSD. From numerous investigations, it is clear that there is no increase in ACTH levels in PTSD (12–14), a finding recapitulated in chronic pelvic pain (15), making primary adrenal insufficiency unlikely. Similarly, the HPA axis responds at least normally, if not in an exaggerated manner, to a range of stressful and pharmacological stimuli, suggesting no central anergy of the HPA axis (16–18).

Glucocorticoid Sensitivity

In contrast, a number of studies in PTSD have suggested increased sensitivity to feedback by synthetic steroids such as dexamethasone, implying that the low levels of cortisol have increased action on target tissues; note that dexamethasone appears predominantly to test feedback sensitivity at the pituitary rather than the brain, which it accesses poorly due to partial exclusion by the ABCB1 multidrug resistance efflux membrane pump (19). Glucocorticoid action on target genes in leukocytes is also exaggerated in PTSD (20). Although leukocyte glucocorticoid receptors (GR) are down-regulated by glucocorticoids, so up-regulation in the face of lower circulating cortisol is predictable, nonetheless the PTSD-associated increase in leukocyte sensitivity to glucocorticoid persists *in vitro* when glucocorticoid levels are controlled (20, 21). Thus increased GR sensitivity may be a fundamental state. Leukocyte GR hypersensitivity in PTSD appears to reflect higher GR density and perhaps also affinity, although any mechanism of the latter remains obscure (20). Intriguingly, younger age at traumatization correlates with greater rises in leukocyte GR again suggesting a developmental component. Indeed, studies in which GR changes are not observed tended to employ older subjects exposed in trauma in adulthood (17) or be confounded by comorbid conditions such as depression (22). The pituitary in PTSD appears similarly hypersensitive to glucocorticoids (20, 23, 24).

The increased GR function in leukocytes and pituitary of course begs the question of whether the same pertains in the brain. In young subjects with PTSD, acute cortisol administration causes a greater decline in hippocampus-associated verbal declarative memory and cortex-associated working memory than in matched healthy controls. These glucocorticoid-mediated changes in cognition correlate negatively with leukocyte GR density (25). In contrast, elderly PTSD victims have improved memory with cortisol administration (26), although again this appears to be an exaggeration of the effects seen in age-matched controls. Intriguingly, a positron emission tomography study suggests striking regional differences in brain glucose metabolism in PTSD patients given cortisol (27) with responses not so much blunted or exaggerated as opposite to those in controls. Overall, the main effect of exogenous low-dose cortisol in PTSD is to normalize brain metabolism. So, although in leukocytes and pituitary cells, the product of low cortisol × increased tissue GR responsiveness appears to increase the signal to target genes, in the brain, the signal varies by subregion. Thus, the low circulating cortisol levels in PTSD and related disorders plausibly yields an inadequate signal to at least some key brain regions, and hence, function may, in part, be restored by cortisol replacement, at least acutely.

Developmental Programming

The particular association of changes in cortisol and tissue sensitivity with traumatization early in life suggests a role for developmental programming (28). Intriguingly, GR gene expression is a particular target for programming by early-life events, with an increasingly well-defined epigenetic mediation by persistent changes in the frequency of cytosine methylation in tissue-specific alternate GR gene promoters in the rat and human brain (29–31). Moreover, although prenatal glucocorticoids/stress persistently alter

receptor density in the rodent brain, the direction of change varies by subregion, with reduced receptors in hippocampus but increased GR in amygdala (32), a key locus for fearfulness that shows hyperfunctioning in PTSD (33). Indeed, amygdala GR acting via CRH is essential for fear conditioning (34), and early-life events set the tone of this amygdala CRH system (32) as well as the hypothalamic CRH that regulates the HPA axis (35). Overall, there appear to be a subset of subjects with PTSD who have a developmental origin component to their symptoms and who are characterized by low cortisol and tissue-specific alterations in glucocorticoid sensitivity. These may reflect the human equivalent of animal models where early-life stress can persistently lower glucocorticoid levels throughout the lifespan and predispose to fear-related behaviors on retraumatization (36).

Peripheral Metabolism and Intracrine Effects

So far, so conventional. However, a further level of control of tissue action of steroids bears consideration, intracellular metabolism in target cells. Such intracrine controls are mediated by enzymes that activate or inactivate ligands. For glucocorticoids, the best characterized are the 11β-hydroxysteroid dehydrogenases (11β-HSD). In addition, 5α- and 5β-reductases (A-ring reductases) might play analogous roles, especially in the liver where they are highly expressed (37).

Glucocorticoid-metabolizing enzymes may have an impact on tissue glucocorticoid action by two distinct mechanisms. First, they act to gate steroid access locally to intracellular receptors (an intracrine effect). A good example of this is 11β-HSD type 2, which catalyzes the rapid inactivation of cortisol (corticosterone in rodents) to inert cortisone (11-dehydrocorticosterone). This excludes glucocorticoids from intrinsically nonselective mineralocorticoid receptors (MR) in the distal nephron, thus allowing the nonsubstrate aldosterone exclusive access to the receptor. Inhibition or gene deletion of 11β-HSD2 allows cortisol illicitly to bind and activate MR causing salt retention, hypokalemia, and hypertension (the syndrome of apparent mineralocorticoid excess) (38). 11β-HSD type 1 catalyzes the reverse reaction and thus amplifies glucocorticoid levels in target cells (39).

Second, enzymes may contribute to bulk glucocorticoid metabolism, either anabolism (*e.g.* 11β-HSD type 1) or catabolism (11β-HSD2, A-ring reductases). Changes in metabolism may alter HPA axis activity merely to maintain circulating cortisol levels in the face of altered steroid clearance. This effect is strikingly observed in deficiency/inhibition of 11β-HSD1. In humans, 11β-HSD1 in the splanchnic bed contributes around 30–40% of daily cortisol production (40, 41). Loss of 11β-HSD1 necessitates increased HPA axis activity (and thus higher ACTH) merely to maintain circulating cortisol levels (42). The enzyme is primarily expressed in liver, although also in adipose, brain, pituitary, and other tissues (43). Although the central nervous system (CNS) sites might have an impact via intracrine mechanisms on HPA axis negative feedback, and 11β-HSD1 knockout mice and humans treated with selective inhibitors have increased ACTH levels and adrenal hypertrophy (44, 45), rescuing enzyme expression only in liver on the knockout background fully restores HPA axis function, despite the persistence of the intracrine defect in brain and pituitary (46). Apparently metabolism predominates, but is this of relevance to low cortisol in PTSD?

Glucocorticoid Metabolism in PTSD

Recent data suggest that peripheral glucocorticoid metabolism is strikingly altered in some people with PTSD. In elderly Holocaust survivors, many of whom have PTSD, total glucocorticoid production is markedly reduced. These individuals were exposed to the almost unimaginable physical, nutritional, and psychological challenges of the Holocaust early in life. Survivors show strikingly (3-fold) lower 5α-reduction of cortisol, indicating less hepatic 5α-reductase type 1, as well as a reduced urinary ratio of cortisone to cortisol, suggesting a relative deficiency of 11β-HSD2 in the kidney (47). The greatest reductions in these enzymes are seen in those who were youngest at exposure to the Holocaust, suggesting there may be a developmental programming window in early life during which adversity down-regulates these enzymes. Indeed, in pregnant rats, exposure to excess glucocorticoids reduces offspring 11β-HSD2 in the kidney from birth through to midlife, suggesting that this gene may be programmed (48). The promoter of the *HSD11B2* gene is subject to methylation (49), which is increased by prenatal adversity (50), plausibly reducing expression in the longer term. Moreover, the offspring of pregnant women who ate a highly unbalanced diet during pregnancy also show alterations in methylation of both GR and 11β-HSD2 gene promoters that correlates with the degree of dietary aberration 40 yr earlier (Drake, A. J., R.C. McPherson, K.M. Godfrey, C. Cooper, K.A. Lillicrop, M.A. Hanson, R.R. Meehan, J.R. Seckl, and R.M. Reynolds, *et al.*, unpublished data).

These changes make some teleological sense. With early-life exposure to extreme stress and starvation, a metabolic

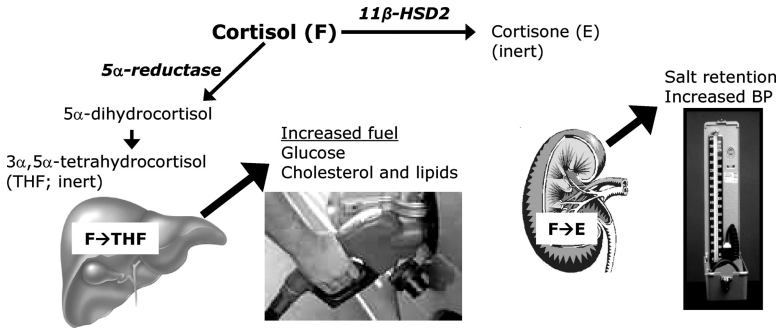

FIG. 1. Intracrine effects. Environmental exposures (including psychological trauma and/or physical adversity, including starvation) result in a lowering of 5α-reductase and 11β-HSD2. One effect of lowered enzyme activity is the prolongation of local intracellular glucocorticoid action without elevation of circulating glucocorticoids. In the liver, persisting intracrine glucocorticoid activity via deficient 5α-reductase (type 1) promotes metabolic fuel production. In the kidney, reduced 11β-HSD2 leads to sodium retention via exposure of MR to cortisol. Consistent with the model of developmental programming, the effects are particularly enhanced and enduring in those who experience extreme environmental adversity at a younger age.

shift to reduce cortisol inactivation in liver (by 5α-reductase-1) would prolong intracrine glucocorticoid action in the liver, thus maximizing glucocorticoid drive to produce scarce metabolic fuels for body and brain (Fig. 1). Attenuation of renal 11β-HSD2 allows cortisol to persist in distal nephron epithelia and activate renal MR, maximizing sodium retention in the face of the anticipated extreme dietary deficiency of salt. Such adaptations are likely honed by evolution because ancestral environments presumably often involved calorie and salt deficiency. Couple these exaggerated local actions of cortisol in liver and kidney with normal or slightly lowered plasma cortisol levels to minimize the deleterious catabolic effects of glucocorticoids on brain and muscle, and such changes appear to mold physiology *in extremis* to promote immediate and longer-term survival and thus Darwinian fitness. The fact that this appears to have persisted throughout the lifespan in Holocaust survivors is typical of developmental programming effects.

In terms of neuropsychiatric risk, this may be a selected component of the early-life challenge phenotype (promoting behaviors aiding survival to reproductive age) or a mere bystander to the overriding needs to survive the fundamental mortal stress of severe nutritional deprivation. The finding that the healthy (*i.e.* no neuropsychiatric impairments) children of Holocaust survivors, themselves born at least a decade after the Holocaust, show not only lowered plasma cortisol levels, if the mother had PTSD (51), but also similar changes in steroid metabolism in the absence of neuropsychiatric disease suggests that these changes in metabolism are trait rather than state and may reflect a basal vulnerability to later challenge. It also implies that some intergenerational transmission has occurred, as seen in in-bred animal models for both metabolic variables and HPA axis function (52, 53). Transmission of these effects down the male line (*i.e.* a male animal exposed *in utero* to stress hormones, when mated with a control female, produces offspring with altered physiology) implies epigenetic effects rather than any mediation via the uterine environment *per se*.

Of course, Holocaust survivors have suffered prolonged trauma, and it is difficult to ascribe subsequent pathophysiology to a particular event or time. We have had the opportunity to study women who were pregnant and in, or immediately adjacent to, the World Trade Centre during the September 11, 2001 (9/11), atrocity in New York. Around 50% of these women developed PTSD. Intriguingly, their offspring showed lower salivary cortisol levels at 1 yr of age (54). This rather bypasses the concerns that changes seen in the children of Holocaust survivors reflect altered rearing or vicariously traumatization by histories related by their parents. In the case of the 9/11 offspring, however, PTSD was not the only delimiting factor, exposure in the third trimester was also critical, suggesting that it is not simply child-rearing style but that there is a developmental programming window in the latter part of gestation during which, and delimited by maternal PTSD, a low cortisol state can be transmitted to the offspring. Intriguingly in 9/11-exposed individuals, low 5α-reductase activity in exposed individuals predicted their response to psychotherapy for PTSD, those with low 5α-reductase failing to respond to therapy and those with higher 5α-reductase showing therapeutic responses (55).

Overall, the data suggest there is a vulnerability diathesis of reduced tissue-specific glucocorticoid metabolism and lower cortisol levels, programmed by early-life events, which underpins at least a subset of vulnerability to PTSD and perhaps other disorders. This human biology echoes older preclinical literature showing that 5α-reductase is programmed by early-life events in rodents (56, 57) and is particularly influenced by nutritional cues, increasing with high calorie intake/obesity and decreasing with starvation/leanness (58, 59).

How Might Altered Metabolism Associate with Low Cortisol and Contribute to Neuropsychiatric Disorders

Beyond the intracrine effects, deficiencies of 11β-HSD2 and 5α-reductase type 1 slow the body's clearance of cortisol (Fig. 2). In consequence, activity of the HPA axis will

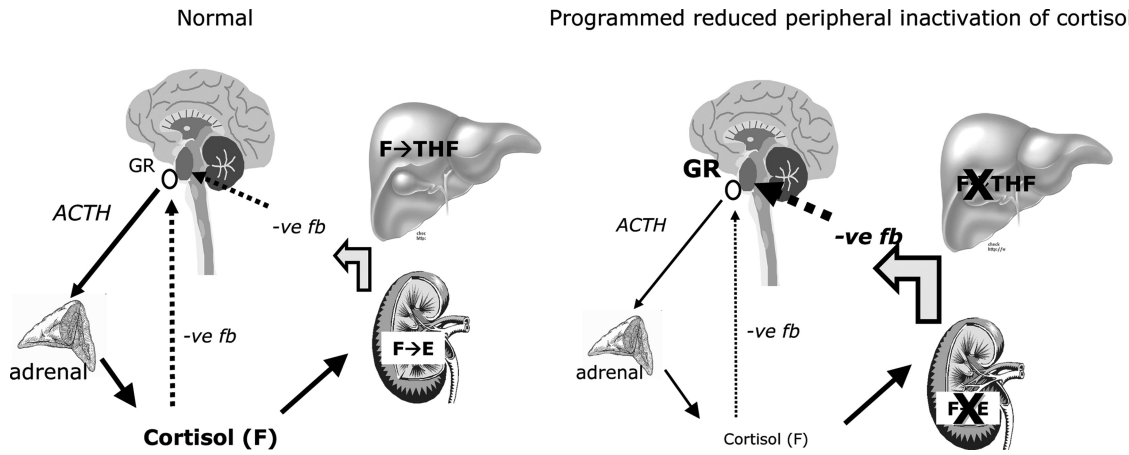

FIG. 2. Endocrine effects. 5α-Reductase and 11β-HSD2 catalyze major pathways of cortisol catabolism. Deficiency of these enzymes, programmed by early-life exposure to severe challenge, will therefore result in reduced cortisol clearance. In consequence, basal activity of the HPA axis is reduced merely because less cortisol needs to be produced because its peripheral degradation is attenuated. Over and above any intracrine effects of these enzymes in sites of glucocorticoid negative feedback (-ve fb), this may contribute to subtle lowering of circulating cortisol levels simply because the initial response of the HPA axis (*e.g.* to diurnal cues) is reduced. Coupled with increased GR sensitivity in some tissues, including HPA axis feedback at the pituitary, itself also plausibly programmed by early-life events, and summative processes appear likely to contribute to basal hypocortisolemia. Of course, the HPA axis is responsive to severe stress if necessary.

be reduced, merely because less cortisol needs to be secreted by the adrenals to maintain normal blood levels. The consequent subtle adrenal hypoplasia may allow mild hypocortisolism to ensue, especially if local glucocorticoid effects in the liver contribute to glucocorticoid feedback via provision of fuels or hepatic vagal afferents, both of which suppress HPA function (60, 61). Of course, reduced adrenal output can be overcome if HPA drive increases during severe stress.

This state may make the brain vulnerable to major challenge. Glucocorticoids are crucial for fear conditioning and trauma-associated learning (62). It is plausible that an individual, made vulnerable by their genetic make-up or programmed epigenetically after early-life challenge, with reduced glucocorticoid metabolism and therefore necessarily a less active HPA axis, will, when exposed to severe trauma, make inadequate initial glucocorticoid responses, fail appropriately to both learn and subsequently to modulate and expunge traumatic memory, and be left with persisting stressful recall of an initiating event, which in another individual would be recalled, processed, filed, and gradually lost from the forefront of cognition. From an evolutionary perspective, this may have had benefit in adverse environments, promoting an anxious and hypervigilant phenotype when frequent challenges are anticipated; in the modern world, such behaviors are pathological but are perhaps not so maladaptive in a famine-stricken war zone. Associated with this may also be a programmed thrifty phenotype which, when mismatched in contemporary calorie-dense environments, may promote cardiometabolic disorders. These indeed associate with PTSD (63), although comorbidity with depression makes the link uncertain. Naturally, such early programmed changes in tissue glucocorticoid sensitivity and steroid metabolism are unlikely to be the only route to a complex neuropsychiatric state such as PTSD but perhaps describe a distinct and identifiable subset of vulnerable individuals.

This notion has some predictive implications. It might be possible, perhaps early in life, to identify individuals with reduced glucocorticoid metabolism who are at increased risk of PTSD and related disorders on exposure to trauma later in life. To test this, it will be helpful prospectively to follow cohorts such as the offspring of women pregnant and traumatized during 9/11. It also implies that use of glucocorticoids either at the time of trauma or during the early phase of development of symptoms may aid reversal in such vulnerable individuals. Indeed, recent clinical evidence suggests that this might be the case (64–67).

A final thought occurs. 5α-Reductase type 1 is also expressed in the brain where, *inter alia*, it activates neurosteroids such as allopregnanolone (3α-hydroxy-5α-pregnan-20-one) with potent anxiolytic actions. Cerebrospinal fluid allopregnanolone levels are reported to be lower in women with PTSD (68). Moreover, in a mouse model, lower 5α-reductase-1 and allopregnanolone levels in corticolimbic regions correlate with behaviors reminiscent of PTSD (69). If early-life events or other forces that cause vulnerability to PTSD do engender long-term decreases in this enzyme in the CNS, perhaps the effects on peripheral metabolism are mere markers for events occurring in parallel in the brain itself. Indeed, postnatal starvation lowers regional CNS 5α-reductase activity (70). Conversely, because the fundamental challenge driving such adaptations in the mammalian maternal environ-

ment is most likely to have been malnutrition, parallel changes in 5α-reductase in liver and brain may have shaped the offspring in a predicted dangerous, calorie-restricted world to have metabolic efficiency and a behavioral strategy of wariness and vigilance. PTSD may merely be the exaggerated outcome of an efficient multi-organ change designed to engender a set of physiological adaptations in early life to give a survival edge in tough circumstances. Interesting thoughts indeed.

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