Biology of Posttraumatic Stress Disorder

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An understanding of the biological basis of posttraumatic stress disorder (PTSD) requires an examination of the underlying neurobiology of fear and the factors that might contribute to an unsuccessful termination of the fear response in some individuals. Several factors may lead to an inadequate termination of a stress response, and the failure to contain the biological alterations initiated by stress may have long-term adverse consequences. In particular, a prolonged continuation of biological responses following stress may lead to an inappropriate pairing of the traumatic memory with distress and may then initiate a cascade of secondary biological alterations. This article examines some of the biological alterations in PTSD and develops a framework for understanding the development progression of the neurobiology of this disorder. *(J Clin Psychiatry 2000;61[suppl 7]:14–21)*

Posttraumatic stress disorder (PTSD) is a psychiatric condition that can occur in individuals who experience a traumatic event. According to the most recent definition in DSM-IV, a traumatic event is one that involves a threat to one's life or physical integrity and a subjective response of fear, helplessness, or horror.[1] A question that immediately arises in trying to understand the biological consequences of trauma exposure is the definition of a traumatic event, and the distinction between traumatic experiences and stressful ones. Current information suggests that exposure to stress results in a myriad of negative health outcomes, including psychiatric symptoms.[2] It is therefore of interest to consider the extent to which this extant literature on stress and stress-related disturbance is relevant to understanding the biological underpinnings of PTSD.

THE RELATIONSHIP BETWEEN STRESS AND TRAUMA

A commonsense approach in considering the relationship between traumatic events and stressful ones has been to consider the former events as more extreme versions of the latter. Although DSM-IV, and prior versions of this manual, attempted to differentiate trauma from stress, most people would tend to view these life experiences as occurring on a continuum. This tendency is particularly strengthened by the belief that the severity of stressful or traumatic experiences is best defined by subjective emotional responses in addition to objective characteristics of the events.

And yet, from the very beginning of the establishment of PTSD it was deemed important to differentiate traumatic events from stressful ones from a qualitative as well as a quantitative perspective. In early formulations of PTSD, a traumatic event was considered one that was unusual or substantially out of the range of normal life experiences and was markedly distressing.[3] More current definitions have emphasized the idea that trauma exposure involves life threat, or at least substantial threat to one's body, and is accompanied by extreme fear, helplessness, or horror. This definition of trauma is fairly specific and is intended to rule out a variety of more common stressful life events, such as divorce, job loss, coping with chronic illness, and occupational stress. It is clearly understood that both stressful and traumatic events are associated with negative consequences. However, one of the fundamental differences between a traumatic event involving life threat and other types of chronic stressful events is that removing the "stress" (remarrying, changing jobs, etc.) often alleviates, if not removes, the negative consequences of stressful events. Indeed, it is often the case that physicians who believe life stress to be an important contributor to a patient's current condition will prescribe a regimen that includes stress reduction (or removal). In contrast, PTSD describes adverse effects associated with exposure to trauma that continues even decades after the event has passed. In PTSD, the patient has usually already distanced himself or herself physically from the focal trauma. However, the memory of the event lingers on, and this memory and the concomitant arousal caused by the memory produce a biological situation that is as difficult to bear as the

one associated with the stress as it was occurring. As such, the biological basis of PTSD must describe long-term consequences associated with a failure of the body to recover from a traumatic situation or the biological consequences occurring in response to memories of events that are not occurring in real time.

THE BIOLOGY OF FEAR

By its very nature, then, the biology of PTSD is fundamentally different from the biology of stress because it describes a process that occurs well after the stress is no longer physically present. Thus, the essential question of the biology of this disorder is one of delineating why there has been a failure of the body to return to its pretraumatic state. It appears to be less important to consider the actual biology of stress in addressing this issue because PTSD is not an inevitable outcome of stress. Indeed, about 25% of individuals develop PTSD in response to trauma (however, importantly, this percentage increases or decreases depending on the severity of the event).[4,5] More than half of those who develop PTSD also appear to recover from this disorder. Thus, understanding the biological response that occurred during the traumatic event may not necessarily address the biology of PTSD. Rather, the central issue appears to be one of determining why there is recovery in some survivors, but not others. This said, the biology of stress represents an important starting place for inquiries into the biology of PTSD because examining why a stress response resolves in some individuals and not others requires an understanding of this response. Indeed, the symptoms of PTSD have been conceptualized as resulting from the cascade of biological and psychological responses following the activation of fear-related and other brain systems.[6]

Exposure to traumatic stress results in a fear response, which involves the initiation of concurrent and instantaneous biological responses that help assess the level of danger and then organize an appropriate behavioral response (Figure 1). The amygdala is the brain organ that serves as the major interface between the sensory experiences, such as seeing an aggressor and perceiving indications of his or her harmful intentions, and the biochemical and behavioral systems that ultimately respond to this information.[7] The amygdala therefore essentially determines whether there should be a stress response and, if so, begins the process of activating the neurochemical and neuroanatomical circuitry of fear. The time frame for this response is several milliseconds. In this very short time, projections from the amygdala to the reticularis pontis caudalis potentiate the startle response[8] and initiate defensive behaviors not requiring the direct action of the sympathetic nervous system. Projection from the amygdala to the lateral hypothalamus and then to the rostral ventral medulla initiate sympathetic nervous system (and catecholamine) responses,[9] and projections from the amygdala to the solitary

Figure 1. Neuroanatomy of Fear[a]
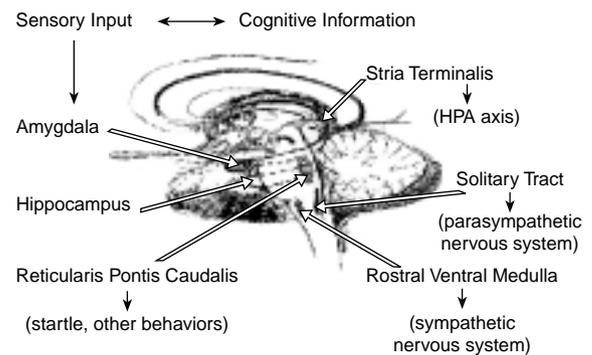
[a]Arrows indicate "activation" of specified system.
Abbreviation: HPA = hypothalamic-pituitary-adrenal.

tract stimulate parasympathetic responses.[10] Projections from the central amygdala to the bed nucleus of the stria terminalis initiate the hypothalamic-pituitary-adrenal (HPA) axis response.[11]

One of the most immediate responses to stress is the coordinated sympathetic discharge that causes increases in heart rate and blood pressure, initially described by Walter Cannon as the "fight or flight" reaction.[12] These reactions result in increased blood flow and glucose availability to skeletal muscles that allow for effective flight from adverse situations or, if necessary, optimal interactive responses to threat.[13] The parasympathetic response constrains these reactions in a variety of target tissue, but operates independent of the sympathetic nervous system. Finally, the HPA axis is also activated by brain neuropeptides that stimulate the hypothalamus to release corticotropin-releasing factor (CRF) and other regulatory neuropeptides (which stimulate the pituitary release of adrenocorticotropic hormone [ACTH]) and stimulate the adrenal gland to release cortisol.[14]

Stress—particularly acute stress—results in a dose-dependent increase in both catecholamines and cortisol. The greater the severity of the stressor, the higher the levels of both hormones.[15] However, the actions of these two systems are synergistic. Whereas catecholamines facilitate the availability of energy to the body's vital organs, cortisol's role in stress is to help contain or shut down sympathetic activation and other neuronal defensive reactions that have been initiated by stress.[16] In one sense, then, cortisol functions as the mediator of the termination of the stress response. As stress-activated biological reactions shut down as a result of cortisol inhibition, elevated cortisol levels also suppress the further release of cortisol itself.[17] That is, through negative feedback inhibition, cortisol acts on the pituitary, hypothalamus, hippocampus, and amygdala, sites initially responsible for the stimulation of cortisol release.[18] Indeed, these sites contain a large con-

centration of cortisol, or glucocorticoid, receptors and are important targets of action of cortisol.[19] Once the acute stressor has been removed and no external threat is detected, negative feedback inhibition of the HPA axis is activated, leading to the restoration of basal hormone levels.[20]

DIFFERENCES BETWEEN FEAR RESPONSE AND BIOLOGY OF PTSD

In individuals with PTSD, there are many biological alterations reminiscent of the original stress response. Trauma survivors with PTSD show an enhanced startle response to both neutral and trauma-related cues.[21] There is abundant evidence for increased sympathetic nervous system activation in PTSD. First, most studies have demonstrated increased physiologic responses to loud tones[22] as well as trauma-related cues.[23] Consistent with this finding, there have been demonstrations of increased peripheral catecholamine levels in PTSD under basal[24] and stimulated conditions.[25] The most compelling evidence of noradrenergic dysregulation in PTSD is that administration of the α_2-antagonist yohimbine increases both PTSD symptoms and levels of the noradrenergic metabolite 3-hydroxy-4-hydroxyphenylglycol (MHPG) in trauma survivors with PTSD.[26]

Parasympathetic alterations in PTSD have not been well studied. However, studies of heart rate variability indicate a reduction in parasympathetic activity as evidenced by decreased respiratory sinus arrhythmia.[27] The presence of parasympathetic alterations in PTSD can also be inferred from the increased heart rate in response to loud tones in the absence of increased skin conductance.[28] Thus, the startle response and sympathetic and parasympathetic alterations in chronic PTSD are similar to those that might have been observed at the time of the trauma. These findings have led to the idea that PTSD may represent a state of sustained fear and arousal following trauma.

As mentioned above, an important component of the fear response is the activation of the HPA axis that culminates in the release of cortisol. Normally, cortisol levels are directly proportional to the level of cortisol released from the pituitary, which, in turn, is related to the amount of CRF that is released from the hypothalamus. In PTSD, however, ambient cortisol levels have been found to be lower than normal[29,30] rather than higher, as would be expected under conditions of sustained stress.[31] Thus, in contrast to the above mentioned alterations in PTSD, which do parallel alterations associated with activation of a stress response, the cortisol levels in PTSD do not resemble those in classic descriptions of stress responses.

WHY CORTISOL LEVELS ARE LOW IN PTSD

Initially, low cortisol levels in PTSD were explained as reflecting a chronic adaptation to stress. Indeed, it was certainly plausible to consider the possibility that the HPA axis became tonically inhibited owing to a chronic adaptation to the stressor. Selye[15] referred to such a phenomenon as "adrenal exhaustion." It became particularly important to consider the idea of chronic adaptation in PTSD as findings of reduced hippocampal volume in PTSD emerged.[32] These findings raised the possibility of trauma-related hippocampal damage secondary to cortisol toxicity in PTSD.

Data from several studies have challenged the idea of a chronic adaptation of the HPA axis in PTSD, and therefore this idea is not likely to be the true explanation of why cortisol levels are lower than normal in those with this condition. Under conditions of chronic adaptation, CRF levels would be expected to be low. In contrast, cerebrospinal fluid (CSF) concentrations of CRF appear to be higher in PTSD compared with those in healthy volunteers.[33] The observations of increased CRF in the CSF are supported by the findings of an increased ACTH response to metyrapone administration in individuals with PTSD compared with that in healthy subjects, which particularly implicate hypothalamic CRF as being hyperreleased in PTSD.[34]

More recent data from two prospective, longitudinal biological studies of trauma survivors have also challenged the idea that cortisol levels were at one time extremely elevated in PTSD, only to have chronically adapted over time. Both studies examined the cortisol response to trauma within hours after the trauma occurred. In the first,[35] the cortisol response to motor vehicle accidents was measured in persons appearing in the emergency room in the immediate aftermath (usually within 1 or 2 hours) of the trauma. Six months later, subjects were evaluated for the presence or absence of psychiatric disorder. In subjects who had developed PTSD, the cortisol response in the immediate aftermath of the motor vehicle accident was significantly lower than the cortisol response of those who subsequently developed major depression, even after covariates such as minutes postaccident, time of day, severity of trauma, and past PTSD were controlled for. The mean cortisol level after motor vehicle accidents in those who did not subsequently develop psychiatric disorder was in between that of those who developed PTSD and that of those who developed major depression. This study suggests that PTSD-like HPA axis alterations are present in the immediate aftermath of a traumatic event.

A second study[36] demonstrated that women with a prior history of rape or assault had relatively lower cortisol levels immediately after rape than women without such history. Thus, cortisol levels in the immediate aftermath of a traumatic event may be predicted by factors that precede trauma exposure. The data are important because they suggest that ultimately it may be possible to predict the development of PTSD from the acute biological response to a traumatic event.

PREDICTING PTSD FROM THE
ACUTE TRAUMATIC RESPONSE TO STRESS

In the above-mentioned prospective studies, the observation of low cortisol levels in the immediate aftermath of the trauma was similar to what has been described in the literature for individuals with chronic PTSD. However, it is certainly possible that there would be biological predictors of PTSD based on responses that occur in the immediate aftermath of the trauma, which then dissipate as PTSD develops (and as such would not necessarily then be measurable in chronic PTSD). In a remarkable study, Shalev et al.[37] collected heart-rate data from trauma survivors who appeared at the emergency room in the immediate aftermath of a traumatic event, but who did not have significant physical injury. Mean heart rate levels at the time of the trauma were significantly higher in the 23.4% (of 86 subjects) who developed PTSD as determined at a 4-month follow-up. The mean heart rate in the PTSD group remained higher at the 1-week follow-up; however, by 1 month and 4 months, there were no group differences. Importantly, subjects who did not develop PTSD also had elevated heart rate (83.2 beats per minute) at the emergency room because they were expressing a stress response. The groups did not differ in initial blood pressure, and the differences remained significant when adjusted for age, event severity, intensity of the subjective response, and peritraumatic dissociation.

It is interesting to consider in tandem the observations that low cortisol levels and elevated heart rate were separately associated with the development of PTSD, particularly in light of the role sympathetic nervous system (SNS)–HPA axis interactions play in stress.[38] Under normal stress-activated conditions, cortisol levels would ultimately inhibit the adrenergic system. However, it may be that some trauma survivors have higher heart rates in the immediate aftermath of a traumatic event because there has been a failure of cortisol to contain this specific response. In support of this idea is the observation that cortisol and MHPG levels—measured from the same blood sample in the aforementioned rape survivors—appeared to be related to different aspects of the traumatic experiences.[39] Whereas cortisol levels were related to prior history, MHPG levels in these rape victims were associated with the severity of the trauma. Moreover, in the women who did not subsequently develop PTSD, there was a significant correlation between cortisol and MHPG levels, which is consistent with the normal stress response, whereas in the women who did subsequently develop PTSD, this relationship was lacking. Thus, the HPA and sympathetic nervous system responses to trauma may literally be "disassociated" in those who subsequently develop PTSD. These preliminary data suggest a possible mechanism for why only some individuals would develop a PTSD-like response, whereas others may recover. They

also offer a testable hypothesis regarding the role of risk factors in determining whether or not there will be a normative stress response.

Indeed, it may be that those who show characteristic risk factors for PTSD such as prior exposure to trauma may respond differently from individuals who do not develop PTSD to a similar trauma. One question raised by these studies is whether or not individuals may have had low cortisol levels even before the traumatic event or had some abnormality that accounts for their aberrant response to the traumatic event they sustained. In this regard, we have previously demonstrated that cortisol levels are low in the high-risk group of adult children of Holocaust survivors.[40] Adult children of Holocaust survivors are 3 times more likely to develop PTSD compared with demographically matched comparison subjects.[41] Risk of PTSD is greater in offspring whose parents had chronic PTSD than in those whose parents did not develop or sustain PTSD.[42] Although low cortisol levels were present in offspring with PTSD, these levels were also associated with the specific risk factor of parental PTSD in the offspring and were present in high-risk offspring (those with parental PTSD) who had not been exposed to traumatic events and therefore had not developed PTSD. These types of studies need to be performed on a wider scale with multiple high-risk groups before this issue is resolved. Ultimately, the best resolution of this question will necessitate prospective studies that assess cortisol levels in persons before and after they experience traumatic events or the study of other groups at risk for PTSD (e.g., those with increased familial risk for the development of PTSD).[43]

"SECONDARY" BIOLOGICAL CHANGES IN PTSD

One of the problems in attempting to study the pathophysiology of PTSD using a retrospective, cross-sectional approach is the difficulty obtaining perspective regarding the "staging" of biological alterations. It is certainly possible that changes in one system initiate a cascade of biological alterations. It becomes important to conceptualize a model of the biology of PTSD that recognizes this possibility and accounts for change over the longitudinal course of PTSD.

Prospective studies have certainly provided important insights into the essential questions of PTSD pathophysiology. One of the most illuminating observations has been that in contrast to elevated heart rate and lower cortisol levels, which were early predictors of PTSD, other alterations associated with chronic PTSD did not distinguish trauma survivors in the immediate aftermath of the trauma. For example, auditory startle responses obtained 1 week posttrauma did not predict PTSD at 4 months, as did heart rate obtained from the same subjects.[44] Auditory startle responses have been very well documented as present in chronic PTSD patients.[45] However, startle re-

sponses became clearly differentiated only at 1-month posttraumatic assessment. Interestingly, by this time, heart rate measures were no longer significantly different in these 2 groups. These data suggest that there is a progressive development of the abnormal startle response that occurs somewhere after the first week, but before the first month, in those who develop chronic PTSD. More importantly, however, the data show the importance of understanding PTSD as an illness with a progressively changing biology.

PROGRESSIVE BIOLOGICAL CHANGES IN PTSD

Because of the paucity of longitudinal biological studies, little is known about the developmental time course of biological changes in PTSD over time. However, it seems possible that the biological alterations in this disorder do evolve over time. Indeed, there are certainly biological consequences associated with prolonged states of arousal, as reflected by the findings of catecholamine alterations in PTSD, as well as findings associated with alterations in the HPA axis.

Although we have observed low cortisol levels in trauma survivors with both acute and chronic PTSD symptoms, there are other alterations within the HPA axis that appear to reflect a progressive sensitization of this stress system over time. Our current work in aging trauma survivors has identified patterns of hormonal alterations that appear to be different in older trauma survivors with PTSD compared with those in younger ones.[46] It is not clear to date whether changes in older trauma survivors reflect the chronicity of the disorder or whether they directly address the issue of changes over time as opposed to changes associated with aging. Regardless, the studies demonstrate that the important biological systems in PTSD may certainly change while PTSD symptoms are maintained and suggest that the issue of progressive change be explored in subsequent research studies.

MODELS OF BIOLOGICAL SENSITIZATION IN PTSD

The model we have previously set forth is that the failure of cortisol to completely contain the SNS response results in the initial problem of a failure of normal memory consolidation.[47] Indeed, there is substantial evidence that catecholamines, particularly epinephrine, enhance memory consolidation in laboratory rats.[48,49] This effect appears to be at least in part modulated by adrenal steroids, since removing the adrenal glands of animals makes them more sensitive to the effect of epinephrine on memory consolidation.[50] Furthermore, when such animals are given replacement doses of glucocorticoids, they become less sensitive toward the memory-enhancing effects of epinephrine.[51]

Pitman[52] has hypothesized that PTSD results from an exaggerated response of neuropeptides and catecholamines at the time of the trauma. He has suggested that the increased levels of these stress hormones initiate a process in which memories of the traumatic event might be "overconsolidated" or inappropriately remembered owing to an exaggerated level of distress. This is indeed possible, because the primary mechanism through which catecholamines facilitate memory formation is the maintaining of organisms in a heightened state of arousal.[53] Certainly, the failure of cortisol to shut down other neuropeptides would facilitate this effect and also explain why non-PTSD patients do not "overconsolidate" their traumatic memories. Importantly, the proposed mechanism allows not only for the increased formation of distressing memories, but also explains why reminders of the traumatic event are accompanied by distress in individuals with PTSD.

One could further theorize that the increased distress that accompanies traumatic reminders might activate stress responsive systems and, primarily, CRF. Thus, CRF would be expected to be hyperreleased owing to the intense anxiety brought about by memories that have been inappropriately paired with distress, which are then accompanied by higher levels of catecholamines. We have previously suggested that CRF hypersecretion activates the pituitary to release cortisol. However, because there is an increased sensitivity of glucocorticoid receptors in PSTD (which account for why cortisol levels might be low in the first place), the HPA axis becomes progressively more sensitive to cortisol (and stress) as it continues to be exposed to CRF.[54]

ENHANCED NEGATIVE FEEDBACK INHIBITION IN PTSD

The enhanced sensitivity of glucocorticoid receptors appears to explain one of the most replicable and also intriguing findings in PTSD—that of an enhanced negative feedback of cortisol (as assessed by the exaggerated cortisol response to low doses of dexamethasone administration).[55] Glucocorticoid receptors are proteins located in the cytosol of cells that bind to cortisol and allow this hormone to exert biobehavioral effects.[56] Our group has demonstrated that there may be critical individual differences in the number[57] and functional activity[58] of glucocorticoid receptors, which might, in turn, potentially explain why everyone does not respond to stress in the same manner. For example, persons with PTSD seem to have an increased number of glucocorticoid receptors (as measured on white blood cells), whereas persons with major depressive disorder seem to have a reduced number of these receptors.[59] The reduced number of receptors in major depression may account for why these patients are "resistant" to the effects of steroids. Indeed, many patients with major depression have high lev-

Figure 2. Cortisol Suppression in Subjects With Posttraumatic Stress Disorder and Healthy Controls on Administration of Low-Dose Dexamethasone
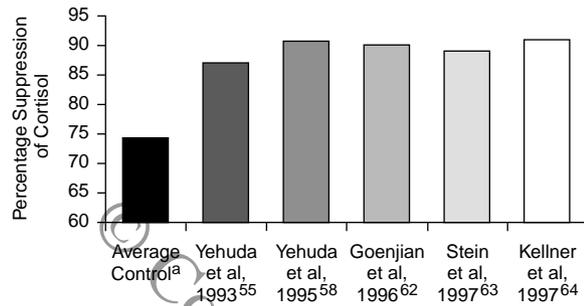
[a]Average percent suppression in studies that had a normal control group.

els of cortisol, but do not show evidence of Cushing's disease, an endocrinological disorder.[60] The best evidence for glucocorticoid resistance in major depression is that, following the administration of dexamethasone, cortisol levels do not decrease to the same extent as in persons without major depression. This phenomenon, known as dexamethasone nonsuppression, has been observed in up to 60% of patients with major depression.[61] In contrast, persons with PTSD show an exaggerated response to dexamethasone administration, which appears to be mediated directly by glucocorticoid receptor activity. The increased responsiveness to dexamethasone, as evidenced by an exaggerated decline in cortisol levels, has now been observed in several studies (Figure 2).[55,58,62–64]

IMPLICATIONS OF ENHANCED NEGATIVE FEEDBACK INHIBITION FOR OTHER BIOLOGICAL ALTERATIONS IN PTSD

If the brain glucocorticoid receptors are more sensitive in those with PTSD, it might explain some of the recent findings of smaller hippocampal volumes in patients with this disorder. The hippocampus is an area rich in glucocorticoid receptors.[20] The current explanation promulgated in the literature is that smaller hippocampal volumes occur as a result of increased cortisol, released in response to the traumatic event, that causes neurotoxicity and ultimately reduced volume.[32] However, as stated above, cortisol levels are not higher in the immediate aftermath of a trauma in persons who will most likely develop PTSD nor during chronic PTSD. However, if PTSD were characterized not only by increased sensitivity of lymphocyte glucocorticoid receptors but also of hippocampal glucocorticoid receptors, the vulnerability of the hippocampus to atrophy could be increased even if cortisol levels were not increased.[65] Indeed, the activation of receptors that lead to the cascade results in the events (i.e., primarily activation of glutamate receptors) that contribute to the neuronal de-

generation following stress.[66,67] That glucocorticoid responsiveness is a more relevant contributor to hippocampal alterations than cortisol per se also explains why not all trauma survivors develop smaller hippocampal volumes after trauma exposure.

CLINICAL RELEVANCE OF THESE CONSIDERATIONS

The implication of these data for treatment of trauma survivors is profound. The most common complaint of trauma survivors with PTSD is that they feel misunderstood—by family members, loved ones, friends, and even, unfortunately, mental health workers. In fact, many well-intentioned people urge trauma survivors to move on with their lives, often citing examples of other similarly traumatized persons who have managed to do just that. These words are meant to provide support and encouragement, but often convince the survivor that he or she is even more alone. Biological studies of trauma survivors suggest that there are many different kinds of responses to adverse events, and a person with PTSD is dealing with a particularly intransigent and difficult set of symptoms that reflect a biological response that has gone awry. Many trauma survivors complain that they cannot put their experiences in the past—a complaint compatible with the biological observations which suggest that some aspects of the biological stress response were never properly terminated. Thus, everyday reminders of the trauma result in mini-retraumatizations and, worse, further biological dysregulation. In many persons, this disorder continues to get worse if left untreated. With time, however, it becomes less obvious that the symptoms that are troubling to the patient are related to past trauma exposure. Trauma survivors with PTSD need to talk about the effects of their experiences and also actively attempt to influence some of the biological processes that have become altered in the aftermath of their experiences. The latter may require the use of medications that have been demonstrated to be effective in the treatment of PTSD.

Becoming actively involved in a therapeutic process helps many trauma survivors to realize that they are, in fact, safe now and that their lives are very much under their control. This can be accomplished in several ways with the help of therapists trained in the latest techniques of individual and group therapies for trauma survivors. Talking about the trauma—even with friends and family—can also be helpful, as the repeated telling of the story of what happened in now safe surroundings often results in removing some of the distress associated with memories of a past trauma. But most importantly, trauma survivors should never feel that their symptoms represent a character weakness or failing on their part. The biology indicates that this is certainly not the case.

CONCLUSIONS

To date, several important statements can be made about the biology of PTSD. First, the biology of PTSD does not appear to completely reflect the biological alterations that are observed at the time of the traumatic event. Second, not all of the biological alterations in PTSD reflect similar aspects of the traumatic experiences. Indeed, some biological alterations may be related to risk for PTSD and actually explain the development of other biological responses. Some alterations may be secondary consequences of the traumatic stress response or may develop in response to PTSD symptoms. Third, the biology of PTSD seems, in many respects, to be different than biological alterations observed in other psychiatric disorders, particularly major depressive disorder. This is particularly interesting since so many symptoms of PTSD are similar to symptoms in major depressive disorder, and trauma survivors frequently meet the diagnostic criteria for both disorders.

There are many gaps in our knowledge about the biology of PTSD, largely because we have not, as a field, mapped out developmental changes using prospective, longitudinal approaches. Such research is necessary if we are to ultimately understand the evolution of biological alterations in PTSD. Indeed, as our understanding of the biology of PTSD grows, we will be able to understand mechanisms of actions of various treatments. Even more promising, however, is the opportunity to develop treatments that are geared specifically toward restoring biological systems.

Disclosure of off-label usage: The author has determined that, to the best of her knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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