This review explores the neurobiology of stress and its possible role in the etiology of schizophrenia. Major life events may play a role in onset and relapse in schizophrenia. Other data suggest that early stress exposure increases schizophrenia risk, especially in individuals with latent vulnerability. Animal research has led to an elucidation of the mechanisms by which stress and cortisol are toxic to the hippocampus and impair cognition. Associations among these factors have been found in a variety of human conditions, including psychiatric illness and normal aging. These mechanisms are plausible in schizophrenia, which is characterized by a degree of cortisol dysregulation, hippocampal abnormality, and cognitive impairment. Characterization of the role of the stress cascade in schizophrenia has implications for novel pharmacologic and other treatment, especially for cognitive symptoms, which are debilitating and largely refractory to treatment. (Journal of Psychiatric Practice 2001;7:3–14)

KEY WORDS: schizophrenia, stress, animal research, cortisol dysregulation, hippocampal abnormality, cognitive impairment

Stressful life events can worsen symptoms and precipitate relapse in a host of psychiatric conditions, including postpartum mood and psychotic disorders, affective illness, and alcohol dependence. However, stress may be particularly deleterious for patients with schizophrenia; the death of a parent, a change in therapist, a move from one apartment to another—these events seem to trigger multiple symptoms, such as anxiety, depression, and increasing psychosis, which may lead to hospitalization. Even seemingly mild stressors, such as a job interview or a date, may have a profound effect in some patients with schizophrenia, suggesting that such patients may be more vulnerable to life events. In this article, we will explore the biological mechanisms that may underlie the role of stress in the pathophysiology of schizophrenia.

The idea that stress and schizophrenia are inextricably linked is well supported in the literature, beginning with Brown and Birley’s seminal paper from 1968, which argued that stress may precipitate the onset of schizophrenia. These authors found that 46% of 50 patients with acute-onset schizophrenia had been exposed to stressful life events in the preceding 3 months compared to only 14% of 325 controls: the difference was most pronounced in the 3 weeks leading up to hospitalization. In their 1993 review, Norman and Malla found a significantly higher incidence of recent life events in patients with schizophrenia as compared with healthy controls in 43% of all the studies they examined. A salient critique of these reviews is that the authors establish association, not causation (i.e., schizophrenia may increase vulnerability to life events). However, exposure to life events does not appear to simply be an effect of having schizophrenia, since the association between stressful life events and relapse persists when patients with schizophrenia are their own controls (relapse versus baseline) and when “relapsing” patients are compared with “nonrelapsing” patients.

The association between stress and illness is certainly not unique to schizophrenia. A wealth of evidence from animal and human research shows that stress can lead to persistent biological changes via the stress hormone, cortisol, which at high levels can be harmful to many organs in the body, including the brain. There are physical and psychological sequelae/costs/repercussions involved in the adaptation to stress, termed the “allostatic load” of stress by Bruce McEwen, an expert in stress research. For example, psychological stress is associated with relapse or exacerbation in a variety of medical illnesses, including ulcerative colitis, genital herpes, asthma, vaginal candidiasis, multiple sclerosis, psoriasis, and “tension-type” headaches.

In this article, we review what is known about the biology of stress and its impact on the brain and cognition, provide further evidence of an association between stress...
and schizophrenia risk, present models for mechanisms that may underlie this association, and, finally, discuss possible novel pharmacological and nonpharmacological interventions.

THE NEUROBIOLOGY OF STRESS

An intact stress response is adaptive and enhances survival, but an unrestrained physiological stress response can injure the brain. Recently, a great deal of scientific effort has been devoted to teasing apart the molecular and cellular events in the stress response that can lead to neural damage (Figure 1). The cascade of events initiated by the perception of stress includes the release of corticotropin-releasing hormone (CRH) throughout the brain, especially in the hypothalamus and in the locus coeruleus and sympathetic nervous systems located in the brainstem. Physiological effects from sympathetic nervous system output include increased cardiac output, shunting of blood from the digestive system, and the release of norepinephrine by the adrenal medulla, in preparation for the “fight or flight” reaction to acute danger. CRH stimulates norepinephrine release within the brain, enhancing arousal and vigilance. CRH release in turn triggers adrenocorticotrophic hormone (ACTH) release from the pituitary, which induces secretion of cortisol by the adrenal cortex. Cortisol is the major mediator of the physiologic effects of stress. In addition to its myriad effects throughout the body, cortisol acts centrally to inhibit serotonin, norepinephrine, and dopamine, which ultimately results in the inhibition of further cortisol release. The hippocampus (Figure 2), which is crucial for encoding and retrieving memory, is also an important modulator of the hypothalamic-pituitary-adrenocortical (HPA) response to stress.19 The hippocampus sends neuronal projections to the hypothalamus to initiate the cascade of cortisol release and is itself a major target organ for glucocorticoid action in the brain.20 Although basal levels of cortisol are required for the health and normal functioning of the hippocampus, an ongoing stress response (and consequent elevation of cortisol) is associated with hippocampal dysfunction and volume reduction, as well as deficits in hippocampus-dependent memory.

Animal Models

Our initial understanding of the toxic effects of stress and cortisol on the hippocampus derived from preclinical studies in diverse species. These findings were first observed in primates: vervet monkeys that died spontaneously following severe stress from poor and overcrowded housing had damage to the CA3 hippocampal subfield.21 This damage was subsequently related to cortisol,22 which across species has been demonstrated to decrease dendritic branching23 and cause neuron loss24 in a steroid- and tissue-specific manner.25, 26 In rats, stress from physical restraint likewise causes atrophy of the apical dendrites in CA3 hippocampal pyramidal cells (Figure 3)27 and leads to impairments in spatial memory, which is hippocampus-dependent.28 Exposure to high levels of cortisol in rats also causes the same hippocampal29 and spatial memory deficits,30 demonstrating that the
The effects of stress are mediated by cortisol. Further, reducing cortisol exposure prevents the hippocampal cell loss induced by chronic stress.31, 32 The degree of hippocampal cell loss in rats is correlated with cognitive deficits: the degree of impairment in new learning of maze escape behaviors is related to the extent of damage to the CA3 region of the hippocampus.33 A putative mechanism for these deficits may be stress-induced impairment in long-term potentiation (LTP),34 which is the neurophysiological process that underlies memory and learning. The
impairments in hippocampus-dependent memory that result from stress can persist beyond the resolution of the stress response and the normalization of cortisol levels.\(^{35}\)

While damaging effects of cortisol on CA3-specific synapses\(^{36}\) and inhibition of neurogenesis in the dentate gyrus\(^{37}\) are potentially reversible in the rat hippocampus, prolonged stress or exogenous cortisol can cause neuronal death in rats and primates.\(^{21, 22}\) High levels of cortisol accelerate energy loss\(^{38}\) and inhibit glucose transport,\(^{39}\) causing the hippocampus to be energetically limited and vulnerable to damage. Excessive excitatory amino acids (EAAs), particularly glutamate, accumulate in the synapse,\(^{40}\) where they activate glutamate receptors and pathologically mobilize free calcium in the postsynaptic neuron. This process has been shown to be NMDA-dependent.\(^{41}\) Decreases in neurotrophic factors and changes in serotonin, precipitated by stress, also may play a role. In rats, stress from physical restraint or high levels of cortisol suppress serotonin 5HT1A receptor binding,\(^{42}\) so that serotonin is not taken up into the neuron. This increase in extracellular serotonin\(^{43}\) further elevates glutamate levels and potentiates toxicity.\(^{41, 44}\)

The degree of physiological response to a stress is related to genetic differences and to exposure to stressful events early in life. Early life sensitization to stress in rats and primates is related, in part, to maternal behavior towards the animals. Rat pups that are not vigorously licked by their mothers after short periods of separation have, as adults, more cortisol dysregulation, greater stress reactivity, more avoidant behavior, and poorer performance in maze tests.\(^{45}\) In contrast, rat pups that are vigorously licked after short separations are largely protected from developing these abnormalities as adults. However, prolonged maternal separation leads to HPA dysfunction in nearly all rat pups, independent of maternal licking after separation. Although there is a genetic basis for maternal licking rate, cross fostering demonstrates intergenerational nongenetic transmission, suggesting a protective effect of high licking even for pups from low-licking lines.\(^{46, 47}\) Levine and his colleagues have shown similar effects of maternal separation in monkeys.\(^{48}\)

**Stress, Cortisol, Memory, and the Hippocampus in Human Conditions**

A number of studies in the last several years have also demonstrated strong associations among stress, high cortisol levels, hippocampal integrity, and memory in humans. These data complement the animal studies in suggesting that these elements may likewise be linked in a causal pathway that is initiated by perceived psychological and/or physiological threat in humans. There is a remarkable consistency in research on these elements across a wide range of human conditions, including exposure to steroid medications, Cushing’s disease, normal aging, depression, posttraumatic stress disorder (PTSD), and Alzheimer’s dementia.

many psychiatric illnesses are known to be associated with cortisol dysregulation.

Many psychiatric illnesses are known to be associated with cortisol dysregulation. While abnormal basal levels of cortisol may indicate an abnormality, the more sensitive test of cortisol function is the dexamethasone suppression test (DST). This test examines the level of cortisol released by the adrenal cortex into the blood in response to the exogenous steroid dexamethasone. Normally, dexamethasone inhibits cortisol secretion through feedback inhibition of the HPA axis. Patients with psychiatric illness are more likely to have persistently elevated cortisol levels following administration of dexamethasone, indicating a failure of inhibition of cortisol secretion. Abnormal DST results are seen in a significant percentage of patients suffering from depression and have been found to be associated in depression with small
hippocampal size. In depression, baseline levels of cortisol in the urine are correlated with cognitive impairment. Further, middle-aged patients with chronic refractory depression have smaller hippocampi than do age-matched healthy controls and the total lifetime duration of depression (but not age) correlates with smaller bilateral hippocampal volumes and lower verbal memory scores. Patients with depression have been reported to have a statistically significant 16% smaller left hippocampus than comparison subjects.

Individuals with PTSD, who, by definition, have had a significant exposure to stress, show associations among cortisol, hippocampal volume, and cognition. Veterans with PTSD score significantly lower on hippocampal-dependent memory measures, such as the Wechsler Memory Scale and the Selective Reminding Test and these deficits correlate with reduction in right hippocampus volume. Adult survivors of childhood abuse also show deficits in immediate and delayed verbal recall and smaller hippocampi, but no difference in size of the amygdala, temporal lobe, or caudate, suggesting a neural specificity to the volume reduction. However, unlike the elevated and unregulated cortisol levels seen in depression and other conditions, cortisol levels in patients with PTSD are reduced. One hypothesis to explain this puzzling finding is that stress may cause an acute hypocortisolemia at the time of trauma and then subsequent chronic cortisol dysregulation, which later, at the time of diagnosis, is characterized by low serum cortisol but high CRF and ACTH.

HPA dysfunction in AD is most studies have been negative. It is likely that HPA-related cognitive changes in AD are small compared to those resulting from the disease process itself.

Glucocorticoids may impair hippocampus-dependent memory in humans. This effect is demonstrated in individuals who chronically take 5–40 mg/day of prednisone for medical indications and in healthy research subjects administered fixed doses of dexamethasone or prednisone for just 4 days. In Cushing's disease, a condition marked by high levels of endogenously released cortisol, patients' hippocampal volumes are inversely correlated with plasma cortisol levels (r = −0.73, p < 0.05). These reductions in hippocampal volume are also correlated with lower scores in verbal memory, specifically paired associated learning and recall corrected for full-scale IQ. Of note, memory deficits that occur in patients with Cushing's disease have been shown to be reversible.

Associations among stress, cortisol, hippocampal volume, and cognition are also demonstrated in normal aging. Healthy elderly individuals with increasing/high cortisol levels (measured annually) were found to have impairments in hippocampus-dependent explicit memory and in selective attention, as measured by Wechsler scales, cued recall, and a visual search task. In an analogous study, another group with increasing or high cortisol over time demonstrated a 14% reduction in hippocampal volume (p < 0.001); the annual rate of cortisol increase correlated negatively with hippocampal volume (r = −0.8, p < 0.01). Hippocampal size is also inversely related to delayed memory performance in normal human aging. Explicit memory impairments in aging individuals can be transiently induced by stress: when healthy elderly subjects were assigned the stressful task of giving a videotaped public presentation, those individuals who secreted more cortisol in anticipation did more poorly on explicit memory. However, these transient effects may be a consequence of impaired working memory and thus poor encoding, rather than a deficit in

### Table 1. Associations among hippocampal volumes, cortisol, and memory in various conditions

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Hippocampal Atrophy and Abnormal Cortisol</th>
<th>Memory Impairment and Abnormal Cortisol</th>
<th>Hippocampal Atrophy and Memory Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cushing's</td>
<td>↑cortisol↑65</td>
<td>↑cortisol↑65</td>
<td>(+)↑65</td>
</tr>
<tr>
<td>Aging</td>
<td>↑cortisol↑52</td>
<td>↑cortisol↑67</td>
<td>(+)↑68</td>
</tr>
<tr>
<td>Depression</td>
<td>Abnormal DST↑49</td>
<td>Abnormal DST↑60</td>
<td>Both correlate with duration of illness↑52</td>
</tr>
<tr>
<td>PTSD</td>
<td>Abnormal DST↑60 GT↑61</td>
<td>(+)↑62 (-)↑60</td>
<td>(+)↑70</td>
</tr>
</tbody>
</table>

DST = Dexamethasone Suppression Test  GTT = Glucose Tolerance Test  (+) = positive findings  (-) = negative findings

08 Corcoran 01-01.qxd  1/8/01  1:17 PM  Page 7
These elements of the stress cascade—cortisol dysregulation, reduced hippocampal volumes, and impairment in hippocampus-dependent memory—occur in a significant number of patients with schizophrenia.

Cortisol Dysregulation and Schizophrenia

Cortisol dysregulation occurs at a higher rate than normal in schizophrenia even though the abnormalities are not specific for schizophrenia. A meta-analysis of 46 studies yielded an overall rate of 26.4% of DST nonsuppression in schizophrenia versus 5% in controls and another meta-analysis of 25 studies found DST nonsuppression in 19% of subjects with schizophrenia and 7% of healthy subjects, compared with 51% of those with depression. The varying rates of DST nonsuppression found in schizophrenia may result from differences in the types of populations studied and variance in their illness stage and course. Dexamethasone nonsuppression in schizophrenia has been associated with negative and cognitive symptoms, ventricular enlargement, poorer prognosis, and movement abnormalities. Of interest, most authors do not find depressive symptoms to be associated with dexamethasone nonsuppression in schizophrenia. Cortisol dysregulation may be related to fluctuations in symptomatology and may vary over time in a given individual. In a prospective study, Sachar et al. found that cortisol levels increased by 250% immediately preceding psychotic exacerbation and then decreased to a level between that of pre-episode and recovery. Two studies reported a normalization of cortisol function as psychotic symptoms abated, with DST nonsuppression declining from 71% to 20% in one study and from 39% to 20% in the other. The large variance in cortisol dysregulation in patients with schizophrenia is also consistent with the concept of schizophrenia as a heterogeneous illness, so that the mechanism may characterize distinct subgroups within the schizophrenia diagnosis.

Hippocampal Abnormalities and Schizophrenia

Patients with schizophrenia have smaller hippocampi than comparison subjects. In addition to volume loss, there are neurochemical indices of hippocampal damage that have been observed using magnetic resonance spectroscopy (MRS): reduction in N-acetyl aspartate (NAA), a marker of neuronal integrity, has been significantly associated with illness in a study of 23 patients with schizophrenia and 18 controls. Likewise, functional imaging shows reduced hippocampal activation in schizophrenia during verbal episodic memory retrieval and odor discrimination. Postmortem studies also demonstrate abnormal cytoarchitecture, lower cell counts, disorientation of pyramidal cells, and smaller neurons in the hippocampi of patients with schizophrenia. Such hippocampal findings could result from the effects of stress and cortisol. Neuropathology in the hippocampal CA3 region, which is related to stress or glucocorticoid exposure in animal models, would be consistent with the neurotoxicity of glucocorticoids. In schizophrenia, postmortem studies have found abnormal dendrites on pyramidal cells in another part of the hippocampus, the subiculum (A. Dwork, personal communication, 2000), but to our knowledge the CA3 region has not yet been examined.

Impairment in Hippocampus-Dependent Cognition and Schizophrenia

Although cognitive deficits are not listed as specific criteria for schizophrenia in the DSM-IV, it has become increasingly clear that cognitive impairment is pervasive in schizophrenia. Often refractory to treatment, cognitive deficits are frequently evident very early in the course of illness. Cognitive deficits in schizophrenia exist across many domains, including executive functioning and memory. A recent meta-analysis of 70 studies that examined cognition in schizophrenia showed consistent moderate-to-large effect sizes across studies for memory impairment (specifically recall). Impairment was present in hippocampus-dependent verbal and nonverbal memory, both immediate and delayed. Indeed, cognitive function, specifically hippocampus-dependent verbal memory, is a strong predictor of functional outcome in schizophrenia.

Stress and Dopamine

The dopaminergic system is a mechanism through which stress may interact with schizophrenia vulnerability. In a
recent model that focuses on the possibility of an abnormal dopamine response to stress, Walker and Diforio proposed that stress augmentation of the HPA axis could increase dopamine synthesis and release. Neural systems needed for adaptation to stressors may be damaged by maturation-related abnormal synaptic pruning or myelination or by earlier congenital defects. These defects might not be manifest unless they are called upon to regulate critical neural elements in the stress response, such as subcortical dopamine. In support of this hypothesis, an increased risk of psychosis has been linked to schizophrenia risk, even though the disease becomes manifest and diagnosable years later, usually during late adolescence or early adulthood. High-risk children are more likely to develop schizophrenia if they are exposed to parental maltreatment or live in institutional settings. The adopted children of affected mothers are similarly more likely to develop schizophrenia if their adoptive families are “dysfunctional.” Preclinical studies support a stress-dopamine relationship in schizophrenia: in an animal model of schizophrenia, rats with neonatal hippocampal excitotoxic damage show greatly increased mesolimbic release of dopamine in response to stress. Consistent with the relationship of dopamine to stress, psychosis reactivation in those with a history of methylphenidase psychosis is more likely following major life events, such as divorce, unwanted pregnancy, or physical or sexual abuse.

**Stress and Schizophrenia**

The association of schizophrenia with cortisolemia, hippocampal abnormalities, and impairment of hippocampal-dependent cognition suggests that these indices may be causally related to the disease. Further support for this hypothesis comes from data that show a relationship between stress/life events and illness course and relapse. But what evidence exists that stress plays a role in the etiology of schizophrenia? Interestingly, both prenatal insults and early postnatal psychosocial stress have been linked to schizophrenia risk, even though the disease becomes manifest and diagnosable years later, usually during late adolescence or early adulthood. High-risk children are more likely to develop schizophrenia if they are exposed to parental maltreatment or live in institutional settings. The adopted children of affected mothers are similarly more likely to develop schizophrenia if their adoptive families are “dysfunctional.” Recently, patients with schizophrenia have been found to have a fourfold increased rate of early parental loss (death or permanent separation) compared to controls, particularly if parental loss occurred before 9 years of age.

Thus far, we have principally focused on postnatal and adult effects of stress/cortisol in the induction of neural damage, but stress in utero is also associated with schizophrenia risk. Offspring whose mothers were informed of their husband’s death during the second trimester have an increased risk of psychosis. Animal studies of prenatal stress demonstrate several findings in parallel with schizophrenia. Exposure to stress or stress hormones in utero is associated with elevated cortisol and stress responsiveness, reduced hippocampal weight, and decreased brain N-acetyl-aspartate in rat pups and in primates. Some of the most promising animal models for schizophrenia involve excitotoxic hippocampal insult during development: in the rat, this lesion leads to behavioral abnormalities and hyperresponsivity to stress in adults. Similarly, early hippocampal injury in primates leads to long-lasting impairment of the prefrontal cortex with related abnormal behavior and cognition. In utero stress in primates leads to dermatoglyphic abnormalities, neuroromotor and attentional deficits, and social impairment. The analogous findings in schizophrenia are evident as early as the premorbid phase, long before the development of frank psychotic symptoms. Neonatal hippocampal injury seems to be a workable primate model of schizophrenia, in that it impairs long-term socioemotional behavior, with loss of social affiliation and a protracted emergence of abnormal behaviors, as well as memory impairment. Hippocampal abnormalities in schizophrenia have been ascribed to early neurodevelopmental events: it is conceivable that glucocorticoid toxicity is a final common pathway through which a variety of stressors that have been associated with schizophrenia (antenatal infection, poor nutrition, obstetric complications, and traumatic brain injury) may injury the hippocampus.

Stress is ubiquitous, but schizophrenia is uncommon. It is therefore likely that some other latent vulnerability (either from faulty genes or adverse perinatal events) is essential for stress to cause schizophrenia. The finding of an association between early psychosocial stress and schizophrenia only in high-risk individuals suggests that stress and genetic vulnerability may interact. Perhaps the condition of premorbid schizophrenia, with its psychosocial and sensory data processing impairments, could itself increase exposure and responsiveness to stress. Innocuous stimuli may be misperceived as threatening or dangerous and cognitive dysfunction may impair effective coping with stressful circumstances. It is feasible that a vulnerability to schizophrenia may entail an increased exposure or vulnerability to stress. Psychotic relapse itself may be a major source of stress, since it has been found to lead to PTSD symptoms. Conversely, a recent study found that duration of untreated psychosis in first-episode schizophrenia was not associated with structural brain deficits or cognitive impairment, which suggests that the onset of illness itself may not be inducing stress-related changes in the brain.

Just as schizophrenia is only one of a number of conditions that may be exacerbated by stress, stress is likely only one of many factors that contribute to schizophrenia. The importance of genetic factors in schizophrenia vulnerability is virtually undisputed. As yet, however, no major “schizophrenia gene” has been identified, and it is likely that much of schizophrenia vulnerability may result from multiple genes of small effect that interact.
THE NEUROBIOLOGY OF THE STRESS CASCADE AND SCHIZOPHRENIA

with one another and with environmental exposures at particular stages of development. Stress may be one such relevant environmental factor.

THE POSSIBILITIES FOR INTERVENTION AND TREATMENT

Cognitive deficits are prevalent in schizophrenia and strongly predict functional outcome, yet they are the symptoms that have proven most refractory to treatment. While cognitive impairments are typically viewed as a fixed and early feature of illness, a sort of static encephalopathy, more recent research demonstrates some progression of cognitive dysfunction in schizophrenia. If cognitive impairment is related to the stress cascade, then opportunities may exist for intervention in patient subgroups with stress reactivity.

Furthermore, if hippocampal damage were immutably fixed in early life, then interventions to directly improve hippocampal function would be limited. But if the hippocampus is plastic, then improvement in cognition and outcome for patients with schizophrenia may be possible. Data suggest that dynamic changes can occur in the adult hippocampus, including the genesis of new neurons in the dentate gyrus. These new cells may have an important function in the consolidation of new memory and may offer an antidote to stress-induced injury.

We have described animal data showing that the dendritic branches in the pyramidal cells of the hippocampus may regenerate when a stressor is eliminated or cortisol is reduced. In humans, stress responses may be attenuated by nonpharmacologic interventions. Environmental enrichment, which stimulates hippocampal neuron regeneration in animals, also reduces stress in adults with schizophrenia. Stress management techniques prevent deterioration early in the course of schizophrenia, delay relapse, and reduce anxiety. Identifying a subset of schizophrenia patients with cortisol dysregulation, small hippocampi, and poor cognition introduces the possibility of targeting such treatment for this group to improve cognition.

Numerous neuroactive medications have been shown to prevent stress-induced damage to the hippocampus in animal studies. Tianeptine, an antidepressant and serotonin uptake enhancer, has been found to block cortisol-induced dendritic atrophy in the hippocampus and reverse maze deficits in rats, an effect not seen with fluoxetine and desipramine. NMMA blockers and adrenal steroid synthesis inhibitors reduce stress-induced damage, as may some benzodiazepines.

A significant body of work has shown neuroprotective activity of the anticonvulsant phenytoin. Phenytoin blocks the atrophy of pyramidal cell apical dendrites in the CA3 region of rat hippocampus that is induced by stress or glucocorticoids. The neuroprotective effect of phenytoin is not achieved via a reduction in cortisol levels, as phenytoin remains protective even in the context of high levels of cortisol; also, phenytoin administration does not block the stress-induced weight gain or adrenal enlargement that result from high cortisol levels. Rather, phenytoin appears to inhibit glucocorticoid-induced apical dendritic atrophy of CA3 pyramidal cells by blocking calcium influx and the release of excitatory amino acids. The mechanism may include modifying neuronal nitric oxide synthase (NOS) messenger RNA expression in inhibitory hippocampal interneurons. The role of NOS in memory is likely mediated by its effects on long-term potentiation (LTP).

An additional potential treatment for the cognitive deficits of schizophrenia may be another adrenal steroid, dehydroepiandrosterone (DHEA), which, along with its sulfated ester DHEAS (together abbreviated DHEA(S)), is the most abundant steroid hormone in the body. Like cortisol, DHEA(S) is produced and secreted by the adrenal cortex, but it is also synthesized in the brain, where it acts locally. DHEA(S) is neuroprotective and may act as an endogenous restraint against cortisol: it has been proposed that the ratio of cortisol to DHEA may be a more significant correlate of neurotoxicity than the levels of either hormone alone. For example, the ratio of evening levels of cortisol to DHEA was found to predict persistent major depression, as well as subsequent disappointing life events, in 8 to 16 year olds. DHEA(S) blocks the neurotoxic effects of cortisol on hippocampal cells. In vitro, it protects hippocampal neurons against excitotoxicity from glutamate and NMDA and against oxidative injury. In rats, DHEA(S) increases long-term potentiation (associated with memory and learning) in the dentate gyrus (a part of the hippocampal formation) and enhances activity of hippocampal cells in the CA1 region. It has been found to improve memory to youthful levels in old mice.

Like cortisol, DHEA plasma levels reflect a circadian rhythm. In schizophrenia, abnormal diurnal patterns of DHEA, but not cortisol, aldosterone, or testosterone, differentiated patients from healthy normal subjects with 100% accuracy. The implications of a disturbed circadian rhythm of DHEA in schizophrenia are not clear. The
THE NEUROBIOLOGY OF THE STRESS CASCADE AND SCHIZOPHRENIA

finding is not specific, as morning levels of DHEA have been found to be lower among depressed adolescents, adults, and depressed elderly women (but not men). Treatment with DHEA has been found to be efficacious in depression, improving mood and memory, in both open-label and placebo-controlled double-blind studies. Administration of DHEA to healthy aging individuals, however, has yielded mixed results, with only some studies reporting an improvement in well-being. As yet, there have not been any published reports of DHEA treatment in schizophrenia since 1954, when case reports (unblinded and uncontrolled) claimed that DHEA improved a range of negative symptoms. If cortisol toxicity proves to be an important mechanism in the emergence of schizophrenia symptoms, it will warrant a study of DHEA in the treatment of the cognitive impairments that are so debilitating and refractory in schizophrenia.

CONCLUSION

Although the role of stress as a factor in the onset and course of schizophrenia has been studied for decades, the relationship between stress and illness remains to be elucidated. This will involve a careful assessment of exposure to stress in patients with schizophrenia, including a history of prenatal exposures, obstetric events, early trauma, major life events, and day-to-day stress. It also warrants an investigation of potential associations of stress in schizophrenia with cortisol dysregulation, hippocampal function, and cognitive impairment. There may be a subset of schizophrenia patients who have abnormal cortisol indices, small hippocampi, and memory impairment. Characterizing this subset in terms of timing and nature of CNS exposure to stress may help elucidate the process by which abnormal neurodevelopment leads to the expression of schizophrenia.

Animal studies have demonstrated that both stress and cortisol are toxic to the brain, especially to the hippocampus, and lead to impairments in hippocampus-dependent cognition. This toxicity is mediated through excessive glutamate, which has been hypothesized to play a role in several neuropsychiatric disorders, including schizophrenia. In humans, there is extensive and consistent research that links cortisol, hippocampal volumes, and hippocampus-dependent memory across many conditions, including Cushing’s disease, depression, PTSD, and age-related cognitive impairment. In light of these data and the well-replicated findings of reduced hippocampal volume and impaired cognition in schizophrenia, it is important to examine these associations in patients with schizophrenia.

There are many challenges in understanding the mechanisms by which stress might play a role in schizophrenia. It is a heterogeneous disorder, so it is possible that stress may be a significant etiological factor in some cases of schizophrenia but less important or irrelevant in others. This would certainly impede our attempts to understand its relationship to this disease as a whole. Another challenge is that the relationship between stress and schizophrenia is likely to be complex and bidirectional, unfolding over the course of development and interacting with other factors, such as genetic vulnerability. Yet, despite these obstacles, understanding how stress may affect the onset and course of schizophrenia has important implications for the development of novel treatments, both pharmacologic and nonpharmacologic, for the devastating and so far relatively untreated cognitive impairments distinctive to this illness.

Understanding how stress may affect the onset and course of schizophrenia has important implications for the development of novel treatments, both pharmacologic and nonpharmacologic, for the devastating and so far relatively untreated cognitive impairments distinctive to this illness.

References

THE NEUROBIOLOGY OF THE STRESS CASCADE AND SCHIZOPHRENIA

12. Levenstein S, Prantes C, Varvo V, et al. Stress and exacerbation in ulcerative colitis: A prospective study of patients enrolled in remis-
17. Mazzeotti M, Mozzetta A, Soavi GC, et al. Psoriasis, stress and psychi-
18. Wittrock DA, Myers TC. The comparison of individuals with recurrent tension-type headache and headache-free controls in physiological response, appraisal, and coping with stressors: A review of the litera-
26. Packan DR, Sapolsky RM. Glucocorticoid endangerment of the hip-
33. Arbel I, Kadar T, Silbermann M, et al. The effects of long-term corti-
34. Diamond DM, Fleshner M, Rose GM. Psychological stress repeated-
39. Virgin CJ, Jr., Ha TP, Packan DR, et al. Glucocorticoids inhibit glu-
40. Stein-Behrens BA, Lin WJ, Sapolsky RM. Physiological elevations of glucocorticoids potentiate glutamate accumulation in the hippocam-
41. Armanini MP, Huthins C, Stein BA, et al. Glucocorticoid endanger-
ment of hippocampal neurons is NMDA-receptor dependent. Brain Res 1990;532:7–12.
43. McKittrick CR, Blanchard DC, Blanchard RJ, et al. Serotonin recep-
44. Sapolsky RM, Meaney MJ, McEwen BS. The development of the glu-
46. Plotsky PM, Meaney MJ. Early, postnatal experience alters hypothalamic corticotropin-releasing factor (CRF) mRNA, median emi-
47. Francis DD, Caldji C, Champagne F, et al. The role of corticotropin-
49. Axelson DA, Doraiswamy PM, McDonald WM, et al. Hyper-
51. McKittrick CR, Blanchard DC, Blanchard RJ, et al. Serotonin recep-
52. Axelrod DA, Doraizwamy PM, McDonald WM, et al. Hyper-
54. Shah PJ, Elmeheier KP, Glabus MF, et al. Cortical grey matter reduc-
tions associated with treatment-resistant chronic unipolar depres-
THE NEUROBIOLOGY OF THE STRESS CASCADE AND SCHIZOPHRENIA

THE NEUROBIOLOGY OF THE STRESS CASCADE AND SCHIZOPHRENIA


