Stress and Glucocorticoid

In his Perspective "Why stress is bad for your brain" (1), Robert M. Sapolsky concludes that glucocorticoid (GC) excess, sometimes a result of sustained stress, is a "likely culprit in causing [hippocampal] atrophy [in humans]." Although the data demonstrating reduced hippocampal volume in Cushing's disease provide supporting evidence for this hypothesis, the other clinical studies cited do not. For example, although hippocampal volumes are reportedly smaller in trauma survivors with posttraumatic stress disorder (PTSD) as compared with those in survivors without PTSD and in nonpsychiatric (control) subjects, the amount of circulating GC is actually chronically *lower* in people with PTSD as compared with these other groups (2). Furthermore, although there has been a general presumption that the concentration of cortisol present at the time of the trauma is higher in trauma survivors who develop PTSD as compared with that in those who do not, recent evidence suggests that the opposite might be correct.

For example, a longitudinal study of rape victims found that cortisol responses (obtained from emergency room blood samples within hours after the rape) were attenuated in women who had prior trauma and who were more likely to develop PTSD, as compared with the cortisol responses of similarly traumatized women who did not develop PTSD (3). Motor vehicle accident victims who subsequently developed PTSD also showed reduced amounts of cortisol within hours following this trauma, as compared with amounts in such victims who had no subsequent psychiatric disorder or who developed major depression (4). Higher concentrations of cortisol at the time of the accident were associated with subsequent major depression (4). Although the blood cortisol samples were not obtained in studies (3, 4) while the trauma was actually occurring, making it technically impossible to rule out that concentrations of cortisol were higher during the trauma in those who subsequently developed PTSD, it seems unlikely that these concentrations would be high enough to permanently damage the hippocampus for the brief duration (minutes to hours) during which these traumatic events actually occurred, even though this brief duration was enough to precipitate PTSD.

GC excess may also not be the underlying cause of the smaller hippocampal volumes observed in a study by Sheline *et al.* of remitted depression (5). Although it is well established that about half of depressed patients are hypercortisolemic, the only study that directly examined this issue found no differences between depressed patients and normal controls (6). Although Sheline *et al.* observed smaller hippocampi in their study group, the remitted depressed subjects were not hypercortisolemic at the time of the hippocampal volume assessment. Furthermore, there is no evidence that subjects were ever hypercortisolemic, even though they had a past history of depression. Because subjects were elderly (with a mean age of 68) and had psychiatric treatment histories, a number of factors other than GC excess may have contributed to the smaller hippocampal volumes.

Although Cushing's disease, PTSD, and depression have been associated with smaller hippocampal volumes, it is unlikely that a common etiology explains the neuroanatomical findings, because each disorder presents a different clinical picture. In Cushing's there is clearly GC excess, but not necessarily stress exposure. Because successful treatment reverses some of the hippocampal atrophy (7), this effect appears to be at least partially state-dependent, and may not be associated with permanent or long-term consequences. In PTSD, patients have been exposed to traumatic stress, but there is little evidence of GC excess. The most ambiguous observations are those made of depressed patients. However, unlike the data on Cushing's disease, the findings presented in the Sheline *et al.* study suggest a more permanent, nonstate-dependent phenomenon, because smaller hippocampi were observed in the absence of both an excess of GC and clinical symptomatology, whereas these changes may be less obvious while patient are depressed and actively hypersecreting GC (6).

One way to approach these studies is to use them as an opportunity to critically examine some of our assumptions about the relationship between stress and GC excess. Given that sustained stress and trauma are often associated with low cortisol in humans, stress should no longer be defined by GC excess any more than GC excess should be taken as evidence of stress. These terms, therefore, should not be used interchangeably. In the aggregate, the data suggest that it is necessary to search for biologic mechanisms other than cortisol toxicity that might account for hippocampal atrophy (for example, excitatory amino acids). Moreover, because the effects of stress do not appear to be uniform, it would be appropriate to carefully delineate the conditions under which stressors are more or less likely to influ-

ence brain plasticity, as well as the risk factors that account for individual differences in GC responses to stress (8).

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Response: A literature stretching back decades demonstrates the deleterious effects of stress and of GCs in the hippocampus of laboratory animals. My Perspective considered recent evidence that the same might occur in humans. Yehuda, a leading PTSD researcher, has questioned some of this evidence.

How could GCs cause the hippocampal atrophy seen in patients with depression and PTSD, when circulating GC concentrations are normal in the former and below normal in the latter? The absence of elevated GC at the time of study (as noted in my Perspective) is not a problem. The study of Sheline *et al.* (1) was not of depressives, but of ex-depressives. In the case of PTSD, it is not the period of the posttraumatic stress disorder that is the alleged culprit, but the period of the traumatic stress itself. No one knows what GC concentrations are during a traumatic stress in a human, but 60 years of research suggests that concentrations will be elevated, a likelihood Yehuda appears to accept. It is the hippocampal atrophy—found many years after the (well-documented) GC hypersecretion seen in approximately half of depressives and after the (likely) CG hypersecretion during the traumatic stressors—that was so striking in these studies.

With regard to the relative brevity of the stressor, I would not anticipate finding hippocampal atrophy in rape or accident victims. The literature comes from combat veterans (2, 3) and from individuals with a history of childhood abuse (4). These are not traumas of brief duration, but of months to years. As the most explicit example of this, in one study (3) the extent of atrophy was predicted by the severity of

the combat exposure, a measure reflecting repeated trauma (with questions such as "How often were you in danger of being injured or killed in the line of duty?") (5). As Yehuda points out, all stressors and all stimuli of GC secretion are not the same, and duration of stress is certainly relevant.

In my Perspective, I raised a challenge to those studying the biological correlates of PTSD, which is to determine whether these correlates are a consequence of the trauma or if they predispose the individual towards being in the subset of trauma victims who suffer PTSD. This issue confounds the current discussion. However, among combat veterans both with and without PTSD (3), greater severities of combat exposure were associated with smaller hippocampi—thus, amid the complexities of trying to understand cause and effect in PTSD, it was combat stress, and not the subsequent PTSD in a subset of individuals, that was relevant to the instances of hippocampal atrophy.

Yehuda notes an earlier study that did not find hippocampal atrophy in hypercortisolemic depressives. That 1993 imaging study used magnetic resonance imagers (MRIs) with one-tenth the resolution of current ones (5.0 versus 0.5 mm, respectively), and could not distinguish hippocampus from amygdala. It was the development of newer MRIs that prompted the current spate of studies.

Yehuda notes that in considering the hippocampal atrophy in Cushing's disease, depression, and PTSD, "it is unlikely that a common etiology explains the neuroanatomical findings." I agree. The closest animal model for the reversible atrophy in the Cushing's patients is excitatory amino acid–dependent retraction of dendritic processes, while the closest model for the more persistent atrophy in the other two cases is neuron loss.

Much more work is needed—given that there are now only a handful of human studies—particularly in differentiating between depression with or without GC hypersecretion, in carrying out prospective studies of trauma victims, and in determining whether actual neuron loss has occurred in cases of persistent atrophy.

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