Why Stress Is Bad for Your Brain

Robert M. Sapolsky

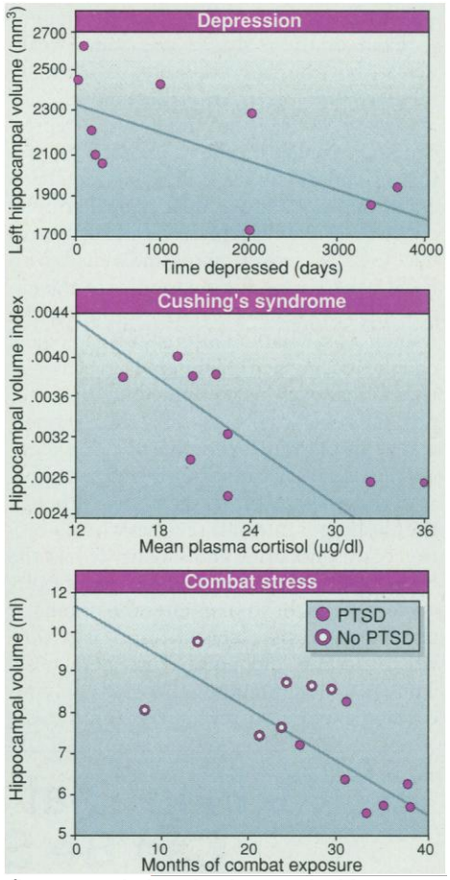
Sustained stress can have numerous pathologic effects. Among the molecules that mediate such effects are the adrenal steroid hormones, including the human glucocorticoid (GC) hydrocortisone. Along with epinephrine (adrenaline) and norepinephrine, GCs are essential for surviving acute physical stress (evading a predator, for example) but they may cause adverse effects when secretion is sustained, such as when waiting to hear about a grant renewal (*1*).

Excessive exposure to GCs has adverse effects in the rodent brain, particularly in the hippocampus, a structure vital to learning and memory and possessing high concentrations of receptors for GCs (*2*). A few days of stress or GC overexposure "endangers" hippocampal neurons, compromising their ability to survive seizures or ischemia; as the likely underpinning of this, the steroids worsen the poor regulation of glutamate and calcium that occurs during such neurologic insults. Over the course of weeks, excess GC reversibly causes atrophy of hippocampal dendrites, whereas GC overexposure for months can cause permanent loss of hippocampal neurons. Although a few studies suggest that similar effects occur in the brains of primates (*3*), there has been virtually no evidence for GC-induced damage in the human. Some new, exciting studies present the first such evidence.

A first example, recently published by Sheline and colleagues at Washington University School of Medicine, concerns major depression (*4*). Approximately half of depressive patients studied secrete abnormally high amounts of GCs. Although investigators had searched with magnetic resonance imaging (MRI) for hippocampal atrophy in depressives, these studies could not distinguish the hippocampus from neighboring structures or used geriatric depressives with brain-wide atrophy from an array of diseases. The authors of the new study report MRIs with far more resolution than in previous studies and have excluded individuals with neurologic, metabolic, or endocrine diseases. They have found significant reductions in the volume of both hippocampi (12% in the right and 15% in the left) when comparing individuals with a history of depression to age-, education-, gender-, and height-matched controls. No change in overall brain volume was observed. The individuals studied had been depression-free for months or decades and, at the time of the study, had normal GC concentrations. The investigators ruled out several confounding variables: alcohol or substance abuse, electroconvulsive therapy, and current use of antidepressants. Remarkably, there was a significant correlation between the duration of the depression and the extent of atrophy (see figure, top panel).

A similar relation is seen in patients with Cushing's syndrome: GCs are overproduced as a result of a hypothalamic, pituitary, adrenal, or pulmonary tumor, and there is bilateral hippocampal atrophy (*5*). Unfortunately, for control values the authors of this study had to rely on comparisons with published data from MRI scans. However, as an impressive internal control, among the Cushingoid individuals, the extent of GC hypersecretion correlated with the extent of hippocampal atrophy (which also correlated with the extent of impairment in hippocampal-dependent cognition) (see figure, middle panel). No atrophy occurred in the caudate nucleus, a brain region with few GC receptors (*6*).

Additional evidence of the relation between GCs and hippocampal function has emerged from studies of individuals with posttraumatic stress disorder (PTSD). In Vietnam combat veterans with PTSD, Bremner and colleagues found a significant 8% atrophy of the right hippocampus (and near significant atrophy of the left) (*7*). In a study in *Biological Psychiatry* (in press), Gurvits, Pitman, and colleagues also examined Vietnam veterans with PTSD and found significant 22 and 26% reductions in volumes of the right and left hippocampi, respectively (*8*). Finally, in another study, also in press in *Biological Psychiatry*, Bremner *et al.* found a 12% atrophy of the left hippocampus in adults with PTSD associated with childhood abuse (with near significant atrophy in the right hippocampus) (*9*). The studies controlled for age, gender, education, and alcohol abuse—and the Bremner studies—ruled out depression as a confounding variable as well. There is some uncertainty as to the anatomical specificity of the effect. In the studies by Bremner, the results were only presented as absolute hippocampal volume, and there were nearly as large (but nonsignificant) reductions in volumes of the amygdala, caudate nucleus, and temporal lobe. However, the study by Gurvits *et al.* showed hippocampal atrophy after correction for whole-brain volume, with no atrophy in the amygdala.



Do stress-induced glucocorticoids cause brain atrophy? Relation between hippocampal volume and (**top**) duration of depression among individuals with a history of major depression [from (*4*)], (**middle**) extent of cortisol hypersecretion among Cushingoid patients [adapted from (*5*)], and (**bottom**) duration of combat exposure among veterans with or without a history of posttraumatic stress disorder [from (*7*)]. Cortisol is another term for the human GC hydrocortisone.

It is not clear whether the atrophy is associated with trauma (combat or abuse) or with succumbing to PTSD (which occurs in 5 to 20% of such traumatized individuals). In the Gurvits study, control groups consisted of healthy volunteers (matched for age, education, and other characteristics) and matched veterans with a history of combat exposure but no PTSD. In the combat veterans, both with and without PTSD, longer durations of combat were associated with smaller hippocampi (see figure, bottom panel). However, because the PTSD patients sustained longer combat exposure than did the controls who had experienced combat but did not have PTSD, it was impossible to dissociate combat from PTSD as a predictor of atrophy. In contrast, in the Bremner combat study (in which there was no non-PTSD combat control group), combat duration did not predict extent of atrophy. Finally, in the childhood abuse study (in which there were no non-PTSD childhood abuse controls), it was not pos-

The author is in the Department of Biological Sciences, Stanford University, Stanford, CA 94305, USA.

sible to dissociate the PTSD from the trauma.

Each of these studies has some weaknesses, but they are countered by complementary strengths in the other studies.

Are GCs the damaging agents? Depression is accompanied by numerous physiological abnormalities, and it has not been demonstrated that the hippocampal atrophy occurs only among depressives who overproduce GCs. Moreover, among individuals with PTSD, there is no information as to the extent of the GC stress response during the trauma (or what additional physiological changes occur then). Thus, in these cases, it is not clear whether GCs mediate the atrophy. However, as noted, the defining abnormality in Cushing syndrome is GC excess, making it a likely culprit in causing atrophy.

How persistent are the changes? Although the Cushingoid atrophy reverses with correction of the endocrine abnormality (6), in the PTSD and depression studies, the atrophy occurred months to years after the trauma or the last depressive episode, and at a time when patients did not hypersecrete GCs. Thus, these long-standing changes could conceivably represent irreversible neuron loss.

The PTSD and depression studies present a problem of causality. Given the cognitive role of the hippocampus, a smaller hippocampus might be more likely to lead to being assigned frontline combat duty rather than a skilled task at headquarters. Furthermore, given the evidence of depression as a disorder of "learned helplessness," a smaller hippocampus might predispose toward depression (that is, less cognitive capacity to detect efficacious coping responses and thus greater vulnerability to learned helplessness). Finally, PTSD individuals, before joining the military, had high rates of learning disorders and delayed developmental landmarks that could reflect cerebral atrophy (*10*). Thus, a small hippocampus could be a cause, rather than a consequence, of the trauma or stressor in these studies. However, there is no plausible way in which a small hippocampus predisposes one toward the pituitary or adrenal abnormalities of the Cushingoid patients, or toward being a victim of childhood abuse.

Should this literature ultimately show that sustained stress or GC excess can damage the human hippocampus, the implications are considerable. It would then become relevant to question whether the high-dose GC regimes used to control many autoimmune and inflammatory diseases have neuropathological consequences. (Both therapeutic and experimental administration of GCs to humans results in memory impairment.) In addition, in the rodent the extent of lifetime GC exposure can influence the likelihood of "successful" hippocampal and cognitive aging (*11*); similar issues must be examined concerning our own dramatic differences in cognitive aging.

References

1. A. Munck *et al.*, *Endocr. Rev.* **5**, 25 (1984).
2. B. McEwen, *Prog. Brain Res.* **93**, 365 (1992); R. Sapolsky, *Semin. Neurosci.* **6**, 323 (1994).
3. H. Uno *et al.*, *J. Neurosci.* **9**, 1705 (1989); R. Sapolsky *et al.*, *ibid.* **10**, 2897 (1990); A. Magarinos *et al.*, *ibid.* **16**, 3534 (1996).
4. Y. Sheline *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **93**, 3908 (1996).
5. M. Starkman *et al.*, *Biol. Psychiatry* **32**, 756 (1992).
6. M. Starkman, personal communication.
7. J. Bremner *et al.*, *Am. J. Psychiatry* **152**, 973 (1995).
8. T. Gurvits *et al.*, *Biol. Psychiatry*, in press.
9. J. Bremner *et al.*, *ibid.*, in press.
10. T. Gurvits *et al.*, *J. Neuropsychiatry Clin. Neurosci.* **5**, 183 (1993).
11. M. J. Meaney *et al.*, *Science* **239**, 766 (1988); A. Issa *et al.*, *J. Neurosci.* **10**, 3247 (1990).

STATs Find That Hanging Together Can Be Stimulating

Stewart Leung, Xiaoxia Li, George R. Stark

Transcription factors activate the synthesis of messenger RNAs from DNA, thereby changing the function of cells. A few years ago, a new family of transcription factors—the STATs (signal transducers and activators of transcription)—was described that mediates the action of a large and vastly important class of signaling molecules, the cytokines and growth factors. Each cytokine or growth factor activates a distinct set of genes to produce very distinct effects on the cell, yet there are only a limited number of STATs to mediate these signals. How do these few STATs generate a specific response for each cytokine or growth factor? Part of the answer to this puzzle is provided in a report by Xu *et al.* in this week's issue of *Science* (*1*).

The STATs exist as latent transcription factors in the cytoplasm. After binding of the growth factor or cytokine to its receptor, the STAT is activated by tyrosine phosphorylation (*2–4*); it then migrates to the nucleus, binds to specific DNA elements, and activates the transcription of nearby genes. The six STAT family members form homo- or heterodimers in which the phosphotyrosine of one partner binds to the SH2 (SRC homology 2) domain of the other (*5*). These dimers bind to palindromic GAS sequences that have similar affinities for different STATs.

The new work by Xu *et al.* (*1*) describes how each cytokine elicits a specific transcriptional response when each must use a limited number of factors and when the target DNA elements distinguish relatively poorly among these factors. In investigating a region of the human interferon-γ (IFN-γ) gene that contains clusters of GAS elements, these authors found that homodimers of STATs 1, 4, 5, and 6 all bind, but with different footprints. Their observations suggest that STAT dimers may cooperate in binding to clustered GAS elements and that the details of this cooperation may help to determine the cytokine specificity of the response.

The STAT proteins share blocks of homology, arrayed over their entire 800–amino acid length, and it is likely that similar domains have similar functions: (i) The SH2 domain near residue 600 is highly conserved, as is a tyrosine near residue 700, which becomes phosphorylated upon activation. In addition to binding the phosphotyrosine of another STAT, the SH2 domain also mediates the binding of STATs to specific phosphotyrosine residues of activated cytokine receptors (*6–8*). (ii) The COOH-termini of STATs mediate transcriptional activation, and phosphorylation of a serine residue in this region of STATs 1α, 3, 4, and 5 enhances this activity (*9*). In contrast, the acidic COOH-terminal region of STAT2 can activate transcription without phosphorylation (*10*). (iii) STATs contain a DNA binding domain near residues 400 to 500 (*11*). (iv) STAT2-STAT1 heterodimers bind to an additional protein, p48, to form the major transcription factor generated in response to IFN-α. The region comprising residues 150 to 250 of STAT1 interacts with p48 (*12*). Other STAT dimers may also interact with p48 (or similar proteins) to form more complex oligomeric transcription factors.

Xu *et al.* (*1*) have found a new function for the NH_2-terminal domains of STATs 1 and 4: Mediating cooperative binding of these STATs to tandem GAS sites. Deletion of 90 amino acids from the NH_2-terminus of STAT4 did not affect its binding to a single GAS site but abolished the cooperative binding of two STAT4 dimers to a double site. Furthermore, a peptide representing the

The authors are in the Department of Molecular Biology, Research Institute, Cleveland Clinic Foundation, Cleveland, OH 44195, USA. E-mail: starkg@cesmtp.ccf.org