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Chronic Stress-Induced Hippocampal Vulnerability: The Glucocorticoid Vulnerability Hypothesis

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Synopsis

The hippocampus, a limbic structure important in learning and memory, is particularly sensitive to chronic stress and to glucocorticoids. While glucocorticoids are essential for an effective stress response, their oversecretion was originally hypothesized to contribute to agerelated hippocampal degeneration. However, conflicting findings were reported on whether prolonged exposure to elevated glucocorticoids endangered the hippocampus and whether the primate hippocampus even responded to glucocorticoids as the rodent hippocampus did. This review discusses the seemingly inconsistent findings about the effects of elevated and prolonged glucocorticoids on hippocampal health and proposes that a chronic stress history, which includes repeated elevation of glucocorticoids, may make the hippocampus vulnerable to potential injury. Studies are described to show that chronic stress or prolonged exposure to glucocorticoids can compromise the hippocampus by producing dendritic retraction, a reversible form of plasticity that includes dendritic restructuring without irreversible cell death. Conditions that produce dendritic retraction are hypothesized to make the hippocampus vulnerable to neurotoxic or metabolic challenges. Of particular interest is the finding that the hippocampus can recover from dendritic retraction without any noticeable cell loss. When conditions surrounding dendritic retraction are present, the potential for harm is increased because dendritic retraction may persist for weeks, months or even years, thereby broadening the window of time during which the hippocampus is vulnerable to harm, called the Glucocorticoid Vulnerability Hypothesis. The relevance of these findings is discussed with regard to conditions exhibiting parallels in hippocampal plasticity, including Cushing's disease, Major Depressive Disorder (MDD), and Post-Traumatic Stress Disorder (PTSD).

Introduction

An individual's survival relies upon the successful activation and termination of a stress response. The stress response occurs following a real or perceived threat (stressor) and includes the activation of the sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenal (HPA) axis. The SNS is responsible for the rapid stress response, involving the release of catecholamines (epinephrine and norephinephrine) within seconds of the onset of the stressor. The HPA axis is responsible for the slower onset stress response, involving the release of glucocorticoids (Cortisol in humans and corticosterone in rodents) within several minutes of stressor onset. A critical feature of the stress response is that it terminates itself when the stressor has ended or is no longer perceived as a threat. The termination of the stress response is critical because the continued activation of the SNS and the HPA axis can wreak havoc on the body. A racing heart and high blood pressure triggered by epinephrine to maximize blood flow is critical for assisting in escaping the stressor, but a persistent racing heart and high blood pressure increases the risk of heart failure and arteriosclerosis. Elevated glucocorticoids are

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essential for the redistribution of energy resources, but the long-term elevation of glucocorticoids starves some tissues of necessary resources and hinders immune function, increasing the susceptibility to disease. While the stress response is critical for the successful adapatation to a real or perceived threat, a persistent stress response can be detrimental.

In the 1930's, Hans Selye stumbled upon the discovery that chronic stress can shorten the lifespan. With the publication about the General Adaptation Syndrome (GAS) and the Diseases of Life, the connection that chronic stress can cause poor health received widespread acknowledgment /see 136/. In the years that followed the original publication, aspects of the GAS were inconsistent with new discoveries: among the notable findings was that glucocorticoids reduced inflamation instead of exacerbating it. Not until decades later did interest in chronic stress re-emerge to support a key concept of Selye's hypothesis that persistent stress can weaken the body.

Several findings beginning in the late 1960s revealed that prolonged exposure to stress or glucocorticoids harms the brain. Glucocorticoid function was first identified in peripheral tissue, hence, the name "glucocorticoid" reflects effects on energy metabolism. Subsequent studies revealed that the brain is an important target of glucocorticoids, with the forebrain and limbic structures containing a high proportion of specific receptors /87,88/. In line with this revelation was the finding that the brain responded poorly to extended and elevated glucocorticoid levels. Guinea pigs injected daily with glucocorticoids for four weeks exhibited brain damage in the hypothalamus and hippocampus /4/. In the late 1970's and early 1980's, studies began to link stress and glucocorticoids with poor hippocampal aging. Age-related hippocampal pathology, as measured by reactive astrocytes, positively correlated with plasma glucocorticoid levels in rats /74/. Importantly, reducing glucocorticoids by adrenalectomy at mid-age attenuated glial reactivity and neuronal loss commonly observed in aged rats /75/. These studies were followed by a series of reports showing that the dysfunctional hippocampus contributes to an impaired HPA axis response in aged rats /117–120,123/. These findings were consistent with reports showing that the hippocampus provides negative feedback to the HPA axis, with hippocampal stimulation and lesions causing decreases and increases in HPA axis activity, respectively /36,40,43,58,85/. Consequently, some investigators renamed the HPA axis, calling it the "LHPA" axis to acknowledge the influence of the limbic "L" region /as examples, see 78,106/. Collectively, these studies demonstrated that chronic stress and glucocorticoids impaired hippocampal function, which in turn contributed to the dysregulation of the HPA axis.

In 1986, the Glucocorticoid Cascade Hypothesis was proposed to describe the dynamic relationship between glucocorticoids and the hippocampus with aging /127/. This seminal hypothesis states that glucocorticoids secreted during periods of stress desensitize the hippocampus to further glucocorticoid exposure by downregulating glucocorticoid receptors, an effect that is self-correcting and therefore reversible. At some point, however, the downregulation of glucocorticoid receptors precipitates further hypersecretion of glucocorticoids until permanent hippocampal cell loss occurs. This irreversible hippocampal damage was proposed to make the hippocampus irreversibly insensitive to further glucorticoid elevations, creating a feed-forward cycle of elevated glucocorticoids and continued hippocampal destruction as an individual ages. While elegant, the glucocorticoid cascade hypothesis had some inconsistencies /see 2/. The purpose of this review is to discuss the seemingly inconsistent findings concerning the effects of prolonged elevation of glucocorticoids on hippocampal health and to discuss the interpretation that a chronic stress history, which includes repeated elevation of glucocorticoids, may make the hippocampus vulnerable to potential injury.

Brief Historical Account of the Glucocorticoid Cascade Hypothesis and its Caveats

A series of studies starting in the 1980's showed that acute stress and the concurrent elevation of glucocorticoids exacerbated damage to the hippocampus caused by neurochemical or metabolic challenges. Glucocorticoids enhance hippocampal damage following neurotoxin insult /kanic acid, also known as 3-acetyl-pyridine, 125,126/, or metabolic challenge /hypoxia, 156/, /hypoglycemia, 156/, /ischemia, 124/. Glucocorticoids can aggravate hippocampal damage when steroid titers are elevated just prior to, during, or immediately after the neurotoxic challenge /122/. Reducing glucorticoids via adrenalectomy or by metyrapone administration can attenuate glucocorticoid-induced exacerbation of hippocampal damage from a neurotoxin challenge /121,124,141,148/. Down-regulating the HPA axis with repeated glucocorticoid injections to produce low glucocorticoid titers during a hypoxia/ischemia challenge helps to protect against hippocampal damage /72/. While glucocorticoids can influence hippocampal susceptibility indirectly through their well-known effects on peripheral energy metabolism, in vitro tissue culture work demonstrates that glucocorticoids can also directly exacerbate hippocampal cell loss following hypoxia and hypoglycemia /128,156/, by compromising energy use /130,162/. Collectively, these studies show that acute glucocorticoid elevations exacerbate hippocampal damage when glucocorticoid elevations coincide with challenges that compromise energy use.

The Glucocorticoid Cascade Hypothesis illustrates the mechanism underlying the shift from reversible glucocorticoid receptor downregulation to permanent cell death in the hippocampus / 127,130/. Under conditions of acute stress and high glucocorticoid levels, the hippocampus has reduced energy stores to respond effectively to a challenge, such as a metabolic event. Under most circumstances, high glucocorticoid levels occur without such a metabolic challenge and subsequently subside without any severe consequence to hippocampal health. Indeed, most young individuals rarely exhibit metabolic challenges, such as stroke, ischemia, hyperglycemia, hypoxia, etc., which could compromise hippocampal integrity. In contrast, aged individuals have a lifetime of experiences with elevated glucocorticoids and are more likely to experience a metabolic event that coincides with high glucocorticoid levels. Thus, the probability of any one of these elevated glucocorticoid events occurring around the same time as a metabolic event is greater in the aged than in the young. The transition from reversible glucocorticoid receptor downregulation to permanent cell death requires just one concurrent incident of glucocorticoid elevation and metabolic challenge. Once these two events coincide, hippocampal damage occurs, and HPA axis regulation by the hippocampus becomes progressively less effective, leading to ever-increasing glucocorticoid levels. Subsequent glucocorticoid elevations can become even more common, as each single stressful event is prolonged due to faulty the negative feedback, causing glucocorticoids to stay elevated longer in an individual with hippocampal damage. Consequently, because the duration of glucocorticoid elevation is prolonged, the probability of elevated glucocorticoids occurring around the same time as the next metabolic challenge is increased. Therefore, a damaged hippocampus makes itself even more susceptible to a metabolic challenge than a healthy hippocampus, creating a downward spiral of increased chances of potentiated hippocampal damage with each metabolic episode and this risk increases with age.

At the time that the Glucocorticoid Cascade Hypothesis was proposed, the supporting studies utilized rats. However, subsequent studies using rats and other models did not consistently find hippocampal damage with prolonged glucocorticoid or stress expsoure. Some studies reported that chronic stress or glucocorticoids contributed to hippocampal cell death in adult rats /33, 123/ and non-human primates /129,157/, while others failed to find hippocampal cell loss in rats /8,21,142/, tree shrews /47,163/, non-human primates /76/, and humans /93/. The mounting

conflicting evidence clearly shows justification to question whether chronic stress and glucocorticoid elevations are sufficient to kill hippocampal neurons with age.

In corroboration with this concern, some studies began to show inconsistencies in glucocorticoid responsivity in aged individuals. In a test of HPA axis activity, cortisol levels before and after a psychological test were compared between men in their twenties and sixties. Regardless of age, comparable endocrine response patterns were observed, which failed to support the hypothesis of the breakdown of the HPA axis with age /73/. In other studies, cortisol levels were measured in patients with Alzheimer's disease and healthy adults following an exogenous challenge with dexamethasone, a synthetic glucocorticoid that should inhibit the HPA axis via negative feedback, reducing the subsequent release of endogenous cortisol /45, 154/. Both studies found that control subjects and patients with Alzheimer's disease had comparable HPA axis response patterns. Moreover, Swanwick and colleagues (1998) repeated the dexamethasone challenge at 9-month intervals and were unable to predict the HPA axis response in the Alzheimer's disease patients based upon their previous history, suggesting that hypercortisolism and cell loss was not a cofactor in further degeneration. The inconsistencies between the rodent and human literature drew into question the relevance of the Glucocorticoid Cascade Hypothesis for humans /see 165/.

Some of the difficulty in understanding the mechanisms by which chronic glucocorticoids influence the hippocampus may arise from species-specific differences in stress steroid receptor expression. Glucocorticoids bind with a low affinity to the glucocorticoid receptor (GR) and with nearly ten fold higher affinity to the mineralocorticoid receptor /MR, 3/. While these names may appear counter-intuitive, the receptors for glucocorticoids were originally described after characterizing their peripheral actions; glucocorticoids produced robust effects on peripheral tissues expressing GR, without noticeable effects on tissues expression MR (i.e. kidney), mainly because the kidney contained 11β-hydrosteroid dehydrogenase Type II to convert active glucocorticoids into inactive forms /48,135/ and to permit selective access of aldosterone to MR. Consequently, glucocorticoid receptors were named based upon ligand effectiveness in the peripheral tissues. In contrast to these tissues, 11β-hydrosteroid dehydrogenase is nearly absent in the brain /134/, which expresses both GR and MR /113/. Moreover, the limbic regions highly express GR and MR, both of which confer functional consequences in response to glucocorticoids /37/. However, controversy arose because in the rodent brain, GR and MR were particularly concentrated within the hippocampus /113/, while differences were found in the nonhuman primate hippocampus /116/. Specifically, Rhesus monkeys express relatively few GR in the hippocampus, despite their relative abundance within the hypothalamus and pituitary /116/. This lack of robust hippocampal GR expression is problematic because glucocorticoids are proposed to bind to GR-sensitive tissue to mediate subsequent neuronal death within the hippocampus. Sánchez and colleagues /116/ hypothesized that MR may mediate the detrimental effects of chronic glucocorticoid exposure because MR are expressed in relatively high levels within the hippocampus. Alternatively, they suggested that the hypothalamus could be a putative target, given the high numbers of GR it contained. Unlike the Rhesus monkey, high levels of GR and/or MR are found within the hippocampus of the squirrel monkey /103/, macaque /17/, marmoset /63/ and human /131/. Patel and colleagues suggest that riboprobe sensitivities may have contributed to the differences in the Rhesus monkey, noting that human riboprobes were used in this study. For the human work, a potential confound is that the temporal lobes were excised to treat epileptic seizures, making it unclear whether GR expression represents the typical human hippocampus. The equivocal findings for primate GR levels within the hippocampus raise doubt as to whether chronic glucocorticoid exposure causes hippocampal damage via GR in humans. These conflicting outcomes contributed to the reduced interest in the Glucocorticoid Cascade Hypothesis to explain hippocampal decline with aging.

Chronic Stress Endangers the Hippocampus: The Glucocorticoid Vulnerability Hypothesis

If repeated elevation of glucocorticoids through a lifetime fails to kill neurons within the hippocampus, then do glucocorticoids contribute to hippocampal endangerment? Glucocorticoids may not be necessary for hippocampal damage, but they are an important contributing variable to hippocampal vulnerability to damage. A history of chronic stress is proposed to alter the hippocampus by elevating glucocorticoids and these alteration(s) extend the window of time, during which the hippocampus is susceptible to damage. A critical difference between the Glucocorticoid Cascade Hypothesis and the current Glucocorticoid Vulnerability Hypothesis is that glucocorticoids need not be elevated at the time of the metabolic challenge: a history of chronic stress is proposed to leave an “imprint” on the hippocampus, making the hippocampus vulnerable even when glucocorticoids are not elevated at the time of the metabolic challenge. As a consequence, chronic stress and glucocorticoids are not the sole determinant for hippocampal cell loss but play a critical role in priming the hippocampus to be more susceptible to subsequent insults.

A recent history of chronic stress is a significant variable contributing to the susceptibility of the hippocampus to degeneration. As described earlier, work in the 1980’s showed that acute glucocorticoid elevations that coincided with a metabolic challenge produced more hippocampal damage than did metabolic challenge alone /130/, revealing the vulnerability of the hippocampus to simultaneous threats. Recently, work in our lab revealed that a chronic stress history could compromise hippocampal health as well. In one study, we exposed male rats to chronic immobilization stress for six hours/day for 21 days, then a few days later, we challenged the CA3 region of the hippocampus with ibotenic acid (IBO), a neurotoxin that is thought to act upon the glutamate system through NMDA receptors /67/. Rats with a history of chronic stress showed more CA3 damage from IBO compared to non-stressed controls /28/. To determine whether these effects were produced by circumstances surrounding the chronic stress history or from potential glucocorticoid elevation caused by the last day of restraint, we exposed rats to a single restraint episode (acute stress) at the time when chronically-stressed rats received their last day of restraint, then assessed IBO-induced hippocampal CA3 damage /28/. Only chronic stress, but not acute stress, exacerbated IBO-induced CA3 damage, which confirmed that waiting several days following the end of the last day of restraint permitted glucocorticoid elevations from the last restraint session to subside. These data support the interpretation that acute glucocorticoid elevations from restraint were unlikely to have exacerbated IBO-induced CA3 damage and emphasize that the history of chronic stress was critical for hippocampal susceptibility to the IBO challenge.

A caveat is that the surgical procedures to infuse IBO into the CA3 region of the hippocampus may have elevated stress hormones differently in chronically-stressed rats compared to controls. Such an interpretation would suggest that the surgical-induced elevations of stress hormones that were differentially primed from the chronic stress history mediated IBOinduced hippocampal damage. Specifically, the HPA axis response changes with chronic stress history /34,35/. Rats exposed repeatedly to the same chronic stress stimulus (homotypic stressor) begin to habituate to that stimulus and show attenuated HPA axis responses. In contrast, rats exposed repeatedly to the same chronic stress stimulus and then presented with a novel stressful stimulus (heterotypic stressor) exhibit potentiated HPA axis responses to the novel stimulus. In our paradigm, chronic restraint is homotypic and would produce a blunted HPA axis response to restraint, but infusing IBO under surgical anesthesia cause a heterotypic stress response. Consequently, the chronically-stressed rats may have had exacerbated CA3 damage in response to IBO because of a potentiated HPA axis response during the procedures to infuse IBO. To address this concern, we performed another study to infuse IBO at a time removed from the exposure to the potential heterotypic stressor of surgical anesthesia; cannulae were implanted

to target the CA3 region before treatment, and after recovery, rats were exposed to chronic glucocorticoids for 21 days, allowed to rest for several days, then infused with IBO through the pre-implanted cannula while alert /31/. We found that a history of chronic corticosterone exacerbated CA3 damage from the IBO challenge even without the potential heterotypic stressor of surgical anesthesia. The procedure of infusion through the cannula could still be construed to be a mild and novel heterotypic stressor for the rats. However, this seems unlikely as measurements of endogenous corticosterone responses to a mild and novel stressor in another circumstance (acute saline injection) produced similar cortiocosterone responses in the control and chronic corticosterone-treated rats. These findings are significant because they show that homotypic stress leaves an "imprint" on the hippocampus that extends the window of time during which the hippocampus is vulnerable to damage.

Conditions Producing Hippocampal Dendritic Retraction Confer Susceptibility to Damage

While the literature reveals inconsistencies with regards to chronic stress producing hippocampal neuronal death, many laboratories using a variety of species report reliable chronic stress effects on other hippocampal measures. These stress/glucocorticoid-induced hippocampal changes include decreasing neurogenesis /62,108,115/, altering dendritic spine density /97,153,155/, hindering synaptic plasticity /62,115/, impeding long-term potentiation /105/, changing the inhibitory and excitatory tone /62,102,112/, downregulating GR /69,170/, and reducing dendritic complexity /70,82,167/. Of these changes, hippocampal CA3 dendritic retraction, characterized by reduced dendritic complexity and total dendritic length, is an important indicator of a chronic stress history because it occurs following chronic stress or glucocorticoid exposure /30/, but not following acute stress, even when that acute stress is repeated for up to two weeks in some paradigms /80,91/. In contrast, the other chronic stressinduced changes within the hippocampus can be produced following acute stress/glucocorticoids /19,29,39,52,89,104/. Moreover, hippocampal CA3 dendritic retraction lasts for at least four days following the end of chronic stress /27,164/. Therefore, chronic stress alters the hippocampus, including CA3 dendritic retraction, and these changes are present relatively long (many days) after stress hormone elevations have subsided compared to stress-induced glucocorticoid elevations that return to baseline very quickly (within hours of the stressful event).

We investigated whether a history of chronic stress and the subsequent structural changes, as measured by dendritic retraction within the hippocampus, conveyed susceptibility to a neurotoxic challenge. We first compared the effects of an IBO challenge to the CA3 and CA1 hippocampal regions after chronic restraint stress. These two regions are critical because hippocampal CA3 neurons undergo dendritic retraction at three weeks following chronic stress or glucocorticoid treatment /91/, while CA1 neurons do not express dendritic retraction at this time /82,166,169/. We found that chronic stress exacerbated cell loss in the hippocampal CA3, but not CA1, region following an IBO challenge /28/. We also compared IBO-induced CA3 damage following chronic stress in both sexes because the extent of chronic stress-induced CA3 dendritic remodeling differs: chronic stress alters the larger apical region in males as opposed to the smaller basal region in females /49/ with evidence of ovarian hormones being neuroprotective /90/. We found that chronic stress exacerbated IBO-induced CA3 damage in males, but not females /28/. These findings suggest that chronic stress and its subsequent imprint on the hippocampus as measured by dendritic retraction may contribute to the vulnerability of the CA3 region to the IBO challenge.

To further investigate the contribution of chronic stress/glucocorticoid-induced dendritic retraction to hippocampal susceptibility to a neurotoxic challenge, we blocked CA3 dendritic retraction. Stress levels of corticosterone were administered to rats in the drinking water for

three weeks to produce CA3 dendritic retraction. Half of the rats were treated daily during the three weeks with the antiepileptic drug, phenytoin (Dilanton), to block chronic stress- and glucocorticoid-induced hippocampal CA3 dendritic retraction, as described by others /83, 166/. A few days after corticosterone exposure ended, rats received IBO infusions into the CA3 region via previously implanted cannuale. We confirmed that the glucocorticoid treatment produced CA3 dendritic retraction, which was prevented with phenytoin /31/. Importantly, we found that only conditions producing CA3 dendritic retraction (corticosterone + vehicle) showed exacerbated hippocampal CA3 cell loss by an IBO challenge /31/. Treatments that did not produce hippocampal CA3 dendritic retraction did not show IBO-induced exacerbation of hippocampal damage, including the chronic corticosterone group treated with phenytoin. Moreover, phenytoin did not exert its neuroprotective effect by altering the HPA axis because corticosterone profiles were similar among rats treated with corticosterone and phenytoin versus corticosterone and vehicle. Altogether, these findings show that chronic stress or glucocorticoid elevation that produces structural changes in hippocampal dendritic arbors also makes the hippocampus vulnerable to neurotoxic challenges, even when glucocorticoids are unlikely to be elevated during the neurotoxic challenge.

The mechanism by which chronic stress confers susceptibility to a neurotoxic challenge is unknown, but dendritic retraction may provide insight. Dendritic remodeling is essential for normal, healthy development and is an important part of plasticity in adult brains as well. In hibernating ground squirrels, for example, dendritic retraction occurs during hibernation, and dendritic complexity increases upon waking /109,110/. The decrease in dendritic complexity during a time of reduced forebrain function suggests that dendritic retraction may disrupt information processing. Consistent with this idea is the finding that dendritic complexity is correlated with synaptic input /111/. Hippocampal dendritic restructuring may be significant because a major source of input to the apical dendrites of CA3 neurons is glutamate, which is released from the commissural pathway (contralateral hippocampus), entorhinal cortex, and the mossy fibers of the dentate gyrus. However, unregulated glutamate can be neurotoxic / 20/, and glucocorticoids increase extracellular glutamate levels /62,92,150/. Consequently, dendritic retraction may be an adaptive response to reduce the exposure of CA3 neurons to glucocorticoidinduced glutamate elevation. However, the price of dendritic retraction can be substantial. At the systems level, studies consistently show that CA3 dendritic retraction corresponds with impaired spatial ability /30,91/, a hippocampus-mediated function /98/. At the cellular level, slow functioning may hinder the ability of neurons to respond quickly or effectively to a neurotoxic or metabolic challenge. CA3 dendritic retraction is hypothesized to be a compensatory response to avoid over-exposure to elevated glucocorticoids and the subsequent increase in glutamate, but this dendritic restructuring has a cost: neurons that retract dendrites may be unable to respond adequately to an unexpected metabolic challenge, leading to exacerbated hippocampal damage.

If dendritic retraction has such a high cost of potentially irreversibly damaging the neurons, then why do neurons undergo this process? CA3 dendritic retraction is proposed to occur in response to an event that is certain: the bombardment of glutamate induced by elevated glucocorticoids, which makes adjusting to the potentially lethal exposure to glutamate paramount. In contrast, the potential for damage in response to a metabolic challenge is uncertain. Specifically, neuronal death from glutamate over-exposure is highly probable during increased glutamate release, whereas a metabolic event may not occur. Another factor to consider is that stress-induced CA3 dendritic retraction is reversible; neurons return to the prechronic stress condition within 10 days after the termination of chronic stress /27,164/. Consequently, CA3 dendritic retraction may be triggered by repeated, high glucocorticoid exposure, but then returns to baseline once glucocorticoid levels return to normal. Therefore, CA3 dendritic retraction is proposed to be a relatively low-risk, temporary neuroplastic response to combat the immediate looming threat of elevated glutamate.

Another interpretation is that chronic stress-induced changes in the MR/GR ratio within the hippocampus may confer susceptibility to a neurotoxin challenge. A dual role for MR and GR was proposed to describe HPA axis regulation /41,101/, then was extended to describe cognitive function as well /25,26,29,38,100/. Altering MR and/or GR expression can influence the HPA axis and perhaps susceptibility to a potential challenge to the hippocampus. Low MR expression within the CA2/3 region produced by chronic unpredictable stress corresponds with elevated basal levels of glucocorticoids /78/. Conversely, high MR expression within the hippocampus in a predisposed Lewis rat strain is associated with hyporesponsiveness to stress /101/. In either situation, the ability to detect changes in glucocorticoid levels is compromised because elevated basal glucocorticoids may reduce the sensitivity of MR to detect basal glucocorticoid fluctuations /38,41/ and over-expression of MR may hinder a robust stress response. Using our model of chronic restraint stress, we found reduced GR expression across the hippocampus and elevated glucocorticoids during cognitive testing /170/. This finding is consistent with reports showing impaired glucocorticoid feedback with chronic stress /5,119,120/ or with glucocorticoid agonists /57/; however, not all studies report decreased MR or GR with chronic stress /59,143/. Instead, the ratio of MR/GR expression may be critical for regulating hippocampal function, such that a MR/GR ratio imbalance is hypothesized to contribute to cognitive dysfunction and susceptibility to disease /38,81/. Indeed, suicide victims exhibit lower MR/GR ratios within the hippocampus than controls /78/. Consequently, MR/GR ratio balance may be an important variable that contributes to hippocampal dysfunction.

The significance of these findings is that a history of chronic stress or glucocorticoid elevation, which produces alterations within the hippocampus, extends the window of time during which the hippocampus is susceptible to damage. Prior work demonstrated that a neurotoxic challenge that coincided with elevated glucocorticoids produced more damage than either event alone /121/. The current findings reveal that glucocorticoid elevations are necessary to produce hippocampal structural changes, but glucocorticoids need not be elevated at the time of the neurotoxic challenge to confer heightened susceptibility to damage. Importantly, the relatively long-lasting persistence of structural changes, including CA3 dendritic retraction in response to the transient stress-induced elevation of glucocorticoids is significant because it presents an extended opportunistic window during which the hippocampus is vulnerable. Therefore, chronically-stressed individuals are at increased risk for potential hippocampal damage because they are exposed to repeated elevation of glucocorticoids and the potential subsequent structural alterations within their hippocampus confer extended susceptibility.

An important factor to consider is the type of insult to the hippocampus. In our experimental studies, we used IBO neurotoxin. While the likelihood of an individual experiencing neurotoxicity is probably very low, this paradigm could be extrapolated to situations involving metabolic challenges. In the acute glucocorticoid exposure model, the presence of high glucocorticoid levels exacerbated hippocampal damage following exposure to a neurotoxin / kainic acid, 3-acetylpyridine, 121,122/, as well as to episodes of ischemia /124/, hypoxia /156/, or hypoglycemia /156/. These results illustrate that the hippocampus was susceptible to damage whether it was challenged with neurotoxin or a metabolic event, emphasizing that glucocorticoid-enhanced susceptibility can be generalized to a neurotoxic or metabolic insult. Since our current findings reveal that chronic stress conditions can also increase hippocampal susceptibility to a neurotoxic challenge, our results may be extrapolated to suggest that chronic stress conditions may also increase hippocampal susceptibility to metabolic events, although empirical testing will be important to address this issue.

Significance for Metabolic Challenges and Clinical Conditions

The finding that a history of chronic stress can exacerbate hippocampal damage in response to a neurotoxic/metabolic challenge has many implications for a variety of conditions that show

similar dynamics in hippocampal plasticity, including Cushing's disease, Major Depressive Disorder (MDD), and Post-Traumatic Stress Disorder (PTSD). Cushing's disease is a rare disorder characterized by the hypersecretion of glucocorticoids /95,96/. When undiagnosed, individuals show a high degree of susceptibility to mood disorders, such as MDD, and these symptoms improve with treatment /144/. MDD is among the most common psychiatric disorders /7,77/ and predominately involves changes in mood, but also includes alterations in cognition, HPA axis function, motivation, sleep, anhedonia, appetite and weight /42,56/. PTSD has received a great deal of attention recently due to current world events and is an anxiety disorder that can develop in response to real or perceived trauma. PTSD is characterized by hypo-HPA activity and episodes of reliving the trauma through intrusive memories (DSM-IV). Common features for all three conditions include small hippocampal volume and HPA axis disruption /13–15,46,54,61,94,137,145,149,160,161/. The relationship between hippocampal volume and glucocorticoid levels in these human conditions provides strong evidence that parallels our observations with chronic stress and dendritic retraction within the hippocampus of rodents.

A consistent characteristic of these conditions is that symptom severity correlates with hippocampal size, which shows plasticity by improving with treatment. Patients with Cushing's disease show reduced hippocampal volume that inversely correlates with glucocorticoid levels /145/. Following intervention to reduce glucocorticoids, Cushing's disease patients show nearly 10% hippocampal volume increases after 1.5 to 2 years /11,60, 146/ and improvement in function /147/. In patients with MDD, hippocampal volume is negatively correlated with symptom severity /137/. Antidepressant treatment can prevent or restore hippocampal volume loss because MDD individuals on long-term antidepressants show no significant differences in hippocampal volume compared to controls /138/. In Vietnam veterans with PTSD, smaller hippocampal volumes correlate with longer combat exposure / 54,158/. Similarly, PTSD patients exposed to childhood sexual abuse or other trauma show smaller hippocampal volumes that are correlated with symptom severity /149,161/, demonstrating that these characteristics of PTSD extend to non-combat exposure. These findings are consistent with the animal literature showing that chronic antidepressant treatment increases neurogenesis /84/ and triggers synapse formation in hippocampal neurons /55/. It should be noted that some reports fail to find reduced hippocampal volumes in PTSD patients / 9,107,133/, but a meta-analysis of 23 published studies on PTSD confirms that hippocampus volumetric differences covary with PTSD severity /65/. Importantly, antidepressant treatment can increase hippocampal volumes in PTSD patients /10,159/. In all conditions, the hippocampus is particularly vulnerable to volumetric changes, as many other brain regions are unaffected /15,54,61/. Taken together, the reversibility of hippocampal volume in all of these conditions suggests that neuron loss may be less important /32,79,152/, than other processes that may include changes in glial cells, connections and spine formation /93/, which are consistent with altered dendritic structure and are capable of plasticity. Consequently, hippocampal dendritic retraction produced by chronic stress in rodents and reduced hippocampal volumes observed in Cushing's disease, MDD, and PTSD are dynamic and have the capacity to recover.

Another important consideration is that individuals with Cushing's disease, MDD and PTSD show HPA axis disruption. For Cushing's disease and MDD, glucocorticoid levels correspond to symptom severity, such as mood /18,68/, changes in hippocampal volume /18,145/, and disturbance in hippocampal-dependent cognition /18,51,53,145/. Resolving the hypersecretion of glucocorticoids can improve symptoms /86,144,147/. Some have even suggested that antiglucocorticoid therapy may be a useful treatment for MDD /114/. Unlike Cushing's disease and MDD, individuals with PTSD are often characterized with a hyporesponsive HPA axis / 172/, which may be an important symptom in the immediate aftermath of the trauma for developing PTSD /173/, and suggests that correcting the subthreshold glucocorticoid levels

may reduce the possibility of developing PTSD. A paradox is that glucocorticoids appear to be problematic when they are either too high (Cushing's disease or MDD) or too low (PTSD), but only high levels of glucocorticoids are traditionally thought to reduce hippocampal volumes. Also, studies on MDD typically find negative correlations with hippocampal volume and glucocorticoid levels, suggesting that low glucocorticoid levels are optimal for large hippocampal volume. However, a recent study on aged individuals with MDD reveals that hypo- and hyper-secretion of glucocorticoids can reduce hippocampal volumes /12/. Moreover, the animal literature shows that reduced glucocorticoids via adrenalectomy causes neural degeneration within the hippocampal dentate gyrus, /22–24,140/, which can be detected by volumetric measures /23/. Consequently, glucocorticoids can reduce hippocampal volume and plasticity when their levels are either too high or low. The overall message is that the effect of glucocorticoids on hippocampal size in these psychiatric conditions is described by an inverted U-shaped function, emphasizing the importance of regulating glucocorticoids at moderate levels so that extremes of glucocorticoid secretion are minimized.

Taken together, these findings show that patients with Cushing's disease, MDD, or PTSD exhibit a small hippocampus and dysregulated HPA axis, and these conditions are consistent with hippocampal dendritic retraction following chronic stress in rodents. If the conditions that apply to hippocampal susceptibility following chronic stress in rodents are extended to individuals with Cushing's disease, MDD, and PTSD, then the data suggest that the hippocampus of these untreated individuals is primed for susceptibility to permanent damage.

Metabolic events may be problematic when compounded with Cushing's disease, MDD, PTSD, or even a history of chronic stress. Metabolic events can include, for example, small blocked vessels or restricted blood flow, and/or low sugar or oxygen levels. While these may seem like ailments of older individuals, the demographics of the typical American suggest that young adults and children are also at risk. The average American is heavier than ever, with over half of adults considered to be overweight and nearly one-third obese /44/; children show obesity trends as well /99/. Health risks associated with obesity include arteriosclerosis and Type II diabetes, which contribute to restricted blood flow and blood sugar imbalance, respectively. Both types of risks reflect metabolic challenges that damage the brain and compromise function. Indeed, heart transplant patients show increased risk for hippocampal atrophy /168/, emphasizing that the hippocampus is susceptible to restricted blood flow. Some metabolic events may be innocuous in isolation, without necessarily causing noticeable brain damage. could be problematic in a susceptible individual. Specifically, subthreshold metabolic events that are benign to the hippocampus of a healthy individual may be harmful to people with Cushing's disease, MDD, PTSD or a history of chronic stress because these latter individuals exhibit a vulnerable hippocampus that may be less able to respond effectively to an anomalous metabolic challenge. Moreover, these individuals are potentially vulnerable for an extended period because hippocampal plasticity can be compromised for weeks, months, or even years. The longer a hippocampus is compromised, the higher the probability that a metabolic event will occur, and the end result may be permanent hippocampal cell loss and an inability to recover, despite antiglucocorticoid or antidepressant treatment. In summary, a metabolic challenge in isolation may be innocuous to the healthy hippocampus, but with a history chronic stress or predisposition to Cushing's Disease, MDD, or PTSD, the brain and hippocampus in particular may be less resilient.

Despite the potential for individuals with Cushing's disease, MDD, and PTSD to have increased susceptibility for irreparable damage to the hippocampus, there are many possibilities for intervention and prevention. As already described, antidepressants have positive effects on mood and hippocampal volume in MDD /138/ and PTSD /16/. While some studies suggest that small hippocampal volume may reflect predisposition to develop MDD /61/ and PTSD /71,174/, the finding that both respond to treatment shows that hippocampal plasticity is possible

regardless of whether or not hippocampal volume is a cause or a consequence. Diet may also be an important contributing variable, as obese individuals typically consume high fat foods, which has been linked to many of the potentially detrimental events that can cause hippocampal damage. In the animal literature, a history of a high fat diet exacerbates stress-induced hippocampal dendritic retraction /6/ and impairs hippocampal function /50,64/. Reducing fat intake and eating healthy foods may reduce the risk of hippocampal vulnerability. Finally, the theory of Cognitive Reserve is used to explain the finding that individuals with more mental activity develop better, more elaborate neuronal connections that can withstand a greater amount of pathological damage before succumbing to disease /66,151/. Individuals engaging in intellectually-stimulating activities throughout their lives maintain their cognitive abilities when others begin to show cognitive decline /1,132,139/. In the animal literature, housing rats in enriched environments to provide opportunities for social interactions, exercise, and novel visual stimulation prevents the detrimental effects of chronic stress on hippocampal function /171/, and studies are underway to investigate the neurobiological substrates underlying this effect.

Taken together, compelling findings suggest that a small hippocampus may confer susceptibility to potential damage, without necessarily reflecting neuronal loss. A small hippocampus may have altered neuronal morphology, which is dynamic and reversible, as emphasized by responding to treatments and interventions that include antidepressant therapy, diet, and cognitive challenges. The problem is that the probability for permanent neuronal damage within the hippocampus is increased because this vulnerable period can extend over weeks, months, or years. This interval during which the hippocampus is susceptible provides an opportunistic window for a seemingly minor, innocuous metabolic event to cause permanent harm in a small “compromised” hippocampus. On the other hand, some individuals may recover without incident because the vulnerable period may not have coincided with a metabolic challenge. Consequently, a lack of consistent findings in the literature regarding hippocampal cell death and aging may be more indicative of a small hippocampal volume conveying susceptibility to damage rather than neuronal loss.

Key Words

CA, Cornu Ammonis; DSM IV, Diagnostic and Statistical Manual of Mental Disorders Fourth Version; GAS, General Adaptation Syndrome; GR, Glucocorticoid Receptor; HPA, Hypothalamic-Pituitary-Adrenal; IBO, Ibotenic Acid; MDD, Major Depressive Disorder; MR, Mineralocorticoid Receptor; PTSD, Post Traumatic Stress Disorder; SNS, Sympathetic Nervous System.

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