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What Is the Functional Significance of Chronic Stress-Induced CA3 Dendritic Retraction Within the Hippocampus?

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Abstract

Chronic stress produces consistent and reversible changes within the dendritic arbors of CA3 hippocampal neurons, characterized by decreased dendritic length and reduced branch number. This chronic stress-induced dendritic retraction has traditionally corresponded to hippocampus-dependent spatial memory deficits. However, anomalous findings have raised doubts as to whether a CA3 dendritic retraction is sufficient to compromise hippocampal function. The purpose of this review is to outline the mechanism underlying chronic stress-induced CA3 dendritic retraction and to explain why CA3 dendritic retraction has been thought to mediate spatial memory. The anomalous findings provide support for a modified hypothesis, in which chronic stress is proposed to induce CA3 dendritic retraction, which then disrupts hypothalamic-pituitary-adrenal axis activity, leading to dysregulated glucocorticoid release. The combination of hippocampal CA3 dendritic retraction and elevated glucocorticoid release contributes to impaired spatial memory. These findings are presented in the context of clinical conditions associated with elevated glucocorticoids.

Keywords

hippocampus; spatial memory; brain plasticity; chronic stress

Chronic stress has been proposed to compromise the hippocampus, a region in the brain important for memory processing (Eichenbaum, 1997; O'Keefe & Nadel, 1978). Chronic exposure to stress steroids, glucocorticoids (GCs), was originally hypothesized to make hippocampal neurons vulnerable so that excessive GC exposure over a life span would eventually kill neurons (Sapolsky, 1992; Sapolsky, Krey, & McEwen, 1986). Early studies showed that GCs secreted in response to chronic stress or administered exogenously might kill neurons within the hippocampus (de Leon et al., 1988; Kerr, Campbell, Applegate, Brodich, & Landfield, 1991; Landfield, Waymire, & Lynch, 1978; Sapolsky, Krey, & McEwen, 1985; Uno et al., 1994; Uno, Tarara, Else, Suleman, & Sapolsky, 1989) and hypothalamus (Aus Der Mühlen & Ockenfels, 1969). Although GC attenuation reduced this hippocampal damage (Landfield, Baskin, & Pitler, 1981), complete GC removal via adrenalectomy destroyed another region of the hippocampus, the dentate gyrus (Conrad & Roy, 1993, 1995; Sloviter et al., 1989), demonstrating that GC tone must be balanced. However, some studies showed inconsistencies in whether chronic stress and GCs killed hippocampal neurons, even under conditions in which GC dose and duration were similar (cell death/pyknosis observed: Arbel, Kadar, Silbermann, & Levy, 1994; Clark, Mitre, & Brinck-Johnsen, 1995; Dachir, Kadar, Robinson, & Levy, 1993; Mizoguchi, Kunishita, Chui, & Tabira, 1992; Sapolsky, Uno, Rebert, & Finch, 1990; cell death not observed: Bardgett, Taylor, Csernansky, Newcomer, & Nock, 1994; Bodnoff et al., 1995; Leverenz et al., 1999; Sousa, Madeira, & Paula-Barbosa, 1998;

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Vollmann-Honsdorf, Flügge, & Fuchs, 1997). Later, it was determined that in some species, such as the tree shrew and the aged primate, the hippocampus failed to show consistent cell death with chronic stress, GCs, or aging (Fuchs et al., 2001; Leverenz et al., 1999; Vollmann-Honsdorf et al., 1997). Moreover, GCs bind to two receptors, the mineralocorticoid (MR) and glucocorticoid receptor (GR), and the primate hippocampus has much fewer GRs than typically observed in the rodent hippocampus (Jacobson & Sapolsky, 1991; Mar Sanchez, Young, Plotsky, & Insel, 2000), suggesting that the mechanism of stress-induced cell death in the hippocampus may differ between primates and rodents (see Belanoff, Gross, Yager, & Schatzberg, 2001).

Unlike hippocampal cell loss, dendritic retraction of hippocampal neurons in response to chronic stress is expressed in several species and can be reversed. Chronic stress produces dendritic retraction within the hippocampus in rats (Watanabe, Gould, Cameron, Daniels, & McEwen, 1992; Watanabe, Gould, Daniels, Cameron, & McEwen, 1992; Watanabe, Gould, & McEwen, 1992) and tree shrews (Magariños, McEwen, Flügge, & Fuchs, 1996) and returns to control levels within 10 days after the termination of chronic stress (Conrad, Magariños, LeDoux, & McEwen, 1999). For this reason, many have referred to dendritic retraction as “remodeling.” Dendritic retraction may be a compensatory response to chronic stress that goes unnoticed during uneventful periods because it recovers shortly after stress ceases. However, hippocampal neurons expressing dendritic retraction may be vulnerable to other life events that occur at the same time. For example, rats that were chronically stressed by restraint to produce dendritic retraction within the hippocampal CA3 region show exacerbated hippocampal cell death following a neurotoxin challenge compared to non-stressed controls (Conrad, Jackson, & Wise, 2004). This may explain why the hippocampus is vulnerable to damage when chronic stress precedes or coincides with other conditions, such as AIDS (Oberfield et al., 1994), obesity (Raber, 1998), depression (Sheline, Wang, Gado, Csernansky, & Vannier, 1996), and Alzheimer’s disease (de Leon et al., 1993). These studies suggest that chronic stress and GCs contribute to but are not the sole determinant for hippocampal cell death in rodents and humans (see Sapolsky, 2000b). In human conditions that hypersecrete GCs, such as depression (Sheline et al., 1996), Cushing’s disease (Starkman, Gebarski, Berent, & Schteingart, 1992), and in a subset of aged individuals (Lupien et al., 1998), hippocampal volumes are reduced (Sheline et al., 1996; Starkman et al., 1992). Treatment with antidepressants can protect against hippocampal volume loss in depression (Sheline, Gado, & Kraemer, 2003), and attenuating GC elevations can help increase hippocampal volumes in Cushing’s disease (Starkman et al., 1999). Thus, chronic stress-induced hippocampal dendritic retraction in rodents is a useful model for understanding the dynamics between chronic stress/GC exposure and the hippocampus in humans.

The purpose of this review is to discuss the relevance of studying structural changes to the dendritic arbors of neurons, delineate the functional significance of chronic stress-induced changes in hippocampal neurons, and propose a mechanism by which chronic stress influences hippocampal function.

CHRONIC STRESS AND THE MECHANISM OF HIPPOCAMPAL CA3 DENDRITIC RETRACTION

A stress response allows organisms to respond appropriately to a continually changing environment. Many diverse species have a stress response, emphasizing that this mechanism is conserved and integral for survival. The stress response includes the release of epinephrine (adrenaline) through the sympathetic nervous system, which Walter Cannon (1871–1945) described as mediating the flight-or-fight response to escape or face a threat. This system redistributes energy resources to tissues that need them (skeletal muscles, heart) from those functions that can be temporarily delayed (digestive and reproductive systems). The stress

response also includes the hypothalamic-pituitary-adrenal (HPA) axis. The hypothalamus releases corticotrophin-releasing hormone and arginine vasopressin into a local hypophyseal portal blood system, which stimulates the anterior pituitary to release adrenocorticotropin hormone (ACTH) into the general blood supply. ACTH triggers the adrenal gland to release GCs, which include corticosterone in rats and mice and cortisol in humans and primates. GCs complement the sympathetic nervous system response by mobilizing energy stores to provide energy substrates within the blood, in addition to many other actions that include inhibiting inflammatory responses. These events necessitate that GCs be tightly regulated by inhibitory feedback mechanisms at the hypothalamus and pituitary, as well as at higher cognitive neural structures (for review, see Herman, Figueiredo, et al., 2003).

Chronically activating the stress response can produce maladaptive changes, which have been postulated to contribute to disease (for review, see de Kloet, Joels, & Holsboer, 2005; McEwen & Wingfield, 2003; Smith, 1996). A transition into maladaptive changes includes dendritic remodeling, which can be produced under a variety of chronic stress conditions: 6 hours of daily restraint in wire mesh for 21 days (Watanabe, Gould, Cameron, et al., 1992; Watanabe, Gould, Daniels, et al., 1992; Watanabe, Gould, & McEwen, 1992), daily predator stress combined with a high-fat diet for 21 days (Baran et al., 2005), social defeat stress every other day for 21 days (Kole, Costoli, Koolhaas, & Fuchs, 2004), continual social stress and competition for resources over 14 days (McKittrick et al., 2000), 2 hours in bag restraints daily for 10 days (Vyas, Mitra, Rao, & Chattarji, 2002), and daily activity stress combined with food restriction over 6 days (Lambert et al., 1998). Although chronic stress predominately reduces dendritic arbors in CA3 neurons, dendritic retraction has been observed in other brain regions. When chronic unpredictable stress continues for 4 weeks, CA1 and dentate gyrus neurons express dendritic retraction (Sousa, Lukoyanov, Madeira, Almeida, & Paula-Barbosa, 2000). In addition, CA3 and CA1 dendritic retraction occurs in as little as 6 days following activity stress combined with food restriction (Lambert et al., 1998). Prefrontal cortical neurons also express dendritic retraction following 3 hours of restraint for 1 to 3 weeks (S. M. Brown, Henning, & Wellman, 2005; Radley et al., 2004). Chronic stress-induced CA3 dendritic remodeling has been proposed to be a maladaptive response because it is associated with susceptibility to damage and cognitive dysfunction (discussed later). However, another interpretation is that CA3 dendritic remodeling may be a compensatory response to protect against extended excitatory amino acid stimulation, which can compromise and kill neurons.

The mechanism underlying stress-induced CA3 dendritic retraction is illustrated in Figure 1 and is discussed in other reviews (McEwen, Magarinos, & Reagan, 2002; Smith, 1996). GCs acting through the GR mediate stress-induced CA3 dendritic retraction. Chronic administration of stress levels of GCs produces CA3 dendritic retraction (Magariños, Orchinik, & McEwen, 1998; Woolley, Gould, & McEwen, 1990), and GC attenuation with cyanoketone blocks CA3 dendritic retraction (Magariños & McEwen, 1995b). These studies indicate that corticosterone, rather than other hormones of the HPA axis or enhanced activity of the sympathetic nervous system, mediates CA3 dendritic retraction.

Excitatory amino acid release influences stress-induced CA3 dendritic retraction. Phenytoin (Dilantin), an antiepileptic that interferes with excitatory amino acid release and action (Crowder & Bradford, 1987; Griffith & Taylor, 1988; Skerritt & Johnston, 1983), prevents stress-induced CA3 dendritic retraction (Magariños et al., 1996; Watanabe, Gould, Cameron, et al., 1992). These data are consistent with stress-enhancing glutamate release (Gilad, Gilad, Wyatt, & Tizabi, 1990; Lowy, Gault, & Yamamoto, 1993) and up-regulating glutamate transporter expression within glia of the CA3 region (Reagan et al., 2004).

Selective changes in regions showing dendritic remodeling may help identify glutaminergic afferents contributing to CA3 dendritic plasticity following chronic stress because

glutamatergic afferents are topographically organized. The mossy fibers from the dentate gyrus granule cells form synapses on excrescences, postsynaptic structures located proximal to the CA3 soma (T. H. Brown & Zador, 1990; Martinez & Barea-Rodriguez, 1997). Afferents located distally from the CA3 soma form synapses on “spines” and include the commissural fibers from the contralateral hippocampus, recurrent axon collaterals from CA3 neurons, and the perforant path from the entorhinal cortex (T. H. Brown & Zador, 1990; Martinez & Barea-Rodriguez, 1997; Witter & Amaral, 2004). Chronic stress produces drastic remodeling within the middle part of the apical CA3 dendritic tree (Kole et al., 2004), which corresponds to the region expressing chronic stress-induced changes in the N-methyl-D-aspartate (NMDA) glutamatergic receptor sensitivity (Kole, Swan, & Fuchs, 2002). Consequently, these two studies implicate the commissural-associational collaterals as contributing to CA3 dendritic retraction. Another study showed that entorhinal cortical lesions, which project to the distal portions of the apical CA3 region, protect against CA3 dendritic retraction following chronic stress (Sunanda, Meti, & Raju, 1997). Moreover, dendritic retraction typically occurs on the CA3 apical region, not the CA3 basal tree (Conrad et al., 1999; Magariños et al., 1996; Magariños & McEwen, 1995a; McKittrick et al., 2000), and the former region receives the majority of mossy fiber inputs from the dentate gyrus, indicating that selective damage to the dentate may also prevent stress-induced CA3 dendritic remodeling. Dendritic retraction has been observed in both the apical and basal regions, but this robust dendritic retraction typically occurs under extreme conditions that combine chronic restraint with food restriction (Kleen, Sitomer, Killeen, & Conrad, in press) or ovariectomy in females (McLaughlin, Baran, Wright, & Conrad, 2005). Finally, chronic stress-induced decreases in CA3 dendritic complexity occur in conjunction with increased density of both excrescences and spines (Sunanda, Rao, & Raju, 1995), implicating compensatory mechanisms of both mossy fiber and nonmossy fiber afferents. Altogether, these studies indicate that chronic stress interacts synergistically with a variety of glutamatergic afferents to remodel CA3 dendritic morphology.

Serotonin may be implicated in CA3 dendritic retraction. Chronic stress increases brain serotonergic levels (Chaouloff, 1993) and down-regulates the transporters that remove serotonin from the synapse, a process that can enhance extracellular serotonin (McKittrick et al., 2000). Reducing extracellular serotonin by enhancing its uptake with tianeptine prevents stress-induced CA3 dendritic retraction (see Figure 2; Conrad et al., 1999; Magariños, Deslandes, & McEwen, 1999; Watanabe, Gould, Daniels, et al., 1992). Antidepressants that enhance serotonin, such as fluoxetine, fail to alter stress-induced CA3 dendritic retraction (Magariños et al., 1999). However, recent studies suggest that tianeptine may prevent CA3 dendritic retraction through actions on the glutamatergic system (Fuchs, Czeh, Kole, Michaelis, & Lucassen, 2004; McEwen & Chattarji, 2004), which includes altering NMDA receptor sensitivity (Kole et al., 2002) and changed expression of glutamate transporter within glial cells (Reagan et al., 2004). These studies show that enhanced serotonergic tone, or perhaps actions on the glutamatergic system, contributes to chronic stress-induced CA3 dendritic retraction.

Enhancing the inhibitory tone may also attenuate stress-induced CA3 dendritic retraction. The majority of interneurons within the hippocampus are inhibitory (Feldblum, Erlander, & Tobin, 1993; Woodson, Nitecka, & Ben-Ari, 1989), and activating gamma-aminobutyric acid (GABA)_A receptors with adinazolam, a benzodiazepine agonist, block CA3 dendritic retraction caused by chronic stress (Magariños et al., 1999). Paradoxically, chronic stress enhances GABAergic systems (Bowers, Cullinan, & Herman, 1998; Qin, Karst, & Joels, 2004), but these effects may be region specific. For example, GABA can be altered within the interneurons of the dentate gyrus without changing GABA in other hippocampal regions (Herman, Renda, & Bodie, 2003). This latter finding supports the interpretation that altered inhibitory tone is not uniform and that region-specific effects may disrupt overall inhibitory tone.

Neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), neurotrophin (NT)-3, and NT-4, can also contribute to hippocampal dendritic plasticity. Postsynaptic neurons release neurotrophic factors, which are retrogradely transported to the nucleus of the presynaptic neuron to influence gene expression (Smith, 1996). The hippocampus expresses the highest levels of BDNF mRNA in the brain (Hofer, Pagliusi, Hohn, Leibrock, & Barde, 1990), and BDNF promotes neuronal connectivity (Klintsova & Greenough, 1999; Lewin & Barde, 1996), especially dendritic differentiation and complexity in nonpyramidal interneurons of the hippocampus (Marty et al., 1996; Vicario-Abejon, Collin, McKay, & Segal, 1998), neocortex (Jin, Hu, Mathers, & Agmon, 2003), striatum (Ventimiglia, Mather, Jones, & Lindsay, 1995), and cerebellum (Mertz, Koscheck, & Schilling, 2000). Indeed, GABAergic influence is facilitated by BDNF and prevented by BDNF inhibitors (Jin et al., 2003). Although chronic stress also enhances GABAergic systems (Bowers et al., 1998), stress or isolation down-regulates BDNF (Scaccianoce et al., 2006) and up-regulates NGF and NT-3 (Smith, Makino, Kvetnansky, & Post, 1995). The effects of stress on NGF and NT-3 are proposed to be compensatory mechanisms (Smith, 1996). Overall, many of the changes produced by BDNF are opposite those produced by glutamate and chronic stress (Smith, 1996).

To demonstrate that many pharmacological manipulations do not act as antiglucocorticoids, other parameters of chronic stress perception are measured to demonstrate that drug actions work downstream from GC release. Chronic stress commonly decreases the weights of the thymus (Bhatnagar & Meaney, 1995; McKittrick et al., 2000) and gonads (Galea et al., 1997) and the rate of body weight gain (Conrad, Mauldin-Jourdain, & Hobbs, 2001; Galea et al., 1997; McKittrick et al., 2000; Watanabe, Gould, Daniels, et al., 1992; Watanabe, Gould, & McEwen, 1992; Wright & Conrad, 2005) while increasing the weight of the adrenals (McKittrick et al., 2000; Watanabe, Gould, Daniels, et al., 1992; Watanabe, Gould, & McEwen, 1992). On some occasions, chronic stress fails to alter the weight of a given target, but the rate of body weight gain tends to be highly reliable (as examples, see Magariños & McEwen, 1995a, 1995b; Vyas et al., 2002). In general, measures from several targets are helpful in demonstrating that the subjects perceive the procedure as stressful.

FUNCTIONAL SIGNIFICANCE OF DENDRITIC COMPLEXITY IN OTHER MODELS

Structural changes in neuron connections are believed to be important components underlying brain plasticity. At the microscopic level, Ramon y Cajal (1852–1934; see Ramon y Cajal, 1988) suggested that protrusions on dendrites, or spines, are involved with mental activity. Hebb (1949) later proposed that synapse dynamics underlie brain plasticity, such as memory formation (for discussion on Hebbian synapses, see Cruikshank & Weinberger, 1996; Martinez & Barea-Rodriguez, 1997). With the average neuron receiving about 10,000 to 30,000 synapses (Malenka & Nicoll, 1999), a reasonable assumption is that macroscopic alterations in dendritic arbors would profoundly influence brain plasticity. Indeed, synaptic input correlates with dendritic geometry (Purves & Lichtman, 1985; Rall, 1964; see Figure 3), and the structure of the dendritic tree affects neuronal firing properties (Mainen & Sejnowski, 1996; Schaefer, Larkum, Sakmann, & Roth, 2003). But the changes in spine shape and number can be independent of dendritic complexity and vice versa (see Fiala, Spacek, & Harris, 2002; Kolb, Forgie, Gibb, Gorny, & Rowntree, 1998). Moreover, dendritic arbors can change appreciably over several weeks within the adult brain (Purves & Hadley, 1985). Enhanced morphological complexity within neurons of the frontal lobes is proposed to contribute to the higher cognitive functions observed in humans (Martinez & Barea-Rodriguez, 1997; see Figure 4). Hebb (1949) noted that rats raised at home performed better on mazes than did rats raised in the laboratory. Many studies have since shown that deprived conditions (Globus & Scheibel, 1967), deafferentation (Deitch & Rubel, 1984; Flores et al., 2005; Nutan & Meti, 1998; Works,

Wilson, & Wellman, 2004), some clinical pathologies, and immune dysfunction (Grossman et al., 2003; Sakic et al., 1998) reduce dendritic arbors. In contrast, extensive training (Chang & Greenough, 1982; Nutan & Meti, 2000; Schallert, Kozłowski, Humm, & Cooke, 1997) or environmental enrichment (Camel, Withers, & Greenough, 1986; Faherty, Kerley, & Smeyne, 2003; Greenough & Volkmar, 1973; Kolb et al., 1998; Volkmar & Greenough, 1972) increase dendritic complexity. Additional studies have empirically confirmed that animals raised in enriched environments have measurable changes in the brain and show improved learning in a variety of mazes (see Rosenzweig & Bennett, 1996). These studies demonstrate that many manipulations can alter dendritic complexity, which can influence function.

Parallels between function and dendritic complexity have been observed in many systems, with a few briefly described here. In some avian species, such as the canary, song production and brain regions devoted to song production undergo dynamic seasonal changes (Nottebohm, 1981). Selective brain regions regularly shrink in size during the winter season with concurrent loss of song function and then are restored with song function when mating season returns. Subsequent studies showed that testosterone enhances the dendritic length and number of branch points of these neurons (DeVoogd & Nottebohm, 1981), which correspond to singing ability. Hibernation is a natural model of sustained brain inactivity (Heller, 1979), and the CA3 dendritic arbors show extensive remodeling between hibernation and the active period. Hibernation reduces dendritic arbors and spines to nearly 50% of the complexity observed in active ground squirrels (Popov, Bocharova, & Bragin, 1992; see Figure 5). Most astonishingly, detectable changes in CA3 remodeling occur within 2 hours of waking from torpor (Popov et al., 1992). This ability of dendritic arbors to change rapidly is consistent across several models. Dendritic changes occur within 2 hours after afferent lesion (Deitch & Rubel, 1984), 4 days following enriched environment exposure (Black, Jones, Nelson, & Greenough, 1998), and 10 days following chronic stress termination (Conrad et al., 1999). Regarding functional outcomes, ground squirrels show the best hippocampus-dependent contextual conditioning at 24 hours after waking when hippocampal dendritic arbors are differentiated compared to ground squirrels tested within a few hours of waking (Weltzin, Zhao, Drew, & Bucci, 2006). Moreover, squirrels that experienced hibernation take longer to navigate a spatial maze compared to squirrels that were prevented from hibernating (Millesi, Prossinger, Dittami, & Fieder, 2001). In mice, short photoperiods that typically coincide with metabolic conservation and the nonbreeding season decrease hippocampal volume and impair spatial learning (Perrot-Sinal, Kavaliers, & Ossenkopp, 1998; Pyter, Reader, & Nelson, 2005). Moreover, photoperiod does not alter nonspatial learning nor the volume of the cortex surrounding the hippocampus (Pyter et al., 2005). Thus, the seasonal changes appear to be selective for alterations in hippocampal morphology and function, with smaller dendritic complexity impairing hippocampal function.

DOES STRESS-INDUCED CA3 DENDRITIC RETRACTION PRODUCE SPATIAL LEARNING AND MEMORY DEFICITS? THE USE OF THE Y-MAZE AND GENERAL FINDINGS OF THE 1990s

My research program has investigated the significance of stress-induced CA3 dendritic retraction for hippocampal function. Given the preponderance of studies showing that enhanced neuronal complexity is associated with improved cognitive functioning, we hypothesized that reduced neuronal complexity in CA3 neurons following chronic stress would be associated with poor hippocampal function. The hippocampus is an integral part of spatial memory processing, whereby multiple cues are used to navigate within an environment (Eichenbaum, Schoenbaum, Young, & Bunsey, 1996; O'Keefe & Nadel, 1978). Damage to the hippocampus impairs the ability of rats to use multiple cues located outside a maze to navigate. In contrast, rats with hippocampal lesions readily locate the goal when it is visible

or when the start and goal locations are held constant. These studies show that hippocampal damage impairs place or spatial learning (complex representations) but spares response or simple associative learning. Thus, we specifically hypothesized that stress-induced CA3 dendritic retraction impairs spatial learning and memory.

To assess the functional consequences of chronic stress-induced CA3 dendritic retraction, we selected a Y-maze task as described by Dellu, Mayo, Cherkaoui, Moal, and Simon (1992). The Y-maze consists of three equilaterally intersecting Plexiglas arms with spatial cues positioned outside the maze. Rats are placed in the Y-maze with one of the arms blocked to prevent access, allowing the rats to explore the remaining two arms. After the rats have explored the two arms for 15 minutes, they are removed from the maze and returned to their home cages. During this intertrial interval, the maze is rotated and the bedding on the floor of the maze is mixed to reduce the use of olfactory cues within the maze, which can facilitate navigation without using the hippocampus. After a delay of 4 hours, rats are reintroduced to the spatial location where they were placed in the first trial and allowed to explore all three arms for 5 minutes. Rats with functional spatial memory will enter the arm located in the unexplored spatial location more, relative to the arms in locations that they had already visited in the initial trial, whereas rats with impaired spatial memory will enter the previously explored and unexplored arms similarly (Conrad, Galea, Kuroda, & McEwen, 1996; see Figure 6).

Although the Y-maze has its advantages and disadvantages, we believe that the advantages outweigh the disadvantages when studying the effects of chronic stress on spatial memory. First, spatial memory must be determined relatively quickly because CA3 dendritic arborization is dynamic, and the dendritic arbors can return to their prestress condition within 10 days after the termination of the chronic stressor (Conrad et al., 1999). In this regard, the Y-maze task can be used to train the rat in one trial, and spatial recognition memory can be determined one trial later, usually within several hours. Second, motivating rats to perform on the Y-maze does not require food restriction, which can be an added confound when investigating the effects of chronic stress on performance. Chronic stress decreases sucrose preference (Rygula et al., 2005) and bar-pressing rate for food at higher fixed ratio schedules (Kleen et al., in press). Moreover, food deprivation can increase circulating corticosterone levels (Broocks, Schweiger, & Pirke, 1990; Stewart, Meaney, Aitken, Jensen, & Kalanr, 1988). Third, the Y-maze is as not overtly stressful as other testing paradigms that involve foot shock (i.e., fear conditioning) or immersion in water (Morris water maze).

Potential disadvantages of the Y-maze are that chronic stress decreases motivation, which may influence the stressed rats' motivation to explore. However, we have found that chronic stress decreases food seeking, whereas Y-maze exploration is unaffected (Kleen et al., in press). Thus, motivation to seek food and sucrose may involve separate neurobiological constructs than those guiding Y-maze exploration. Nonetheless, care is taken to validate that motivation is similar among treatment groups. In the Y-maze, motivation to explore can be determined by comparing the total number of entries into all arms across groups. For example, nonstressed controls may make nine entries overall but show a preference for the novel arm by entering the novel arm six times and the remaining arms three times. In contrast, chronically stressed rats may make nine entries overall but fail to show an arm preference by entering each arm three times. In this example, motivation is suggested to be similar because rats made a similar number of entries even though arm preference differed. Related to this behavior, chronic stress enhances anxiety and produces neophobia, which may interfere with the goal of seeking out the novel arm in the Y-maze. However, rats must recognize the novel arm to avoid it. Nonetheless, some studies have observed that an animal exhibiting fear responses may show an increased alternation rate because it tries to avoid the arm from which it was previously picked up (Gerlai, 2001). Under these conditions, chronically stressed rats may show performance at chance levels to avoid the experimenter. This concern is addressed in several ways. First, animals are handled daily in

novel and familiar locations to expose them to novelty. Second, an investigator handling the rats is different from the investigator restraining the rats to reduce potential negative associations between the investigator and restraint process. Third, we have recently demonstrated that chronically stressed rats will perform well in the Y-maze by entering the novel arm more than the previously explored arm when the task demands are made easier by reducing the intertrial interval from 4 hours to 1 minute (Bellani, Luecken, & Conrad, 2006; Kleen et al., in press) and placing salient cues within the maze (Wright & Conrad, 2005), which is similar in principle to other paradigms that include intramaze cues (Ramos, 2000). Rats that attempt to avoid the novel arm or the investigator should exhibit poor performance regardless of the demands of the Y-maze. However, our findings demonstrate that chronically stressed rats will seek out the novel arm when the demands of the task reduce the reliance on the hippocampus. The Y-maze is probably successful for determining spatial memory in rats because the relatively narrow walls of the Y-maze (19 cm wide) enable rats to exhibit thigmotaxis, the preference to remain near walls and sides of a room. Thus, rats can explore and seek out novelty without interference from competing demands, such as avoiding open spaces that would trigger anxiogenic responses.

The hypothesis that chronic stress impairs spatial memory by remodeling CA3 dendritic arbors generated much support in the 1990s from behavioral paradigms that tested rats under conditions that produce or prevent CA3 dendritic retraction. Temporal time lines have supported the hypothesis that spatial memory is impaired under conditions that CA3 dendritic retraction exists. Six hours of daily restraint in wire mesh for 3 weeks impairs spatial learning and memory (Conrad et al., 1996; Luine, Villegas, Martinez, & McEwen, 1994; Sunanda, Rao, & Raju, 2000) under similar conditions that produce CA3 dendritic retraction (Magariños & McEwen, 1995a; Watanabe, Gould, & McEwen, 1992). However, 6 hours of daily chronic restraint for 7 or 14 days fails to impair spatial learning and memory (Luine, Martinez, Villegas, Magariños, & McEwen, 1996) and does not alter CA3 dendritic arbors (Luine et al., 1996). Moreover, rats that are allowed to recover from chronic stress for at least 10 days show functional spatial memory (Luine et al., 1994), which corresponds to the return of the CA3 dendritic remodeling to the prestress condition (Conrad et al., 1999; Vyas, Pillai, & Chattarji, 2004). Psychosocial stressors that produce CA3 dendritic retraction (Kole et al., 2004; McKittrick et al., 2000) show evidence of impairing spatial memory (Park, Campbell, & Diamond, 2001). Pharmacological interventions also provide compelling evidence that stress-induced CA3 dendritic retraction underlies spatial memory ability. Chronically stressed rats treated daily with tianeptine to prevent serotonin reuptake show functional spatial memory (Conrad et al., 1996; Luine et al., 1994), and a similar paradigm with tianeptine blocks stress-induced CA3 dendritic retraction (Magariños et al., 1999; Watanabe, Gould, Daniels, et al., 1992). Therefore, these studies generated support for the hypothesis that chronic stress remodels CA3 dendrites, which causes a subsequent impairment in spatial memory.

ANOMALOUS FINDINGS REGARDING STRESS-INDUCED CA3 DENDRITIC RETRACTION IMPAIRING SPATIAL MEMORY

Recently, exceptions have been observed whereby chronic stress and GC elevations produced CA3 dendritic retraction that failed to subsequently impair hippocampus-dependent memory. The anomalous findings included chronic corticosterone treatment, fear-conditioning paradigms, and studies with females.

Chronic corticosterone treatment produces anomalous findings in whether spatial memory is impaired. As described earlier, chronic stress-induced CA3 dendritic retraction is mediated by GCs, such as corticosterone: CA3 dendritic retraction is created by exposure to stress levels of corticosterone for 3 weeks (Magariños & McEwen, 1995b; Watanabe, Gould, Cameron, et al., 1992; Woolley et al., 1990) and prevented by blocking corticosterone secretion with

cyanoketone (Magariños & McEwen, 1995b). Thus, if hippocampal dendritic plasticity mediated hippocampal function, then GC-mediated CA3 dendritic retraction should produce spatial learning and memory deficits. However, the literature is mixed regarding chronic GC actions on spatial learning and memory; some studies show deficits (Arbel et al., 1994; Bardgett et al., 1994; Dachir et al., 1993; Endo, Nishimura, & Kimura, 1996; McLay, Freeman, & Zadina, 1998; Ramos-Remus, González-Castañeda, González-Perez, Luquin, & García-Estrada, 2002), others show improvements (Bardgett, Newcomer, & Taylor, 1996; Hebda-Bauer, Morano, & Therrien, 1999), and still others report no significant effects (Bardgett et al., 1996; Bodnoff et al., 1995; Clark et al., 1995; Hebda-Bauer et al., 1999; Krugers et al., 1997; Luine, Spencer, & McEwen, 1993). Some discrepancies may be resolved by the differential treatment protocols. Corticosterone administration beyond a month may compromise neurons and eventually lead to cell death (see Arbel et al., 1994). Other paradigms continue corticosterone treatment during behavioral assessment, which allow GCs to modulate memory through activational effects that are unrelated to dendritic retraction (see Conrad, 2005). Moreover, corticosterone dose and serum levels can greatly vary among studies. Nonetheless, some protocols replicate the conditions in which corticosterone treatment produces CA3 dendritic retraction (Watanabe, Gould, Cameron, et al., 1992; 40 mg/kg daily injections for 3 weeks) without altering spatial memory (Coburn-Litvak, Pothakos, Tata, McCloskey, & Anderson, 2003). Thus, corticosterone-induced CA3 dendritic retraction shows evidence of a disconnection from spatial memory.

In a second example, classical fear conditioning was used to determine whether chronic stress selectively impaired hippocampus-dependent memory compared to hippocampus-independent memory. Lesions to the hippocampus or its afferents attenuate contextual fear conditioning without disrupting cued fear conditioning (Bechara et al., 1995; Kim & Fanselow, 1992; Phillips & LeDoux, 1992, 1995). Thus, freezing to the environment is hippocampus dependent whereas freezing to tone is hippocampus independent. Hence, rats were chronically stressed by restraint (6 hours per day for 21 days) and then submitted to fear conditioning (Conrad et al., 1999). Mild foot shock was paired with a tone, and memory for this event was measured in the environment that was paired with the foot shock (hippocampus dependent) and with the tone (hippocampus independent). We found that chronic stress facilitates fear conditioning to both context and tone (Conrad et al., 1999). In addition, performance appears unrelated to hippocampal CA3 dendritic retraction because tianeptine treatment to prevent CA3 dendritic retraction fails to alter the facilitated fear conditioning of chronically stressed rats (Conrad et al., 1999). Compared to the nonstressed controls, the CA3 dendritic arbors in chronically stressed rats were confirmed to be less complex, an effect that was prevented by tianeptine (Conrad et al., 1999). This last finding was critical because it provided the first demonstration of a disconnection between CA3 dendritic retraction and hippocampal function within the same animals.

Finally, anomalies between structural changes in hippocampal dendritic arbors and spatial ability following chronic stress occur when the subjects are female. Chronic stress produces dendritic retraction in the CA3 region of both males and females but with sexual dimorphisms in the location of dendritic retraction. In males, chronic restraint stress remodels the apical arbors of the CA3 neurons, whereas in females, remodeling occurs in the basal region (Galea et al., 1997). A similar chronic restraint paradigm produces sexually dimorphic outcomes for spatial memory. In males, chronic stress impairs spatial memory, but in females, chronic stress produces temporal deficits on spatial navigation (Conrad, Grote, Hobbs, & Ferayorni, 2003), which may reflect alterations in novelty-seeking behavior as opposed to impaired spatial memory (Frye, 1995). For example, both chronically stressed males and females show impaired Y-maze performance within the 1st minute, but chronically stressed females recover in subsequent minutes, demonstrating that they are capable of using spatial memory to navigate (Conrad et al., 2003). This interpretation is supported by findings using other navigational

tasks, such as the radial arm maze, in which spatial abilities remain intact or are facilitated in females following the chronic restraint protocol (Bowman, Zrull, & Luine, 2001). In a recent study, we investigated the effects of chronic restraint stress on hippocampal morphology and spatial memory within ovariectomized female rats and found that chronically stressed female rats can express functional spatial memory despite robust CA3 dendritic retraction (McLaughlin et al., 2005). This latter study demonstrates that spatial memory can be disconnected from CA3 dendritic remodeling within the same subjects. The mechanism that allows chronically stressed female rats to maintain spatial memory navigation is beyond the scope of this review, but this topic has been discussed elsewhere (Bowman, Beck, & Luine, 2003; Luine, 2002). The main point here is that chronic stress-induced CA3 dendritic retraction does not always produce spatial memory deficits.

WHAT IS THE FUNCTIONAL SIGNIFICANCE OF STRESS-INDUCED CA3 DENDRITIC RETRACTION IN MALES?

Do these anomalous findings from chronic corticosterone treatment, fear-conditioning paradigms, and the use of females indicate that CA3 dendritic retraction lacks functional significance? On the contrary, chronic stress and the subsequent CA3 dendritic retraction is thought to indirectly impair spatial memory: Chronic stress is proposed to create CA3 dendritic retraction, which then disrupts HPA axis regulation and elevates GC levels, causing the impaired spatial memory observed from a compromised hippocampus (see Figure 7A, B). To support this hypothesis, the following must be demonstrated: (1) the hippocampus regulates HPA axis activity, (2) altered HPA axis activity influences spatial memory, (3) chronic stress disrupts HPA axis activity, and (4) manipulating the HPA axis following chronic stress alters spatial memory, which is independent of CA3 dendritic retraction.

The role of the hippocampus in regulating the HPA axis has been demonstrated in a variety of ways. Stimulating the hippocampus generally inhibits the HPA axis (Dunn & Orr, 1984; Mandel & Walter, 1963), and destroying part or all of the hippocampus or its efferents enhances HPA axis activity (Daniels, Jaffer, Engelbrecht, Russell, & Taljaard, 1990; Feldman & Conforti, 1980; Fischette, Komisaruk, Edinger, Feder, & Siegel, 1980; Herman et al., 1989; Sapolsky, Krey, & McEwen, 1984a; Wilson, Greer, & Roberts, 1980). These data indicate that the hippocampus participates in the regulation of the HPA axis through an inhibitory role (for review, see Herman, Figueiredo, et al., 2003).

Corticosteroids have long been known to influence cognition, including spatial memory. The limbic structures, especially the hippocampus, express the highest levels of receptors for GCs in both the rodent brain (McEwen, Weiss, & Schwartz, 1968, 1969) and primate brain when both receptor subtypes are included (Mar Sanchez et al., 2000), causing the hippocampus to be highly sensitive to GCs. Indeed, stress and GCs greatly influence the learning and memory processes that are mediated by the hippocampus (Bremner & Narayan, 1998; Conrad, 2005; Kim & Diamond, 2002; Luine, 1997). GCs influence spatial memory in a biphasic fashion, with low to moderate GC levels positively correlating with spatial memory and moderate to high GC levels negatively correlating with spatial memory (Conrad, 2005; Park, Campbell, Smith, Fleshner, & Diamond, in press; Yau, Olsson, Morris, Meaney, & Seckl, 1995). Moreover, GC actions can differ depending on the stage of memory processing (acquisition, consolidation, retrieval; Conrad, 2005; Conrad, Lupien, Thanasoulis, & McEwen, 1997; Oitzl & de Kloet, 1992) and the receptor subtype activated (Lupien & McEwen, 1997; Oitzl & de Kloet, 1992). Thus, the HPA axis clearly influences spatial memory in a complex, nonlinear fashion (see Figure 7A).

Chronic stress can produce numerous changes throughout the HPA axis, especially within the hippocampus, to disrupt HPA axis activity. The potential for chronic stress and GC

hypersecretion to disrupt the HPA axis has been extensively studied and reviewed (McEwen, 2001; Sapolsky, 1992, 1996, 2000a). Briefly, chronic stress and GCs down-regulate mRNA and protein for GC receptors within the hippocampus (Meyer, van Kampen, Isovich, Flügge, & Fuchs, 2001; Nishimura, Makino, Tanaka, Kaneda, & Hashimoto, 2004; Sapolsky, Krey, & McEwen, 1984b) and for corticotropin-releasing factor within the hypothalamus (Albeck, Hastings, & McEwen, 1994; Nishimura et al., 2004; Szot et al., 2004). These imbalances in GR and MR expression are proposed to alter the hippocampus regulation of the HPA axis (Dallman, 1993; de Kloet, 1991). Moreover, chronic stress reduces GABAergic input to hypothalamic neurons that participate in regulating the HPA axis (Verkuyl, Hemby, & Joels, 2004). Indeed, chronically stressed rats show an enhanced HPA axis response to novel stressors (Bhatnagar & Dallman, 1998; Harris et al., 2004) and increased sensitivity to an α_2 adrenergic receptor antagonist (Park et al., 2001), suggesting a sensitization of the sympathetic nervous system. These findings clearly demonstrate that chronic stress alters the HPA axis and the response to novel stressors.

Three of the four criteria have been satisfied by demonstrating that (a) the hippocampus regulates HPA axis activity, (b) altered HPA axis activity influences spatial memory, and (c) chronic stress disrupts HPA axis activity. For the last criterion, we recently reported that manipulating the HPA axis can restore spatial memory in chronically stressed rats (see model, Figure 7B). We followed a paradigm that reliably produces hippocampal CA3 dendritic retraction (Conrad et al., 1999; Magariños & McEwen, 1995a; Watanabe, Gould, & McEwen, 1992), whereby rats were chronically stressed by restraint for 6 hours/day for 21 days and then spatial memory was assessed using the Y-maze 1 day after chronic restraint ended (Wright, Lightner, Bellani, Harman, & Conrad, 2004; Wright et al., 2005; Wright, Lightner, Harman, Meijer, & Conrad, in press). On the day of Y-maze exposure, a subset of rats received a single injection of metyrapone to prevent stress levels of GCs from being released. We found that the highest dose of metyrapone (75 mg/kg) restored spatial memory ability in chronically stressed rats (see Figure 8A). Moreover, chronic stress increased the corticosterone response to the Y-maze (see Figure 8B) and down-regulated GR mRNA within the hippocampus, demonstrating that the HPA axis was dysregulated. A potential concern is that metyrapone could have influenced each stage of memory processing (acquisition, consolidation, retrieval), as well as motivational/motor abilities because metyrapone was given prior to training. However, total entries made during Y-maze exploration were similar among conditions, indicating that motivational differences were unlikely to have caused the improvement in Y-maze performance. Future studies will be performed to determine the stages of memory processing that are influenced by metyrapone treatment. Retrieval is a putative target because injecting metyrapone prior to retrieval restores spatial memory in rats with lesions to the CA3 region (Roozendaal, Phillips, et al., 2001). These studies show that altering the HPA axis can correct memory deficits in individuals with a hippocampus compromised by remodeled dendrites or even neuron loss.

If CA3 dendritic retraction produced by chronic stress alters the HPA axis to impair spatial memory, then why would CA3 dendritic retraction produced by chronic corticosterone treatment fail to impair spatial memory? The key is whether chronic corticosterone alters the HPA axis similarly as chronic stress because HPA axis dysregulation is proposed to be an important step linked to spatial memory ability. The key is whether chronic stress corticosterone alters HPA axis in a similar way as chronic stress, because HPA axis dysregulation is proposed to be an important step linked to spatial memory ability. There are differences in how chronic stress and corticosterone influence the HPA axis: The HPA axis is activated by chronic stress and inhibited by chronic corticosterone treatment. Consequently, chronically stressed rats typically have enlarged adrenals from the enhanced HPA axis demands (Kleen et al., in press; Magariños et al., 1998; Uno et al., 1989; Verkuyl et al., 2004; Watanabe, Gould, Cameron, et al., 1992; Watanabe, Gould, Daniels, et al., 1992), whereas chronic

corticosterone-treated rats show atrophied adrenals (Cerqueira et al., 2005; Coburn-Litvak et al., 2004; Magariños et al., 1998, 1999). Thus, a novel situation that mildly activates the HPA axis, such as testing on the Y-maze, can have dramatically different outcomes on spatial memory, which is sensitive to GC levels. GCs typically have an inverted U-shaped relationship with hippocampus-dependent memory (for review, see Conrad, 2005). However, a novel situation can trigger the enlarged adrenal, in chronically stressed rats, to secrete GCs at levels that typically impair memory, and the atrophied hippocampal dendrites may be less discriminating. Indeed, the HPA axis is proposed to be sensitive to a novel stressor following chronic stress (Dallman, 1993). In contrast, rats treated chronically with corticosterone may fail to exhibit an exaggerated GC response to a novel situation because their adrenals are atrophied. Rats that are injected daily with corticosterone (10, 20, or 40 mg/kg) for 21 days have a suppressed corticosterone response following the novel stress of forced swimming (Johnson, 2006). Hence, the attenuated or absent GC response in chronic corticosterone-treated rats may allow them to navigate in hippocampus-dependent spatial tasks (see Figure 7C).

INFLUENCE OF AMYGDALA ON COGNITIVE ABILITY FOLLOWING CHRONIC STRESS

Unlike the conditions surrounding spatial memory assessment using the Y-maze, the amygdala is recruited in highly emotional events, which affects performance. As already discussed, chronic stress is proposed to create CA3 dendritic retraction, which then disrupts HPA axis regulation. Then, during an emotionally arousing event, such as fear conditioning, HPA axis dysregulation feeds back onto the amygdalar neurons to enhance memory modulation (see Figure 9). Evidence has already been presented to support the interpretation that the HPA axis is regulated by the hippocampus and disrupted by chronic stress. Here, findings will be presented to show that (a) the amygdala is involved in highly aversive (emotional) events, (b) the amygdala is necessary for spatial ability in emotionally arousing conditions, and (c) HPA axis activity influences amygdalar and hippocampal function. Finally, a mechanism will be presented that outlines how chronic stress influences contextual fear conditioning.

Many reviews have reported that the amygdala is involved in highly aversive conditions and is considered part of the repertoire of emotional responses (Cahill, 2000; Cahill & McGaugh, 1996; LeDoux, 2000). Amygdalar lesion or inactivation prevents fear conditioning to both cue and context (Conrad, MacMillan, et al., 2004; Phillips & LeDoux, 1992). In contrast, hippocampal lesions impair contextual conditioning, but spare cue conditioning (Phillips & LeDoux, 1992). Thus, the amygdala is necessary for fear conditioning in general, and the hippocampus plays a more limited role in contextual conditioning.

Several studies show that the contribution of the amygdala can have a profound effect on hippocampus-dependent performance. When rats learn a stressful version of a water maze task, the amygdala is activated; rats that fail to learn the stressful version also fail to show activation of the amygdala (Akirav, Sandi, & Richter-Levin, 2001). In another study, amygdalar stimulation facilitates hippocampal long-term potentiation, which is a model of brain plasticity (Akirav & Richter-Levin, 1999). These studies show that hippocampus-dependent learning can be greatly facilitated by the contribution of the amygdala.

The HPA axis is instrumental in the modulation of hippocampus-dependent memory by the amygdala. The amygdala has a rich supply of GC receptors (Reul & de Kloet, 1986; Sarrieau et al., 1985; Waremboourg, 1975), indicating that GCs can directly influence the amygdala. Intra-amygdala infusions of GR agonists enhance passive avoidance, a hippocampus-dependent task that uses foot shock (Rozenendaal & McGaugh, 1997; Rozenendaal, Quirarte, & McGaugh, 2002). Moreover, disruption of the amygdala blocks memory facilitation from GR

agonists (Roozendaal, de Quervain, Ferry, Setlow, & McGaugh, 2001; Roozendaal & McGaugh, 1996).

Finally, chronic stress and the HPA axis alter the amygdala to influence fear conditioning. Although the majority of studies on chronic stress have focused on structural changes within the hippocampus, chronic stress has opposite effects in the basolateral nucleus of the amygdala (BLA), where it increases the dendritic complexity of neurons (Vyas et al., 2002, 2004). Moreover, chronic stress still produces hippocampal dendritic retraction in these animals, demonstrating that BLA hypertrophy is not a product of a unique rat strain or altered perception of the restraint procedure (Vyas et al., 2002). Hence, chronic stress enhances BLA dendritic arborization, which may make amygdalar neurons more sensitive to elevated GCs. During emotionally arousing situations, chronically stressed individuals secrete more GCs than controls do, and the hypertrophied BLA neurons contribute to facilitated memory, which may mask the memory impairment produced by the hippocampus that is typically observed under non-emotionally arousing conditions. Chronic stress has already been shown to facilitate hippocampus-dependent contextual conditioning under emotionally arousing conditions (Conrad et al., 1999). However, when corticosterone is attenuated during training of chronically stressed rats on fear conditioning, contextual conditioning is eliminated without abolishing tone conditioning (Conrad et al., 2001). A subsequent study demonstrated that the GR within the BLA is important in regulating contextual conditioning (Conrad, MacMillan, et al., 2004). These studies show that chronic stress facilitates memory under emotionally arousing situations and that reducing GC secretion during the emotionally arousing exposure will unmask the hippocampus-dependent memory deficit in chronically stressed subjects. Thus, in chronically stressed rats, the hypertrophied BLA is more sensitive to factors that modulate emotional memory, such as GCs.

CONCLUSION AND SIGNIFICANCE

In conclusion, chronic stress has many structural effects on the brain, which include dendritic remodeling within the hippocampus, amygdala, and even prefrontal cortex. In the hippocampus, neuronal dendritic retraction has indirect functional consequences on spatial memory: chronic stress-induced dendritic retraction disrupts the hippocampus from properly regulating the HPA axis, and this HPA axis dysregulation impairs spatial memory under benign conditions that are not emotionally arousing. Correcting the HPA axis hypersecretion can improve spatial memory despite CA3 dendritic retraction. Under emotionally arousing conditions, the amygdala becomes important. Chronic stress enhances dendritic complexity of amygdalar neurons, which may make these neurons more sensitive to memory modulation than nonstressed controls. In chronically stressed individuals, the dysregulated HPA axis and enhanced dendritic complexity within the amygdala may facilitate memory in highly aversive paradigms, including those that involve hippocampal function such as contextual fear conditioning.

Acute stress is thought to help maintain homeostasis, defined as the stability of physiological systems that sustain life (McEwen & Wingfield, 2003). For example, acute stress helps regulate blood glucose levels and body temperature through tightly controlled mechanisms. Allostasis is defined as achieving stability through change (McEwen & Wingfield, 2003). Thus, dendritic remodeling following chronic stress or GCs may be one mechanism that allows the hippocampus to maintain stability through change. Allostatic load refers to the toll on the body as it tries to reinstate homeostasis, and this toll may make individuals vulnerable to disease. For example, CA3 dendritic retraction may make individuals susceptible to spatial memory deficits and even cell damage following exposure to neurotoxins. These latter events may have life-threatening repercussions if memory is critical for locating food resources (in the former example) or if a metabolic challenge coincides with chronic stress. Other individuals may

experience stress-induced CA3 dendritic retraction uneventfully, and they will recover from chronic stress without any significant long-term ramifications of cognitive decline or cell loss.

Genetic predisposition and life events will greatly affect how individuals respond to chronic stress (for review, see de Kloet et al., 2005; see Figure 10). Individuals with genetic anomalies or exposure to unique life events may be more susceptible to the debilitating effects of chronic stress. Using a hypothetical genetic example, the underexpression of BDNF may make one more susceptible to stress-induced CA3 dendritic retraction than if BDNF levels were higher because neurotrophins appear to protect against neuronal damage. In terms of behavioral phenotype, rats that are characterized as high anxiety, based on a commonly used behavioral paradigm that determines emotionality in rodents, show spatial memory deficits following chronic stress compared to low-anxiety rats (Bellani et al., 2006). Regarding life choices, chronic stress combined with a high-fat diet produces robust CA3 dendritic retraction compared to either condition alone (Baran et al., 2005). Hence, highly anxious individuals who prefer high-fat, fast food may be prone to the effects of chronic stress compared to less anxious individuals who eat balanced meals. All of these studies demonstrate that genetics and life events influence susceptibility to chronic stress.

Many features of chronic stress on the brain, physiology, and behavior parallel those found in clinical conditions, such as major depression. Chronic stress produces hippocampal dendritic retraction in animal models, and hippocampal volumes are reduced in individuals diagnosed with depression (Sheline, Sanghavi, Mintun, & Gado, 1999; Sheline et al., 1996; Videbech & Ravnkilde, 2004). Chronic stress increases adrenal size and GC secretion, which matches the adrenal hypertrophy observed in individuals with depression (Nemeroff et al., 1992). Chronic stress decreases motivation on appetitive operant conditioning, which is consistent with anhedonia and decreased motivation (Barr & Phillips, 1998; Konkle et al., 2003), hallmark features of depression (Frazer & Morilak, 2005; Henn & Vollmayr, 2005). Finally, chronic stress impairs long-term spatial recognition memory, which is consistent with the memory decline of clinically depressed patients (Seeman, McEwen, Singer, Albert, & Rowe, 1997). Indeed, chronic stress is used in animals to model physiological and behavioral parameters that underlie clinical depression (Katz, 1981; Willner, 1997). The information gained from animal models suggests that the dysregulated HPA axis in clinical populations with a compromised hippocampus may be a mediator of hippocampus-dependent cognitive deficits and altered memory under emotionally arousing conditions.

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Figure 1. Mechanism of CA3 Dendritic Retraction Following Chronic Stress

NOTE: Repeated glucocorticoid (GC) elevations from chronic stress directly influence the CA3 pyramidal cells and CA3 afferents (dentate gyrus granule cells, commissural/associational fibers [C/A], entorhinal cortex [E.C.]) because all of these cells express receptors for GCs. The glucocorticoid receptor (GR) most likely mediates dendritic retraction in rodents, but the mineralocorticoid receptor (MR) probably plays a role in primates. Excess glutamate (Glu via N-methyl-D-aspartate [NMDA] receptor) and serotonin (5-HT) as well as altered inhibitory tone from interneurons and gamma-aminobutyric acid (GABA) modulate CA3 dendritic retraction. Reduced levels of brain-derived neurotrophic factor (BDNF), which is retrogradely transported to CA3 neurons, may permit CA3 dendritic remodeling. Solid arrows = enhanced tone permits CA3 dendritic retraction; open arrows = reduced tone permits CA3 dendritic retraction.

Figure 2. Camera Lucida Drawings of Hippocampal CA3 Pyramidal Cells

NOTE: Chronic restraint stress for 6 hours/day for 21 days decreased the complexity of the CA3 apical dendritic tree (Str-Veh). Daily tianeptine injections (10 mg/kg, intraperitoneally) prior to each daily restraint session prevented the CA3 apical dendritic retraction (Str-TIA) and produced dendritic arbors that were indistinguishable from controls injected with vehicle (Con-Veh) or tianeptine (Con-TIA). The CA3 basal dendritic arbors were unaffected by these manipulations. SOURCE: Reprinted with permission from Conrad, Magariños, LeDoux, and McEwen (1999).

Figure 3. Camera Lucida Drawings of Complex Superior Cervical Cells

NOTE: The cells are arranged from left to right according to total dendritic length. The estimate of the number of inputs received by each cell is indicated beside the axon (which extends much farther than shown). The geometrically simpler cells (A) receive fewer inputs than more complex neurons (B).

SOURCE: Reprinted excerpt with permission from Purves and Lichtman (1985), the American Association for the Advancement of Science.

Figure 4. Camera Lucida Drawings of Pyramidal Neurons From the Motor Cortex

NOTE: These are the same kind of neuron, represented from different species. The pyramidal neurons from the motor cortices of different mammals are drawn to the same scale. Enhanced morphological complexity, as observed in dendritic arbors, is proposed to contribute to higher cognitive function.

SOURCE: With permission from Rosenzweig, Breedlove, and Watson (2005).

Figure 5. Camera Lucida Drawings of Hippocampal CA3 Neurons From Ground Squirrels

NOTE: Short (A) and long-shafted neurons (B, C) found in ground squirrels. The long-shafted neurons showed the greatest structural reactivity to hibernation, with the CA3 neurons of awakened ground squirrels (B) showing greater structural complexity than those of ground squirrels in hibernation (C). This observation that the long-shafted neurons have a greater response to remodeling than short-shafted neurons do is similar to observations of differential responsivity of CA3 neuronal subtypes following chronic stress in female rats (McLaughlin, Baran, Wright, & Conrad, 2005).

SOURCE: Reprinted from Popov, Bocharova, and Bragin (1992), with permission from Elsevier.

Figure 6. Schematic and Principle of the Y-Maze

NOTE: A rat is placed in one arm of a symmetrical Y-maze and allowed to explore two arms whereas the third arm is inaccessible (blocked with the same Plexiglas material as the Y-maze). After 15 minutes of exploration, the rat is returned to its home cage so that the Y-maze can be rotated and the bedding on the floor of the maze mixed to reduce the potential use of intramaze cues. After the designated intertrial interval (ITI), the rat is reintroduced to the same start location and allowed to explore all three arms. At 1-minute ITI, rats with or without a compromised hippocampus readily explore the arm in the previously unexplored location. In contrast, at 4-hour ITI, rats with a compromised hippocampus enter the arms of the unexplored and explored locations similarly. Not shown are the salient cues located outside the Y-maze that help with navigation, and these include posters, shelving, and laboratory equipment. Regarding Trial 2, please note that the previously inaccessible arm is now located in a previously explored room location (indicated as "b"), and the previously inaccessible room location is now occupied by a previously explored arm (indicated as "a"). If intramaze (hippocampus-independent) cues guide exploration of the arms, then rats are expected to explore location "b" more than location "a." However, preference for location "b" is rarely observed because rats either prefer the novel location "a" or show no preference.

A. Hippocampus-Dependent Memory Following Acute Stress

B. Hippocampus-Dependent Memory Following Chronic Stress

C. Hippocampus-Dependent Memory Following Chronic GC

Figure 7. Model of CA3 Dendritic Retraction and Spatial Memory Deficits

NOTE: (A) Acute stress influences the hippocampus, which feeds back to inhibit the stress response. Glucocorticoids (GCs) secreted during a stress response can influence spatial memory with low GC levels positively correlating with spatial memory and high GC levels negatively correlating with spatial memory. (B) Chronic stress remodels CA3 dendritic arbors, which makes the hippocampus less effective in regulating the hypothalamic-pituitary-adrenal (HPA) axis. A dysregulated HPA axis leads to GC hypersecretion. During spatial memory processing, this GC hypersecretion can be sufficiently high to reach the negative slope of the inverted U-shape function between GCs and spatial memory. (C) Chronic GCs remodel the CA3 neurons in a similar fashion as chronic stress. However, exogenous GCs inhibit the HPA axis, which contrasts to the effects of chronic stress activating the HPA axis. During spatial memory processing, GCs are not hypersecreted, and the typical inverted U-shaped function with GC levels and spatial memory is observed. For spatial memory assessment using the Y-maze, spatial memory is functional because the Y-maze is fairly benign and does not produce highly emotionally arousing responses.

Figure 8. Attenuating Glucocorticoid (GC) Hypersecretion in Chronically Stressed Rats Restores Spatial Memory

NOTE: (A) Spatial memory on the Y-maze is restored in chronically stressed rats when given a single injection of metyrapone (SM75) on the day of Y-maze training. Spatial memory is concluded to be intact when entries into the novel arm exceed entries into the other arm, whereas motivation is unaltered (i.e., similar total entries made into all arms). (B) Total serum corticosterone levels were elevated in chronically stressed rats (SV, SM35, SM75) compared to controls (CV, CM35, CM75). Metyrapone reduced serum corticosterone levels in both control (CM75) and chronically stressed rats (SM75). Trunk blood for corticosterone determination was collected after the first trial of Y-maze training (Training) or after the second trial on Y-maze testing (Testing). CV = control + vehicle; CM35 = control + metyrapone 35 mg/kg; CM75 = control + metyrapone 75 mg/kg; SV = stress + vehicle; SM35 = stress + metyrapone 35 mg/kg; SM75 = stress + metyrapone 75 mg/kg. Means with different symbols

indicate statistical significance. SOURCE: Reprinted with permission from Wright et al. (2005); Wright, Lightner, Harman, Meijer, and Conrad (in press).

Emotionally-Arousing Memory Following Chronic Stress

Figure 9. Model of CA3 Dendritic Retraction and Spatial Memory Deficits Under Emotionally Arousing Conditions

NOTE: The process for chronic stress producing CA3 dendritic retraction is described in Figure 1. Chronic stress enhances dendritic arborization of the neurons within the basolateral nucleus (BLA) of the amygdala. The amygdala is more sensitive to emotionally arousing events following chronic stress than to control, nonstressed conditions. The combined hypersecretion of glucocorticoids (GCs) and the increased sensitivity of BLA neurons produce facilitated memory under emotionally arousing conditions. HPA = hypothalamic-pituitary-adrenal.

Figure 10. Gene-Environment Interactions Produce a Vulnerable Individual

NOTE: Responses to multiple and/or long-lasting stressors in adulthood depend on genetic predisposition and are modulated by the history of the individual. Vulnerable individuals might display changes in corticosteroid receptor expression, atrophy of hippocampal cells, reduced hippocampal neurogenesis within the dentate gyrus, altered monoaminergic signaling, reduced synaptic plasticity, and impaired learning ability. All of these can ultimately lead to a disease state. DG = dentate gyrus; GR = glucocorticoid receptor; LTP = long-term potentiation; MR = mineralocorticoid receptor; 5-HT_{1A}/5-HT_{2C} = 5-hydroxytryptamine, or 5-HT, receptors. SOURCE: Reproduced with permission from de Kloet, Joels, and Holsboer (2005), *Nature Reviews Neuroscience*, Macmillan Magazines Ltd.