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Remodeling of neuronal networks by stress

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1. ABSTRACT

Stress can be a threat to the physiological and psychological integrity of an individual and may result in psychic and behavioral changes. The stress response is mediated through in-concert activity of many brain areas and there is experimental evidence that stress induces structural changes in neuronal networks, in particular in the hippocampus, the prefrontal cortex and the amygdala. Within the hippocampal formation, stress exposure results in remodeling of dendrites of the CA3 pyramidal neurons and in reduced numbers of synapses on these neurons. Furthermore, stress inhibits adult neurogenesis in the dentate gyrus and appears to modulate the GABAergic system. In the prefrontal cortex, repeated exposure to stress causes dendritic retraction and loss of spines in pyramidal neurons whereas in the amygdala stress can elicit dendritic hypertrophy. These microscopically detectable changes in neuronal structures indicate the reorganization of neuronal networks. Moreover, molecular studies show that stress modulates expression of genes involved in neuronal differentiation and/or structural remodeling. Since a wealth of data documents the adverse effects of stress on emotions and cognition these alterations are commonly interpreted as the deleterious effect of chronic stress on the central nervous system. However, it is also possible that at least part of these changes reflect adaptive responses, as the network system rearranges its connections in order to cope with the changing requirements from the internal or external environment.

2. INTRODUCTION

Challenging events in an individual's environment initiate a cascade of adaptive physiological and psychological processes that constitutes the stress response involving a myriad of physiological, neuroendocrine, immune and neurochemical changes. There are, however, two major systems that mediate the stress response. The first mediating link between brain and body is the hypothalamic-pituitary-adrenal (HPA) system which stimulates the adrenal cortex to release glucocorticoids into the blood. These steroid hormones, notably cortisol in primates including man and corticosterone in rodents, affect many types of cells in both body and brain through intracellular signaling mechanisms involving at least two distinct nuclear receptors. By influencing gene transcription and altering electrical activity of excitable cells, corticosteroids are potent modulators of cell physiology and behavior and serve both to alert the organism to an environmental or physiological challenge and to defend its homeostasis (1,2). The second major system that mediates the stress response is the sympathetic-adrenomedullary system that determines the stress reaction by two pathways working in parallel. One pathway is build up by the cholinergic nerve endings that trigger the release of adrenaline from the adrenal medulla into the blood. The second pathway comprises the noradrenergic nerve endings that supply essentially every organ in the body with noradrenaline.

When regarding systemic aspects it should be realized that stress is not necessarily a harmful or pathological factor to be avoided. Only when adaptive mechanisms cannot be recruited, chronic stress will result in a number of deleterious effects and health may be endangered. Since this is a consistent finding across many species including humans where stress increases the possibility to develop psychiatric disorders, it is important to understand the relationship between stress-induced central nervous changes and diseases.

3. DENDRITIC REMODELING AS A RESULT OF STRESS

Repeated stressful experiences have a profound impact on neuronal plasticity in various brain areas, especially in the hippocampal formation, the prefrontal cortex and the amygdala. Probably the most thoroughly investigated anatomical change is the regression of the geometrical length of apical dendrites of pyramidal neurons that was first demonstrated in the hippocampus (3). The hippocampus is part of the limbic-HPA system and plays an active role in the regulation of the stress response. Dendritic remodeling of CA3 pyramidal neurons has been repeatedly documented after chronic stress exposure as well as after corticosterone administration (3-8). Similar shortening of dendritic branches, although to a smaller extent, has been observed in dentate gyrus granule cells and in CA1 pyramidal cells, in chronically stressed and in corticosterone-treated rats (6). The traditional framework for interpreting the functional consequences of such dendritic remodeling is based on the logic that reduced surface of the neuron will diminish the availability for synaptic input (9). Indeed, a significant loss of synapses on the CA3 pyramidal cells and profound changes in the morphology of their afferent mossy fiber [1] terminals were detected in chronically stressed or corticosterone-treated animals (6,10,11). Interestingly, even a brief social defeat stress (1 hour on 2 consecutive days) with a long time delay after stress (3 weeks without further treatment) can reduce the apical dendritic length to 77% of control, while the branches at the basis of the primary dendrites are *increased* in length (167% of control) and show a higher complexity (12). These data suggest that a brief social conflict is sufficient to drive a dynamic reorganization of neuronal networks with site-selective elimination as well as *de novo* growth of dendritic branches, changes that persist throughout several weeks after the acute stress experience.

Chronic stress alters dendritic morphology not only in the hippocampus, but also in the medial prefrontal cortex and the amygdala. The medial prefrontal cortex (mPFC) modulates various higher cognitive and affective functions, whereas the amygdala plays a crucial role in the regulation of emotions such as fear and anxiety and is essential for the formation of emotional memories. Furthermore, both of these structures regulate the activity of the HPA axis. Recent reports demonstrate that three weeks of either daily restraint stress (3 hours/day) or daily corticosterone injections lead to changes of the pyramidal neurons in the mPFC revealing up to 20-35% retraction of the distal dendritic branches, together with a significant (16%) decrease in apical dendritic spine density (13-16). Interestingly, even repeated vehicle injections result in similar although less pronounced changes, indicating that the mPFC reacts even more sensitive to external influences compared to the hippocampus with respect to morphology of neurons (17). In contrast in the amygdala, a similar chronic stress paradigm that causes dendritic retraction and debranching in hippocampal CA3 pyramidal neurons enhances dendritic arborization of the pyramidal and stellate neurons in the basolateral amygdaloid complex (7).

4. STRESS INHIBITS NEUROGENESIS IN THE ADULT HIPPOCAMPAL FORMATION

A central hypothesis of neuroscience has been that in the mammalian brain, the production of neurons occurs only during development and stops before puberty, and that new neurons cannot be formed in the adult brain (18,19). This widely held belief has been challenged in recent years by extensive evidence from many mammalian species including non-human primates as well as humans showing that certain brain areas retain the capability to generate new neurons in the adult brain (20-23). Adult spontaneous neurogenesis takes place only in selected regions such as the subgranular zone of the hippocampal dentate gyrus (20) and the subventricular zone of the lateral ventricle (24). In the dentate gyrus, newly generated granule cells become incorporated into the granule cell layer and attain the morphological and biochemical characteristics of neurons (25). The neuronal nature of these cells documents itself by the formation of synapses on the cell bodies and dendrites (26), extension of axons into the CA3 region (27) and generation of action potentials (28). However, the newborn cells have distinct morphological and electrophysiological properties compared to mature granule cells (29), e.g., they present a lower threshold for induction of long-term potentiation (LTP) and display robust LTP (30).

The observations on neurogenesis were facilitated by the advent of a novel method for detecting cell proliferation and migration, the 5-bromo-2'-deoxyuridine (BrdU) labeling technique (31). BrdU is a thymidine analog that can be applied systematically to become incorporated into the DNA during the S phase of mitosis and can therefore be used to label proliferating cells and their progeny. BrdU can be visualized by immunocytochemical means, and if BrdU labeling is combined with other cell markers to identify specific cell types, it allows determination of the phenotype of the newly generated cells. Using such methods, it has been demonstrated that the majority of adult-generated cells in the dentate gyrus differentiate into neurons, e.g., it has been shown that the BrdU-labeled cells express the neuronal marker molecule neuron-specific nuclear protein (NeuN) (see Figure 1). Only a small proportion of the newborn cells express markers for glial cells such as glial fibrillary acidic protein (GFAP). Furthermore, BrdU labeling has allowed to estimate the number of newly born neurons using stereological methods showing that every day, thousands of new neurons are added to the mammalian brain (32). Although the new neurons are a minuscule

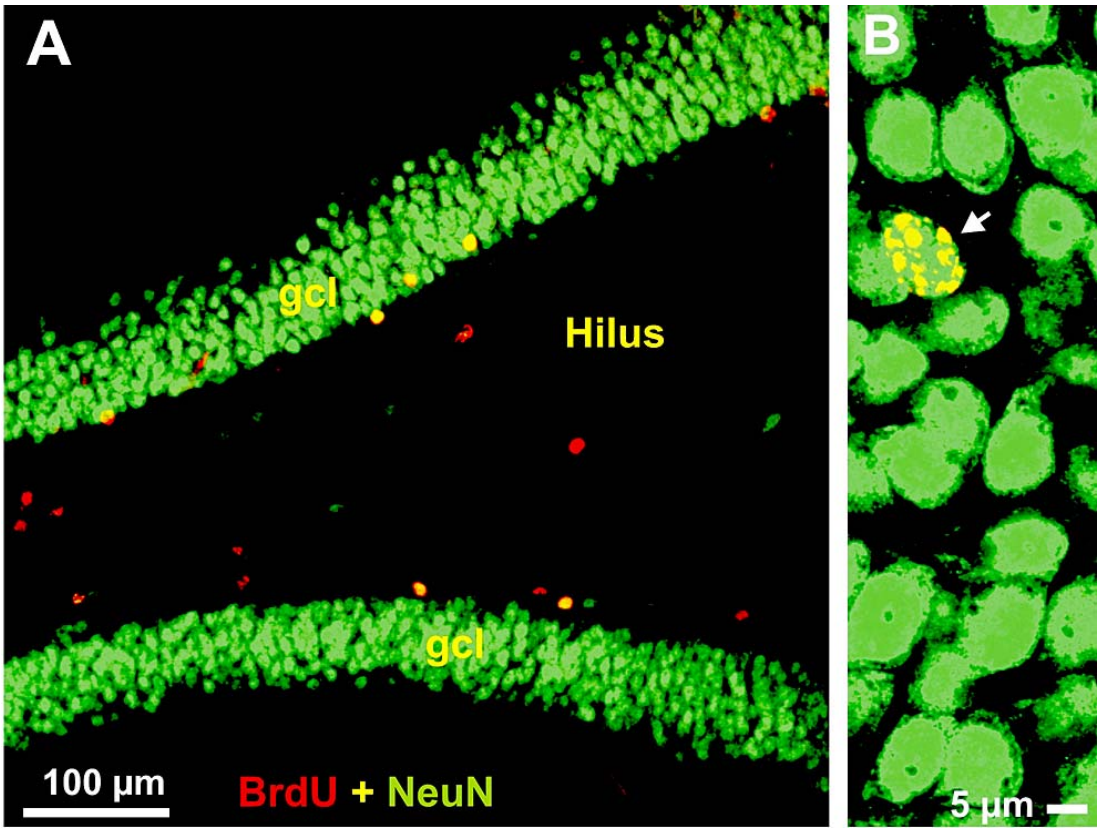

Figure 1. Colocalization of BrdU immunoreactivity with the neuronal marker NeuN. A. Representative image of a double stained hippocampal dentate gyrus (region of the hilus) at low magnification (BrdU: *red-yellow*, NeuN: *green*). The majority of newborn (BrdU-labeled) cells is found in the subgranular zone and in the granule cell layer (gcl) of the dentate gyrus. B. Double labeling with BrdU and the neuronal marker NeuN with a high magnification displaying a BrdU+/NeuN+ newborn neuron (arrowhead). BrdU: 5-bromo-2'-deoxyuridine; NeuN: neuron-specific nuclear protein; gcl: granule cell layer.

proportion of the total neuronal population, their continual addition over the entire life-span implies considerable structural changes within the neuronal network. The magnitude and ubiquity of adult neurogenesis across vertebrates suggests that it is functionally significant and not merely a vestige of development.

Since the hippocampal formation plays a central role in the acquisition and consolidation of episodic-declarative memories (33), the fact that continuous neurogenesis takes place here may indicate that newborn neurons could participate in learning. Indeed, a continually rejuvenating population of new neurons seems well suited for the proposed transient role of the hippocampal formation in information storage. An increasing number of reports provide evidence, although so far only correlational, that adult hippocampal neurogenesis is involved in learning and memory (34-36). However, the exact functional role of these newborn neurons remains to be proven.

Adult neurogenesis in the dentate gyrus is modulated by a large number of environmental and endogenous factors (37), but stress is one of the most potent environmental parameters known to suppress adult neurogenesis, as it was shown in several different species using various stress paradigms (Figure 2) (38-48). Chronic stress not only suppresses the rate of continuous adult dentate cytogenesis but results also in a smaller size of cell clusters formed by the newly generated neurons. If the experimental animals are investigated shortly (e.g. 2-24 hours) after injection of BrdU, the newborn BrdU-labeled cells generally occur in duplets or small groups compromising up to 14 cells in a cluster (see Figure 3). Exposing animals to five weeks of psychosocial stress alters cluster formation in the dentate subgranular zone so that in the stressed animals, newly generated cells form smaller clusters (Figure 3). Furthermore, it appears that there is an age-dependent susceptibility of adult dentate cell proliferation to stress with older animals being more sensitive (49).

Adult neurogenesis in the dentate gyrus is also accompanied by a constant occurrence of cell death that results in a continuous cell turnover in this brain area (50,51). Experimental data indicate that both these processes are modulated by stress (48,52,53). The suppression of cell turnover following chronic stress predicts that the age of the granule cell population, connectivity of the neurons and the resulting properties of the neuronal circuits might be substantially different from

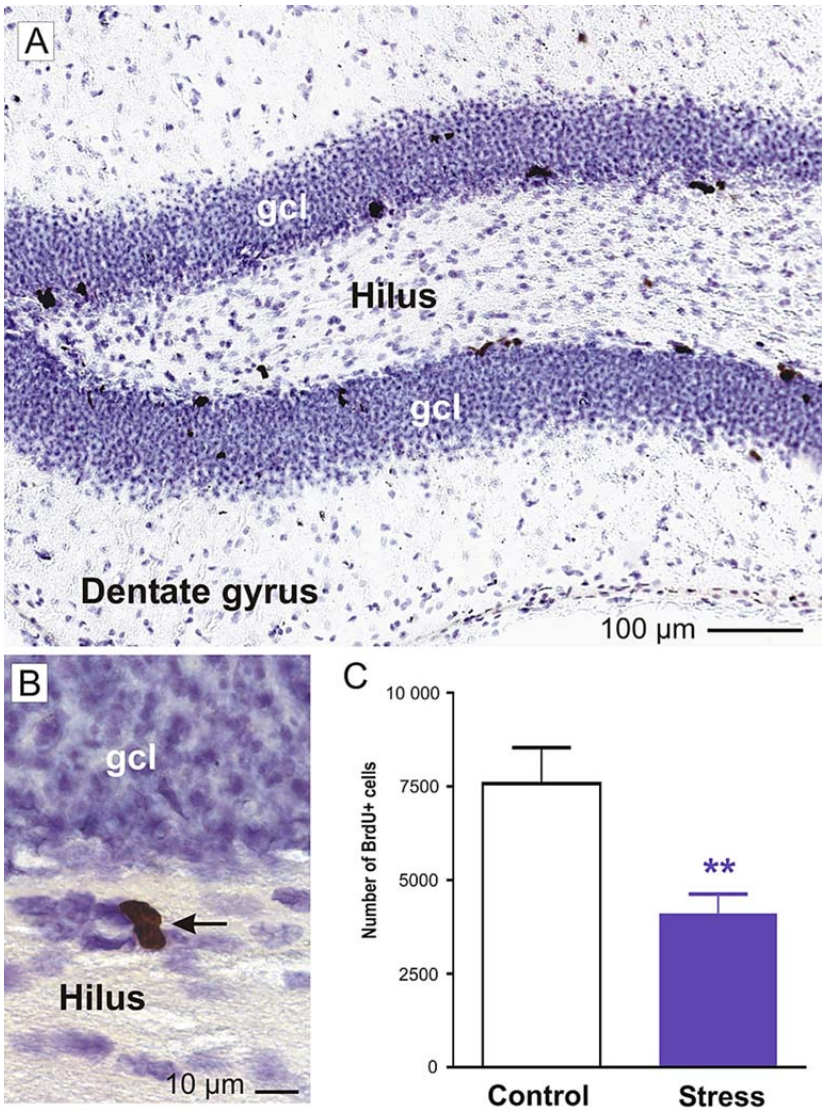

Figure 2. Cell proliferation in the hippocampal dentate gyrus of the tree shrew was quantified with the use of BrdU immunohistochemistry.A. A representative photomicrographs of a control animal. The majority of proliferating cells is found predominantly in the subgranular zone defined as a two-cell-body-wide zone between the granule cell layer (gcl) and the hilus. B.Positively labeled cells (arrow) generally occurred in duplets or cell clusters. C. Chronic psychosocial stress significantly suppressed cell proliferation in the hippocampal dentate gyrus. Results are given as mean ± SEM number of BrdU-positive cells in the hippocampal dentate gyrus. Student *t*-test: ** $p < 0.01$.

control situations with potentially important functional consequences. Indeed, clear changes in various neurophysiological parameters were found in electrophysiological studies employing a chronic stress model (54,55).

5. PLASTICITY OF THE HIPPOCAMPAL GABAERGIC SYSTEM AFTER CHRONIC STRESS OR GLUCOCORTICOID TREATMENT

As generally accepted, stress increases extracellular glutamate levels and thus enhances excitatory activity, e.g. of the principal cells in the hippocampal formation (56). However, a growing number of data indicate that also the main inhibitory system in the brain, the GABAergic system, changes due to environmental challenges in that stress or artificially elevated glucocorticoid levels up-regulate the GABAergic elements. Chronic stress and glucocorticoid treatment increase GAD^2 expression in the hippocampus, presumably leading to enhanced GABA synthesis (57,58) and raise hippocampal GABA receptor expression, most probably to facilitate inhibitory neurotransmission (59). However, we recently provided evidence that *long-term* psychosocial stress reduces the number of parvalbumin-immunoreactive neurons that are regarded as GABAergic interneurons. This effect occurred in the dentate gyrus and in the CA3 regions of the Ammon's horn, whereas the CA1 subfield was not

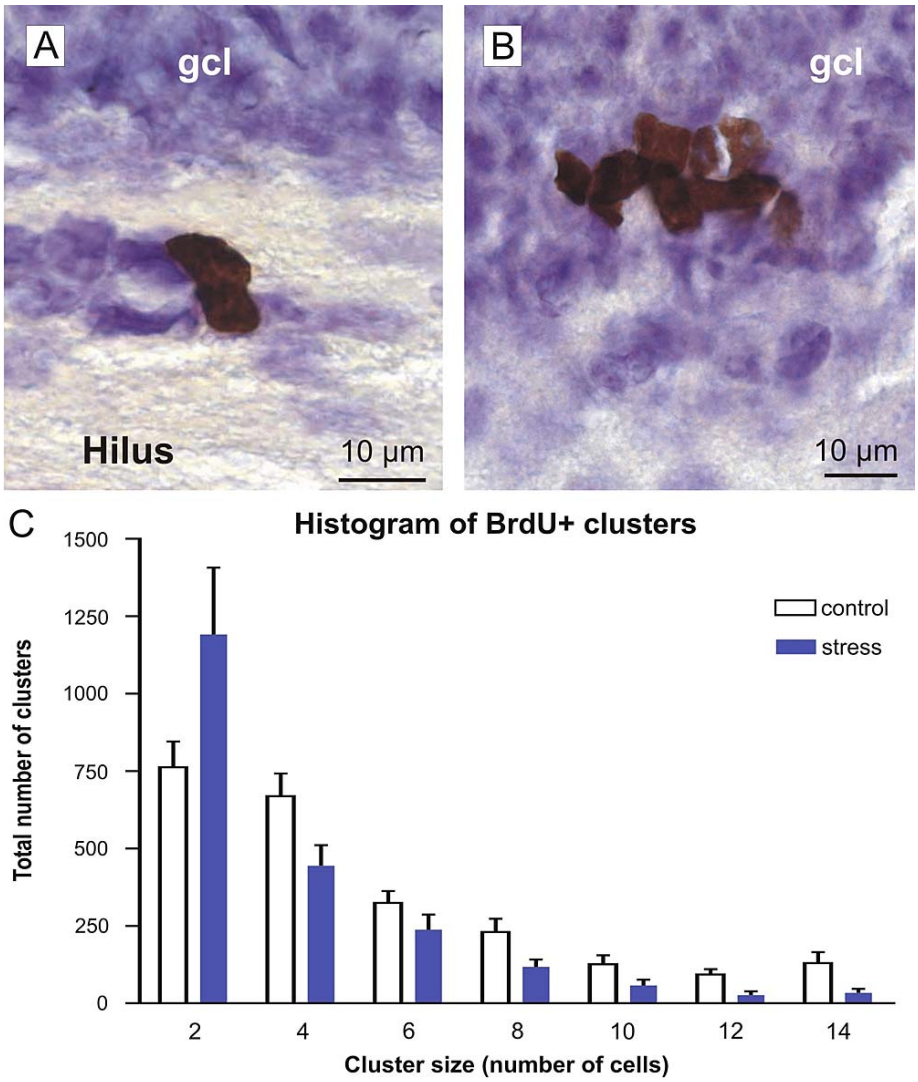

Figure 3. Chronic stress affects the cluster size of the proliferating cells. A-B. Taking brains shortly (e.g. 24 hours) after the animals have been injected with the mitotic marker BrdU allows evaluation of the number of proliferating cells, or cytogenesis. Newborn BrdU-positive cells generally occur in duplets or cell clusters compromised of up to 14 cells in a cluster. C. After five weeks of psychosocial stress, cluster formation in the dentate subgranular zone is altered. In the stressed animals, newly generated cells form smaller clusters than controls (smaller number of cells in a given cluster). Abbreviations: BrdU: 5-bromo-2'-deoxyuridine; NeuN: neuron-specific nuclear protein; gcl: granule cell layer.

affected (60) (Figure 4). To our knowledge this is the first report showing that chronic stress may alter the number of interneurons in the hippocampus. Moreover, parvalbumin-positive interneurons may not be the only members of the hippocampal GABAergic network that are affected by stress, as a recent report demonstrated reduced number of NPY-positive interneurons in the dentate gyrus of rats exposed to another type of stress in the learned helpless paradigm (61).

What can be the explanation for a reduction in cell number after chronic stress? Since stress is known to increase extracellular glutamate levels in the hippocampus it has been hypothesized that neurons are dying due to excitotoxic effects of glutamate (56). Several years ago, it has been argued that prolonged stress may induce loss of CA3 pyramidal neurons (62,63). In the recent years, however, stereological studies challenged these findings as *post mortem* studies on brain tissue from severely depressed patients, or from steroid-hormone treated subjects revealed no major cell loss nor any neuropathologic changes. In addition, apoptosis was observed only to a very limited extent in depression, for example in entorhinal cortex, subiculum, and dentate gyrus but not in hippocampal subregions predicted to be at risk for corticosteroid hormone overexposure, such as the CA3 area (64,65). These data are consistent with those from other preclinical studies that failed to find neurotoxic effects of hypercortisolemia or chronic stress on the hippocampus of several species including rats, tree shrews

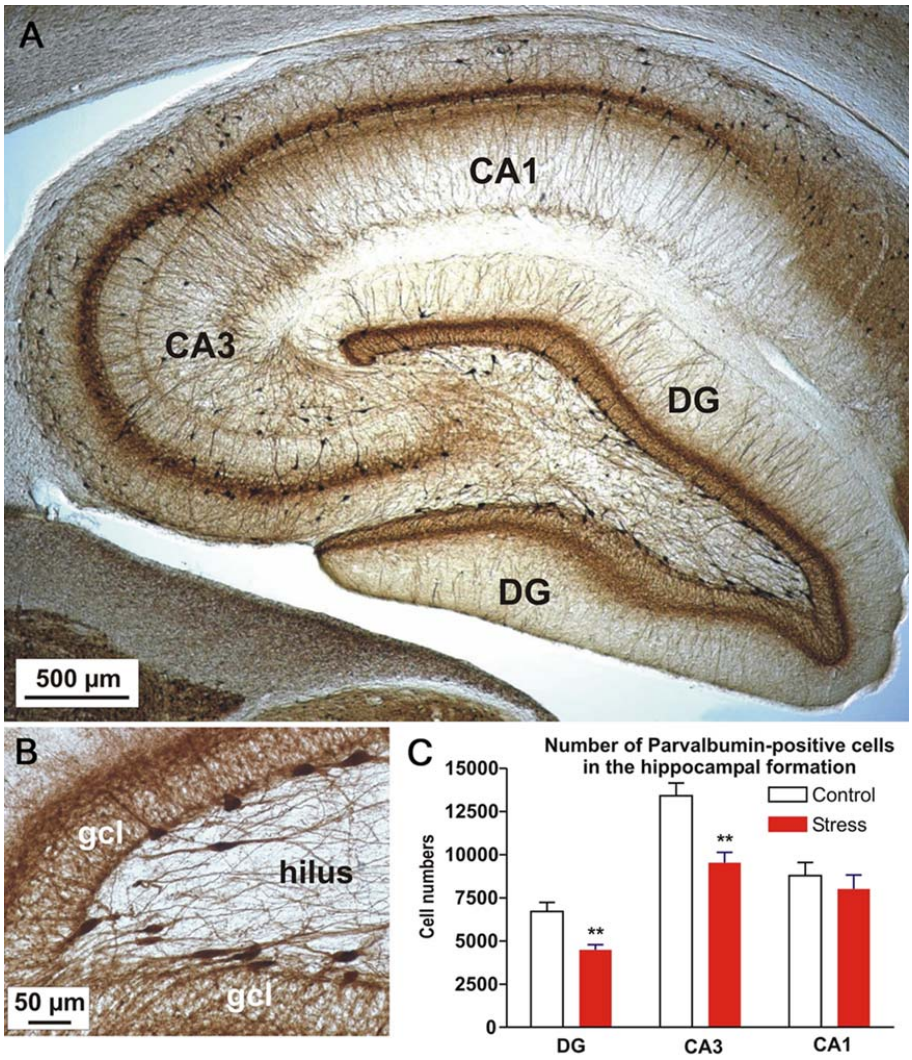

Figure 4. A. Representative example of a parvalbumin stained horizontal section of the tree shrew hippocampal formation. Parvalbumin-immunoreactive (PV-IR) neurons were present exclusively as non-principal cells. Note that all hippocampal subregions and layers are clearly distinguishable. B: Detailed image of the dentate gyrus from a representative control animal. Most of the parvalbumin-positive interneurons were aligned at the border of the granule cell layer (gcl) and the hilus.C: Stress significantly decreased the number of PV-IR cells in the dentate gyrus and in area CA3, whereas the CA1 region was not affected.*Statistics*: one-way ANOVA, followed by Tukey's *post-hoc* analysis: ** < 0.01 *versus* Control. DG: dentate gyrus; gcl: granule cell layer.

and non-human primates (6,66-68). It should be noted though that possible changes in the number of interneurons or hilar cells were not specifically addressed in these studies. We also quantified the incidence of apoptosis in animals exposed to chronic social stress. Unexpectedly we found a significant increase in the number of apoptotic cells in the hilus and a non-significant increase in the granule cell layer, whereas in region CA3, apoptosis was decreased (52). Considering these results on numbers of apoptotic cells, excitotoxic cell death may explain the reduced number of parvalbumin-containing interneurons in the dentate hilus. Thus, we cannot rule out the possibility that long-term stress may induce excitotoxic interneuron loss, however, the number of principal neurons in the hippocampus is obviously not affected by stress.

Another explanation for a reduced number of parvalbumin-immunoreactive neurons in the hippocampal formation is a decreased content of intracellular parvalbumin below levels detectable by the immunocytochemical method. Changing the cell phenotype, e.g. by re-adjusting the cell's calcium-buffering system, might be regarded a special form of neuroplasticity. The exact physiological role of the calcium-binding protein parvalbumin (PV) is not yet clear, but results from studies on PV-deficient mice show that low levels of parvalbumin in the axon terminals correlate with increased GABA release indicating that PV modulates Ca^{2+}-dependent GABA neurotransmission (69). It has also been demonstrated that, after repeated epileptic seizures, the density of hippocampal PV-immunoreactive neurons

decreases rapidly without changing the density of GABA-immunoreactive neurons in the same area (70). This indicates that in response to seizure activity, the perikaryal PV content falls below levels detectable by immunohistochemistry. A reduction of the calcium-buffering system within the cells may potentially correlate with a functional impairment of the PV-containing interneurons, but it might also be a compensatory mechanism. Hypothetically, this could reflect a kind of somatic 'plasticity' in that PV-positive inhibitory cells might be able to down-regulate their parvalbumin content to facilitate GABA release. Such an adaptive change may help the GABA system to prevent excessive firing of the principal cells in response to repeated stress exposure. It is a common idea that neurons of the hippocampal formation may modify their physiology in response to extreme conditions. Changes in the phenotype of cells in the hippocampus of the macaque monkey have been reported recently after chronic (1 year) treatment with cortisol (71). As demonstrated, this longlasting cortisol exposure increased calbindin expression in the dentate granule cells. Calbindin is a marker for inhibitory neurons and, like parvalbumin, a protein that buffers excess calcium and thus may protect against neurodegeneration resulting from overabundant intracellular calcium.

Granule cells of the dentate gyrus are primarily glutamatergic and their axons, the mossy fibers, constitute a major excitatory connection within the hippocampal formation (72). Interestingly, dentate granule cells possess a functional dual glutamatergic - GABAergic phenotype, as they also contain GABA and the enzyme glutamatic acid decarboxylase (GAD) (73). In the recent years experimental evidence revealed that these cells can become inhibitory in response to changes in the milieu such as extreme hyperexcitability due to epileptic seizures (73,74). Thus, GABAergic neurotransmission in mossy fiber synapses appears to represent a compensatory mechanism in response to seizures. Since calbindin is found primarily in GABAergic neurons (75) the findings of McMillan et al.(2004) (71) showing that cortisol induced an up-regulation of calbindin in dentate granule cells and mossy fibers suggests that chronic cortisol exposure may promote a GABAergic phenotype analogous to that reported under hyperexcitability conditions such as epileptic seizures. In other words, by increasing their calbindin expression granule cells may adopt an inhibitory phenotype which seems to be a compensatory feedback mechanism to dampen the initial excitatory effects of glucocorticoids (71). From these results one may hypothesize that under conditions such as persistent stress – which is characterized by constantly elevated glucocorticoid plasma concentrations - the hippocampal network attempts to counterbalance the chronic over-excitation by changing the cellular phenotype in order to facilitate GABA release and thus counterbalancing enhanced excitatory activity.

6. GENE EXPRESSION IN RELATION TO STRESS-INDUCED CHANGES IN THE NEURAL NETWORK

The stress-induced changes in shape and number of neurons imply that brain cells adjust their biosynthesis pathways to the requirements, e.g., concomitant with retraction of dendrites there is a reduced need for structural proteins in the neuronal membranes, or when neurogenesis is inhibited, proteins building up newborn neurons are not required. Related adaptational processes take in part place on the level of transcription. Due to the methods currently available for identification of genes that are differentially regulated by stress, namely cDNA microarrays, serial analysis of gene expression and subtractive hybridization, the genes known to be regulated by stress still look rather heterogeneous (see 76). However, from the lists of the respective genes it is already clear that some observations concerning gene transcription are consistent with what has been found with other methods.

In the hippocampal formation, expression of several genes known to be involved in neuronal differentiation was found to be down-regulated by chronic social stress in the hippocampal formation, e.g. those encoding the membrane glycoprotein M6A, CDC-like kinase 1 (that phosphorylates serine- and arginine-rich proteins of the spliceosomal complex; is involved in RNA splicing in the nucleus), and a DNA sequence encoding a distinct subunit of certain G-proteins, GNAQ (77). All these genes play a role in neurite outgrowth and neuronal differentiation supporting the view that alterations in neuronal morphology and/or formation of neurons are primary effects of stress, at least in the hippocampal formation (78). Furthermore, the expression of neural cell adhesion molecule (NCAM) was found to be down-regulated after chronic restraint stress (79). It is known that NCAM regulates neurite outgrowth and target recognition in the developing nervous system by mediating cell adhesion and signal transduction (80).

Neuronal plasticity is accompanied by dynamic changes in elements of the cytoskeleton. Alpha-tubulin, which is the major component of microtubules, can be post-translationally modified, and both the tyrosinated (tyr-tub) and acetylated (acet-tub) forms are considered markers of dynamically changing or stable microtubules, respectively. Sub-chronic restraint stress (4 days) decreases the expression of tyr-tub and increases the expression of acet-tub in the hippocampus (81).

Neurotrophic factors are known to regulate neural growth and differentiation during development but they are also potent regulators of neuronal and glial plasticity and survival in the adult brain (82). Several studies have investigated the regulation of growth factors and their receptors in response to stressful situations. Nerve growth factor (NGF) expression was reduced after chronic social stress (77), and levels of mRNA for brain derived neurotrophic factor (BDNF) were decreased after various forms of stress (83,84) although BDNF down-regulation was not found in all studies (77). On the other hand, expression of the receptor for BDNF, TrkB, was upregulated by both immobilization and unpredictable stress (85).

It is well known that stress increases the activity of central nervous monoamine systems which has

widespread effects on neuronal excitability. Imbalances between the central nervous monoamine systems are thought to contribute to stress-related central nervous disorders (see 86). Hyperactivity of the noradrenergic system reflects itself by reduced expression of alpha-2 adrenergic autoreceptors in the locus coeruleus, an important noradrenergic center in the brain. In contrast, long-term stress leads to upregulation of postsynaptic alpha-2 adrenoceptors, e.g. in the prefrontal cortex, probably as compensatory mechanism in response to a deficit in noradrenaline and/or adrenaline (87).

As pointed out in the Introduction, the hyperactivity of the HPA-axis and thus elevated glucocorticoid levels are main neuroendocrine features of stress (1). Like the other steroid hormones, these corticosteroids regulate transcription of specific target genes via interaction with intracellular receptors forming steroid-receptor complexes that bind to DNA. There are two types of receptors that are activated by glucocorticoids: The mineralocorticoid (MR) and glucocorticoid receptor (GR) both being expressed in the brain, especially in the hippocampus. Regulation of the GR and MR genes has been well studied. The majority of the corticosteroid-responsive genes are regulated by either activated GR or MR, while only a few genes are responsive to both receptor complexes (88). As shown in several species, different forms of stress including psychosocial stress down-regulate GR mRNA in the dentate gyrus and hippocampal subfields CA1 and CA3 (89,90). Since the activated glucocorticoid receptor functions as transcription factors alterations in GR expression have 'downstream effects' on expression of many genes (88). Also the transcription factor CREB has been shown to be regulated by stress (91).

As discussed above, stress increases extracellular glutamate levels in the hippocampus and this excitatory amino acid neurotransmitter plays a role in dendrite remodeling and in suppression of neurogenesis. Several glutamate receptors have been analyzed in relation to stress including the ionotropic AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor. Depending on the duration of restraint stress and on the brain region, mRNA for certain AMPA receptor subunits were either up- or down-regulated suggesting that different assemblies of AMPA receptors subunits and isoforms may underlie the neuroplastic changes induced by stressful stimuli (92). Furthermore, the same form of stress upregulated the glial glutamate transporters GLT-1 and GLT-1b (93). These data show that different target molecules of the glutamatergic system are affected by stress.

Stress-induced changes in the hippocampal GABAergic system have already been described above. Apart from those data, it was found that the level of mRNA for the GABA-A receptor subunit beta2 was increased after chronic non-habituating stress in hippocampal subfields CA1, CA3 and in the dentate gyrus (94). Chronic intermittent stress also upregulated the GABA-synthesizing enzyme glutamic acid decarboxylase GAD67 in the hippocampus (57).

Nerve terminal vesicles and their integral membrane proteins play a critical role in synaptic plasticity (95). Five days of immobilization stress in rats resulted in a reduction of the synaptic vesicle protein synaptophysin and an increment of synaptotagmin mRNA levels in all hippocampal subfields (96). Mss4, a gene that encodes a guanine nucleotide (GTP) exchange factor interacts with GTPases of the rab family, small proteins that play a role in recycling of synaptic vesicles. Chronic mild stress in rats during 3 weeks decreased Mss4 transcript levels (97).

Cytokines are low molecular weight proteins that are produced in response to antigens and functions as chemical messengers for regulating the immune system. They modulate brain function through multiple signaling pathways originating from peripheral and central nervous cells. Brain cytokines increase following stress exposure and have been implicated in brain plasticity. Mice subjected to chronic psychosocial stress show decreased interleukin (IL)-1beta and tumor necrosis factor (TNF)-alpha mRNA levels in the hippocampus (98).

7. FUNCTIONAL CONSEQUENCES

The ability of the brain to undergo functionally relevant adaptations following external and/or internal stimuli is generally referred to as neural plasticity. These dynamic processes are based on the capacity of neural systems, single neurons, glia cells, synapses, receptors and other components to adapt and change their structural or functional repertoire in response to alterations in the internal and/or external environment. Neural plasticity is absolutely necessary for adequate functioning of an individual in the continuously changing environment. However, as demonstrated by the altered structure and functions in the brains of patients with mood disorders it became clear that neural plastic changes are not always beneficial. Neuroimaging studies have demonstrated selective structural changes across various limbic and non-limbic circuits in the brains of depressed individuals; e.g., volume of prefrontal and cingulate cortex are reduced, while with further progression of the syndrome also hippocampal atrophy occurs (99,100). These findings led to a modification of the earlier hypotheses on the pathophysiology of major depression usually based on altered neurotransmitter availability in the synaptic cleft, and that assumed antidepressants to exert their primary biochemical effects by readjusting the intrasynaptic concentrations of serotonin and/or norepinephrine. More recent preclinical and clinical studies suggest that major depressive disorders are associated with cellular resilience and an impairment of synaptic and structural plasticity and antidepressant medications may act by correcting this dysfunction (91,101). This concept together with clinical observations that stress often precipitates depressive episodes (102) has increasingly attracted research efforts that may result in new treatment strategies for psychiatric disorders, such as major depression.

The effect of chronic stress on cognition is most commonly interpreted as being adverse. This interpretation is based on numerous experimental observations

demonstrating impairments of hippocampal dependent learning in animals that were chronically exposed to stress (reviewed by 103,104). These cognitive deficits have been attributed to numberless structural, molecular and physiological alterations, some of which have been presented above. However it appears, that although the relationship between stress, glucocorticoids and memory loss is empirically supported, there are other factors, such as the experimental conditions, gender of the affected subject, the type of learning paradigm used as well as individual differences within groups, that influence interactions between these variables, and there are cases when specific memory processes not only remain intact, but indeed are facilitated by chronic stress (105-107).

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Footnotes: [1] Mossy fibers are the axonal projections of the granule cells of the dentate gyrus projecting to the pyramidal cells of the hippocampal CA3 area, [2] GAD: glutamic acid decarboxylase is the enzyme that catalyzes the synthesis of the inhibitory neurotransmitter GABA (gamma-aminobutyric acid). GABA is the most important and abundant inhibitory neurotransmitter in the brain (it's an amino acid classified as a neurotransmitter).

Key Words: Hippocampus, Neurogenesis, GABAergic System, Chronic Stress, M6A, CDC-like kinase, HPA axis, Parvalbumin, Dendrites, Antidepressants, Animal Models, Pyramidal Neurons, Interneurons, Review

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