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Lucassen, P.J.; Fitzsimons, C.P.; Vreugdenhil, E.; Hu, P.; Oomen, C.; Revsin, Y.; Joëls, M.; de Kloet, E.R.

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6 Regulation of Structural Plasticity and Neurogenesis During Stress and Diabetes; Protective Effects of Glucocorticoid Receptor Antagonists

Q1 Paul J. Lucassen, Carlos P. Fitzsimons, Erno Vreugdenhil, Pu Hu, Charlotte Oomen,
Yanina Revsin, Marian Joëls, and E. Ron• De Kloet

In this chapter, we will review changes in structural plasticity of the adult hippocampus during stress and exposure to glucocorticoids (GCs). We further discuss the protective and normalizing role of glucocorticoid receptor (GR) antagonist treatment under these conditions and its implications for disorders such as depression and diabetes mellitus.

6.1 The Stress Response

Stress represents an old, yet essential alarm system for an organism. Whenever a discrepancy occurs between an organism's expectations and the reality it encounters, stress systems are activated; particularly when it involves a threat to, or disturbance of its homeostasis, well being, or health. Loss of control, or unpredictability when faced with predator threat in animals, or psychosocial demands in humans, can all produce stress signals. The same holds true for perturbations of a more physical or biological nature, such as energy crises, injury, or inflammation. Upon exposure to a stressor, various sensory and cognitive signals converge to activate a stress response that triggers several adaptive processes in the body and brain which aim to promote restoration of homeostasis.

In mammals, Selye [1] noted that the effect of stressors develops in a stereotypic manner. The first phase largely involves activation of the sympathoadrenal system through the rapid release of epinephrine and norepinephrine from the adrenal medulla; these hormones elevate basal metabolic rate and increase blood flow to vital organs like the heart and muscles. At a later stage, the limbic hypothalamo-pituitary-adrenal (HPA) system is activated as well, a classic neuroendocrine circuit in which limbic and hypothalamic brain structures integrate emotional, cognitive, neuroendocrine, and autonomic inputs, that together determine the magnitude and duration of the organism's behavioral, neural, and hormonal response to a stressor.

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Q2104 6 Regulation of Structural Plasticity and Neurogenesis During Stress and Diabetes

6.2 HPA Axis and Glucocorticoids

Stress-induced activation of the HPA axis starts with the production of corticotropin-releasing hormone (CRH) in parvocellular neurons of the hypothalamic paraventricular nucleus (PVN), which induces the release of adrenocorticotrophic hormone (ACTH) from the anterior pituitary gland; this in turn causes release of GCs from the adrenal cortex into the general circulation. This stress-induced secretion is superimposed on the hourly pulsatile secretory bursts of steroid release under basal conditions. This ultradian rhythm in the HPA axis is important for maintaining tissue responsiveness. The amplitude of this rhythm is low at the end of the active period and increases again toward the next activity period. The rhythm becomes disordered in old age so that the coordinating and synchronizing action of GCs becomes compromised [2].

6.3 Glucocorticoid Actions

Upon their release, GCs (cortisol in primates, corticosterone in most rodents) cause a wide range of actions and have an important effect on many organs and organ systems in the body, including the brain. In the periphery, GCs mobilize energy by raising glucose levels. They further affect carbohydrate and lipid metabolism and can have a catabolic effect on muscle and bone tissues and affect cognition, for example. GCs also exert a "permissive" influence that enhances sympathoadrenal activity, in contrast to the generally slow genomic action of the latter. If stress becomes chronic, an imbalance may occur and GCs can overshoot and have deleterious effects by inducing muscle wasting, gastrointestinal ulceration, hyperglycemia (diabetes mellitus), and atrophy of the immune system.

6.4 Feedback Regulation

After the discovery that the hippocampal formation holds large numbers of GC receptors [3], a large body of evidence has been gathered, demonstrating that stress via elevated GC levels can affect both, hippocampal structure and function [4–6]. Cerebral impacts of GCs are considered to predominantly involve slow genomic actions following activation of mineralocorticoids (MRs) and GRs. These receptors act as transcriptional regulators of responsive genes. The MR has a high affinity for aldosterone and corticosterone. It is predominantly expressed in the hippocampus, lateral septum, and amygdala. In contrast, the GR has a 10-fold lower affinity for corticosterone and is ubiquitously distributed, with enrichments in the hippocampus, PVN, and pituitary; that is, the main feedback sites through

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which GCs regulate their own release [7]. Also, other brain regions such as the amygdala and prefrontal cortex, modulate HPA feedback and (re)activity.

Owing to these differences in affinity, the degree of MR and GR occupation depends on circulating GC levels that fluctuate over the course of the day. When at rest, circulating GC levels are low and activate mainly the MR while occupying only a small fraction of the GRs. Only after stress, or at the circadian peak prior to the onset of the activity period, do GRs become activated. Under these circumstances, changes in the degree of MR and GR activation influence gene expression in the hippocampus and may result in persistent changes in the electrophysiological properties of the hippocampal network. The variable MR/GR ratio is particularly relevant for neurons that express both receptor types; that is, CA1 pyramidal neurons and dentate gyrus (DG) granular neurons. In the CA3 region, very few GRs are present.

Recently, fast actions of the GC have been discovered, which are putatively mediated by membrane receptors. These fast actions are thought to contribute to the organization of the stress response [8]. These membrane receptors appear to be variants of the classical nuclear receptors MR and GR. In limbic regions, the membrane MR was found to boost excitatory neurotransmission accompanying the initial stress-induced rise of corticosterone. Electrophysiological, endocrinal, and behavioral data suggests that fast-acting corticosterone organizes the initial stage of the stress response through the MR [9]. Interestingly, there is also evidence for a fast-acting GR that requires endocannabinoids [10].

The hippocampus is not only very sensitive to circulating GC levels, it is also important in emotional processing and key aspects of learning and memory, where adult neurogenesis (AN) has also been implicated [6, 7]. Short-term exposure to stressors induces behavioral adaptation and is considered harmless. Although prolonged GC (over)exposure is often thought to be associated with deleterious alterations in hippocampal excitability, long-term potentiation (LTP), and hippocampus-related memory performance, many positive effects of stress have been described as well, that depend on the type of stressor and its convergence in space and time [5, 8, 11].

Prolonged exposure to stress may induce alterations in HPA feedback that can overexpose the brain and body to aberrant GC levels. Even though feedback is largely mediated through the GR, chronic stress may also alter the function of the MR that is implicated in tonic inhibitory control of the HPA axis and modulates AN [5, 7].

6.5 Stress and Depression

Exposure to severe, repetitive, uncontrollable stressors may facilitate the development of psychopathologies. Major depressive disorder is one among these illnesses known to result from an interaction between environmental stressors and genetic/developmental predispositions [12]. Typical observations in depressed

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patients suggest a hyperactive HPA axis: reduced GR function as tested in the dexamethasone (DEX) suppression test is commonly found, as well as elevated cortisol levels particularly during the trough of the circadian rhythm, increased adrenal size, reduced hippocampal volume, and various other aberrations at different levels of the neuroendocrine system [6, 7, 13].

Many brain structures mediate the different symptoms of depression, and *in vivo* imaging studies on patients with emotional disorders have repeatedly indicated that structures other than the hippocampus are also involved, such as the prefrontal cortex, subgenual cingulate cortex, and amygdala [14]. Altered hippocampal function is likely to influence the activity of other brain structures, in particular, the prefrontal cortex and the amygdala which are key areas in emotional regulation and can, in turn, be influenced by these structures as well. Since the hippocampus indirectly provides negative feedback control of the HPA axis through a poorly understood trans-synaptic network [15], altered hippocampus function may contribute to HPA axis dysregulation, which is common in almost 50% of depressed patients [16].

While depressive and related affective disorders are considered to have a neurochemical basis, recent studies suggest that impairments of structural plasticity, particularly when induced at an early age, contribute to the pathophysiology as well [6, 17–19]. In this review, we will focus on the hippocampal formation, because of the volume changes in depression [20] and the occurrence of AN in this structure.

6.6

Stress-Induced Viability Changes in the Hippocampus: Effect on Function, Volume, Cell Number, and Apoptosis

Loss of hippocampal volume is well documented in stress-related disorders such as depression, and in patients treated with synthetic GCs, or suffering from Cushing's syndrome [20–23]. When stress exposure is prolonged, reductions in neuropil and hippocampal volume have also been reported in animal models. Magnetic resonance imaging (MRI) and morphometric studies, for example, show that chronic psychosocial stressors result in a mild reduction in hippocampal volume, that is around 10% in tree shrews [20]. Effects of stress on hippocampal volume and hippocampal cell number are, however, relatively mild and subregion-specific and occur shortly after stressor onset, but prior to cognitive disturbances [6].

The traditional explanation for this stress-induced hippocampal volume decrease was that elevated GCs in rodents have neurotoxic effects on the hippocampus. Neuronal death in the CA3 and CA1 subregions, in particular, was emphasized [23, 24]. More recent studies however, used state-of-the-art methodology and failed to find evidence for stress-induced massive loss of the principal hippocampal cells [6, 20, 25]. The fact that major neuronal loss cannot explain the hippocampal volume changes observed after stress is consistent with observations that many of the stress-induced structural changes are transient and, for example, spontaneously disappear when animals are subjected to a recovery period [26], or when elevated

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corticosteroid levels are normalized again [6, 20, 22]. As major cell loss in the CA and DG neuronal layers is not responsible for the hippocampal volume changes observed after stress, these must therefore be derived from other factors. Candidate cellular mechanisms are the somatodendritic components, neurogenesis, and glial changes but factors such as shifts in fluid balance cannot be excluded either [18, 20].

6.7 Effects of Stress on Dendritic Atrophy, Spine, and Synaptic Changes

Structural substrates for the stress-induced functional alterations are not necessarily the same and may involve axonal changes, synapse loss, alterations in postsynaptic densities, and dendritic reorganization. The most thoroughly documented stress-induced structural change is the dendritic reorganization that occurs parallel to the loss of spines and synapses and together with alterations in postsynaptic densities, suggesting general changes in neuronal connectivity. Chronic stress or experimentally increased corticosterone concentrations induce retraction of the apical dendrites of the CA3 and, to a lesser extent, of CA1 pyramidal cells and dentate granule cells [6, 27, 28]. Alterations in CA3 synapses and in the morphology of their mossy fiber terminals have also been described [27–29]. These changes in neuronal morphology are likely to contribute to various cognitive deficits occurring as a result of chronic stress exposure. Another possible functional outcome of dendritic retraction may be a disturbance of HPA axis regulation, leading to up-regulated GC release [29]. Recent studies show that such dendritic alterations in hippocampal neurons can already occur within a very short period of time, particularly in relatively immature cells [30]. This synaptic remodeling may also extend to cortical areas, where changes in cell adhesion, molecule expression, attention, spatial memory, and fear conditioning often occur in parallel. The latter dendritic changes appear to occur relatively early and to last for long periods of time [31].

6.8 Adult Hippocampal Neurogenesis

AN refers to the production of new neurons in an adult brain and is a prominent example of the adult neuroplasticity that occurs in most vertebrate species studied today, including humans. In young adult rodents, thousands of new granule neurons are generated every day, though significant differences exist even within different mouse strains [32]. The process of AN is dynamically regulated by various environmental factors and rapidly declines with age [6, 33]. Neurogenesis also occurs in the subventricular zone (SVZ) of the ventricle wall in many mammals and has been reported in the human brain as well [34, 35].

Several independent groups have observed low levels of neurogenesis in other brain structures also, such as the amygdala, striatum, and neocortex but negative results exist as well [36, 37]. Part of the difficulty in studying AN in these regions as such could reside in the fact that new cortical neurons, for example, probably belong to small subclasses of interneurons dispersed in large neocortical volumes [37].

In contrast to its abundance during embryonic development, neurogenesis in the adult is much less frequent but follows a similar, complex multistep process starting with the proliferation of progenitor cells, followed by their morphological and physiological maturation (often referred to as the “*survival*” process). This ends with a fully functional neuron that is integrated into the preexisting hippocampal network [38]. The existence and number of true multipotent neural stem cells residing in the adult DG is still a disputed issue (Figure 6.1). Experimental data

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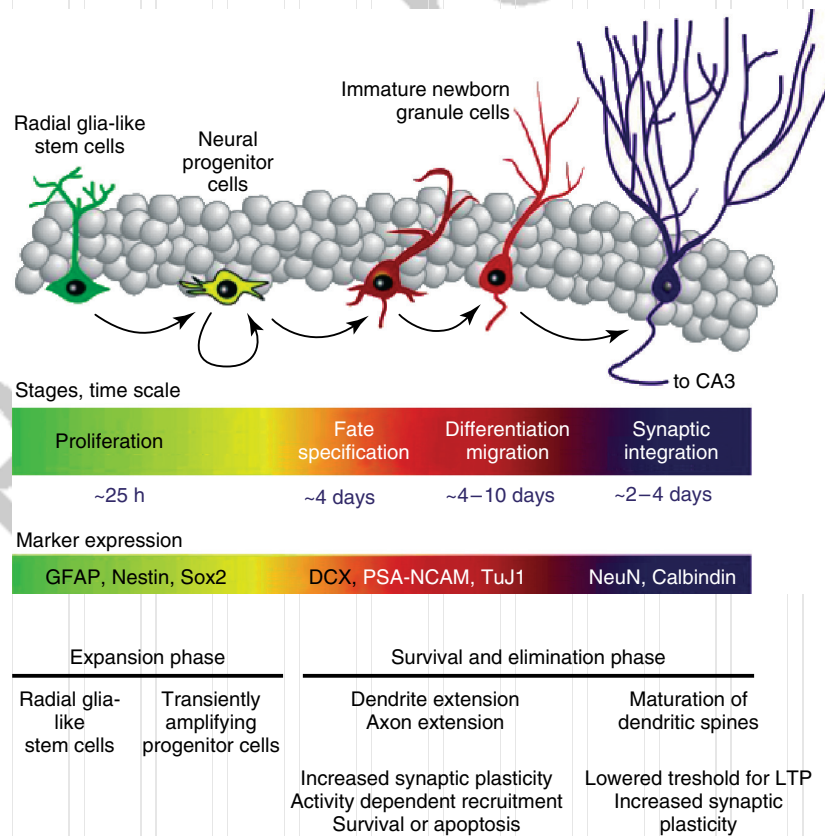


Figure 6.1 Schematic representation of the different stages of neuronal differentiation of newborn cells in the adult dentate gyrus of the hippocampus. Abbreviations: GFAP, glial fibrillary acidic protein; Sox2, sex determining region Y (SRY)-box 2; DCX, doublecortin; PSA-NCAM, polysialylated form of the neural cell adhesion molecule; TuJ1, β -tubulin III; NeuN, neuronal nuclear antigen. (Reproduced from Lucassen *et al.*, 2009.)

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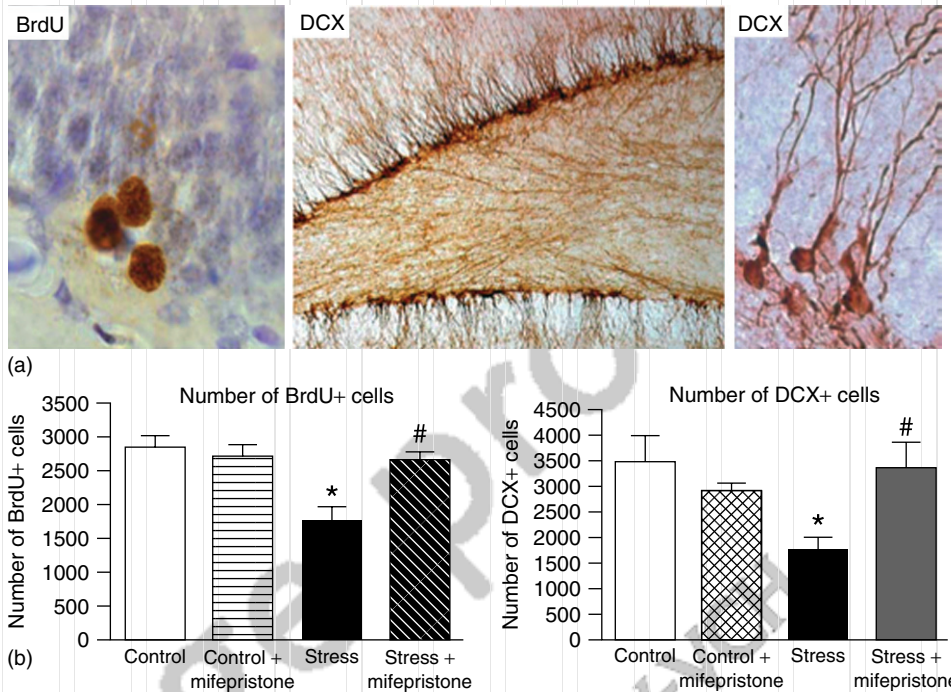


Figure 6.2 (a) Show examples of bromodeoxyuridine (BrdU+) and doublecortin (DCX+) immunostained cells in the DG. DCX-positive somata are located in the subgranular zone (SGZ) with extensions (arrowheads) passing through the granular cell layer. (b) Display BrdU- and DCX-positive cell numbers in rats subjected to 21 days of chronic unpredictable stress. The significant

reduction in both BrdU- (21 day old cells) and DCX-positive cell numbers after chronic stress or corticosterone treatment is normalized by four days of high dose treatment with the GR antagonist mifepristone, whereas application of the drug alone to control animals has no effect (see Mayer *et al.* [66] and Oomen *et al.* [45] for details). (Reproduced from Lucassen *et al.* 2009.)

Q5

report that a heterogeneous population of precursor cells is located and proliferates in the subgranular zone, a narrow layer located between the dentate granule cell layer and hilus. These precursor cells show a characteristic phenotype of radial astrocytes. Daughter cells of these progenitors proliferate at high frequency, often observed as bromodeoxyuridine (BrdU)-positive cell clusters and have been named amplifying neural progenitors •(Figure 6.2). As the newborn neurons mature, they extend axons and dendrites, followed by the formation of spines and functional synapses [6, 38].

New neurons display characteristic functional properties such as lower threshold for induction of LTP and robust LTP [39]. Recent data indicate that the subsequent survival of the newly generated neurons is regulated by their input-dependent activity [40]. There is significant overproduction of newborn cells and many of

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them are rapidly eliminated by apoptotic cell death. A significant turnover of granule cells thus occurs in the DG of young rodents. In monkeys, this turnover rate is significantly lower while no quantitative data are as yet available for humans [41].

AN in the DG is regulated by a large variety of hormonal and environmental factors. AN is, for example, potently stimulated by learning, voluntary exercise, and enriched environmental housing [6]; interestingly, under these circumstances, enhanced neurogenesis is associated with elevated GC levels, whereas in general the reverse is true.

The exact functional role of the newborn granular neurons remains to be determined but numerous reports suggest that AN is involved in learning and memory, especially in the acquisition of spatial learning, in pattern separation, and in anxiety, as reviewed in detail elsewhere [19, 42–44].

6.9 Effect of Stress on Adult Hippocampal Neurogenesis

Stress is one of the most potent inhibitors of AN, as shown in several different species and using various stress paradigms; psychosocial and physical stressors all inhibit one or more phases of the neurogenesis process [6, 26, 28, 45]. Both acute and chronic stress exposure have a potent suppressive effect on proliferation, while continued stress exposure appears to interfere with all stages of neuronal renewal and inhibits both, proliferation and survival, possibly also in depression [18].

Stress-induced reductions in proliferation could result, for example, from apoptosis of progenitor cells or from cell cycle arrest. After acute stress, a reduction in proliferation was paralleled by increased numbers of apoptotic cells, yet no distinction was made between apoptosis of newborn or mature cells. Following chronic stress, both proliferation and apoptosis were reduced, parallel to increases in the cell cycle inhibitor p27Kip1, indicating that more cells had entered cell cycle arrest and that the granule cell turnover had thus slowed down [26, 46].

The exact underlying cellular mechanisms mediating the inhibitory effect of stress are unknown. The adrenal GC hormones have been pointed out as key players in this process and both GR as well as NMDA receptors have been identified on early progenitor cells [47, 48]. At the same time, several examples of a persistent and lasting inhibition of AN exist after an initial stressor, despite a later normalization of GC levels. These findings suggest that while GCs may be involved in the initial suppression of cell proliferation, particularly in early life when neurogenesis is abundant, they are not always necessary for the maintenance of this effect. A large number of other factors may also mediate the stress-induced inhibition of AN. The stress-induced increase in glutamate release via NMDA receptor activation is another leading candidate in this process [47].

Stress is also known to affect the levels of various neurotransmitters that have been implicated in the regulation of AN: GABA, serotonin, noradrenaline, and dopamine, to name a few examples. Other neurotransmitter systems, such as the

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6.10 Normalization of the Effects of Stress on the Hippocampus by Means of GR Blockade 111

cannabinoids, opioids, nitric oxide, and various neuropeptides may contribute as well (see [6, 38] for reviews). Furthermore, stress reduces the expression of several growth and neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), insulin-like growth factor-1 (IGF-1), nerve growth factor (NGF), epidermal growth factor (EGF), and vascular endothelial growth factor (VEGF), that all can influence neurogenesis [49]. Gonadal steroids can also be involved [50]. The proximity of the precursors to blood vessels further suggests a strong interaction with the vasculature and it is this population that is particularly sensitive to stress [51]. Also, astrocytes are important in this respect as they support the survival of developing neurons, possess GRs, and are significantly affected by some [52] but not all types of stress [53].

Many of the symptoms of stress or HPA hyperactivity can typically be reversed with antidepressant (AD) treatment in both human and animal models. The observation that different classes of ADs with distinct mechanisms of action can block the behavioral effects of stress and restore normal levels of adult hippocampal neurogenesis [6, 54] supports the possibility that stimulating neurogenesis is a common pathway through which ADs exert their behavioral and therapeutic effects, although exceptions have been reported [18, 54–57].

6.10 Normalization of the Effects of Stress on the Hippocampus by Means of GR Blockade

As outlined above, excessive GC levels and chronic GR activation have been implicated in the pathogenesis of depression because of their role in increased arousal and psychotic disorganization [58, 59]. Thus, a current experimental treatment strategy is to identify drugs blocking (the effects of) the stress system. Indeed, modulators of the HPA axis often approved for different clinical applications can transiently block GC synthesis in the adrenals or block the access of GCs to their receptors in the brain and are associated with beneficial clinical effects in the treatment of psychosis while antidepressant effects have also been reported. These include cortisol synthesis inhibitors such as ketoconazole and metyrapone, corticotropin-releasing factor (CRF) antagonists, and GR antagonists such as mifepristone.

Interestingly, short-term treatment (four days) with mifepristone has been successfully applied to treat/ameliorate symptoms of psychotic depression in clinical trials [60]. It was found that mifepristone not only reduced symptoms in a subset of severely psychotic depressed patients, it was also especially helpful in treating psychosis secondary to Cushing's disease [61]. Given the fact that psychotic depressed patients tend to be the most resistant to the effects of traditional ADs, these findings seem promising. Thus, patients who are unresponsive to ADs alone and only partially responsive to an antidepressant–antipsychotic combination may benefit from treatment with GR antagonists. However, only high doses of mifepristone were effective, doses that are occasionally associated with adverse effects, although not uniformly across patient populations. Even higher doses are

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associated with skin rash, endometrial hyperplasia, and hot flashes in women. Other inhibitors of HPA axis function are associated with more severe side effects. One concern is mifepristone's clinical efficacy, as highlighted by studies comparing treatment with mifepristone to placebo or other antidepressive and antipsychotic treatments (for a review see [62]).

Q6 In a series of recent experimental studies [45, 63–66], mifepristone was also effective in rats that were exposed to 21 days of chronic multiple unpredictable stressors, a paradigm that altered many structural and functional parameters in the hippocampus (Figure 6.3●) [5, 8]. Interestingly, treatment with a high dose of mifepristone during the final 4 days of this 21 day paradigm rapidly normalized the stress-induced reduction in adult generated cell numbers and neurogenesis in the hippocampal DG [45, 66]. In similar studies with the same design, the increased amplitude of high-voltage activated Ca-currents in CA1 neurons [63, 64] as well as the impaired induction of LTP in the CA1 region that occurred after 21 days of chronic stress [65] were all normalized already after 4 days of high dose mifepristone application. Interestingly, application of mifepristone alone, that is in the absence of concomitant stress exposure, was in all cases ineffective, indicating that mifepristone selectively interferes with pathways activated by chronic stress only, and, for example, does not appear to stimulate compensatory processes [5, 8]. Accordingly, it is not surprising that “clamping” corticosterone levels throughout life by means of adrenalectomy followed by a fixed suppletion, does not lower neurogenesis [67]. This implies that other mediators of the stress axis may also affect neurogenesis. This is indeed the case; both, a CRH-R1 and a vasopressin-1b antagonist were found to reverse lasting chronic stress-induced suppression of neurogenesis when given three weeks after the start of a seven weeks' mild stress paradigm [68].

A wide variety of different types of ADs including 5-HT reuptake modulators and substance P antagonists have been successfully applied to reverse effects of chronic stress on brain cells such as dendritic retraction in the CA3 region. Almost all ADs reverse suppressions of neurogenesis after chronic stress and promote neurogenesis in naive, nonstressed animals. In general, beneficial effects of ADs are seen only after several weeks of treatment and these effects are thought to be crucial for their clinical effectiveness. As such, they most likely do not directly interfere with stress-activated pathways but rather exert counteractive or compensatory effects [6, 7, 38, 49, 54].

Q7 Compounds that affect local excitability can also prevent chronic stress-induced changes. This has been mainly studied for CA3 dendritic morphology where application of a competitive NMDA receptor antagonist during chronic restraint stress prevented CA3 dendritic retraction. Modulation of this same pathway by agmatine also affected neurogenesis. Benzodiazepine application was effective in preventing stress-induced dendritic atrophy, as was daily treatment of tree shrews or rats with phenytoin both regarding CA3● dendritic morphology and LTP in CA1. Finally, a variety of nonspecific interferences have been described, ranging from transcranial magnetic stimulation, electroconvulsive seizures to learning experiences. In general, these treatments by themselves evoke an effect opposite

6.10 Normalization of the Effects of Stress on the Hippocampus by Means of GR Blockade 113

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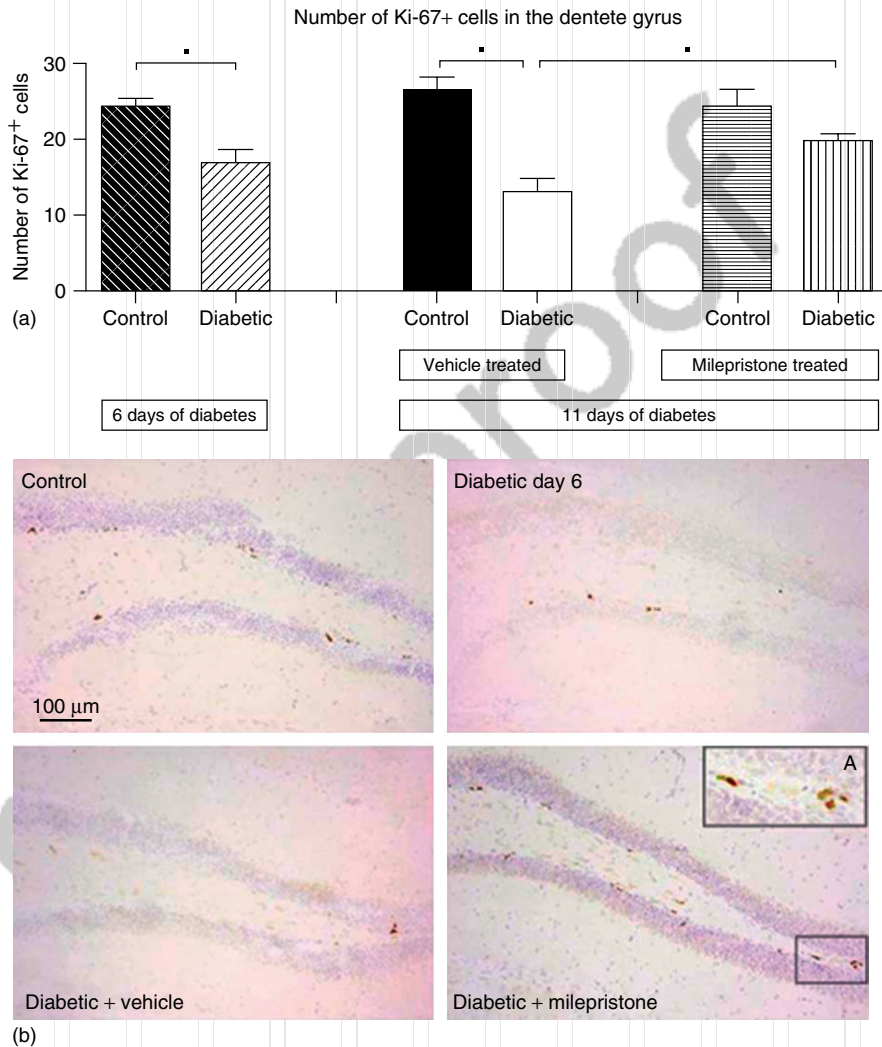


Figure 6.3 Cell proliferation in the sub-granular zone (SGZ) of the dentate gyrus of diabetic animals treated with mifepristone. (a) Quantitative analysis of the immunocytochemistry for Ki-67 in the SGZ. Values

expressed mean \pm SEM, $n = 6-8$, $*p < 0.05$; (b) microphotographs of the different experimental groups. Insert I: 4 times magnification of Ki-67+ cells. Control refers to a control + vehicle-treated mouse.

to that of chronic stress, for example, on neurogenesis or spinogenesis. Also, a recovery period after chronic stress tends to reverse effects on neurogenesis or dendritic remodeling in the CA3 area and prefrontal cortex, though not in the BLA [5, 6, 8, 26, 28].

In conclusion, many treatments can reverse effects of chronic stress on neurogenesis, cell morphology, or cell function. Yet, nearly always, these treatments

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need to be maintained for weeks and seem to act in an indirect manner, usually by exerting effects opposite to those of chronic stress.

6.11 Normalization of Hippocampal Alterations during Diabetes Mellitus Using the GR Antagonist Mifepristone

In recent studies, hippocampal morphology and function was studied in a mouse model for type 1 diabetes (T1D) generated by treating mice with streptozotocin, a compound that destroys the β cells in the pancreas and hence, circulating insulin levels drop. The lack of insulin causes hyperglycemia and cellular starvation, a condition known as *metabolic stress*. One of the concomitant hormonal changes to cope with this metabolic stressor is a profound activation of the adrenal GC secretion [69]. Interestingly, this increased secretion of the adrenals develops through hyperresponsiveness of the adrenals to circulating ACTH rather than elevated levels of ACTH *per se* [70, 71]. As a result of hypercorticism, cells including the neurons in the central nervous system are further deprived of glucose, causing a sustained elevation of corticosterone in these mice. Then the question arose whether this endocrine adaptation in T1D leads to a more fragile state of the brain in which GC excess may enhance the potential for damage and attenuate a protective mechanism, thus facilitating cognitive impairment.

Indeed, uncontrolled diabetes is known to produce signs of hippocampal pathology, which proceeds together with changes in other brain structures such as hypothalamus and cerebral cortex. The hippocampus of the diabetic mice exhibited increased neuronal activation, signs of oxidative stress, and astrogliosis [72–74]. Cognitive deficits were also observed in the hippocampus-dependent novel object-placement recognition task [75], in which mild hippocampal alterations can be tested under conditions of novelty exposure. Nondiabetic control mice preferred the exploration of the object placed in a novel location while the diabetic mice did not, indicating impaired spatial object-placement memory. This mild disturbance is typically observed at early stages of diabetes, while during a more prolonged disease state more severe behavioral deficits were established [76, 77].

Q8 While seeking to clarify the role of hypercorticism in the hippocampus of STZ•diabetic mice, Revsin discovered that the GR antagonist mifepristone administered for four consecutive days (from day 6 to 10 after onset of diabetes in the STZ model) partly prevented and/or reversed hippocampal functional deficits and morphological abnormalities [75]. The antagonist prevented astrogliosis and excessive neuronal activation and reversed the suppressed markers for neurogenesis in the hippocampus induced by the diabetic state and associated high corticosterone [66, 75]. Cognitive deficits observed at day 11 of diabetes were also ameliorated resulting in a performance even better than the untreated controls [75]. These

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findings are supported by another recent study demonstrating that signs of hippocampal deficits did not develop in the diabetic mouse as long as the circulating corticosterone levels were kept low, rather than the excessively high concentrations seen during diabetes. This was achieved by adrenalectomizing the diabetic animals and replacing with corticosterone to achieve physiological levels of the circulating steroid [78].

Hence, remodeling of the structure of the hippocampus is accelerated and its vulnerability to cognitive dysfunctions is enhanced during diabetes in a process that can be blocked by antiglycocorticoid therapy. Previously, hyperglycemia and insulin deficiency were thought to underlie the hippocampal deficits (see [76, 77] for reviews), but these possibilities can be excluded in view of the experiments of Revsin *et al.* [75, 78], although synergy between these conditions and the deleterious effect of hypercortisolemia cannot be ruled out. A rationale behind this observation is that the blockade of the GR would allow a more prominent function of neuroprotective MR-mediated actions [9]. Hence, this would predict that during GR blockade in the face of high circulating GCs, the maintenance of hippocampal integrity is a necessary condition for hippocampal-dependent behavioral performance.

6.12 Concluding Remarks

Chronic stress and stress hormone exposure alters many aspects of brain structure and function including long-term potentiation, neurogenesis, and dendritic complexity. Similar to its rapid effects in clinical studies with psychotic depressed patients, many of the chronic stress- or chronic corticosterone-induced changes in hippocampal structure and function in rodent models could all be normalized by brief treatment with the GR antagonist mifepristone. The same treatment also prevented the occurrence of hippocampal pathology induced by a diabetic state.

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Disclosure

ERdK is a member of the scientific advisory board of Corcept Therapeutics Inc and owns stock.

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Abstract

Keywords

adult neurogenesis; stress; glucocorticoid; depression; diabetes; mifepristone; hippocampus

Affiliation

Affiliation for the author: Paul J. Lucassen¹, Carlos P. Fitzsimons^{1,2}, Erno Vreugdenhil², Pu Hu^{1,4}, Charlotte Oomen¹, Yanina Revsin², Marian Joëls^{1,3}, and E. Ron De Kloet²

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¹ University of Amsterdam, Centre for Neuroscience, Swammerdam Institute of Life Sciences, P.O. Box 94214, 1090 GE Amsterdam, The Netherlands

² Leiden University, Division of Medical Pharmacology, Leiden Amsterdam Center for Drug Research, Leiden, The Netherlands

³ University Medical Center Utrecht, Department Neuroscience and Pharmacology, The Netherlands

⁴ University of Science and Technology of China, Hefei National Laboratory for Physical Sciences at Microscale and Department of Neurobiology and Biophysics, Hefei, Anhui, PR China

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