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SPECIAL ISSUE

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What causes the hippocampal volume decrease in depression?

Are neurogenesis, glial changes and apoptosis implicated?

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Abstract Even though in vivo imaging studies document significant reductions of hippocampal volume in depressed patients, the exact underlying cellular mechanisms are unclear. Since stressful life events are associated with an increased risk of developing depression, preclinical studies in which animals are exposed to chronic stress have been used to understand the hippocampal shrinkage in depressed patients. Based on morphometrical studies in these models, parameters like dendritic retraction, suppressed adult neurogenesis and neuronal death, all due to elevated levels of glucocorticoids, have been suggested as major causative factors in hippocampal shrinkage. However, histopathological studies examining hippocampi of depressed individuals have so far failed to confirm either a massive neuronal loss or a suppression of dentate neurogenesis, an event that is notably very rare in adult or elderly humans. In fact, many of the structural changes and the volume reduction appear to be reversible. Clearly, more histopathological studies are needed; especially ones that (a) employ stereological quantification, (b) focus on specific cellular elements and populations, and (c) are performed in nonmedicated depressed patients. We conclude that mainly other factors, like alterations in the somatodendritic, axonal, and synaptic components and putative glial changes are most likely to explain the hippocampal shrinkage in depression, while shifts in fluid balance or changes in the extracellular space cannot be excluded either.

Key words hippocampus · depression · mood disorder · neuroplasticity · glia

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Introduction

Major depressive disorder (MDD) is a common and life-threatening illness, but despite extensive investigations, little is known about its underlying fundamental biology [74]. The traditional neurobiological concept on the etiology of depressive disorders has been the monoamine hypothesis, but during recent years, it has become evident that factors other than monoamine deficiency or imbalances between various neurotransmitter systems must be taken into account when describing the neurobiological basis of major depression. Contemporary theories place emphasis on the intracellular and structural changes, and suggest that disturbed neuroplasticity, including impaired adult hippocampal neurogenesis, might be implicated in the biological basis of major depression [9, 24, 66].

These novel theories are based on a number of clinical and preclinical observations. Numerous in vivo imaging studies report selective functional and structural changes in limbic structures such as the prefrontal cortex and hippocampus in patients with major depressive disorder [5, 22, 67, 91, 92]. Probably the most reproduced finding is a small (10–15%) but significant reduction in hippocampal volume as documented by in vivo magnetic resonance imaging (MRI) studies [6, 106]. Moreover, duration of the depressive episode is closely paralleled by volumetric changes, with longer periods of depression generally corresponding to smaller hippocampi [92, 93, 61].

Even though the possibility cannot be excluded that a smaller hippocampal volume might be a trait characteristic of MDD [73], it should be noted that hippocampal shrinkage is not specific to depression and has been reported in various other stress-related psychiatric disorders, including posttraumatic stress disorder (PTSD) [95], borderline personality disorder associated with early abuse [23], and possibly with dissociative identity disorder [105]. In addition, reduced hippocampal volume has been demonstrated in a number of other neuropsychiatric and neurological disorders including schizophrenia [39], dementia, Alzheimer's, Parkinson's, and Huntington's diseases, epilepsy, chronic alcoholism, herpes simplex encephalitis, and traumatic brain injury [30].

As the exact mechanisms remain obscure, the aim of the present study is to review and discuss the putative cellular alterations that may contribute to or underlie hippocampal shrinkage in depressed patients. Since stressful life events are associated with the risk of developing depression in genetically predisposed individuals [49, 8] and availability of human postmortem histopathological analyses is limited, it has been proposed that similar cellular changes as observed in animal models of prolonged stress occur in depressed individuals as well [69]. Consequently, for many years, dendritic remodelling and even death of neurons because of elevated levels of glucocorticoids have been put forward as major causative factors underlying this volume reduction [85] (Fig. 1). This assumption was based on various clinical observations indicating that the HPA-axis is hyperactive in depressed individuals [101], and on preclinical studies that reported a massive loss of CA3 pyramidal cells in the hippocampi of severely stressed rats and monkeys [86, 87, 102].

During recent years, however, it has become evident that massive neuronal loss resulting from hypercortisolism can be excluded, because in human postmortem brain tissue of depressed and of steroid-treated subjects, no major cell loss was apparent, nor could any neuropathology be found [58, 71, 77, 99]. It should be noted, however, that no stereological quantification was performed in these studies. Currently, unbiased stereological cell-counting techniques are the method of choice for evaluating changes in cell numbers in a specific brain structure. However, such methods require the analysis of entire, intact brain structures of interest, which are often difficult to obtain.

Another difficulty when investigating the pathophysiological basis of depression is the limited availability of brain tissue of nonmedicated depressed subjects. Such tissue is extremely rare but would be preferred given the fact that many antidepressant drugs (AD) affect structural hippocampal plasticity [25], and AD treatment may hence ameliorate or obscure the cellular changes that could initially have contributed to the hippocampal volume reductions in depression. Other mechanisms that could affect hippocampal volume may involve somatodendritic, axonal, and synaptic components of the hippocampal neural network, or changes in adult glio- or neurogenesis. As we will discuss, the degree to which particularly the latter two alterations could contribute to the hippocampal volume loss is disputable.

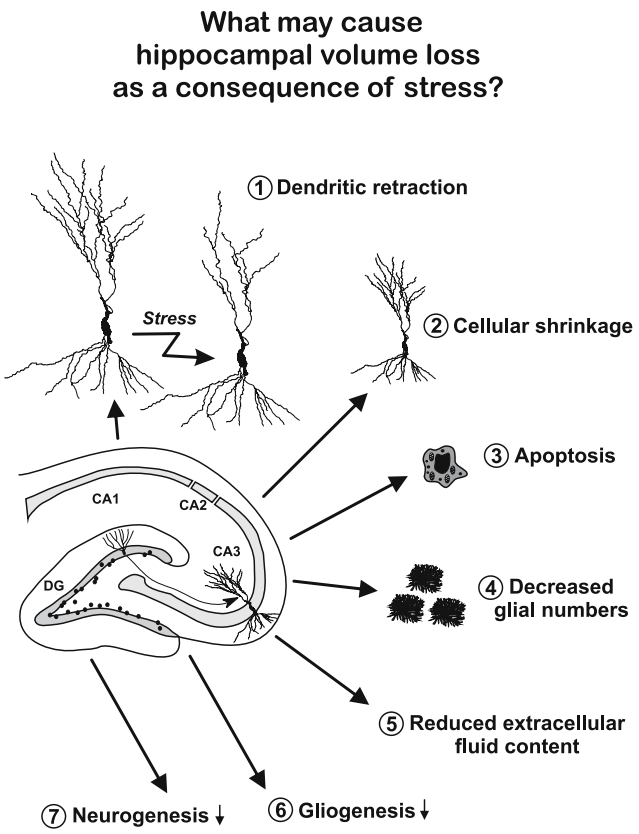

Fig. 1 Stress-induced cellular changes reported in animal studies suggest the various possibilities that could underlie hippocampal shrinkage in depressive disorders. (1) Dendritic debranching after chronic stress exposure is the best-documented phenomenon in preclinical studies. (2) Cellular shrinkage has been reported for both neurons and glia. (3) Apoptosis used to be the major candidate for volume reduction, but recent studies could not demonstrate massive neuronal loss either after chronic stress exposure in animals or in depressed patients. (4) Decreased numbers of astroglia have been reported in an animal study after chronic stress. (5) Clinical data suggest that shifts in fluid balance between the ventricles and brain tissue could significantly contribute to the hippocampal volume reduction. (6) Reduced gliogenesis has been reported in animal studies after stress or glucocorticoid exposure. (7) Reductions in dentate neurogenesis have been suggested as playing a role in hippocampal shrinkage. However, such a cellular change is simply too small to be a significant modulator of the significant changes in volume of the entire hippocampus. Reduced neurogenesis was paralleled by increased incidences of apoptosis after acute stress exposure, whereas after chronic stress, both neurogenesis and apoptosis are reduced in the dentate gyrus, slowing down the neuronal turnover. Results from animal studies suggest that many of these changes can be reversed by recovery or antidepressant treatment

Can stress-induced reduction in neurogenesis contribute to hippocampal volume loss?

Reduction in the rate of neurogenesis in the adult hippocampal dentate gyrus has been suggested to play a role in hippocampal shrinkage [40] (Fig. 1). As

shown in various animal species, stress, and glucocorticoids are among the most potent inhibitors of neurogenesis in the adult dentate gyrus [28, 29, 15, 78, 108, 37, 68, 70]. Chronic stress appears to have an age-dependent effect when suppressing adult dentate cell proliferation in such a way that middle-aged and old animals that show much lower levels of neurogenesis already [36] are generally more vulnerable to the inhibitory effect of stress [90].

Parallel to these findings, a growing number of studies demonstrate that in chronic stress paradigms and various animal models of depression, the suppressed adult neurogenesis can be reversed by different types of classical antidepressant treatments including electroconvulsive stimulation and blockade of the glucocorticoid receptor [2, 14, 43, 46, 64, 68, 103]. At least in some cases, the reduction in volume was also reversed [2, 14, 103]. This is consistent with the general clinical experience with depressive patients, in whom treatment can relieve the depressive symptoms, several of the HPA alterations, and even hippocampal volume loss. Also, reversible changes are difficult to reconcile with a concept of permanent cell loss.

These findings have sparked great enthusiasm and excitement among researchers, resulting in much work on the concept that altered neurogenesis may contribute to the pathogenesis of depression and may play a significant role in, for example, the cognitive symptoms occurring in this disorder [21, 24, 42, 48, 65, 109]. So far, the most crucial experimental evidence supporting this theory is the demonstration that in mice, selective disruption of neurogenesis in the dentate gyrus by X-ray irradiation blocked the behavioral effects of chronic antidepressant treatment [84]. At the same time, others point to indirect effects and vigorously dispute the functional significance of newly generated neurons in the pathophysiology of mood disorders [40].

It is important to point out that reducing neurogenesis itself by means other than stress—for example, directly by X-ray irradiation—does not yield depressive symptoms in an animal. Furthermore, X-ray irradiation may affect hippocampal synaptic plasticity or learning [88] by directly inhibiting neurogenesis, but it may also induce microaneurysms and inflammatory changes that can indirectly affect cell proliferation and hippocampal function. Clearly, the most convincing evidence for a central role of reduced neurogenesis in the pathogenesis of depression would come from the visualization of neurogenesis in live subjects using, for example, PET imaging. Although recent animal work is promising [89], these approaches are so far technically not sensitive, practical or specific enough for human studies.

Another option is the direct examination of postmortem brain tissue of depressed patients. However, this will be very difficult given the very limited availability of such material and the extensive variation in the type, dose, and duration of the antidepressant medication between depressed patients. Given their role in structural plasticity, drugs would be expected to have normalized initial reductions, if any, in neurogenesis or other structural parameters [14, 16]. Moreover, in adult and elderly individuals, neurogenesis is a very rare phenomenon (Fig. 2), while additionally, methodological aspects like postmortem delay and fixation are critical for the visualization of some of the marker proteins, like doublecortin, that identifies newborn neurons [3].

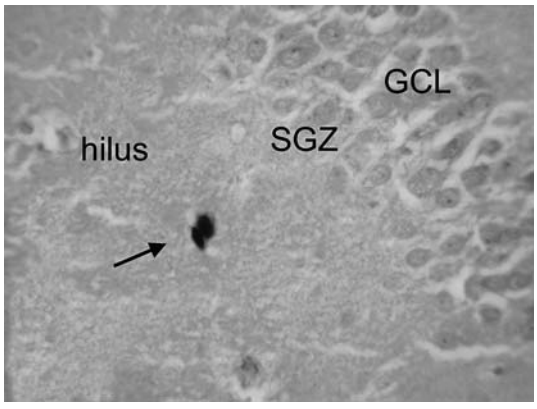

Fig. 2 A proliferating cell identified by PCNA (proliferating cell nuclear antigen) immunocytochemistry in the human hippocampus of a control subject aged 56 years; note its isolated and rare occurrence. GCL; granular cell layer, SGZ; subgranular zone. Arrow points to a dividing PCNA positive doublet

So far, there is only one reported study [80, see also Reif et al. in this issue) that compares the level of neural stem cell proliferation in postmortem hippocampal samples from psychiatric patients with controls. The authors confirmed the very rare occurrence of proliferation in the adult human brain [26, 3] but failed to find any change in depressed patients, and neither did antidepressant treatment result in an increase of neural stem cell proliferation. As this study was based on a relatively small sample size, further studies are warranted. So far, there is therefore no clinical evidence that an altered rate of adult dentate neurogenesis is critical to the etiopathology of affective disorders.

Another problem with the concept that reduced dentate neurogenesis significantly contributes to the hippocampal volume loss in depressed humans is the magnitude of the expected cellular change. Even though neurogenesis can be stimulated several fold in animals in response to environmental stimuli [47], the rates of stem cell proliferation and neurogenesis in adult and elderly individuals are very low [3, 26, 36, 51]. When the stress-induced reduction in new neuron numbers is estimated and compared with the total hippocampal cell population, it is unlikely that such minute alterations can significantly contribute to the 10–15% reduction in the entire hippocampal volume that has been detected in the human brain using MRI.

To estimate the potential contribution of suppressed neurogenesis to total hippocampal volume, one has to consider that the human dentate gyrus contains ~15 million granule cells, together with an additional ~16 million pyramidal cells of the CA1 region, and ~2.7 million pyramidal neurons in the CA2-3 region, plus ~2 million neurons located in the hilus [112]. Thus, in total there are approximately 36 million neurons within the entire hippocampal formation. To our knowledge, the exact frequency of adult dentate neurogenesis so far has not been assessed in humans, thus we can only rely on estimates originating from nonhuman primates. Kornack and Rakic [50] estimated that in the hippocampal formation of adult rhesus monkeys, approximately 0.004% of the total granule cell population is generated per day. In other words, there is one newborn neuron per 24,000 existing granule neurons per day. This number is several magnitudes lower than the cell proliferation rate in experimental rodents. In juvenile rats, approximately 9,000 new cells are generated daily, which is equivalent to one new cell per 130 mature granule neurons each day [7]. It should be noted that this number already decreases rapidly from six weeks of age onwards [36].

As demonstrated previously, the human hippocampus also retains its ability to generate neurons throughout life [26]. This study examined hippocampal samples from elderly cancer patients who had been injected with the thymidine analog bromodeoxyuridine (BrdU), which labels DNA during the S phase. According to their findings, there were up to 300–400 newborn cells per mm^3 sample volume in the germinative zone of the dentate gyrus (Fig. 2 in [26]). Other studies confirm that cell proliferation rates in the adult and aged human dentate gyrus are very low [19, 3]. It appears that the higher the position of a given species in the phylogenetic tree, and the longer its life span, the lower the rate of adult neurogenesis.

Considering these data, we expect that in humans, the incidence of adult neurogenesis is at least one order of magnitude lower than in nonhuman primates. Even if we are optimistic and assume that a similar rate occurs in humans as in rhesus monkeys, this would result in 625 newborn granule cells per day in the human dentate gyrus compared with 15 million existing granule cells. Over a month, this may accumulate to ~18,000 newly generated cells, but based on rodent data [18], a fair estimate is that approximately only 20–30% of these new cells will eventually survive and actually differentiate into a neuronal phenotype.

Thus, the result of our careful estimate—which is likely to be an overestimation—about 5,000 new granule cells appear in the human dentate gyrus per month. This accounts for 0.03% of the entire granule cell population of the dentate gyrus, and to 0.017% of the entire neuron population within the hippocampal formation. Even though animal studies suggest that these cells, and the earlier generated newborn cell populations, do incorporate into the hippocampal circuit and will contact thousands of other cells in CA3 and CA1, it is very unlikely that reductions in this minute renewal rate can significantly contribute to hippocampal shrinkage. Moreover, neurogenesis only occurs in the dentate gyrus, which accounts for only 6% of the volume of the human hippocampus [45], which makes it even more unlikely that altered rates of neurogenesis can significantly contribute to volume changes of about 10–15%, as observed in major depression.

At the same time, it is important to realize that its low frequency does not necessarily imply that the functional consequences of a change in neurogenesis rate after, for example, stress, are also modest. Given its strategic location within the trisynaptic circuit of the hippocampal formation, changes in neurogenesis will, over time, be amplified by subsequent structural adaptations in the projection areas of the dentate gyrus. Relatively small changes in structural parameters like synaptic terminal structure or dendritic arborization, can, after amplification influence properties in subsequent subregions and have considerable functional consequences for critical hippocampal subregions like the dentate gyrus and CA3. For instance, the temporary slowing down of proliferation and neurogenesis after chronic stress will affect the overall composition, average age and identity of dentate granule cells, and thus have considerable consequences for the connectivity and input properties of the hippocampal memory circuit [44, 37].

In summary, changes in adult dentate neurogenesis, if they exist at all in depressed patients, are likely to be too small to contribute to the considerable hippocampal volume reductions in depressed patients.

Could alterations in gliogenesis, glial number and morphology contribute to hippocampal volume reduction?

During recent years, abnormalities of glial function have been shown to contribute to the impairments of structural plasticity and overall pathophysiology of mood disorders [12, 13]. Glial cells slightly outnumber neurons in the human hippocampus [45], thereby constituting a substantial hippocampal volume fraction. Because of this, changes in glial number or morphology can significantly affect hippocampal volume. During pathophysiological conditions, specific glial subtypes may become activated, or may undergo fast migration; they may also die, or, similarly to the dendritic debranching documented in neurons, may retract their elaborate branching processes, and by doing so reduce their cellular volume.

Despite the growing recognition of the importance of glial cells in physiological and pathological condi-

tions, relatively little attention has been paid so far to possible numerical, or morphological changes in glia cells, or to alterations in gliogenesis in the hippocampi of depressed patients. In fact, earlier histological studies expected gliosis in the brains of patients with mood disorders, but until now, no such histopathology, or other classic neuropathology could be demonstrated [17, 71, 77]. Instead, reductions in glial number appear to be common in related limbic structures like the amygdala and prefrontal, orbitofrontal and cingulate cortices of depressed patients [4, 12, 32, 79]. In contrast to these findings, similar analyses of hippocampal postmortem samples have so far failed to find major reductions in glial cell numbers [34, 58, 71, 99].

However, a recent study assessing changes in total cell numbers in the pyramidal layer of the CA1 region reported a reduced ratio of glia per pyramidal neuron, which suggests a slight glial reduction in MDD patients [11]. Another alteration related to glia was a reduced glial fibrillary acidic protein (GFAP) staining of astrocyte cell bodies in the CA1/CA2 portion of the hippocampus of both steroid-treated and depressed patients [71]. Once again, in most of these studies, the depressed patients were not free of antidepressant medication, which could have been a confounding factor, while also only limited numbers of sections were examined. As such, these findings represent initial and qualitative observations. To establish whether glial numbers are altered in depression, more systematic and quantitative studies are needed that examine the entire hippocampal formation of non-medicated depressed patients and evaluate the different glial subtypes separately.

Future studies are warranted as glial abnormalities are obviously present in other limbic structures (see above). Moreover, there is experimental evidence indicating that stress and antidepressant treatment can induce changes in gliogenesis, glial morphology, and cell numbers [1, 16, 111]. For example, reduced gliogenesis has been reported in the adult rat hippocampus after glucocorticoid treatment [1, 111], and electroconvulsive seizure treatment could reverse this effect [111]. In a chronic social defeat stress model in the tree shrew, specific, differential changes were found in the number of apoptotic glial cells in various hippocampal subregions, many of which were affected by treatment with the antidepressant drug tianeptine [55, 59].

Recently, our group reported that when tree shrews were subjected to the chronic social defeat model of depression, their numbers of GFAP-positive astrocytes were significantly reduced, but concomitant treatment with fluoxetine could block this effect of stress [16] (Fig. 3). Furthermore, in the same paradigm, both stress and drug treatment altered the somal volume of the astrocytes [16]. Astroglia are the most abundant type of glia and account for about one-third of the mass of the brain, and their ratio to

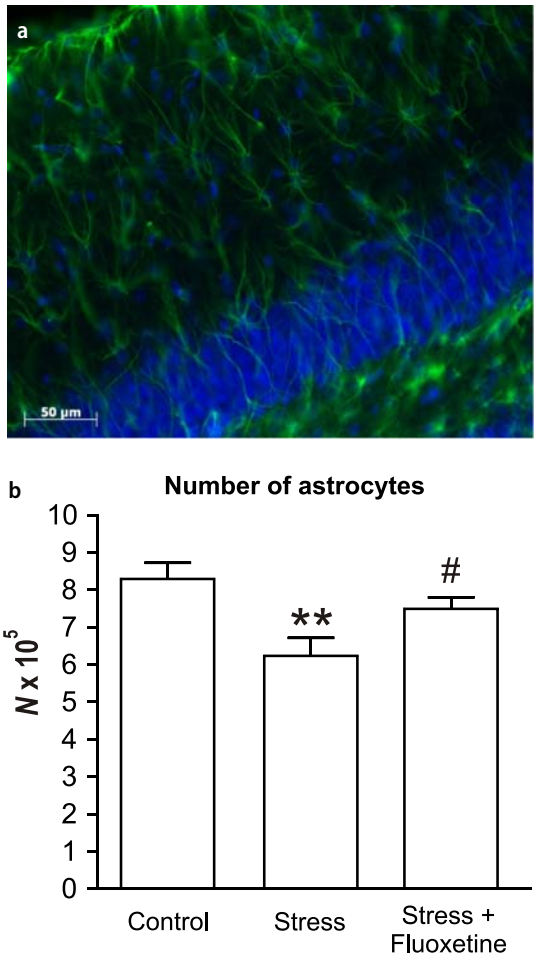

Fig. 3 Effects of chronic psychosocial stress and concomitant fluoxetine treatment on the total number of GFAP-immunoreactive astrocytes in the hippocampal formation: (**A**) representative example of glial fibrillary acidic protein (GFAP) stained astroglia (green) in the hippocampal dentate gyrus of a tree shrew. Neuronal labeling with DAPI (blue). Scale bar: 50 µm. (**B**): Stress significantly decreased the number of GFAP-IR astrocytes, whereas fluoxetine treatment resulted in a partial normalization of GFAP-positive glial numbers. Results are given as mean total numbers ($\times 10^5$) ± SEM. $^{**}P < 0.01$ versus Control; $\#P < 0.05$ versus Stress

neuronal numbers rises profoundly with increases in phylogenetic distance [72]. In humans, specialized types of astrocytes are unique to the primate neocortex, and some even argue that astrocytic complexity may distinguish the human brain from rodent and primate species [76].

Astrocytes provide a structural framework for the brain, maintain pH and ion homeostasis in the extracellular space, supply energy and nutrients to the neurons, clear neuronal waste, and through their end feet on blood vessels are involved in monitoring of peripheral changes in blood composition. Furthermore, recent studies have revealed that besides these "housekeeping" functions, astrocytes are in fact dynamic regulators of synaptic strength, synaptogenesis and neuronal production in the adult dentate gyrus [35, 72]. Astrocytes also possess receptors for neurotransmitters and steroid hormones that, similarly to

receptors in neurons, can trigger electrical and biochemical events in the astrocyte [27, 35]. Thus, structural changes of astrocytes are likely to have an important functional significance for neuron–glia and neuron–neuron communication and are also of particular relevance for hippocampal volume changes.

Could apoptosis or cell death contribute to the hippocampal volume reduction in depressed patients?

In addition to adult neurogenesis, apoptosis continues to occur in the adult dentate gyrus, albeit with very low numbers detectable per tissue section. In fact, a large percentage of the newborn cells in the hippocampus die within a few days after their birth [18].

A wide range of studies have addressed the consequences of chronic stress and prolonged glucocorticoid (GC) exposure for hippocampal structural and functional integrity. GC excess creates functional alterations, for example in hippocampal long-term potentiation and learning and memory [20, 44]. Initial studies indicated that GCs exert deleterious effects on structural parameters ranging from initial, and still reversible, retraction of the dendritic tree of particularly CA3 and, although to a lesser extent, also the CA1 pyramidal and dentate granule neurons, that is paralleled by reversible remodeling of synaptic terminal structures [86, 87, 97] (Fig. 1). At later stages, shrinkage of the hippocampus as a whole occurs, and an increased vulnerability to metabolic insults and possibly neuronal death of CA3 neurons may occur in cases of extreme and prolonged stress [85, for reviews see: 57, 96, Fig. 1).

Although necrosis has also been implicated, stress-induced excitotoxic cell death in the hippocampal CA3 region was initially expected to be mediated through apoptosis [82, 85]. Of interest, linkage studies have recently identified APAF1, the gene for apoptosis protease activating factor1, as a predisposing factor for major depression [33]. Furthermore, antidepressants and stress regulate various neurotrophic factors involved in survival pathways that control apoptosis mediators like CREB, BDNF and MAP kinases [10, 67].

Apoptotic cell death is, however, extremely rare in tissue sections because of its short duration, i.e., hours, during which the cell death process is completed. In the rat brain, for example, steroid-related apoptosis was detectable for a maximum of 72 h [41]. Hence, the chance of detecting apoptosis in thin tissue sections obtained from a chronic brain disorder is very low. Another methodological problem with the detection of apoptosis is not only that the commonly used TUNEL technique is fixation sensitive [54, 56] but also that it basically relies on the detection of massive DNA fragmentation, which is only part of the last stage of an apoptotic cell's demise. At this stage, the cell has shrunken and is often pyknotic and has significantly reorganized its cellular constituents. As a result, most structural proteins are altered or lost altogether, which makes phenotypical analysis of apoptotic cells detected with TUNEL difficult if not impossible in in vivo models or in the human brain. In future studies, immunocytochemistry for specific executioner caspases may be beneficial in this respect.

Either way, accumulating over time, the contribution of apoptosis to hippocampal structural changes can be considerable. Parallel to adult neurogenesis, stress modulates apoptosis and hence DG turnover and total cell numbers that are often correlated, also in non-rodent animal models for chronic stress [37, 59, 104] (Fig. 1). Most of these structural plasticity changes are, however, transient and generally reversible after appropriate recovery periods, following cessation of the stress or corticosteroid exposure, or as a result of antidepressant treatment [37, 55, 59].

To address the neuropathological correlates of cortisol exposure for the human hippocampus and to examine whether apoptosis might be involved, previous studies on hippocampal tissue from major depressed patients and a group of nondepressed individuals who have been treated with synthetic steroids, like prednisone or dexamethasone, revealed that their hippocampus was structurally intact and no indications for massive cell loss could be observed in either the depressed or the steroid-treated group [58, 71]. Apoptotic cells were detected in very low numbers, and were notably absent from areas at risk for glucocorticoid damage like CA3, and mostly found in the dentate gyrus, indicating that apoptosis probably contributes only to a very minor extent to the volume changes in depression.

This is consistent with various recent animal studies in which the effects of chronic stress exposure or cortisol treatment were studied using a stereological approach that revealed no neuropathological effects or massive cell loss [53, 96, 107, 104]. However, despite the methodological limitations associated with the detection of apoptosis, the possibility cannot be excluded that increases in apoptosis, either in neurons or glia, may have occurred in earlier stages; for example, at the onset of the disorder. Moreover, almost all patients studied here have received antidepressant therapy during their lives, which is known to influence apoptosis as well as neurogenesis [52, 55, 65].

In vivo MRI studies suggest a correlation between hippocampal or brain volume reduction, memory deficits and cumulative glucocorticoid exposure during, for example, aging and depression, although exceptions have also been reported [60, 94, 73]. However, such studies do not provide conclusive evidence for permanent changes, like apoptosis-mediated cell loss. Hippocampal volume reductions

during high steroid doses or in Cushing's disease, for example, were shown to be reversible after a decrease or cessation of the steroid exposure or blockade of the glucocorticoid receptor [98, 101]. Hence, reversible and adaptive rather than neurotoxic or apoptotic phenomena are expected to underlie the hippocampal volume shrinkage.

Other possible factors

The conclusion of the latest postmortem studies investigating cellular changes in the hippocampi of depressed patients has been that even though neuronal loss is absent, a significant reduction in neuropil and a slight glial reduction are apparent [99, 11]. These data are consistent with reductions in glial cell numbers and neuronal body size in the prefrontal and orbitofrontal cortex [12, 79]. As neuropil comprises dendrites and axons as well as glial processes, this would imply that the loss of neuropil could reflect a reduced dendritic branching, reduced spine density and complexity, together with smaller glial processes. Accordingly, diminished arborization of apical dendrites together with a decreased dendritic spine density has been reported in the subiculum of a small group of mixed subjects with bipolar disorder or depression [81], while synaptic pathology has also been described in bipolar disorder but not in major depression [34].

In contrast to the scarce human data, there is a large body of evidence from animal studies that documents dendritic shrinkage of CA3 pyramidal neurons after chronic stress exposure or as a result of corticosterone administration (e.g. 62, 97, 110, 113]. Similar shortening of dendritic branches, although to a smaller extent, has been observed in dentate granule cells and in CA1 pyramidal cells in chronically stressed and corticosterone-treated rats [97]. Furthermore, a significant loss of synapses on the CA3 pyramidal cells and profound changes in the morphology of their afferent mossy fiber terminals were detected in chronically stressed or corticosterone-treated animals [63, 83, 97]. Parallel to these findings, there is evidence that antidepressant treatment can also alter the complexity of dendritic arbor and spine density [31, 75, 110].

As a nonstructural explanation of the hippocampal volume changes, one may also speculate on a shift in fluid balance between the ventricles and brain tissue (Fig. 1). This is supported by numerous clinical studies reporting enlarged ventricles, parallel to lower volumes of different brain structures in patients with affective disorder (reviewed by [67], or by studies reporting on reductions in water content or balance after treatment with high levels of corticosteroids, an effect also observed in the clinic when patients are treated with corticosteroids to reduce edema caused by cancer. Ventricular enlargements and the parallel cerebral atrophy may normalize following cessation of corticosteroid administration. The idea that altered water content is apparent in the hippocampi of depressed patients is further supported by the observation that when frozen, such tissues shrink differently compared with controls [99].

Consistent with the idea of a shift in fluid balance, changes in the extracellular space (ECS) and vasculature should also be taken into account [100]. The vasculature not only is in close contact with astrocytic end feet but also provides a niche for adult neurogenesis, and many peripheral changes—such as stress hormone or growth factor concentrations—are monitored here. Chronic stress in rats, for example, was found particularly to affect vascular associated proliferation as well as protein levels of vascular endothelial growth factor (VEGF) and its receptor in the brain, Flk-1, all in a reversible manner [38]. In addition, the ECS of the central nervous system is the microenvironment of neurons and glial cells, and its composition and size change dynamically during neuronal activity as well as during pathological states. Although the hypothesis of an impact of ECS on hippocampal volume changes is not yet supported by experimental data, it is of interest to consider in future studies.

Summary

The exact mechanisms responsible for the hippocampal volume loss in major depression are so far unclear. Massive neuronal loss can be excluded, as no major cell loss was apparent in human postmortem brain tissue of severely depressed patients, nor was massive neuropathology found. In addition, apoptosis was observed only to a very limited extent in depression and not in subregions expected to be at risk for glucocorticoid overexposure.

Adult neurogenesis has been regarded as another mechanism that might significantly affect hippocampal volume. However, neurogenesis adds relatively few neurons per day, and the suppression of this process, if such inhibition exists at all in depressed patients, is likely to be too modest to provide a significant contribution to the approximately 10–15% hippocampal volume reduction reported in depressed patients. Yet, the slowing down of the neuronal turnover in the dentate gyrus by altering both cytogenesis and apoptosis will affect the overall composition, average age and identity of neurons (or glia) and may have considerable consequences for the connectivity, input, and output properties of the hippocampal circuit, and hence for hippocampal function.

Other factors, such as alterations in the dendritic, axonal, and synaptic components, are likely to contribute to the hippocampal shrinkage. Based on the results of animal experiments, particularly changes in

glial cell numbers and in the complexity of glial processes are worth studying in further detail and receiving more attention, even though they have not yet been confirmed in human postmortem studies. More mechanistic explanations underlying the hippocampal volume change, such as shifts in fluid balance between the ventricles and brain tissue, or changes in the extracellular space, cannot be excluded at present and are of interest to consider in future studies. In summary, various neuropathological and animal studies indicate that depression is a disorder of neuroplasticity and cellular resilience and not a neurodegenerative disease.

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