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ORIGINAL PAPER

Functional Neurochemistry of the Ventral and Dorsal Hippocampus: Stress, Depression, Dementia and Remote Hippocampal Damage

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Abstract

The hippocampus is not a homogeneous brain area, and the complex organization of this structure underlies its relevance and functional pleiotropism. The new data related to the involvement of the ventral hippocampus in the cognitive function, behavior, stress response and its association with brain pathology, in particular, depression, are analyzed with a focus on neuroplasticity, specializations of the intrinsic neuronal network, corticosteroid signaling through mineralocorticoid and glucocorticoid receptors and neuroinflammation in the hippocampus. The data on the septo-temporal hippicampal gradient are analyzed with particular emphasis on the ventral hippocampus, a region where most important alteration underlying depressive disorders occur. According to the recent data, the existing simple paradigm "learning (dorsal hippocampus) versus emotions (ventral hippocampus)" should be substantially revised and specified. A new hypothesis is suggested on the principal involvement of stress response mechanisms (including interaction of released glucocorticoids with hippocampal receptors and subsequent inflammatory events) in the remote hippocampal damage underlying delayed dementia and depression induced by focal brain damage (e.g. post-stroke and post-traumatic). The translational validity of this hypothesis comprising new approaches in preventing post-stroke and post-trauma depression and dementia can be confirmed in experimental and clinical studies.

Keywords Ventral hippocampus · Dorsal hippocampus · Stress · Depression · Stroke · Head trauma

Abbreviations

BDNF	Brain derived neurotrophic factor
CRH	Corticotropin releasing factor, corticoliberin
DG	Dentate gyrus
dHi	Dorsal hippocampus
GR	Glucocorticoid receptor
HPAA	Hypothalamus-pituitary-adrenal axis
LTP	Long term potentiation
MCAO	Middle cerebral artery occlusion
MR	Mineralocorticoid receptor
TrkB	Tyrosine receptor kinase B or BDNF/NT-3 growth factors receptor
vHi	Ventral hippocampus.

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Introduction

The brain is the central organ of stress and adaptation to stress; on the one hand, it recognizes and verifies the threat, on the other hand, it determines and governs molecular, physiological and behavioral responses to the stressor. Amazing structural and functional plasticity of the brain is underlying the excellence in stress response and adaptive ability of living organisms [1, 2]. Hippocampus is the limbic brain structure most remarkable for its sophisticated structure and a variety of functions ensuring the integrative role of the brain in the survival, development and well-being of the organism. According to the precise phrase of McEwen et al. "the hippocampus provided the gateway into much

of what we have learned about stress and brain structural and functional plasticity" [3]. Indeed, this structure includes different parts and cell types demonstrating remarkable plasticity and involved in essential functions, in particular, learning, memory, emotions, adaptation, and neuronal cell rebirth. Not surprising, that pathological alterations in this universal and critical brain structure underlie various mental and neurological diseases, in particular depression, dementia, epilepsy [4]. In fact, the growing body of data suggests a relationship between exposure to stress-induced glucocorticoids and hippocampal impairment. For example, there is strong evidence which associates hypercortisolemia in humans with later cognitive dysfunction, these data being supported by many rodent data [5].

Corticosteroids and Hippocampus

Naturally occurring corticosteroids, cortisol and corticosterone, the key hormones managing stress response and adaptation, are closely associated with hippocampal functions (Fig. 1). They are secreted from the adrenals in hourly pulses and after stress as a result of hypothalamus-pituitary-adrenal axis (HPAA) activity, and maintain normal functioning of the organism and resilience/adaptation. Adrenal glucocorticoids are major modulators of multiple functions, including energy metabolism, stress responses, immunity, and cognition [6]. Corticosteroids act in a cell-specific and context-dependent manner to coordinate individual responses to changing environments. They modulate expression of different genes including Errfi1 and Ddit4 (their up-regulation associated with the altered transcription of genes regulating growth factor and mTORC1 signaling) (Gab1, Tsc22d3, Dusp1, Ndrg2, Ppp5c and Sesn1); genes responsible for progression of the cell cycle (Ccnd1, Cdkn1a and Cables1), regulation of transcription (Klf9, Bcl6, Klf15, Tle3, Cxxc5, Litaf, Tle4, Jun, Sox4, Sox2, Sox9, Irf1, Sall2, Nfkbia and Id1), the selective degradation of mRNA (Tob2), involved in the regulation of metabolism (Gpd1, Aldoc and Pdk4), actin cytoskeleton (Myh2, Nedd9, Mical2, Rhou, Arl4d, Osbpl3, Arhgef3, Sdc4, Rdx, Wipf3, Chst1 and Hepacam), autophagy (Eva1a and Plekhf1), vesicular transport (Rhob, Ehd3, Vps37b and Scamp2), gap junctions (Gjb6), immune response (Tiparp, Mertk, Lyve1 and Il6r), signaling mediated by thyroid hormones (Thra and Sult1a1), calcium (Calm2), adrenaline/noradrenaline (Adcy9 and Adra1d), neuropeptide Y (Npy1r) and histamine (Hdc), synthesis of polyamines (Azin1) and taurine (Cdo1) [7].

Half a century ago, McEwen et al. discovered that tritiated corticosterone administered to adrenalectomised rats is accumulated in neurons of hippocampus rather than those in other brain regions, e.g. hypothalamus [8]. This discovery has marked a critical significance of endocrinology for neurobiology and its implication for the understanding higher brain regions operation. It became clear that glucocorticoids act through the specific receptors and this signal transduction enables the regulation of a wide variety of biological processes. Further, the group of de Kloet has carried out a large series of unique and most elegant experimental and theoretical studies, and the results of their profound investigations formed the basis for our current understanding on the involvement of corticosteroids in behavior and cognition in both normal and pathological situations [9–18]. Brain cells express two types of corticosteroid receptors which differ in distribution and affinity. The diverse actions of corticosterone are mediated by mineralocorticoid receptor (MR) expressed abundantly in the limbic circuitry, particularly in the hippocampus, and glucocorticoid receptor (GR), operating as a binary system in concert with neurotransmitter and neuropeptide signals to activate or inhibit stress reactions. de Kloet described functional profile of the binary brain corticosteroid receptor system as mediating, multitasking, coordinating, and integrating [14]. The high-affinity corticosterone receptor called MR was cloned in addition to the classical GR, both receptors acting as classical gene transcription factors. Later, the function of the brain MR was separated from that of the closely related GR, and, finally, the two faces of brain MR were discovered.

MRs are responsible for the regulation of salt appetite, and reciprocal arousal, motivation and reward by a network of aldosterone-selective MR-expressing neurons, while the limbic-forebrain nuclear and membrane MRs act as a switch in the selection of the best response to cope with a stressor (limbic MR promotes selective attention, memory retrieval and the appraisal process, while driving emotional expressions of fear and aggression) [17]. Limbic MR is down-regulated by chronic stress and during depression but induced by antidepressants; increased MR activity inhibits HPAA. It is suggested that stress-induced growing glucocorticoid concentrations activate GRs in limbic-forebrain circuitry; GR activation underlies executive functions and memory storage, which contributes in balance with MR-mediated actions to homeostasis, excitability and behavioral adaptation. MR and GR variants/genetic polymorphisms add to individual differences in resilience and vulnerability to stressors, and these receptors are potential drug targets for recovery of homeostasis and health [8]. MRs and GRs have been best known for their delayed genomic role; however, it is now evident that their fraction associated with the plasma membrane can act as mediators of rapid, non-genomic signaling [12]. These receptors appear to mediate rapid non-genomic actions on excitatory neurotransmission suggesting that they integrate functions over time. Obviously, rapid corticosteroid actions in the brain through membrane-associated MRs and GRs are required for the realization and coordination of a fast adaptive response to stress. Joëls et al. suggested that the

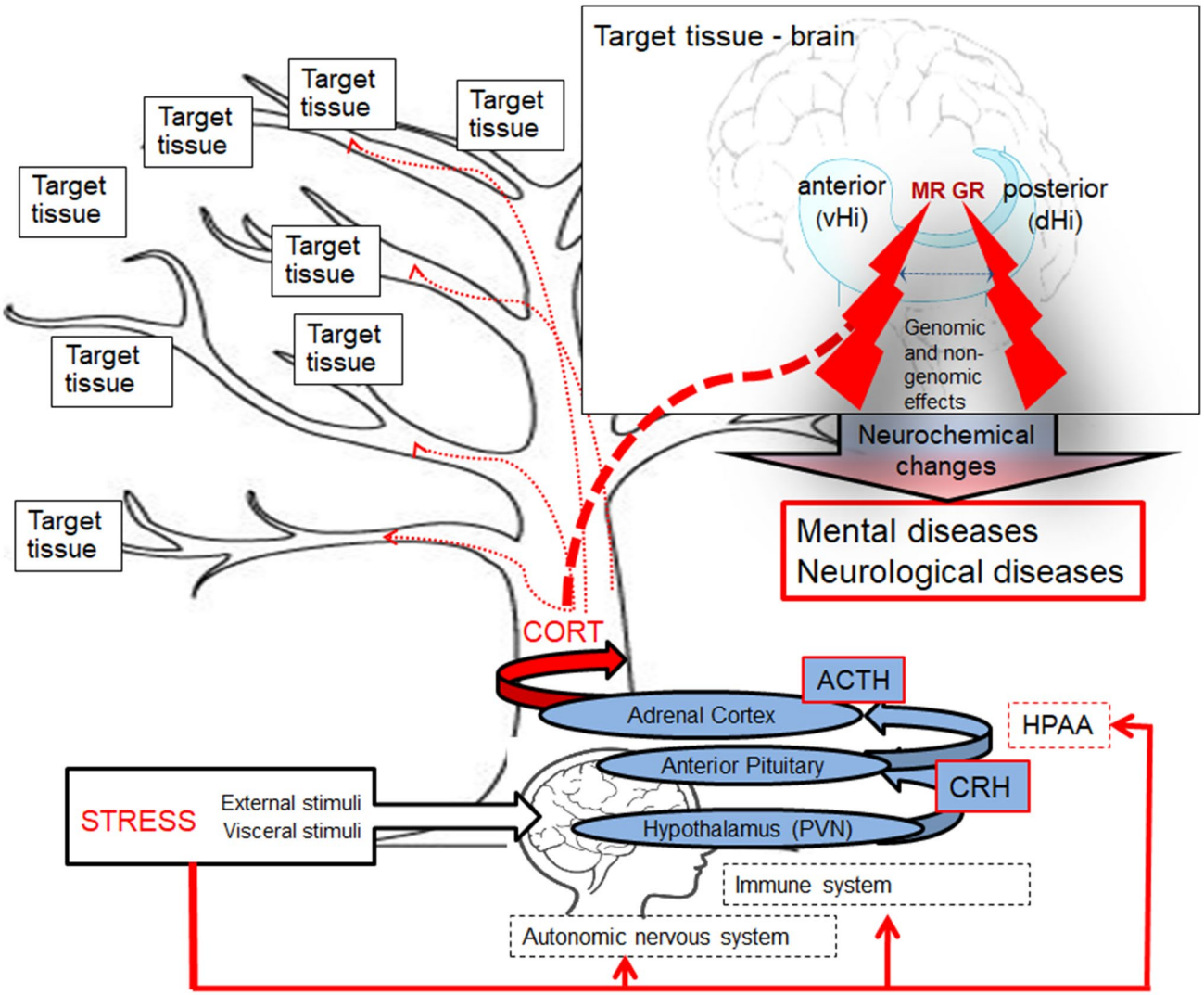

Fig. 1 Brain: the organ perceiving stress and its target. Stress, an adaptive response of the body, is controlled by the brain. In response to a stressful event, the brain activates a comprehensive stress system that engages the organism in an adaptive response to the threat. The major molecular changes in the brain induced by stress factors are biphasic. The initial phase of stress response takes place in the brain which is recognizing stressor and responding by the activating hypothalamic–pituitary–adrenal axis (HPAA) cascade: the release of corticotropin releasing hormone (CRH) from the paraventricular nucleus (PVN) of the hypothalamus inducing secretion of adrenocortical hormone (ACTH) from the anterior pituitary and subsequent stimulation by ACTH of the cortisol/corticosterone (CORT) release from adrenal cortex into the blood. With the blood, CORT reaches all organs and tissues; all cells which express corticosteroid receptors are targets for this hormone. Brain is among major CORT targets; the secreted CORT enters the brain and starts corticosteroid signaling, the second brain-associated phase of stress response. The response of the brain to stress is determined by the balance between corticosteroid actions induced via activation of the mineralocorticoid receptors (MR) and the glucocorticoid receptors (GR) which are most abundant in the hippocampus. MR and GR exert delayed long lasting genomic effect (via cytosolic receptors) as well as rapid, non-genomic signaling (via membrane-associated receptors). The hippocampus is not a homogeneous brain area; a functional dissociation along its septo-temporal axis exists. A longitudinal axis of the hippocampus has been described in both rodents and humans, however, spatial arrangement is different. In mice and rats the hippocampus extends along both a rostrocaudal axis and a dorsoventral axis, the dorsal hippocampus (dHi) being in the septal pole while the ventral hippocampus (vHi)—in the temporal pole of the hippocampus. The most rostral coronal sections of the rodent hippocampus contain dHi only, while more caudal coronal sections contain both the vHi and parts of the dHi. In humans the septal pole is located posteriorly while the temporal pole located anteriorly; therefore, the anterior hippocampus in humans is analogous to the vHi in rodents while the posterior hippocampus is analogous to the rodent dHi [25]. The dHi (posterior in humans) is involved primarily in learning/memory and spatial navigation, while the vHi (anterior in humans) is linked more to emotional behavior and regulation of the neuroendocrine stress axis. Pathological stress-induced functional and molecular changes in the hippocampus underlie the pathogenesis of major mental and neurological diseases, including depression and dementia

low-affinity membrane version of the MR contributes to the initial phase of the stress reaction; this is complemented by the GRs terminating the stress response [10].

During the adaptation process, cortisol and corticosterone affect the appraisal process, which includes the selection of an appropriate coping style and the encoding of the experience for storage in the memory. This action of the stress hormones is mediated by limbic MRs, which are down-regulated by chronic stress and in depression states, and induced by antidepressants [15]. Increased MR activity inhibits HPAA, reduces anxiety and switches circuit connectivity to support coping [17]. Glucocorticoid receptors mediate both rapid non-genomic and slow gene-mediated neuronal actions, therefore stress-induced shifts in corticosteroid level are associated with a complex mosaic of time- and region-dependent changes in neuronal activity [19]. Quick and slow effects of corticosteroids via GRs and MRs enable tuning function allowing to finely regulate all levels of stress response. The rapid non-genomic effects on neurons in the hippocampal CA1 region are mediated by membrane MRs which display a 10-fold lower affinity for corticosterone than the nuclear MRs involved in neuroprotection. Membrane MRs play an important role when corticosteroid levels are high promoting hippocampal excitability, amplifying the effect of other stress hormones and contributing to fast behavioral effects as well as encoding of stress-related information. These fast effects are followed by slower GR-mediated events facilitating suppression of temporary raised excitability, recovery from the stressful experience and storage of information for future use [9]. The balanced function of MRs and GRs crucial for homeostasis can be modified epigenetically by experience of repeated stressors or traumatic early life events. Cortisol levels and emotion/cognition are affected by MR gene haplotypes based on rs5522 and rs2070951. Haplotype 1 (GA) moderates the effects of stressors, while MR haplotype 2 (CA) is a gain of function variant that protects females against depression by association with a resilient phenotype [15]. One of the functional MR gene variants, MR-I180V, is associated with neuroticism and higher feelings of depression [11]. Importantly, corticosteroid signaling disturbances may be significant not only in stress-induced diseases like depressive states. For example, de Kloet considered diabetic encephalopathy as a pathology of imbalanced corticosterone action, which can be corrected in its pre-stage by a brief treatment with the antiglucocorticoid drugs [14].

Upon MR:GR imbalance, dysregulation of the HPAA occurs, which can enhance an individual vulnerability to stress. Such imbalance is characteristic for chronic stress and depression. The intimate involvement of hippocampal GRs and MRs in stress response suggests that the prediction of stress consequences is possible if the details of MR/GR-dependent mechanisms would be deciphered. Kudryashova and Gulyaeva [20] made an attempt to analyze the predictability of stress effects on long term hippocampal plasticity. Stress has been shown to have either stimulatory or inhibitory influences on the efficiency of long term potentiation (LTP) induction, the specific effect depending on the nature, duration, and intensity of the stressor, the time point, the brain structure being studied, and, thus, the involvement in the stress response of the mechanisms underlying LTP. Stress-induced increases in glucocorticoid levels do not obligatory correlate with changes in long-term plasticity, while application of corticosterone in vivo and in vitro may lead to either activation or inhibition of LTP. Existing data provide evidence that changes in LTP are determined by the ratio of MRs and GRs, activation of the latter not so much impairing the mechanisms of generation as increasing the threshold of LTP induction, regulating the metaplasticity of synapses. The practical unpredictability of the effects of stress is also associated with the uncertainty in the involvement of other transmitter systems regulating metaplasticity and its dependence on the animal's individual experience in the stress reaction as well as underlying differences in the processing signals arriving to neurons. Indeed, most, if not all, factors of unpredictability of stress effects may be associated with the lack of specific information regarding the balance and spatial distribution of MRs and GRs in the hippocampus and associated regions.

The hippocampus is involved in the feedback inhibition of the HPAA during stress response. This inhibition is mediated by glucocorticoid feedback due to the expression in the hippocampus of GRs and MRs as well as 11beta-hydroxysteroid dehydrogenase type 1, an enzyme that regulates the conversion of glucocorticoids from inactive to active form. Hyperactivity of the HPAA, a fundamental biological mechanism underlying major depression, is caused by diminished feedback inhibition of glucocorticoid-induced reduction of HPAA signaling and increased corticoliberin (CRH) secretion from the hypothalamic paraventricular nucleus and extra-hypothalamic neurons. Prolonged stress-induced inhibition of systemic feedback significantly changes cytosolic GR levels in the prefrontal cortex and hippocampus, key structures involved in the pathogenesis of depression [21].

Excessive corticosterone accumulation in the brain appears to be closely associated with pro-inflammatory events, and this relation has been revealed in different rodent models of depression [22]. Stress induces secretion of cytokines which, in turn, may induce hormonal changes similar to those observed following exposure to stress. Extended stress responses and overproduction of cytokines impair neuronal plasticity and increase HPAA activity, sensitizing its response to cytokines and stress. Stress situation and induced CRH release evoke a proinflammatory response in the brain, characterized by a complex release of several inflammatory mediators including cytokines, prostanoids,

nitric oxide (NO) and transcription factors, all of them participating in multiple interactions between neuroendocrine and neuroimmune systems [21]. The majority of studies have demonstrated that stress induces significant structural remodelling of microglia and can augment the release of pro-inflammatory mediators from microglia. Many of these effects are believed to be driven by stress-linked signaling molecules, corticosterone and norepinephrine. These signaling molecules can exert both inhibitory and suppressive effects on microglia depending upon the duration and intensity of stress [23]. These stress-induced microglial alterations, rather than being epiphenomena, have behavioural implications, involving microglia in directly regulating definite aspects of cognitive function and emotional regulation.

The hippocampus is selectively vulnerable to neuroinflammation, and this may be one of the bases for the involvement of this structure in the pathogenesis of many mental and neurological diseases. Using different models of stress and a model of focal ischemia in rats, we have demonstrated association of corticosterone accumulation in the hippocampus with the increase in pro-inflammatory cytokines [24–26]. Brocca et al. showed that MRs are associated with pro-inflammatory bias in the hippocampus of spontaneously hypertensive rats [27]. According to the "MR:GR balance hypothesis" [16], inflammatory responses to damage seem to be governed by a balanced MR:GR-mediated action as the initiating, terminating and priming mechanisms involved in stress/adaptation. Since neuroinflammation is regarded as a key mechanism of neuronal cell damage and neurodegeneration, specifying molecular mechanisms of neuroinflammation control by corticosteroids and their receptors is of primary importance for preventing brain diseases.

The dentate gyrus (DG) of the hippocampus maintains production of new neurons throughout the life. Adult neurogenesis is closely associated with hippocampal function, including learning and memory, anxiety regulation and feedback of the stress response [28]. Altered neurogenesis is suggested to be involved in the onset of brain diseases, particularly mental disorders and neurodegenerative diseases. Stress affects all range of hippocampal function, including the production, migration and survival of new neurons. Glucocorticoids have been implicated in stress-induced impairment of adult neurogenesis. It is generally assumed that glucocorticoids have a negative impact on both embryonic and adult neural stem/progenitor cells proliferation, this phenomenon being related to the pathophysiology of brain diseases, such as depression and autism spectrum disorders, as well as impairments of learning and memory [29, 30]. However this view is rather skewed since, depending on the stress nature and severity as well as on the stress response of the organism, increases in corticosterone levels are sometimes associated with enhanced adult neurogenesis in the dentate gyrus, though in other situations they act supressive. Although the effects of acute and mild stress on adult neurogenesis are generally brief and can be quickly overcome, chronic exposure and more severe forms of stress can induce longer lasting reductions in neurogenesis [31]. In these circumstances, the factors that buffer against the suppressive influence of elevated glucocorticoids remain unclear and under debate [28]. There is evidence for both direct and indirect effects of glucocorticoids on neural stem/progenitor cell proliferation and adult neurogenesis and a hypothesis has been formulated that glucocorticoid rhythmicity and oscillations originating from the activity of the HPAA, may be crucial for the neurogenesis in the hippocampus [30].

Ventral Hippocampus: Behavior, Stress, and Psychopathology

The hippocampus is not a homogeneous brain area, and the complex organization of this structure underlies its relevance and functional pleiotropism. There are many important aspects to discuss hippocampal structural and functional complexity; in this article we will focus on one of them—hippocampal dorso-lateral (septo-temporal) gradient. In 2010, Fanselow & Dong published a remarkable paper entitled "Are the dorsal and ventral hippocampus functionally distinct structures?" [32]. The analysis of the literature produced the response of the authors to the question posed: the hippocampus is a functionally heterogeneous structure with the cognitive and emotional signal processing ascribed to the dorsal (dHi) and the ventral hippocampus (vHi) (posterior and anterior hippocampus in humans, respectively). This topic, relevant for fundamental and translational neurobiology and neuroendocrinology, is steadily becoming a hot spot in the field, the studies being performed in both animal models and humans. Recently, this issue has been re-analyzed from different perspectives [33–39]. The data published after the review by Fanselow & Dong [32] show that the functional dissociation along the septo-temporal axis of the hippocampus is much more complex, than just quite a simple "learning vs. emotions" paradigm, though, indeed a converging body of evidence indicates that the dHi is involved *more* in learning/memory and spatial navigation, while the vHi is linked *more* to emotional behavior and regulation of the HPAA. In clinical and translational investigations, the dHi is of primary interest in studies of neurodegeneration and dementia, while a close association of vHi with stress response, depressive and other mental disorders is the main reason for studies of vHi connectivity and stress-induced signal transduction.

In this article, we will primarily focus on the vHi, a region where most important alteration underlying depressive disorders occur. The latest data suggest that the association of the vHi with specific forms of learning and memory

is much more extensive than it has been believed a decade ago and our knowledge about functional variability of vital processes controlled by the vHi and of molecular mechanism involved continues to expand promptly. Notably, the question about the exact physical boundaries of vHi is still a topic of debates. For example, Strange et al. argue that gene expression studies demonstrate multiple functional domains along the hippocampal septo-temporal axis, often with sharply demarcated borders, while anatomical studies and electrophysiological recordings in rodents suggest that the long axis is organized along a gradient [36]. They proposed a model in which functional long-axis gradients are superimposed on discrete functional domains. But in any case, experts are united in recognizing that anatomical connectivity varies along the dorso-ventral axis of the hippocampus, and that differences in the connectivity of the dHi and vHi determine their functional distinction. The dHi and vHi have different connectivity with cortical and subcortical structures, and this issue has been systematically reviewed by Grigoryan and Segal [37]. The vHi has more intense connectivity with the amygdala and hypothalamic endocrine and autonomic nuclei; it projects preferentially to the medial, intercalated, and basomedial nuclei of amygdala and the amygdala-hippocampal transition area, while the dHi has efferents in more lateral regions of the amygdala. The projections from infralimbic and prelimbic cortices involved in emotional regulation approach the vHi via input to the ventromedial parts of the entorhinal cortex, while the anterior cingulate and retrosplenial cortices involved in spatial processing primarily project to the dHi via dorsal and lateral parts of the the entorhinal cortex. dHi projects to the dorsal part of lateral septum and dorsal and medial parts of medial septum, while vHi innervates the larger ventral part of lateral septum and lateral and ventral parts of medial septum. The authors argue that the special character of the hippocampal connectivity forms a difference in the neurotransmitter composition along the axis of the hippocampus, cholinergic and dopaminergic innervation being denser in the dHi, while the concentrations of norepinephrine and serotonin are higher in the vHi [37].

The longitudinal axis of the hippocampus may provide a gradient of representational granularity in spatial and episodic memory in rodents and humans. Brunec et al. suggested that the human hippocampus supports an anterior-to-posterior gradient of coarse-to-fine spatiotemporal representations, implying the existence of a cross-species mechanism, whereby lower neural similarity supports more complex coding of experience [40]. Poppenk et al. [35] propose that various long axis specializations arise out of differences between the anterior and posterior hippocampus in large-scale network connectivity, the organization of entorhinal grid cells, and subfield compositions that bias the anterior (vHi) and posterior (dHi) regions towards pattern completion and separation, respectively. The latter two differences give rise to a property, reflected in the expression of multiple other functional specializations, of coarse, global representations in the anterior (vHi) and fine-grained, local representations in the posterior hippocampus (dHi).

It is generally believed that spatial cognition is associated with the anterior-posterior axis of the hippocampus. Nadel et al. reanalyzed data from a recent fMRI study to determine whether activations in hippocampal regions are affected by the nature of the information being accessed during a scanning session in which participants thought about episodes from their lives [41]. The results confirm the concept about functional differentiation along the hippocampal longitudinal axis in humans matching to that in rats, namely, that the posterior (dHi) is crucial for precise spatial behavior, and the anterior (vHi) is crucial for context coding. Using vHi damage in rats, McDonald et al. [42] showed that the vHi is necessary for the expression of conditioned inhibition, early spatial learning, and discriminative fear conditioning to context when the paired and unpaired contexts have high cue overlap. This suggests a key role for the vHi in the exploitation of broad contextual representations for inhibition and discriminative memory in high ambiguity conditions. Using calcium imaging and optogenetics in freely moving rodents, Jimenez et al. [43] demonstrated that while the CA1 subregion of the dHi is enriched in place cells, CA1 of vHi is enriched in anxiety cells that are activated by anxiogenic environments and required for avoidance behavior. Cell imaging revealed that anxiety cells were enriched in the CA1 population of dHi projecting to the lateral hypothalamic area, and optogenetic activation of CA1 terminals in this area increased anxiety and avoidance. The pathway CA1 of the vHi—lateral hypothalamic area may be a direct route by which the hippocampus rapidly influences innate anxiety behavior. Thus, the vHi is implicated in learning and memory functions that are distinct from those managed by the dHi.

The hippocampus contains one of the few neurogenic niches within the adult brain, the subgranular zone of the DG, permanent adult neurogenesis contributing a lot to remarkable hippocampal plasticity. Using a context fear memory paradigm, Huckleberry et al. showed that adult-born neurons in dHi and vHi contribute to both memory acquisition and recall [44]. The comparatively large behavioral effects of silencing a small number of adult-born neurons suggest that these neurons make a unique and powerful contribution to hippocampal function. vHi, but not dHi inactivation impairs reward memory expression and retrieval in contexts defined by proximal cues. Riaz et al. also examined differential roles of vHi and dHi in reward contextual processing, under conditions in which the context is defined by proximal cues [45]. They studied the effects of transient post-acquisition pharmacological inactivation (using a

combination of GABAA and GABAB receptor agonists) of functionally distinct subregions of the hippocampus (CA1/CA3 subfields of the dHi and vHi) on contextual biconditional discrimination memory retrieval. Robust deficits in task performance and memory retrieval were observed following inactivation of the vHi, but not dHi. Pierard et al. assessed the relative contributions of dHi and vHi regions in mediating the rapid effects of an acute stress on contextual memory retrieval [46]. The results of the study suggest that memory retrieval in non-stress condition involves mainly dHi and that the inversion of memory retrieval pattern after stress is linked to a dHi but not vHi dysfunction. Recent data implicate basolateral amygdala, vHi and medial prefrontal cortex in social defeat, the time courses of the establishment and extinction of social defeat being consistent with the contrasting responses of vHi and basolateral amygdala involved in this process [47]. Pyramidal cells in the dorsal and ventral CA1 of female adolescents are being remodeled differently following single housing [48]. From puberty to end of adolescence the dHi undergoes transient dendritic retractions in stratum radiatum, while the vHi undergoes transient dendritic growths in stratum radiatum; female–female pair housing increases branching in the dorsal and reduces branching in the ventral stratum radiatum.

Mechanisms underlying large scale functional diversification along the hippocampus can be revealed studying specializations of the intrinsic neuronal network between the dHi and vHi, the data remaining to a certain extent contradictory. Higher intrinsic network excitability in the vHi as compared to the dHi is controlled less effectively by GABA(B) receptors, NMDA receptors considerably contributing to this phenomenon [49]. The NMDA and GABA(B) receptors may be involved in differentiation local network dynamics between the dHi and vHi critical for the information processing performed along the septo-temporal hippocampal axis. dHi and vHi slices differ in their basal levels of excitatory synaptic transmission, paired-pulse facilitation, and EPSP-to-spike coupling [50]. As compared to the dHi, slices taken from the vHi have a greater ability to exhibit long-term depression of synaptic transmission and EPSP-to-spike potentiation induced by transient application of a group I mGluR agonist. The data have been reported suggesting relatively higher network excitability of the vHi as compared with dHi and implying vHi as a preferential site of sharp waves initiation. Sharp waves and ripples are regarded as a basic hippocampal network activity associated with memory processing. Kouvaros & Papatheodoropoulos showed that sharp waves recorded from the CA1 field in rat hippocampal slices were larger, shorter and occurred much more frequently in the vHi than in the dHi [51]. NMDA receptors-dependent clusters of sharp waves occurred with higher probability in the vHi and the frequency of occurrence of consecutive intra-cluster events was higher in the vHi (~ 10 Hz) than in the dHi (~ 5 Hz), while ripple oscillation displayed higher amplitude and frequency in the vHi as compared to the dHi. Dorsal–ventral differences in Schaffer collateral synaptic function may be also dependent on differential regulation of NMDA receptor-mediated transmission. Babiec et al. demonstrated that in Schaffer collateral synapses of the mouse vHi and dHi basal synaptic transmission was similar, however, the synapses in the vHi and dHi exhibited distinctly different responses to θ frequency patterns of stimulation [52]. In contrast to the dHi, θ frequency stimulation failed to elicit postsynaptic complex-spike bursting and did not induce LTP at ventral Schaffer collateral synapses. EPSP-spike coupling believed to strongly influence information transfer at synapses, was weaker in ventral pyramidal cells. Taking into account increased mRNA levels for the SK3 subunit of SK-type K+ channels in ventral pyramidal cells, the data suggest that these differences in postsynaptic function are due to an enhanced activation of SK-type K+ channels that suppresses NMDA receptors-dependent EPSP amplification at ventral Schaffer collateral synapses and may underlie the reduced ability of ventral synapses to undergo LTP. A dorsal–ventral difference in SK channel regulation of NMDA receptors activation likely contributes to the distinct roles of the dHi and vHi in different behaviors [52].

Studies on rodent models of stress and depression published during the last decade attempted to find fundamental links between stress, psychiatric diseases and changes in the vHi. The data on key systems (corticosteroid receptors, neurotransmitter systems, neurotrophins, neurogenesis, plasticity/LTP) confirm specific involvement of the vHi in the development of psychopathologies and imply signal transduction pathways and specific molecules involved in the adaptive functions of the vHi (see [38, 39] for review). Corticosteroids modulate synaptic plasticity, expressed as long-term changes in reactivity to afferent stimulation. Maggio & Segal have challenged the classical view of the effects of stress on synaptic plasticity and cognitive functions—an inverted U-shape curve, such that a low stress level facilitates and a high stress level (i.e., corticosterone level) impairs cognitive functions [53]. In a series of studies they showed that stress and corticosterone have immediate and opposite effects on the ability to express LTP in the dHi and vHi. The authors suggested that this differential role of stress may be related to the different functions associated with these sectors of the hippocampus.

Hippocampus is significantly involved in dopamine-dependent behaviors, dopamine being an important modulator of hippocampal synaptic plasticity. The dopaminergic innervation appears to be disproportionally segregated along the hippocampal longitudinal axis. Papaleonidopoulos et al. [54] showed that the expression of D1 receptor mRNA and protein was considerably higher in the vHi as compared to the dHi, while a full D1 receptor selective agonist

significantly enhanced LTP in the vHi but not the dHi. The authors suggest that the dynamic range of D1/D5 receptor-mediated dopamine effects on LTP may be higher in the vHi than dHi and that the vHi may be specialized to acquire information about behaviorally relevant strong stimuli signaled by the dopamine system. Noradrenaline is released in the hippocampus during emotional arousal modulating synaptic plasticity and memory consolidation through activation of β-adrenergic receptors. There are data suggesting that these receptors may act as a switch that selectively promotes synaptic plasticity in the vHi through multiple ways and is involved in mechanisms underlying contribution of the vHi in emotionality [55].

The basic, molecular level of brain plasticity covers numerous specific proteins (enzymes, receptors, structural proteins, etc.) participating in many coordinated and interacting signals and metabolic processes, their modulation forming a molecular basis for neuroplasticity [2]. The immediate early gene Arc known to be involved in neural plasticity and memory is used as one of markers for cell activity. Behavior-driven arc expression was two to threefold reduced in all vHi subfields as compared to CA1, CA3, and DG in the rat dHi [56]. The DG is regarded as a major site for experience-dependent plasticity associated with sustained transcriptional alterations, potentially mediated by epigenetic modifications. Zhang et al. demonstrated a dorsal–ventral asymmetry in DG transcription and methylation that parallels well-known functional and anatomical differences and that may be enhanced by environmental enrichment [57]. They found genome-wide transcriptional and methylation differences between the dHi and vHi, including key developmental transcriptional factors. Peripubertal environmental enrichment increased hippocampal volume, enhanced dorsal DG-specific differences in gene expression and dorsal–ventral differences in DNA methylation. The latter included binding sites of the transcription factor NeuroD1, a regulator of adult neurogenesis. Using RNA-seq-based bioinformatic analysis in conjunction with quantitative real-time polymerase chain reaction analysis and a comparison of in situ hybridization data obtained from the Allen Brain Atlas, Lee et al. provided an analysis of differentially expressed genes in the dHi and vHi at specific developmental ages representing the postnatally maturing hippocampus [58]. Genes associated with particular functional pathways and marker genes for particular neurological diseases were found to be distinctively segregated within either the dHi or vHi at specific or at all developmental ages examined. Floriou-Servou et al. have provided the combined transcriptomic (RNA sequencing) and proteomic (sequential window acquisition of all theoretical mass spectra) profiling of the dHi and vHi in mice [59]. Using different acute stressors, it was demonstrated that these hippocampal regions displayed drastically distinct molecular responses and that, as expected, the vHi was predominantly sensitive to the effects of stress. In particular, protein interaction cluster analyses revealed a stress-responsive epigenetic network around histone demethylase Kdm6b restricted to the vHi, and acute stress reduced methylation of its enzymatic target H3K27me3. Notably, selective Kdm6b knockdown in the vHi induced behavioral hyperactivity/hyperresponsiveness. Deletion of CREB in the dHi resulted in learning and memory deficits in fear conditioning, whereas CREB deletion in the vHi showed an enhancement in learning. Notably, CREB deletion in the vHi, but not dHi resulted in amelioration of nicotine withdrawal-induced anxiety-like behavior, while providing towards the distinct roles of CREB within the dHi and vHi in mediating select nicotine withdrawal phenotypes [60].

Stress differentially regulates glutamate homeostasis in the dHi and vHi. Nasca et al. [61] provided an RNA-seq roadmap for the stress-sensitive DG of the vHi and revealed the involvement of the astroglial glutamate exchanger xCT in stress and antidepressant responses. They suggested a mechanism by which ventral DG protection results in stress resilience and antidepressant responses via epigenetic programming of an xCT-mGlu2 network. Pacheco et al. [62] compared the effect of repeated stress on the expression of AMPA and NMDA receptor subunits in the dHi and vHi. Surprisingly, in their experiments the dHi appeared more sensitive than the vHi to chronic stress exposure, mainly altering the expression of NMDA receptor probably favoring changes in the configuration of this receptor that may influence the function of the dHi. The connections between the glutamatergic and BDNF systems in the brain are numerous and bidirectional, providing for mutual regulation of the systems. It is suggested that it is complex and well-coordinating nature of these connections that secures optimal synaptic and cellular plasticity in the normal brain. Both systems are associated with the pathogenesis of depression, and the disturbance of tight and well-balanced associations between them results in unfavorable changes in neuronal plasticity underlying depressive disorders and other mood diseases [63]. Tyrosine kinase receptor B (TrkB) of the vHi appears to be essential for goal-directed action selection, opposing habit-based behavior otherwise facilitated by developmental stress hormone exposure [64]. In rodents, excess of corticosterone caused a shift in the balance between full-length trkB and a truncated form of this BDNF receptor, favoring the inactive form throughout multiple corticolimbic brain regions; phosphorylation of the trkB substrate extracellular signal-regulated kinase 42/44 (ERK42/44) in the vHi was diminished. Serra et al. studied expression of BDNF and trkB in the hippocampus of a rat genetic model of vulnerability (Roman low-avoidance, RLA) and resistance (Roman high-avoidance, RHA) to stress-induced depression [65]. Significant line-related differences were observed in the DG only in the vHi supporting and specifying the hypothesis

that a reduced BDNF/trkB signaling in the hippocampus of RLA vs. RHA rats may contribute to their more pronounced vulnerability to stress-induced depression. Ergang et al. [66] demonstrated that depending on the stress-susceptibility of the rat strain, stress stimulates the activity of 11beta-hydroxysteroid dehydrogenase type 1, controlling the conversion of glucocorticoids to active form, specifically in the vHi, while stress inhibited GR in the dHi.

Adult hippocampal neurogenesis in the hippocampal DG is implicated in cognitive functioning, stress responses, and in antidepressant action. Given the role of neurogenesis in functions preferentially regulated by the dHi or vHi, it is reasonable to suggest that neurogenesis is predominantly regulated in either the dHi or vHi depending upon the stimulus. The analysis of the literature on the effects of stress and antidepressants on neurogenesis along the hippocampal longitudinal axis suggests that preferential regulation of neurogenesis in the vHi/anterior hippocampus contributes to stress resilience and antidepressant effects [34]. In recent years, both major depression and antidepressant therapy have been linked to adult hippocampal neurogenesis. Tanti & Belzung reviewed data on the relation of models of depression and of antidepressant therapies to adult neurogenesis along the septo-temporal axis of the hippocampus and discussed possible mechanisms underlying functional significance of such regional effects [67]. Expectedly, animal models of depression elicited effects restricted to the vHi more frequently than to the dHi. These effects were stage specific and associated with neurogenesis rather than cell proliferation or survival. Unexpectedly, selective serotonin re-uptake inhibitors acted, as a rule, in a uniform way on adult neurogenesis in the dHi and vHi, though some other compounds with antidepressant action affected the vHi specifically. Non-pharmacological manipulations with antidepressant effects (e.g. environmental enrichment or physical exercise), also acted on the dHi or dHi/vHi neurogenesis. In a rodent model of parkinsonism, MPTP-induced dopaminergic depletion in adult mice impaired the dopamine D1 receptor-mediated early survival of newborn neurons in ventral DG, producing depressive-like behaviors [68].

A hallmark of depressive states is hippocampal volume loss. Chronic stress induces volume loss in the hippocampus in humans and atrophy of CA3 pyramidal cells and suppression of adult neurogenesis in the DG of rodents. Chronic unpredictable restraint stress and inhibition of adult neurogenesis resulted in atrophy of pyramidal cell apical dendrites in dorsal CA3 and to neuronal reorganization in ventral CA3 [69]. Some data suggest that the vHi may be less susceptable to age-related changes. Even in the absence of neurodegenerative diseases, progressing age often coincides with cognitive decline and morphological changes in the hippocampus, in particular, volume loss. Interestingly, in mice age-related cognitive decline coincides with accelerated volume loss of the dHi but not vHi [70]. Specific changes in hippocampal volume, shape, symmetry and activation are reflected by cognitive impairment and linked with neurogenesis alterations, the functional differentiation along the anteroposterior longitudinal axis of the hippocampus being relevant for Alzheimer's disease diagnosis [71].

The vHi is involved in addiction-related behavioral disturbances. Recurrent relapse, a major problem in treating opiate addiction, may be closely associated with vHi function. Wright et al. suggests that alpha7 nicotinic receptors in the vHi play a specific role in the retrieval of associative drug memories following a period of extinction, and this is related to changes in AMPA receptor binding [72]. Association of contextual cues with morphine reward increases neural and synaptic plasticity in the vHi of rats. Alvandi et al. showed an association of morphine-induced reward-related memory with neural and synaptic plasticity changes in the vHi possibly underlying context-induced drug relapse [73]. Morphine-induced conditioned place preference significantly increased the number of Ki67 and DCX-labeled cells in the ventral DG. In the vHi, increased dendritic spine density in both CA1 and DG and an enhancement of BDNF/TrkB mRNA levels were found, Ki67, DCX and spine density significantly correlating with conditioned place preference scores. Hudson et al. summarized clinical and preclinical evidence demonstrating that distinct phytocannabinoids act within the vHi and associated corticolimbic structures to modulate emotional memory processing affecting mesolimbic dopamine activity states, salience attribution, and signal transduction pathways associated with schizophrenia-related pathology [74].

Vulnerability to stress appears to be determined by a re-designed neurovascular unit characterized by increased neural activity, vascular remodeling and pro-inflammatory mechanisms in the vHi. Dampening inflammatory processes by administering anti-inflammatory agents reduces vulnerability to stress [75]. Pro-inflammatory stimuli, especially during the early life, induce life-long disfunction of HPAA and the development of depressive-like behaviors [22, 76, 77]. The data obtained in the studies on the effects of neonatal proinflammatory stress suggest that excessive corticosterone delivery to hippocampal receptors and proinflammatory changes persisting during brain maturation are among the principal molecular mechanisms responsible for neuroplasticity impairments induced by early neuroinflammation [26]. There are very few data on the effects of stress inducing depressive behavior on MR and GR expression in the vHi and dHi, and even less is known about gender specificity of these effects. Kvichansky et al. studied the delayed effect of neonatal proinflammatory stress on the expression of GRs and MRs in the dHi and vHi of female and male rats. In male Wistar rats the basal expression of GR mRNA was higher in the dHi as compared with the vHi [78]. Administration

of bacterial lipopolysaccharide during the neonatal period differentially influenced the expression of GR mRNA in the dHi and vHi of adolescent animals: in males, it increased GR expression in the vHi, whereas, in females, it increased expression in the dHi. In the dHi of juvenile males (but not females), neonatal proinflammatory stress increased the expression of CRH mRNA, while in the vHi of females a trend to an increase in the expression of CRHR2 receptor mRNA was found [79]. Onufriev et al. studied acute effect of a pro-inflammatory stimulus, bacterial lipopolysaccharide administration, on in vivo LTP, corticosterone and pro-inflammatory cytokine levels in adult rat dHi and vHi [80]. Unexpectedly, neuroinflammation was developing faster in the dHi, while corticosterone accumulation—in the vHi; functionally (according to in vivo LTP characteristics) the dHi was suffering first, and then LTP disturbance was spreading to the vHi.

Regrettably, the understanding that the hippocampus is not homogeneous and it is necessary to study its regions separately has not been infiltrated in minds of the majority scientists in the field yet. However, in spite of significantly increasing labor intensity, it is unavoidable for understanding basic mechanisms of both normal behavior and pathogenesis of major brain diseases. Nevertheless the fact that the number of comparative studies including the dHi and vHi is steadily growing is encouraging.

Remote Hippocampal Damage Hypothesis: The Price of Stress?

Distant Damage to the Hippocampus

The distant damage to the hippocampus related to a primary damage to another brain structure was described many years ago. However, so far no rational concept has been proposed to explain selective vulnerability of the hippocampus to such kind of injury. In some cases inter-structure neuronal connectivity could be an explanation, however, no general concept has been suggested yet. Yet, such a theory may be of great importance since remote hippocampal damage appears to underlie cognitive decline as well as depression, specifically, induced by brain injury. Here we propose a new viewpoint which may contribute to the explanation why hippocampus is so vulnerable to damage of this kind.

Forty years ago Ben-Ari et al. described distant hippocampal damage induced by intra-amygdalar injections of kainic acid [81], this injection inducing injury localized in the CA3 and CA1 areas of the hippocampus [82]. Surprisingly, only few studies were devoted to the issue of distant damage to the hippocampus since these first reports. The translational relevance of such studies is obvious since hippocampal dysfunction after stroke or head trauma may be involved in the mechanisms of dementia development, a pathology with high disease burden and with no specific treatment available yet. For example, vascular dementia, incorporating cognitive dysfunction with vascular disease, is a frequent cause of cognitive problems (e.g. it ranks as the second leading cause of dementia in the United States).

Memory impairment after stroke is poorly understood, though accumulating evidence suggests that infarction itself may cause secondary neurodegeneration in remote areas. In elderly stroke survivors memory impairments and the concomitant loss of hippocampal volume are usually explained by coexisting neurodegenerative disease (e.g., amyloid pathology) in interaction with stroke. Most patients after stroke caused by middle cerebral artery occlusion (MCAO) show cognitive deficit that is generally regarded as resulting from damage to the cerebral cortex rather than the hippocampus. There are sporadic studies aimed at understanding whether MCAO induces hippocampal damage and whether this contributes to the cognitive defects. Xie et al. [83] assessed patients with MCAO for hippocampal damage by magnetic resonance imaging and magnetic resonance angiography, as well as the Mini Mental-Status Evaluation and Rey Auditory Verbal Learning Test were used to assess cognitive defects. It was demonstrated that patients with exclusively unilateral MCAO showed hippocampal damage characterized by an infarct-size-independent atrophy and alterations in neuronal and glial metabolites in the ipsilateral hippocampus, in parallel with cognitive impairment. Schaapsmeerders et al. investigated the relation between long-term memory performance and hippocampal volume in young patients with first-ever ischemic stroke [84]. On average 10 years after stroke, patients had smaller ipsilateral hippocampal volumes compared with controls, with most apparent memory dysfunctioning after left-hemispheric stroke. A larger hemispheric stroke was associated with a smaller hippocampal volume. The authors suggest that infarction is associated with remote injury to the hippocampus, which may lower or expedite the threshold for cognitive impairment or even dementia later in life.

The use of rodent ischemic stroke models may help to elucidate the type of lesions that are responsible for cognitive impairment in humans. Focal cerebral ischemia (endovascular MCAO) in rats is considered to be a convenient and reliable model of human ischemic stroke. Both sensorimotor neurological deficit and cognitive dysfunction can be induced in the MCAO model, though sensorimotor deficits may improve with time, whereas available data analyzed by Yang et al. [85] suggest that in rats this model can result in a progressive course of cognitive impairment consistent with the clinical progression of vascular dementia. Coincident to the progressive decline of cognitive function, a delayed neurodegeneration in a remote area, distal to the primary ischemic area, the hippocampus, has been demonstrated in

MCAO models. Rodent MCAO induced delayed shrinkage and pyramidal neuronal death in the ipsilateral hippocampus and an impairment of hippocampal-dependent spatial memory [85]. Already at the acute stage, transient focal cerebral ischemia in rats induced damage of neurons and oligodendrocytes in the ipsilateral hippocampal CA1 [86]. After focal ischemic or excitotoxic lesions of the cortex and/or striatum, delayed secondary changes, including neuronal damage, activation of microglia and astrocytes, expression of pro-inflammatory cytokines were observed in remote areas: the hippocampus, thalamus, substantia nigra, pars reticulata, and spinal cord [87]. A mouse model of recurrent photothrombotic stroke is suitable for the preclinical investigation of multi-infarct dementia. In this model, histological analyses also revealed remote astrogliosis in the hippocampus [88]. Using a nonhuman primate stroke model for studies of secondary lesions in remote areas, Chen et al. found secondary damage in the hippocampus and thalamus [89].

Sharp et al. reported an induction of immediate early genes induced in remote areas, including hippocampus, thalamus, and other brain regions after focal cerebral ischemia. They suggested that these distant changes in gene expression occur because of ischemia-induced spreading depression or depolarization and could contribute to plastic changes in brain after stroke. Tau hyperphosphorylation is an important risk for neurodegenerative diseases. Unilateral transient MCAO induced accumulation of hyperphosphorylated tau and concurrent dephosphorylation of glycogen synthase kinase-3β at serine 9 in the ipsilateral hippocampus, a region of secondary damage remote from primary ischemic regions [90]. Since inhibition of NMDA receptor subunit NR2B, but not NR2A activity in the hippocampus attenuated the accumulation of hyperphosphorylated tau and spatial cognitive impairment in MCAO rats, the authors proposed that excessive activation of NR2B-containing NMDA receptors through entorhinal-hippocampal connection initiated the accumulation of hyperphosphorylated tau in the hippocampus, which subsequently induced cognitive deficit.

Similarly to stroke, traumatic head injury leads to primary (at impact) and secondary (distant) damage to the brain. Mechanical percussion of the rat cortex mimics primary damage seen after traumatic head injury in humans. Traumatic head injury in pups by mechanical percussion induced primary (at impact-cortex) and secondary (distant-hippocampus) damage to the brain [91–93]. The data on the neuroprotection by NMDA- and non-NMDA antagonists suggested that while both NMDA- and non-NMDA-dependent mechanisms contributed to the development of primary damage in the cortex, non-NMDA mechanisms were involved in the evolution of secondary damage in the hippocampus in rats subjected to traumatic head injury. Moderate traumatic brain injury in the cerebral cortex of rats resulted in selective neuronal necrosis not only at the site of injury, but was also present within the CA3 and CA4 hippocampal subsectors [94]. The number of IgG-positive neurons in the rat hippocampus increased bilaterally after a dosed traumatic cortical injury [95]. Traumatic brain injury caused the appearance of astrocytes that showed GFAP- and S100-protein immunopositivity in the hippocampus distant from primary injury [96]. Cortical contusion in rats resulted in a primary cortical lesion and ipsilateral distant remote hippocampal damage, involving primarily CA3-pyramidal cells and accompanied by an increase of neurogenic cells in this structure [97]. Traumatic brain injury can induce the expression of stress-related and neurotrophic genes both within the injury site and in distant regions. These genes may affect severity of damage and/or be neuroprotective. Using moderate fluid-percussion cortical injury in rats, Truettner et al. showed that BDNF was strongly upregulated in the granular cells of the DG and in the CA3 of the hippocampus 2–6 h after injury, while cortical regions at and near the injury site showed no response at the mRNA level [98]. NGF mRNA increased over the granular cells of the DG at early time points. The authors supposed that the induction of gene expression for neurotrophins in regions remote from areas with histopathology may reflect coupling of gene expression to neuronal excitation, which may be associated with neuroprotection and plasticity.

Thus, a number of studies demonstrate that focal brain injuries, e.g. stroke and head trauma in humans and modeled in rodents, induce secondary damage in the hippocampus remote from primary ischemic regions. Since hippocampal damage after focal brain injuries is closely associated with the delayed development of cognitive impairments, including dementia, as well as comorbid depression, it is vitally important to understand precise mechanisms of this remote damage to the hippocampus. The data suggest that there is a common factor underlying the remote hippocampal damage which is not strongly related to the nature and localization of the primary damage. An indirect evidence for this view provide the data reported by Hussein et al. [99]. Limb ischemia–reperfusion injury induced degenerative changes in the pyramidal neuronal perikarya of hippocampal CA3 field: dark-stained cytoplasm, mitochondrial alterations, accumulation of dense bodies, disorganized microtubules, astrogliosis, capillaries with narrow lumen and irregular basal lamina. This suggests that distant hippocampal damage may be associated with damage of other organs and tissues, not necessarily the brain.

Can We Discern Effect of Stress?

There is no universal view on the reasons and mechanisms of selective vulnerability of hippocampus to different forms of stress. We hypothesized that this phenomenon may be mediated by relatively high vulnerability to neuroinflammation

related to impairments of local glucocorticoid metabolism and signaling. We have evaluated inflammatory responses induced by acute or chronic combined stress in the cerebral cortex and hippocampus as well as circulating and brain corticosterone levels [24]. The hippocampus demonstrated higher stress-induced expression of the proinflammatory cytokine IL-1β as compared to the cerebral cortex; even a month after the termination of the chronic stress, when IL-1β mRNA in the cerebral cortex reached control levels, it remained significantly increased in the hippocampus. Under chronic stress, the inflammatory response in the hippocampus was accompanied by a significant increase in local cortecosterone levels and in tissue-to-blood corticosterone ratio in the hippocampus. Thus, the hippocampus appears selectively vulnerable to stress-induced inflammation associated with an increase in hippocampal corticosterone accumulation.

Taking into account the above data, we suggested that, considering remote hippocampal damage, it may be practical to try and dissect the effects of brain injury itself and the effect of stress accompanying brain injury (e.g. stress of trauma) or preceding brain injury recently. One of the main triggers for this idea were the results of Tel Aviv Brain Acute Stroke Cohort (TABASCO) study reported by E. Ben Assayag et al. [100]. The role of stress-related endocrine dysregulation in the development of cognitive changes following a stroke was explored in a longitudinal study on cognitively intact first-ever mild-moderate ischemic stroke/transient ischemic attack survivors using cortisol concentrations in hair obtained during the initial hospitalization as a measure of integrated long-term cortisol levels. Higher hair cortisol at baseline was significantly associated with a larger lesion volume and with worse cognitive results 6, 12 and 24 months post-stroke; it also was found to be a significant risk factor for cognitive decline. Thus, individuals with higher hair cortisol, which reflects higher long-term cortisol release, most likely, as a result of higher stress load, are prone to develop cognitive decline following an acute stroke. Recently, in a longitudinal stroke survivors cohort this group reported that higher bedtime cortisol levels immediately post-stroke were associated with larger neurological deficits, brain atrophy, worse white matter integrity, and worse cognitive results up to 24 months post-stroke [101]. Participants with high admission bedtime cortisol levels continued to present relatively elevated bedtime levels across all examined time-points, and this group had inferior memory and executive functioning scores compared to the lower cortisol group 24 months post-stroke. Thus, hyperactivated HPAA predicted worse cognitive outcome.

Our hypothesis illustrated in Fig. 2 suggests at least two major different lines of events. The first one is associated with the direct primary damage to the brain tissue, and these events are major targets of modern medical treatment. The second one is associated with stress and is represented by stress response events, in particular by excessive cortisol (corticosterone) release and stimulating hippocampal MRs and GRs. No doubt that there are interaction between these "direct damage" and "stress response" branches, however, to understand mechanisms of stress involvement in post stroke or post-trauma hippocampal damage, neurodegeneration and dementia pathogenesis, we should first dissect stress-response and consider it separately. In short, we propose that remote hippocampal damage following cognitive disturbances after different brain injuries is not just a consequence of primary injury, but to a big extent a result of stress load and interaction of glucocorticoids with MRs and GRs of the hippocampus. Hippocampal damage can be associated with both post-injury dementia and depression.

This general hypothesis assumes several working suggestions which can be verified experimentally. Most obvious (though, not all) of these suggestions are listed below:

1. Unilateral lesion of the cortex in a stroke or head trauma model should induce bilateral accumulation of corticosterone in the hippocampus and related neuroinflammation; these events during the acute period after brain injury would with higher probability start in the vHi and later extend to the dHi;
2. Hippocampal lesions should be bilateral, inevitably extending to the contralateral hippocampus (though, not necessarily identical ipsilaterally and contralaterally);
3. Prevention of excessive corticosterone accumulation in the hippocampus (either by decreasing corticosterone level in blood or by blocking hippocampal corticosteroid receptors) should alleviate hippocampal neuroinflammation and related damage as well as cognitive decline and depression.

Does the Ventral Hippocampus Take The First Hit?

Some of these assumptions have been confirmed in the experiments, other ones have to be validated in the future. As mentioned above, most ischemic strokes result from MCAO, which induces focal brain lesions in the neocortex. Secondary damage develops in brain regions located distantly from the infarct area, in particular in the hippocampus, hippocampal lesions most probably underlying cognitive impairments and post-stroke depression [84–86]. Onufriev et al. [20] monitored the time course of changes in the levels of corticosterone and proinflammatory cytokine interleukine-1β in the hippocampus and blood of rats after transient MCAO. At the early stage after MCAO the activation of the HPAA resulted in a release of corticosterone into blood, accompanied by the accumulation of corticosterone in the hippocampi of both the ischemic and contralateral hemispheres. This study demonstrated for the first time that this effect was observed

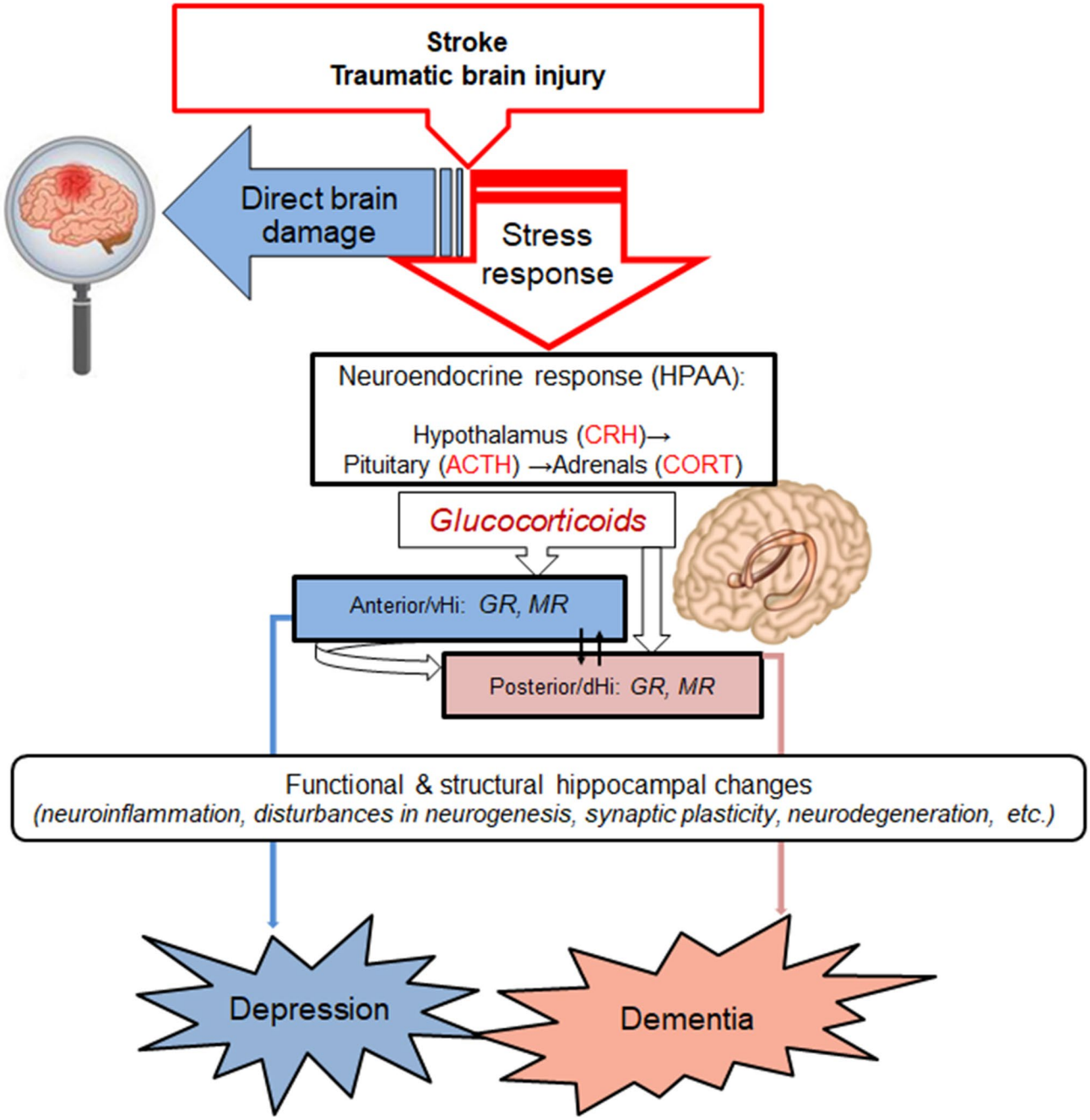

Fig. 2 Stress as a key player in the remote hippocampal damage: a hypothesis. Remote secondary hippocampal damage after stroke and traumatic brain injury is underlying post-stroke and post-trauma dementia and depression. During the post-injury period two major diverse lines of pathological events occur. The first one is associated with the direct damage to the brain tissue, while the second one is associated with stress and is represented by stress response events, in particular by hypothalamic–pituitary–adrenal axis (HPAA) activation, excessive cortisol/corticosterone (CORT) release and stimulation of mineralocorticoid receptors (MR) and glucocorticoid receptors (GR) in the ventral hippocampus (vHi, anterior in humans) and then in the dorsal hippocampus (dHi, posterior in humans). Stress-induced functional and structural changes in the vHi and dHi (neuroinflammation, disturbances in neurogenesis, synaptic plasticity, neurodegeneration, etc.) become a pathogenetic basis for the development of post-injury dementia and depression

primarily in the vHi. MCAO induced accumulation of the proinflammatory cytokine IL-1β, which proceeded in parallel with corticosterone at the early and delayed stages after reperfusion and was also observed in the vHi of both hemispheres. These data show that vHi may be more vulnerable to remote damage induced by MCAO as compared

to the dHi. The fact that corticosterone accumulation and neuroinflammatory process are detected in vHi bilaterally confirms our working hypothesis.

Future Directions

There are several growing points which should be supported by respective experiments. First, to show the validity and translational potency of the head trauma model, similar experiments on the time course of corticosterone and cytokine accumulation in the vHi and dHi should be performed using a brain traumatic injury model. In both stroke and trauma models, it is possible to observe the time course of MR:GR balance and expression of stress-related genes in the dHi and vHi. After finding the critical point(s) and understanding most relevant changes in MR and GR signaling in hippocampal regions it will be possible to elaborate pathogenetically substantiated approaches to reduce the effects of aberrant stress response and protect the hippocampus. Pharmacological tools for modulating MRs and GRs, as well as decreasing glucocorticoid levels are available, at least for experimental studies, and this is encouraging. No doubt, translation of experimental results and performing respective clinical studies would bring us closer to the ultimate goal—prevention of dementia and depression induced by focal brain damage.

Conclusions

Hippocampus is a key structure involved in various types of behavior including a variety of stress-response reactions. The vHi, a part of hippocampus analogous to the anterior hippocampus in humans, is critical for both resilience to stress, adaptation and the development of stress-induced brain pathologies, in particular depression. To understand sequential mechanisms underlying neurophysiological and behavioral manifestations, spatial and temporal alterations in molecular events should be thoroughly monitored in different animal models, primarily, interaction of corticosteroids with different types of hippocampal MRs and GRs, development of neuroinflammation, changes in neuroplasticity in the dHi and vHi. Identifying the involvement of stress response in the remote hippocampal damage after brain injury appears to be one of most relevant growing point possessing important translational significance.

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