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Cellular and Molecular Differences Between Area CA1 and the Dentate Gyrus of the Hippocampus

Karim A Alkadhi [1]

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Abstract

A distinct feature of the hippocampus of the brain is its unidirectional tri-synaptic pathway originating from the entorhinal cortex and projecting to the dentate gyrus (DG) then to area CA3 and subsequently, area CA1 of the Ammon's horn. Each of these areas of the hippocampus has its own cellular structure and distinctive function. The principal neurons in these areas are granule cells in the DG and pyramidal cells in the Ammon's horn's CA1 and CA3 areas with a vast network of interneurons. This review discusses the fundamental differences between the CA1 and DG areas regarding cell morphology, synaptic plasticity, signaling molecules, ability for neurogenesis, vulnerability to various insults and pathologies, and response to pharmacological agents.

Keywords Calbindin · Granule cell · Pyramidal cell · Ischemia · Chronic stress · Alzheimer' disease · Hypothyroidism · Obesity · OZR · Signaling molecules · Functional plasticity · Structural plasticity

Abbreviations

CA1	Corno Amonis
DG	dentate gyrus
I/O	imput/output
LTP	long-term potentiation
E-LTP	early-phase LTP
L-LTP	late-phase LTP
LTD	long-term depression
NO	nitric oxide
NOS	nitric oxide synthase
P-CaMKII	phosphorylated calcium calmodulin kinase II
GTPase	guanidine triphosphotase
UCH-L1	ubiquitin carboxyl-terminal hydrolase-L1
fEPSP	field excitatory postsynaptic potential
GABA	gamma aminobutyric acid
TEA	tetraethylammonium
VDCC	voltage-dependent calcium channel
NMDA	*N*-methyl-D-aspartate
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
BDNF	brain-derived neurotrophic factor
IPSP	inhibitory postsynaptic potential
ERK1/2	extracellular signal–regulated kinase
SRLM	stratum radiatum/stratum lacunosum-moleculare
IPSC	inhibitory postsynaptic current
OZR	obese Zucker rat
A-beta	Amyloid beta
Egr	early growth response protein-1
BLA	basolateral nucleus of the amygdala

✉ Karim A Alkadhi
kalkadhi@uh.edu

[1] Department of Pharmacological and Pharmaceutical Sciences, College of Pharmacy, University of Houston, Houston, TX, USA

Introduction

The unidirectional tri-synaptic pathway of the hippocampus starts with axons of the perforant path neurons synapsing on the granule cells of the dentate gyrus (DG) whose axons form the mossy fibers. The mossy fibers synapse on the pyramidal neurons of area CA3 whose axons form the Schaffer collateral fibers, which synapse on the pyramidal neurons of area Cornu Ammonis 1 (CA1). The dissimilar principal cells of the CA1 and DG areas of the hippocampus are excitatory glutamatergic neurons [1]. The two areas differ strikingly in their vulnerability to various insults, including Alzheimer's disease, stress, and hypothyroidism [2–7]. They also differ in discharge performance, where the presence of a persistent inward rectifier current in the DG, but not in area CA1, may account for the different discharge patterns [8].

Another important difference between the two areas is the DG area's ability for neurogenesis, which may be lacking in area CA1 [9, 10]. Neurogenesis in the DG takes place under both physiological and pathological conditions [11]. Recently, regulation of DG functions by adult neurogenesis at the subgranular zone (SGZ) has been shown to affect cognition with consequential implications for memory and mood [12]. Due to its capacity for neurogenesis, the DG is more heavily regulated by various environmental (e.g., exercise, learning) and neurotrophic factors, including brain-derived neurotrophic factor (BDNF) than other areas of the hippocampus, including area CA1 [13, 14].

The DG is considered the "gateway" to the hippocampus and may play a crucial role in the process of spatial memory formation. Although the DG and CA1 areas of the hippocampus are physically and functionally closely related, they show distinctly different reactions to exterior influences. While the DG is relatively impervious to many offending conditions, area CA1 is noticeably vulnerable to these conditions. Although researchers have been trying to understand the fundamental cause for the differences between the two areas, no conclusive answer to this question has, so far, been reached [5, 8, 15–22]. Most probably, the answer lies in the overall different intrinsic qualities of the dissimilar neurons in the two regions. Area CA1 is constituted of densely packed large pyramidal neurons, whereas the DG region is composed of also densely packed but much smaller granule cells and they differ at the functional, cellular, and molecular levels. Differences between CA1 and DG regions in the gross structure and the expression of certain subcellular proteins may explain their different responses to a variety of offending conditions. The following sections discuss various categories of differences between the two areas of the hippocampus.

Gross Structure, Physiology, and the Effects of Aging

Unlike the small granule cells of the DG, which have relatively short but dense dendrites, the CA1 pyramidal cells are endowed with a more extensive but less compact dendritic tree [23–25]. The pyramidal cell dendrites of area CA1 are nearly three times longer than those of the granule cells of the DG. Therefore, attenuation of the voltage at the distal dendrites is much greater in the pyramidal cells of area CA1 than the granule cells of the DG [26]). Additionally, the entorhinal to DG projections are much more divergent [27, 28] than the Schaffer collateral to area CA1 pathway [29], which may account for the different input-output (I/O) curves of the two areas [30] (I/O graph is a measure of basal synaptic transmission constructed by plotting synaptic response to increasing stimulus strength). Furthermore, the transmitter mobilization capabilities of the Schaffer collateral nerve terminals at the synapses of the CA1neurons exceed those of the lateral perforant path terminals at the synapses of the DG cells. Hence, this may explain the disparities in frequency facilitation and the shape of I/O curves, which are much steeper in area CA1 than in the DG [30].

The difference in gross structure may be seen in the blood supply to these areas. For example, when brain blood flow in the gerbil is interrupted to measure capillary perfusion, the microcirculation capacity of area CA1 is found to be much lower than that of the DG [31]. However, an earlier autoradiographic measurement reports no significant circulatory deficiencies following ischemia in area CA1 [32].

In a transgenic model of Alzheimer' disease, the tTa:APPsi mice, both males and females, show atrophy of the DG only in the dorsal hippocampus. Sex-related differences are seen in the DG but not in area CA1, with females showing more established degeneration than males in this Alzheimer' disease model [33].

In a mouse model of nucleolar stress in neurons, it has been found that nucleolar stress causes progressive neurodegeneration that demonstrates different vulnerabilities in area CA1 and DG [34].

Transcriptional and epigenetic alterations in the hippocampus can contribute to the process of aging of the brain. Aging can cause functional changes, particularly, in hippocampal neurons, which culminate in diminished synaptic plasticity resulting in impaired cognition. Protein synthesis is necessary for LTP and memory consolidation and transcription of early growth response protein-1 (Egr1), which is necessary for these processes. Spatial behavior can cause age-related reduction in the transcription of Egr1 in the DG, but not in area CA1 [35]. More recently, Lardenoije et al. [36] have investigated age-related alterations in epigenetic markers of DNA methylation and hydroxymethylation in the transgenic J20 mouse model of Alzheimer' disease and possible correlations with amyloid plaque load. They report an age-related decrease in DNA methylation in the DG but not in area CA1.

In a study of neural development, the number of cells incorporating BrdU after kainate-induced seizures indicates that area CA1 neural precursors have a greater proliferation capacity than the DG neural precursors [37].

Inhibitory Mechanisms

Responses to paired-pulse stimulation showed that interneurons in the local circuits of the DG react differently to high doses of corticosterone than those of area CA1 [38]. Additionally, corticosterone treatment reduces paired-pulse inhibition and enhances paired-pulse facilitation in the DG but not in area CA1 [38].

The effects of GABA-A receptor antagonists on LTP are more pronounced in the DG than those in area CA1 [39].

When comparing the inhibitory and excitatory monosynaptic responses following LTP-inducing stimuli, it is reported that the balance of the sum total postsynaptic currents causes inhibition in the DG but not in area CA1 [39].

Two types of inhibition are reported in the brain: (a) synaptic and (b) tonic. At the synapse, released GABA acting on GABA-A receptors mediates synaptic inhibition, which is stronger in the DG than in area CA1, because the number of inhibitory neurons is higher in the DG [40]. In contrast, tonic inhibition is believed to be mediated by ambient GABA (in the interstitial fluid) continuously acting on extrasynaptic GABA-A receptors. Tonic inhibition is significantly stronger in the DG than in area CA1, which could result in stronger inhibitory modulation of LTP [39].

Receptors

Differences between the CA1 and DG areas in the expression of certain signaling proteins may explain the different responses of the two areas to a variety of conditions. For example, major differences have been described in the density and/or distribution of T-type calcium channel and glutamate *N*-methyl-D-asparate (NMDA) receptors [22]. Moreover, the glutamate receptor α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) subunit GluA2 level in the DG is lower than its level in area CA1 [41, 42]. This relative paucity of GluA2 subunit in AMPA receptors in the DG [43, 44] may indicate that many AMPA receptors in the DG have high calcium permeability characteristic of AMPA receptor lacking GluA2 subunit [45].

The NMDA receptor GluN1 subunit expression is greater in the DG than in area CA1 [41, 42]. Furthermore, examination of transgenic mice lacking the NMDA receptor GluN2a subunit reveals severe suppression of NMDA receptor current in the granule cells of the DG, which results in significant impairment of synaptic plasticity in the DG, but not in area CA1 [46]. This finding also suggests a higher dependence of DG on NMDA receptors for synaptic plasticity than area CA1. Additionally, in area CA1, there is a greater expression of glutamate NMDA receptor subunit GluN2b than in the DG [41]. This differential expression of GluN2b subunits that may affect the function of NMDA receptor in area CA1, as NMDA receptor with GluN2b subunit has greater affinity for glutamate and glycine, is more selective for Ca^{2+} influx, and it desensitizes slower than GluN2a subunit [41, 47, 48].

The 5′-nucleotidase enzyme (5′-NT, also known as ecto-5′-nucleotidase or CD73) plays a vital role in ending the ATP signaling and the production of adenosine, which is an inhibitory neuromodulator in the nervous system [49, 50]. Histochemical studies have shown that the activity of ecto-5′-nucleotidase is greater in area CA1 than in the DG molecular layers [51, 52]. This may explain adenosine modulation of trains of theta rhythm in area CA1 but not in the DG [30] (theta rhythm or pulse is brain waves involved in spatial navigation tasks in experimental animals). Moreover, theta pulse stimulation erases LTP in area CA1 but not in the DG, although adenosine eliminates potentiation in both areas. This suggests that theta pulse stimulation increases extracellular adenosine to a greater degree in area CA1. Furthermore, adenosine A-1 receptor antagonism has greater impact on theta responses in area CA1 than in the DG [30].

Receptor-binding studies indicate that the neuropeptide Y receptor in the DG is largely of the Y1 type, whereas in area CA1, it is the Y2 type that predominates [53–58]. Since only Y1 is involved in intracellular Ca^{2+} regulation [59], this may suggest a better calcium buffering capacity in the DG.

Calcium Dynamics

The CA1 and DG areas have strikingly different calcium dynamics. For example, the calcium-binding protein, calbindin-D28K (calbindin), which is essential for neural function and plasticity [60], is found in various brain areas, including the DG and CA1 of the hippocampus [61, 62]. However, the pyramidal neurons of area CA1 and granule cells of the DG have strikingly different levels of calbindin. While high concentration of calbindin is present in nearly all granule cells of the DG, it exists in only about one third of the pyramidal neurons of area CA1 [62–65]. This further suggests that the calcium-buffering capacity of the neurons of the DG is superior to that of area CA1. It is well known that excessive activity induces a rise in intracellular free calcium, which may result in cell damage or death (excitotoxic effect); however, neurons that can sequester free calcium would be less vulnerable to damage [66]. For example, prolonged activation of the DG in rats causes degeneration only of neurons that lack calbindin [66]. Interestingly, it has been suggested that lack of calbindin in the DG granule cells of human epileptic subjects may cause hyperexcitability of the DG, which may then function as a driver for temporal lobe seizures [67]. Another study suggests a link between cognitive deficits in Alzheimer's disease and depletion of calbindin in the DG cells [68]. In cultured granule cells of the DG and pyramidal neurons of area CA1, a brief treatment with glutamate or its agonist NMDA induces Ca^{2+} transient currents that recover to baseline much faster in granule cells of the DG than in area CA1 pyramidal neurons, suggesting a more efficient Ca^{2+}-buffering mechanism in the granule neurons of the DG [69].

Synaptic Plasticity

The phenomenon of synaptic plasticity and its reaction to various insults is another important aspect in which area

CA1 and the DG differ markedly. The stimulation parameters required to induce LTP in the DG are typically more vigorous than those required for inducing LTP in area CA1. For example, while a single train of stimuli (100 Hz bursts of four pulses) applied to the Schaffer-collateral quickly evokes a robust LTP in area CA1 [70, 71], the same stimulation protocol applied to the lateral perforant path fails to evoke LTP in the DG [30]. Therefore, the threshold for induction of LTP in area CA1 is much lower than that in the DG [30, 70, 71]. Another example, submaximal tetanic stimulation (2 × 50 Hz/1 s) in slices from control rats elicits LTP at the Schaffer collateral-CA1 synapses but produces no significant change in synaptic responses at the perforant path-DG synapses. Also, enhanced arousal seen in discriminatory avoidance learning paradigm selectively blocks LTP in area CA1, but enhances LTP of the DG [72].

In slices from prenatally morphine-exposed adult male rats, stimulation produces no LTP at the Schaffer collateral-CA1 synapses, whereas the same stimulation protocol elicits long-term depression (LTD) at the perforant path synapses of the DG [73]. Additional differences between area CA1 and DG with regard to LTD are reviewed in Pöschel and Stanton [74].

Certain forms of stimulation intensity and frequency in the basolateral (BLA) nucleus of the amygdala block LTP in area CA1 [75, 76], but identical patterns of stimulation increase LTP in the DG [77, 78]. The same group of investigators shows that activation of BLA nucleus by these forms of stimulation enhances corticosterone level, which positively correlates with the magnitude of LTP in the DG, but not with that of area CA1 [78].

Chronic stress in a preclinical rat model of Alzheimer's disease suppresses not only early-phase LTP (E-LTP) but also nearly abolishes late-phase LTP (L-LTP) in area CA1 [79, 80]. Chronic stress, however, does not significantly affect the magnitude of L-LTP of the DG in this Alzheimer's disease model. Similar differential responses to hypothyroidism or chronic stress are seen as we show that these conditions block E-LTP in area CA1 but not in the DG of the same rats [81, 82].

As mentioned earlier, the importance of glutamate NMDA receptors to the DG function is indicated in experiments where transgenic mice in which NMDA receptor GluN2a subunit is deleted causing severe deficit in NMDA receptor function and significantly impairing both LTP and LTD in the DG, while causing only minor impairment of these responses in area CA1 [46]. Activation of glutamate metabotropic receptors by the non-selective agonist 1-amino-1,3-dicarboxycyclopentane (ACPD) enhances synaptic transmission and LTP in area CA1 but causes only a brief potentiation followed by a long-lasting depression in the DG, probably due to activation of two different classes of these metabotropic receptors in the two areas of the hippocampus [16].

Stress and stress hormones impact LTP of hippocampal area CA1 in a markedly different way than that of the DG [6, 81, 83–88]. For instance, predator stress increases LTP magnitude in the DG [89] but impairs that of area CA1 [85]. Additionally, stress or treatment with corticosterone blocked LTP of area CA1 [87, 90, 91] without affecting LTP in the DG [5, 86, 88]. Thus, while stress and stress hormones have consistently been reported to impair LTP in area CA1 [83–85], their effects on LTP on the DG are more diversified [81, 86, 87].

In the rat hippocampus, the LTD magnitude in area CA1 decreases with age, whereas in the DG, it increases with age [92, 93]. Additionally, LTD is facilitated in area CA1, but not in the DG, when low frequency stimulation is coupled with novel sonic or ultrasonic auditory tones [94].

Molecular Mechanisms

Important enzymes and signaling molecules are distributed differently in these two areas, which consequently affects their functions accordingly. The role of phosphorylated calcium-dependent calmodulin kinase II (P-CaMKII) in the mechanism of generating LTP in the hippocampus is vital. Conserving adequate P-CaMKII levels explains why certain brain disorders diminish LTP in area CA1 but not in the DG of the hippocampus of the same rat. For example, in the hypothyroid or psychosocially stressed rats, P-CaMKII levels are diminished in area CA1 but remain unchanged in the DG despite notable reduction in the total CaMKII level in this region [5, 95], which may explain the preservation of LTP in the DG under these conditions.

To investigate the possible reason for the disparity in P-CaMKII levels between the two areas, we measured the levels and activity of the phosphatase calcineurin. Our work has shown a significant decrease in the basal level of calcineurin in the DG of hypothyroid or stressed rats. This indicates that a lower level of calcineurin in the DG results in curtailed dephosphorylation, thus maintaining adequate level of P-CaMKII. This compensatory mechanism is probably responsible for preservation of LTP in the DG of the hippocampus under these conditions [5, 95]. The absence of a similar compensatory mechanism in area CA1 may be responsible for the impairment of LTP of this region in hypothyroid or stressed rats. Therefore, the reduced levels of calcineurin in the DG of hypothyroid or chronically stressed rats allow adequate level of P-CaMKII to support the expression of LTP [5, 95]. Similar differentials are seen in rats with combined stress and hypothyroidism [81] in addition to other signaling molecules (Table 1). However, the exact mechanism behind the reduced levels of calcineurin in the DG under these conditions remained to be determined.

Ascorbate has important signaling functions in the brain, including functioning as enzyme co-factor and modulating energetic metabolism and glutamate- and

Table 1 Comparison of the effects of hypothyroidism (Hypo), chronic psychosocial stress, and the combination (hypo + stress) on the basal levels of important signaling molecules in the CA1 and DG areas of the hippocampus. (↔) indicates no change, and (↓) indicates significant reduction and (↑) significant elevation ($p < 0.05$) compared with levels in control animals. Modified from Gerges et al. [5, 6], Alzoubi et al. [82, 96]

	CA1			DG		
	Hypo	Stress	Hypo + stress	Hypo	Stress	Hypo + stress
P-CaMKII	↓	↓	↓	↔	↔	↔
Total CaMKII	↓	↓	↓	↓	↓	↓
Calmodulin	↓	↓	↓	↔	↔	↔
PKCγ	↓	↓	↓	↔	↔	↔
Calcineurin	↑	↑	↑	↓	↓	↓
ERK: phospho-P44	↓			↔		
ERK: phospho-P42	↓			↔		

nitric oxide-dependent signaling processes [97, 98]. Using nanocomposite sensors to measure the basal levels of ascorbate in the CA1 and DG of the hippocampus of urethane-anesthetized rats, Ferreira and colleagues [98] report a level of ascorbate in area CA1 that is twice its level in the DG area.

An important mechanism for termination of the action of glutamate at the glutamatergic synapses is an active uptake of glutamate into astrocytes. In the astrocytes, an important enzyme, glutamine synthase, converts glutamate to the less active glutamine [99]. It is known that the expression level of glutamine synthase is higher in the DG than in area CA1 [100]. The uptake of glutamate by the astrocytes involves specific membrane transporters [101, 102]. It has been reported that the expression level of glial glutamate transporter-1 is higher in the DG than in area CA1 of the rat hippocampus [103]. Together, these findings suggest that the management of the essential, but potentially toxic, excitatory neurotransmitter glutamate is more efficient in the DG than in area CA1.

The enzyme ubiquitin carboxyl-terminal hydrolase-L1 (UCH-L1) removes ubiquitin from ubiquitinated proteins, thus controls the process of degradation of proteins and the amount of free ubiquitin [104, 105]. Another enzyme, dynamin-1, is a GTPase protein that exists in nerve terminals where it pinches off fused synaptic vesicles from the plasma membrane after exocytosis of neurotransmitters [106]. Dynamin-1 and UCH-L1 have been reported to be widely expressed in neurons, and immunoreactivities for these proteins have been detected in both CA1 and DG neurons [107, 108]. Interestingly, however, proteomic analysis shows that the expression levels of UCH-L1 and dynamin-1 are higher in area CA1 than in the DG region, which may explain the high level of protein degradation and synaptic vesicle transport in area CA1 [99].

Responses to Endogenous Agents and Drugs

The two hippocampal regions respond quite differently to various drugs and endogenous compounds (summarized in Table 2). The possible reason for this disparity in responding to drugs is the different density and distribution of receptors in these two areas. For example, norepinephrine modulates glutamate release in the DG without significantly affecting such release in area CA1 [109]. Similarly, the β-adrenergic receptor agonist, isoproterenol, increases phosphorylation of synapsins, a family of proteins involved regulation of neurotransmitter release, thus enhances synaptic transmission in the DG but not in area CA1 [15].

Area CA1 and the DG react differently to dopaminergic drugs. For example, antagonism of D1/D5 dopamine receptors with the drug SCH23390 prevents LTP expression [110, 111], and activation of these receptors with agonists (e.g., dihydrexidine) enhances LTP and inhibits depotentiation in area CA1 [112, 113]. However, in the DG, the D1/D5 dopamine receptors do not seem to play a critical role in the expression of LTP and depotentiation [114].

Treatment with the muscarinic cholinergic antagonist scopolamine in rats causes a significant decrease in the enzyme nitric oxide synthase (NOS) activity and an increase in arginase activity and L-ornithine and putrescine levels in the DG, but not in area CA1 [115]. Moreover, microinjection of cholinergic agonist carbachol into area CA1 and DG shows that the drug is more potent in decreasing pre-pulse inhibition in area CA1 than in the DG [116].

Adenosine shows differential effects on responses to theta train in CA1 and DG areas, where it modulates the response in the CA1 but has no significant effect on that response in the DG. Furthermore, the adenosine A1 receptor antagonist DPCPX enhances area CA1 responses without significantly affecting responses in the DG. This may be due to disparity in these hippocampal areas in the levels of the ecto-5′-

Table 2 Differential effects of various drugs on area CA1 and dentate gyrus (DG) of the hippocampus

Drug	CA1	DG
Norepinephrine	No effect on glutamate release	Modulation of glutamate release
Isoproterenol	No effect on synapsins	Increase phosphorylation of synapsins
Adenosine	Modulates theta responses	No effect on theta responses
Midazolam	Inhibitory effect on EPSP and pspike	Much less effect on EPSP and pspike
Muscimol	Hyperpolarize/depolarize	Depolarizes only
Tetraethylammonium	Induces LTP	Induces LTD
Alcohol	Significant loss of cells	Much less loss of cells
Dopamine antagonist	Inhibits LTP	No significant effect
Dopamine agonist	Enhances LTP	No significant effect
Lead	Significant enhancement of LTD	Much less enhancement of LTD
Sevoflurane	Much less enhancement of PPF	Significant enhancement of PPF
L-Tryptophan diet	Increases BDNF	Decreases BDNF
scopolamine	No effect on NOS and arginase	decreases NOS, increase arginase

nucleotidase that converts released ATP into adenosine, where it is greater in area CA1 than in the DG [30, 49, 50].

The benzodiazepines interact with a site on $GABA_A$ receptor, often referred to as the "benzodiazepine receptor." Extracellular recording from rat brain slices treated with the benzodiazepine midazolam reveals the drug to be much more effective in decreasing the amplitudes of orthodromic population spikes and excitatory postsynaptic potential (fEPSP) slopes of pyramidal cells of area CA1 than those of granule cells of the DG [117]. The same group of researchers using intracellular recordings from rat brain hippocampal slices treated with midazolam has shown the drug to be more effective in decreasing the amplitudes of intracellular action potentials of pyramidal cells of area CA1 than those of granule cells of the DG [118]. The differential effects of midazolam may be due to the different types and/or density of $GABA_A$ receptors in area CA1 pyramidal cell and the DG granule cells. Furthermore, whole cell patch-clamp work on the effect of midazolam on inhibitory postsynaptic currents (IPSCs) shows that while it significantly potentiates IPSCs in area CA1, it has no significant effect on those of the DG [119]. Additionally, the $GABA_A$ receptor antagonist bicuculline readily antagonizes the depressant effects of midazolam on action potential generation in area CA1 but is ineffective in antagonizing midazolam effects in the DG [117]. In the same preparation, $GABA_A$ receptor agonist muscimol produces either hyperpolarization or depolarization of the resting membrane potential in pyramidal neurons of area CA1, whereas it consistently produces depolarization of the granule cells of the DG [118].

Recordings from rat brain slices show that the potassium channel blocker tetraethylammonium (TEA), while inducing LTP in area CA1, it produces LTD in the DG [22]. The differential effect of TEA has been clarified by using T-type voltage-dependent calcium channel (VDCC) blockers and NMDA receptor antagonists, which show that TEA induces LTP indirectly by acting on both calcium channels and NMDA receptors in area CA1. In the DG, however, TEA induces LTD by acting only on NMDA receptors. These findings suggest that there is a major synaptic dissimilarity in the distribution of T-type VDCCs and NMDA receptors between CA1 and DG areas [22].

Experiments on rat models of fetal alcohol syndrome have shown that rats treated with ethanol during fetal development when tested in adulthood show that while there is a significant neuronal loss in area CA1, the granule cells of the DG are more resistant or better able of recovery on reaching adulthood [120, 121].

Chronic lead exposure in rats affects the magnitude of LTD differently in these two hippocampal areas. The LTD of the DG is significantly more enhanced by chronic lead exposure than that of area CA1 [92, 122].

Activity-induced external pH shifts are different in the DG and CA1 areas of the developing brain. In area CA1, repetitive stimulation elicits an early alkaline shift associated with a later slow acid shift. However, in the DG, similar stimulation elicits only acidification. This may be responsible for the different seizure susceptibility of the two areas [20].

Other agents show differential effects in the two hippocampal areas; for instance, application of the selective μ-opioid receptor antagonist, funaltrexamine, decreases LTP in the DG of mice but has no effect on LTP of area CA1 [19]. In transverse hippocampal slices from transgenic mice with deleted μ-opioid receptor, tetanization of the lateral perforant pathway produces LTP in the DG, whereas the absence of the μ-opioid receptor in area CA1 does not affect its LTP [19].

Also, high L-tryptophan diet in old rats surprisingly increases BDNF immunoreactivity in area CA1 but causes a drastic decrease in that of the DG [123]. Another example, the volatile anesthetic sevoflurane significantly enhances paired pulse facilitation more profoundly in the DG than in

area CA1 [124]. Furthermore, NMDA drug perfusion-evoked LTD in the two areas also differs in their reaction to bisphenol-A, an estrogen-like synthetic compound, which has been shown to enhance LTD in area CA1 but suppress that of the DG area [125].

Response to Pathologies and Disorders

The granule cells of the DG are more resistant to a number of damaging conditions than are the pyramidal cells of area CA1 [17, 18, 20, 81]. Findings from my lab reveal a notable exception in the differential reaction of CA1 and DG areas to the deleterious effects of sleep deprivation. Following sleep deprivation, LTP in both areas seems to be equally vulnerable to the effect of this disorder [126–130]. However, close examination of the impact of sleep deprivation on cellular structure in the mouse brain reveals a difference in the reactions of the CA1 and DG areas. While sleep loss decreases the density of all subtypes of synaptic spines (thin, stubby, mushroom, filopodia, and branched) in area CA1, the DG sleep deprivation decreases only the thin and branched subtypes [131]. However, the various methods of sleep deprivation used, different times and duration of sleep deprivation, and the diverse animal species studied can be serious confounding factors. Given these differences, additional studies are obviously needed to further elucidate the impact of sleep deprivation on the two areas of the hippocampus.

Ischemia

Transient ischemia impairs NMDA receptor function in area CA1, but not in the DG [17]. It is also known that the granule cells of the DG are more resistant to the harmful effects of anoxia, ischemia, or stress than are the pyramidal cells of area CA1 [17, 18, 20, 81]. Electrophysiological studies have shown that hypoxic-ischemic insults have more profoundly injurious effects on pyramidal neurons of area CA1 than on the granule cells of the DG [17, 18, 20, 81]. Additionally, histological analyses in the gerbil [132] and rat [133–136] show that compared with the DG, the CA1 area is more vulnerable to the damaging effects of global ischemia.

Transient global ischemia causes death of area CA1 pyramidal neurons in the days following reperfusion, whereas the granule cells of the DG neurons remain relatively resistant [137]; (for review, see [138]). Even astrocytes within area CA1 are more sensitive to mitochondrial dysfunction caused by ischemic injury than astrocytes in the DG [137, 139]. For example, in an in vitro hippocampal slice model of ischemia (oxygen-glucose deprivation), whereas field potentials from area CA1 are consistently abolished by hypoxia, similar hypoxic insult has no permanent effect on field responses evoked from the DG [42, 140, 141].

Hypoxia or ischemia produces elevation in intracellular free calcium concentrations of hippocampal neurons, which leads to neuronal damage and death [142]. It has been shown that with hypoxic-ischemic insults, calcium influx is greater in area CA1 neurons than in the DG granule cells [141, 143, 144]. This increase in intracellular free calcium combined with relative paucity of calbindin in area CA1 pyramidal cells [63, 64]; (for review see [65]) make area CA1 more vulnerable to the effect of ischemia. Therefore, the impact of the increase in calcium influx seems to be readily tempered in the granule cells of the DG due to their superior calcium buffering capacity.

Stress and Stress Hormones

Chronic stress negatively impacts brain function, and even mild chronic unpredictable stress causes atrophy of area CA1 of rats but not of the DG of the same rats [145], which may be related to the ability of the DG to replace dysfunctional neurons through neurogenesis. Stress and stress hormones have consistently been reported to impair LTP [83–85, 88] and increase the magnitude of LTD [80] in area CA1, whereas the LTP of DG in the same animals seems to be generally more resistant to stress and stress hormones [81, 86–88]. Remarkably, stress induced by predator exposure impairs LTP of area CA1 [85] but enhances that of the DG [89]. Furthermore, increased release rate of implanted corticosterone severely impairs LTP of area CA1 [90, 91, 145], without affecting LTP of the DG [78, 138]. Moreover, corticosterone at moderate doses causes enhancement of LTP in the DG but not in area CA1. Interestingly, high corticosterone doses changed LTP to LTD in area CA1 without affecting LTP of the DG [38]. Corticosterone also inhibited theta burst stimulation-induced local circuit plasticity in the DG but not in area CA1 [38].

Electrophysiological recording from anesthetized rat brain shows that while chronic psychosocial stress prevents the expression of synaptic plasticity in area CA1, it does not affect that of the DG. For example, in area CA1 of the rat hippocampus, chronic psychosocial stress markedly reduces or abolishes E-LTP; in contrast, no significant change in E-LTP is seen in the DG area [80, 81, 88]. Even when stress is combined with thyroidectomy (hypothyroidism), which abolishes E-LTP of area CA1, the combination of the two insults produces no significant effect on E-LTP of the DG [81]. As mentioned earlier, data from my lab have shown that unlike area CA1 where stress significantly increases the phosphatase calcineurin level in the DG, chronic stress produces a significant decrease in calcineurin levels (Fig. 1, Table 1). These results suggest that in the chronically stressed rats, the DG but not area CA1 is endowed with a defense mechanism whereby calcineurin levels are reduced to curtail dephosphorylation and maintain normal P-CaMKII levels, which may be

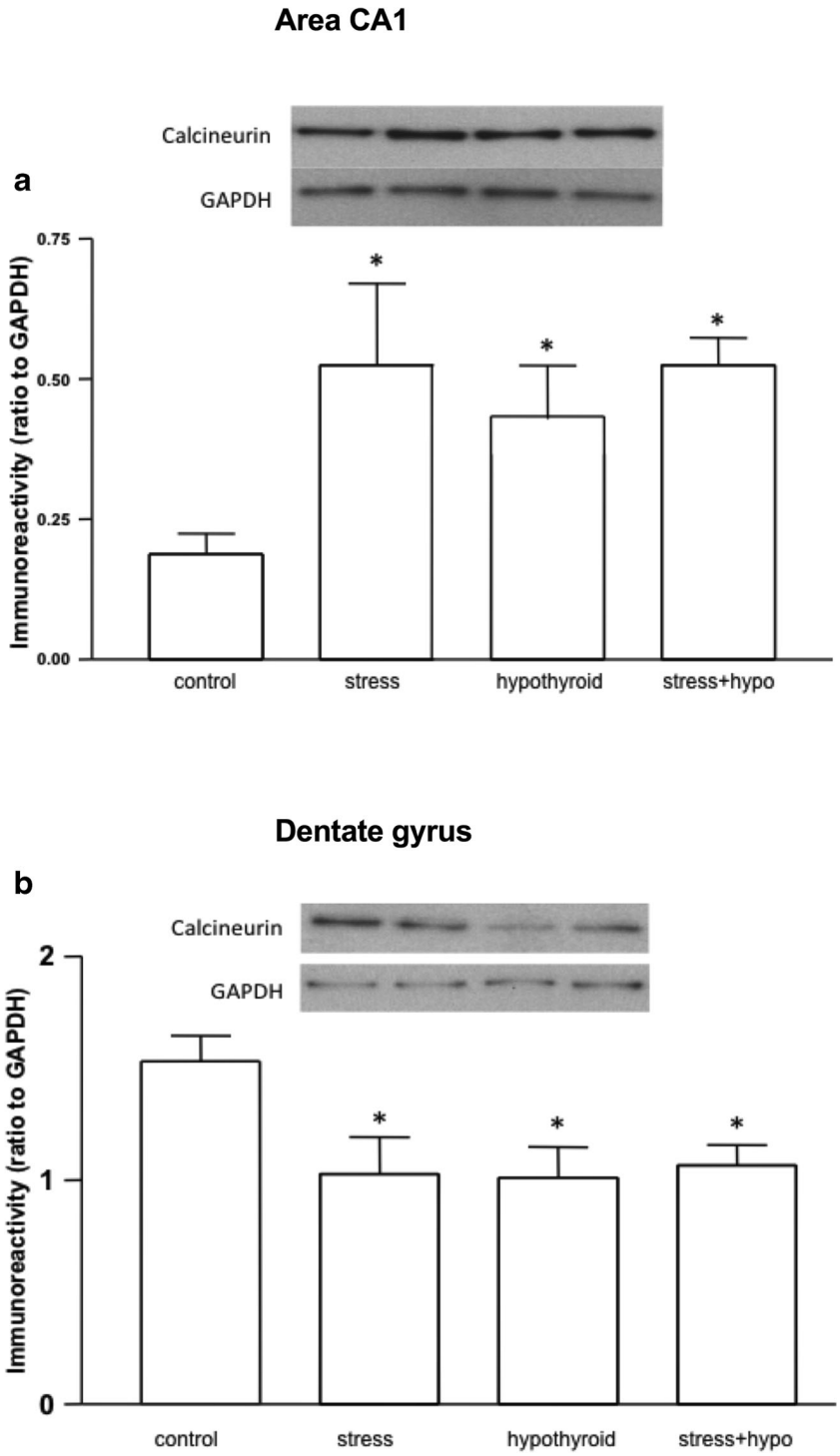

Fig. 1 Comparison of the effects of chronic psychosocial stress, hypothyroidism, and the combination on the levels of the phosphatase calcineurin in area CA1 (**a**) and the dentate gyrus (**b**). * indicates significant difference from control value (one-way ANOVA, Tukey post hoc test). Values are mean ± SEM. Insets are representative Western blots (adapted from Gerges et al. [81, 95, 146])

responsible for the normal E-LTP of the DG of chronically stressed rats [95].

Hypothyroidism

Hypothyroidism markedly impairs E-LTP in area CA1 [6, 82] without significantly affecting that of the DG [6]. As mentioned above, the combination of hypothyroidism and chronic stress does not affect the E-LTP of the DG, while it severely suppresses E-LTP of area CA1 [81]. Similarly, the L-LTP of area CA1 is markedly impaired by hypothyroidism [147–148], but L-LTP of the DG is not significantly impacted [146]. Additionally, hypothyroidism markedly depresses the levels of phosphorylated ERK1/2 (phospho-P44 and phospho-P42) in area CA1 without affecting these molecules in the DG of the same rats (Table 1) [146]. Another interesting

molecular finding is that while hypothyroidism markedly upregulates levels and activity of calcineurin in area CA1 (Fig. 1a), it decreases its level and activity in the DG (Fig. 1b) [6], which may be the reason for preservation of levels of PKC and phosphorylated CaMKII of the DG of hypothyroid rat. Similar effect of hypothyroidism on LTP of the DG has been reported by Sánchez-Huerta et al. [149]. Earlier reports show deficits in synaptic transmission and LTP in the DG in a similar model of adult onset hypothyroidism induced by thyroidectomy [150, 151]. However, these authors have not measured the effect on area CA1 to allow comparison.

Alzheimer's Disease

The apical dendrites of hippocampal area CA1 pyramidal neurons in the stratum radiatum/stratum lacunosum-moleculare (SRLM) are among the earliest targets of Alzheimer's disease. In patients with mild Alzheimer's disease, Kerchner and colleagues [152] report a strong correlation between delayed recall performance and thinning of these dendrites in area CA1 but not in the DG.

Although infusion of Aβ peptides markedly suppresses both E-LTP and L-LTP of area CA1 as measured by both fEPSP slope (a measure of synaptic activity) and population spike (pspike) amplitude (a measure of neurons reaching firing threshold) in the DG of the same rats, the outcome is different. The 14-day infusion of Aβ1–42 severely curtailed the stimulation-induced expression of both E-LTP and L-LTP in area CA1 of anesthetized rat, as measured by the fEPSP or pspike amplitude [153]. However, although E-LTP and L-LTP of the DG as measured by fEPSP are also severely blocked (Fig. 2a, c) [153] when measured by pspike amplitude, these forms of synaptic plasticity are not significantly affected by

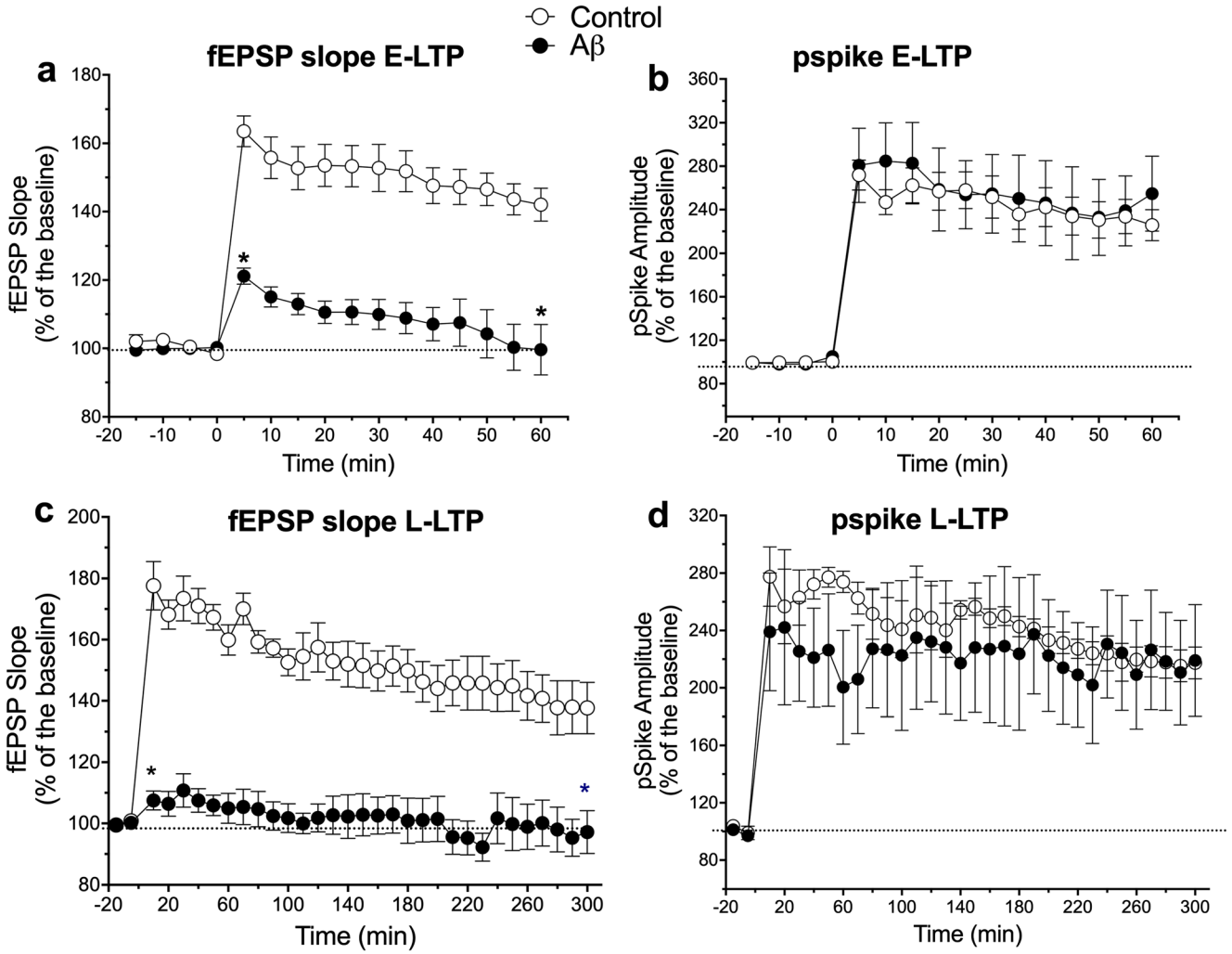

Fig. 2 The effects of infusion of Aβ peptides on E-LTP (**a**) and L-LTP (**c**) measured as fEPSP and as population spike (pspike; **b** and **d**, respectively) recorded from dentate gyrus (DG) of anesthetized rats. All points between the two * are significantly different from control value (one-way ANOVA), Tukey post hoc test). Values are mean ± SEM (adapted from Dao et al. [7, 153]

Aβ infusion (Fig. 2b, d) [153]. At this point, we can only speculate about the cause of the disparity in the results of these measurements. Since the pspike amplitude is a measure of the number of neurons reaching threshold for firing, it is possible that because of its ability for neurogenesis, the DG may produce enough new functional cells to preserve the integrity of the LTP as measured by pspike.

Other Conditions

Both genetic and dietary obesity have deleterious effects on LTP of area CA1 in rodents [82, 154–159]. Electrophysiological recording from anesthetized obese Zucker rat (OZR), a genetic model of obesity, shows E-LTP to be markedly impaired in area CA1 (Fig. 3a, b). However, recording from the DG of the same OZR reveals an intact LTP that is not significantly different than that of the lean control rat (Fig. 3c, d) [82]. We also have investigated the molecular mechanism responsible for impairment of LTP in area CA1 but not in the DG region of this model. Analysis reveals a marked decrease in the levels of P-CaMKII and total CaMKII in the CA1 area of OZR. However, in the DG of the same OZR, reduction is observed only in the levels of total CaMKII, but not in P-CaMKII levels. These findings suggest that the DG is endowed with a compensatory mechanism whereby, despite significant decrease in total CaMKII, calcineurin levels are reduced to allow sufficient P-CaMKII levels to support a normal LTP in the DG of OZR hippocampus [82]. This compensatory mechanism is also seen in the DG of chronically stressed and hypothyroid rats [94].

The CA1 and DG regions exhibit differences regarding biological markers of aging [3, 35, 160–162]. Experiments

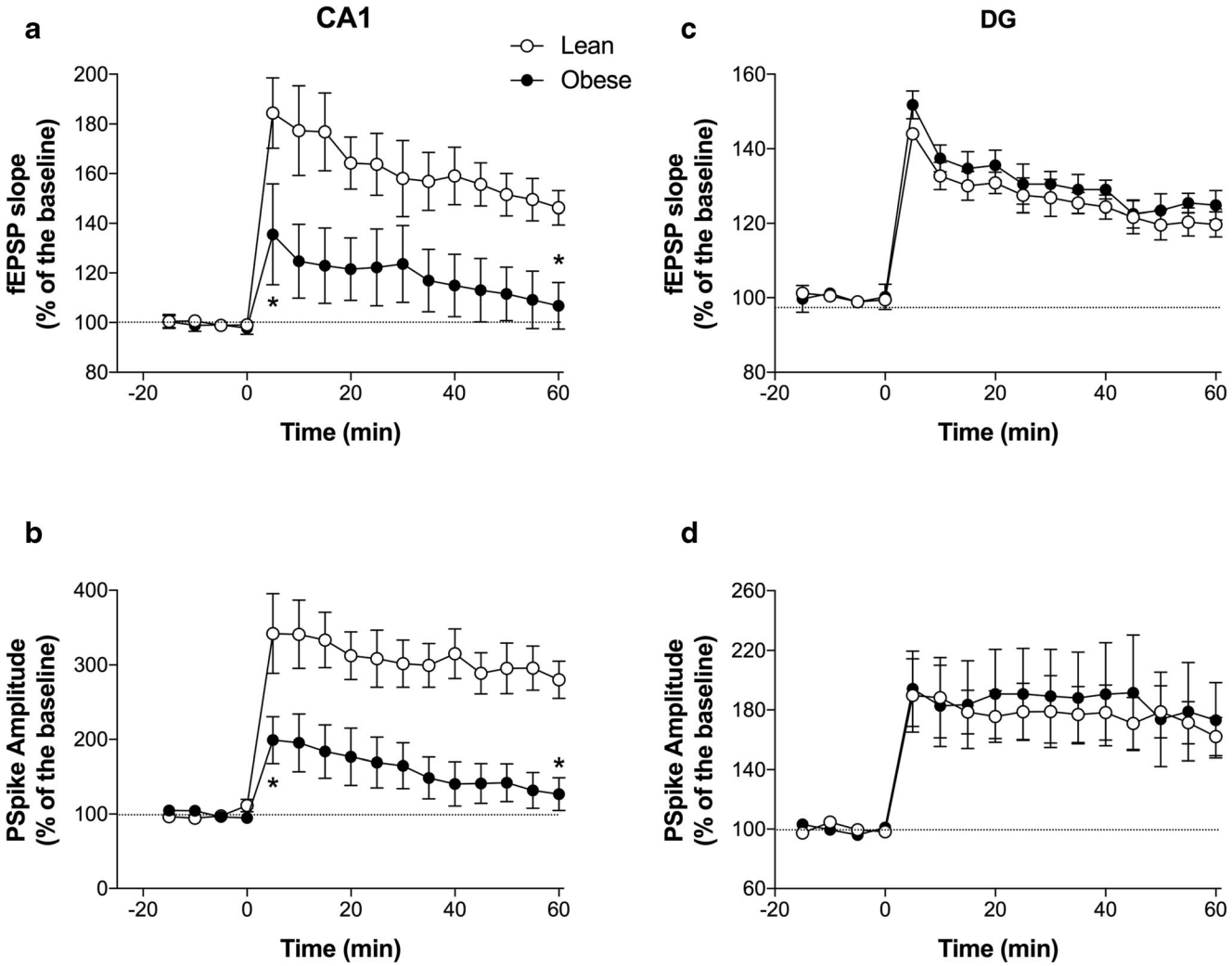

Fig. 3 Comparison of E-LTP recorded from area CA1 (**a** fEPSP, **b** pspike)) and dentate gyrus (DG; **c** fEPSP, **d** pspike) of anesthetized obese and lean Zucker rats. Note that obesity while impairing CA1 E-LTP, it does not impair that of the DG. All points between the two * for obese in **a** and **b** are significantly different from those of the lean rat ($p < 0.05$; unpaired t test test). Values are mean ± SEM (adapted from Alzoubi et al. [82]

in rats show that area CA1 is more susceptible to the deleterious effects of aging, whereas the DG during aging and caloric restriction shows enhanced cell survival signaling pathways. Moreover, area CA1 appears to be more sensitive to oxidative stress and apoptosis seen with age than the DG area [163–165].

Concluding Remarks

The literature consistently shows that the DG granule cells appear to be more resistant than area CA1 pyramidal neurons to several conditions, including stress, anoxia, transient cerebral ischemia, obesity, and hypothyroidism [5, 17, 18, 81, 82]. The intrinsic flow of information within the hippocampal formation necessitates extensive interactions between the CA1 and DG areas. The two areas share similar laminar structure of packed glutamatergic neurons, and both utilize similar NMDA-receptor dependent synaptic plasticity mechanism. However, the CA1 and DG areas markedly differ in the allocation of signaling molecules, receptors, ion channels, and reaction to insults and alteration of function by drugs.

What makes these differences arise between these two closely associated areas? The most logical explanation may be related to the important neurogenic function of the granule cells of the DG in the hippocampal formation. The DG contains the SGZ, one of the few areas in the brain that have active capability for neurogenesis in adulthood. The importance of neurogenesis in the DG for maintaining healthy brain function is obvious. Therefore, this particular region of the brain is endowed with relatively formidable lines of defense to maintain the crucial role of supplying the brain tissue with new cells to ensure integrity and proper functionality of the brain. Interestingly, although there are reports of differences in the effect of sleep deprivation on synaptic spine subtypes, our electrophysiological and molecular results indicated that the DG is just as severely impaired by sleep loss as CA1, which suggests the particularly powerful impact of sleep loss on brain function.

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Compliance with Ethical Standards

Financial Disclosure The author declares no direct or indirect financial or personal relationships, interests, and affiliations relevant to the subject matter of the manuscript have occurred over the last 2 years, and none expected in the foreseeable future.

References

1 Knowles WD (1992) Normal anatomy and neurophysiology of the hippocampal formation. J Clin Neurophysiol 9:252–263
2 Jackson TC, Foster TC (2009) Regional health and function in the hippocampus: Evolutionary compromises for a critical brain region. Bioscience Hypotheses 2:245–251
3 Jackson TC, Rani A, Kumar A, Foster TC (2009) Regional hippocampal differences in AKT survival signaling across the lifespan: Implications for CA1 vulnerability with aging. Cell Death Differ 16:439–448
4 McEwen BS (2001) Plasticity of the hippocampus: Adaptation to chronic stress and allostatic load. Ann N Y Acad Sci 933:265–277
5 Gerges NZ, Alkadhi KA (2004) Hypothyroidism impairs late LTP in CA1 region but not in dentate gyrus of the intact rat hippocampus: MAPK involvement. Hippocampus 14:40–45
6 Gerges NZ, Alzoubi KH, Alkadhi KA (2005) Role of phosphorylated CaMKII and calcineurin in the differential effect of hypothyroidism on LTP of CA1 and dentate gyrus. Hippocampus 15:480–490
7 Dao AT, Zagaar MA, Levine AT, Alkadhi KA (2016) Comparison of the effect of exercise on late-phase LTP of the dentate gyrus and CA1 of Alzheimer's disease model. Mol Neurobiol 53:6859–6868
8 Stabel J, Ficker E, Heinemann U (1992) Young CA1 pyramidal cells of rats, but not dentate gyrus granule cells, express a delayed inward rectifying current with properties of IQ. Neurosci Lett 135:231–234
9 Ormerod BK, Palmer TD, Caldwell MA (2008) Neurodegeneration and cell replacement. Philos Trans R Soc Lond Ser B Biol Sci 363:153–170
10 Pawluski JL, Brummelte S, Barha CK, Crozier TM, Galea LA (2009) Effects of steroid hormones on neurogenesis in the hippocampus of the adult female rodent during the estrous cycle, pregnancy, lactation and aging. Front Neuroendocrinol 30:343–357
11 Sawada M, Sawamoto K (2013) Mechanisms of neurogenesis in the normal and injured adult brain. Keio J Med 62:13–28
12 Anacker C, Hen R (2017) Adult hippocampal neurogenesis and cognitive flexibility linking memory and mood. Nat Rev Neurosci 18:335–346
13 Lee E, Son H (2009) Adult hippocampal neurogenesis and related neurotrophic factors. BMB Rep 42:239–244
14 Yamashima T, Tonchev AB, Vachkov IH, Popivanova BK, Seki T, Sawamoto K, Okano H (2004) Vascular adventitia generates neuronal progenitors in the monkey hippocampus after ischemia. Hippocampus 14:861–875
15 Parfitt KD, Doze VA, Madison DV, Browning MD (1992) Isoproterenol increases the phosphorylation of the synapsins and increases synaptic transmission in dentate gyrus but not in area CA1, of the hippocampus. Hippocampus 2:59–64
16 Davis S, Laroche S (1996) Activation of metabotropic glutamate receptors induce differential effects on synaptic transmission in the dentate gyrus and CA1 of the hippocampus in the anaesthetized rat. Neuropharmacology 35:337–346
17 Hsu JC, Zhang Y, Takagi N, Gurd JW, Wallace MC, Zhang L, Eubanks JH (1998) Decreased expression and functionality of NMDA receptor complexes persist in the CA1, but not in the dentate gyrus after transient cerebral ischemia. J Cereb Blood Flow Metab 18:768–775
18 Yao H, Huang YH, Liu ZW, Wan Q, Ding AS, Zhao B, Fan M, Wang FZ (1998) The different responses to anoxia in cultured CA1 and DG neurons from newborn rats. Sheng Li Xue Bao 50:61–66
19 Matthies H, Schroeder H, Becker A, Loh H, Höllt V, Krug M (2000) Lack of expression of long-term potentiation in the dentate gyrus but not in the CA1 region of the hippocampus of mu-opioid receptor-deficient mice. Neuropharmacology 39:952–960

20 Xiong ZQ, Stringer JL (2000) Extracellular pH responses in CA1 and the dentate gyrus during electrical stimulation, seizure discharges, and spreading depression. J Neurophysiol 83:3519–3524
21 Gilbert PE, Kesner RP, Lee I (2001) Dissociating hippocampal subregions: Double dissociation between dentate gyrus and CA1. Hippocampus 11:626–636
22 Song D, Xie X, Wang Z, Berger TW (2001) Differential effect of TEA on long-term synaptic modification in hippocampal CA1 and dentate gyrus in vitro. Neurobiol Learn Mem 76:375–387
23 Stuart G, Spruston N (1998) Determinants of voltage attenuation in neocortical pyramidal neuron dendrites. J Neurosci 18:3501–3510
24 Stuart GJ, Spruston N (2015) Dendritic integration: 60 years of progress. Nat Neurosci 18:1713–1721
25 Golding NL, Mickus TJ, Katz Y, Kath WL, Spruston N (2005) Factors mediating powerful voltage attenuation along CA1 pyramidal neuron dendrites. J Physiol 568(Pt 1):69–82
26 Schmidt-Hieber C, Jonas P, Bischofberger J (2007) Subthreshold dendritic signal processing and coincidence detection in dentate gyrus granule cells. J Neurosci 27:8430–8441
27 Haberly LB Parallel-distributed processing in olfactory cortex: new insights from morphological and physiological analysis of neuronal circuitry Chem Senses 2001; 26:551–576.
28 Wilson DA, Sullivan RM (2011) Cortical processing of odor objects. Neuron 72:506–519
29 Ishizuka N, Weber J, Amaral DG (1990) Organization of intrahippocampal projections originating from CA3 pyramidal cells in the rat. J Comp Neurol 295:580–623
30 Trieu BH, Kramár EA, Cox CD, Jia Y, Wang W, Gall CM, Lynch G (2015) Pronounced differences in signal processing and synaptic plasticity between piriform-hippocampal network stages: A prominent role for adenosine. J Physiol 593:2889–2907
31 Imdahl A, Hossmann K (1986) Morphometric evaluation of postischemic capillary perfusion in selectively vulnerable areas of gerbil brain. Acta Neuropathol 69:267–271
32 Suzuki R, Yamaguchi T, Kirino T, Orzi F, Klatzo I (1983) The effects of 5-minute ischemia in Mongolian gerbils: I. Blood-brain barrier, cerebral blood flow, and local cerebral glucose utilization changes. Acta Neuropathol 60:207–216
33 Melnikova T, Park D, Becker L, Lee D, Cho E, Sayyida N, Tian J, Bandeen-Roche K et al (2016 Dec) Sex-related dimorphism in dentate gyrus atrophy and behavioral phenotypes in an inducible tTa:APPsi transgenic model of Alzheimer's disease. Neurobiol Dis 96:171–185
34 Kiryk A, Sowodniok K, Kreiner G, Rodriguez-Parkitna J, Sönmez A, Górkiewicz T, Bierhoff H, Wawrzyniak M et al (2013 Nov 11) Impaired rRNA synthesis triggers homeostatic responses in hippocampal neurons. Front Cell Neurosci 7:207
35 Penner MR, Parrish RR, Hoang LT, Roth TL, Lubin FD, Barnes CA (2016 Aug) Age-related changes in Egr1 transcription and DNA methylation within the hippocampus. Hippocampus. 26(8): 1008–1020
36 Lardenoije R, van den Hove DLA, Havermans M, van Casteren A, Le KX, Palmour R, Lemere CA, Rutten BPF (2018 Jan) Age-related epigenetic changes in hippocampal subregions of four animal models of Alzheimer's disease. Mol Cell Neurosci 86:1–15
37 Becq H, Jorquera I, Ben-Ari Y, Weiss S, Represa A (2005 Feb 5) Differential properties of dentate gyrus and CA1 neural precursors. J Neurobiol 62(2):243–261
38 Sharvit A, Segal M, Kehat O, Stork O, Richter-Levin G (2015) Differential modulation of synaptic plasticity and local circuit activity in the dentate gyrus and CA1 regions of the rat hippocampus by corticosterone. Stress. 18(3):319–327
39 Arima-Yoshida F, Watabe AM, Manabe T (2011 May) The mechanisms of the strong inhibitory modulation of long-term potentiation in the rat dentate gyrus. Eur J Neurosci 33(9):1637–1646
40 Frahm C, Draguhn A (2001 Dec 14) GAD and GABA transporter (GAT-1) mRNA expression in the developing rat hippocampus. Brain Res Dev Brain Res 132(1):1–13
41 Coultrap S, Nixon K, Alvestad R, Valenzuela C, Browning M (2005) Differential expression of NMDA receptor subunits and splice variants among the CA1, CA3, and dentate gyrus of the adult rat. Mol Brain Res 135:104–111
42 Lalonde CC, Mielke JG (2014) Selective vulnerability of hippocampal sub-fields to oxygen-glucose deprivation is a function of animal age. Brain Res 1543:271–279
43 Lamsa KP, Heeroma JH, Somogyi P, Rusakov DA, Kullmann DM (2007) Anti-Hebbian long-term potentiation in the hippocampal feedback inhibitory circuit. Science 315(5816):1262–1266
44 Wiltgen BJ, Royle GA, Gray EE, Abdipranoto A, Thangthaeng N, Jacobs N, Saab F, Tonegawa S et al (2010) A role for calcium-permeable AMPA receptors in synaptic plasticity and learning. PLoS One 29:5(9)
45 Weiss JH (2011) Ca permeable AMPA channels in diseases of the nervous system. Front Mol Neurosci 4:42
46 Kannangara TS, Eadie BD, Bostrom CA, Morch K, Brocardo PS, Christie BR (2015) GluN2A$^{-/-}$ mice lack bidirectional synaptic plasticity in the dentate gyrus and perform poorly on spatial pattern separation tasks. Cereb Cortex 25:2102–2113
47 Vicini S, Wang JF, Li JH, Zhu WJ, Wang YH, Luo JH, Wolfe BB, Grayson DR (1998) Functional and pharmacological differences between recombinant *N*-methyl-D-aspartate receptors. J Neurophysiol 79:555–566
48 Dingledine R, Borges BD, Traynelis SF (1999) The glutamate receptor ion channels. Pharmacol Rev 51:7–62
49 Cunha RA (2001) Regulation of the ecto-nucleotidase pathway in rat hippocampal nerve terminals. Neurochem Res 26:979–991
50 Lovatt D, Xu Q, Liu W, Takano T, Smith NA, Schnermann J, Tieu K, Nedergaard M (2012) Neuronal adenosine release, and not astrocytic ATP release, mediates feedback inhibition of excitatory activity. Proc Natl Acad Sci U S A 109:6265–6270
51 Lee KS, Schubert P, Reddington M, Kreutzberg GW (1986) The distribution of adenosine A1 receptors and 5′-nucleotidase in the hippocampal formation of several mammalian species. J Comp Neurol 246:427–434
52 Schoen SW, Kreutzberg GW (1994) Synaptic 5′-nucleotidase activity reflects lesion-induced sprouting within the adult rat dentate gyrus. Exp Neurol 127:106–118
53 Dumont Y, Fournier A, St-Pierre S, Schwartz TW, Quirion R (1990) Differential distribution of neuropeptide Y, and Y, receptors in the rat brain. Eur J Pharmacol 191:501–503
54 Dumont Y, Martel J-C, Fournier A, St-Pierre S, Quirion R (1992) Neuropeptide Y and neuropeptide Y receptor subtypes in brain and periuheral tissues. Prog Neurobiol 38:125–167
55 Dumont Y, Fournier-A S-PS, Quirion R (1993) Comparative characterization and autoradiographic distribution of neuropeptide Y receptor subtypes in the rat brain. J Neurosci 13:73–86
56 Aicher SA, Springton M, Berger SB, Reis DJ, Wahlestedt C (1991) Receptor-selective analogs demonstrate NPY/PYY receptor heterogeneity in rat brain. Neurosci Lett 130:32–36
57 Wahlestedt C, Reis DJ (1993) Neuropeptide Y-related peptides and their receptors-are the receptors potential therapeutic drug targets? Annu Rev Pharmacol Toxicol 33:309–352
58 McQuiston AR, Petrozzino JJ, Connor JA, Colmers WF (1996) Neuropeptide Y1 receptors inhibit N-type calcium currents and reduce transient calcium increases in rat dentate granule cells. J Neurosci 16:1422–1429
59 Silva AP, Carvalho AP, Carvalho CM, Malva JO (2001) Modulation of intracellular calcium changes and glutamate release by neuropeptide Y1 and Y2 receptors in the rat hippocampus: Differential effects in CA1, CA3 and dentate gyrus. J Neurochem 79:286–296

60 Westerink RH, Beekwilder JP, Wadman WJ (2012) Differential alterations of synaptic plasticity in dentate gyrus and CA1 hippocampal area of Calbindin-D28K knockout mice. Brain Res 23(1450):1–10

61 Abrahám H, Veszprémi B, Kravják A, Kovács K, Gömöri E, Seress L (2009) Ontogeny of calbindin immunoreactivity in the human hippocampal formation with a special emphasis on granule cells of the dentate gyrus. Int J Dev Neurosci 27:115–127

62 Sloviter RS (1989) Calcium-binding protein (calbindin-D28k) and parvalbumin immunocytochemistry: Localization in the rat hippocampus with specific reference to the selective vulnerability of hippocampal neurons to seizure activity. J Comp Neurol 280: 183–196

63 Frantz GD, Tobin AJ (1994) Cellular distribution of calbindin D28K mRNAs in the adult mouse brain. J Neurosci Res 37:287–302

64 Müller A, Kukley M, Stausberg P, Beck H, Müller W, Dietrich D (2005) Endogenous Ca^{2+} buffer concentration and Ca^{2+} microdomains in hippocampal neurons. J Neurosci 25:558–565

65 Schwaller B (2010) Cytosolic Ca^{2+} buffers. Cold Spring Harb Perspect Biol 2(11):a004051. https://doi.org/10.1101/cshperspect.a004051 **Epub 2010 Oct 13**

66 Scharfman HE, Schwartzkroin PA (1989) Protection of dentate hilar cells from prolonged stimulation by intracellular calcium chelation. Science 246(4927):257–260

67 Maglóczky Z, Halász P, Vajda J, Czirják S, Freund TF (1997) Loss of Calbindin-D28K immunoreactivity from dentate granule cells in human temporal lobe epilepsy. Neuroscience 76:377–385

68 Stefanits H, Wesseling C, Kovacs GG (2014) Loss of Calbindin immunoreactivity in the dentate gyrus distinguishes Alzheimer's disease from other neurodegenerative dementias. Neurosci Lett 566:137–141

69 Baba A, Yamada MK, Nishiyama N, Matsuki N, Ikegaya Y (2002) Different Ca^{2+} dynamics between isolated hippocampal pyramidal cells and dentate granule cells. J Neurocytol 31:41–48

70 AbrahamWC M-PSE, Logan B (1996) Low-frequency stimulation does not readily cause long-term depression or depotentiation in the dentate gyrus of awake rats. Brain Res 722:217–221

71 Kramar EA, Babayan AH, Gavin CF, Cox CD, Jafari M, Gall CM, Rumbaugh G, Lynch G (2012) Synaptic evidence for the efficacy of spaced learning. Proc Natl Acad Sci U S A 109:5121–5126

72 Izaki Y, Arita J (1996) Long-term potentiation in the rat hippocampal CA1 region is inhibited selectively at the acquisition stage of discriminatory avoidance learning. Brain Res 723:162–168

73 Velísek L, Stanton PK, Moshé SL, Vathy I (2000) Prenatal morphine exposure enhances seizure susceptibility but suppresses long-term potentiation in the limbic systemof adult male rats. Brain Res 869:186–193

74 Pöschel B, Stanton PK (2007) Comparison of cellular mechanisms of long-term depression of synaptic strength at perforant pathgranule cell and Schaffer collateral-CA1 synapses. Prog Brain Res 163:473–500

75 Vouimba RM, Richter-Levin G (2005) Physiological dissociation in hippocampal sub-regions in response to amygdala stimulation. Cereb Cortex 15:1815–1821

76 Vouimba R, Yaniv D, Richter-Levin G (2007) Glucocorticoid receptors and beta-adrenoceptors in BLA modulate synaptic plasticity in hippocampal DG but not in CA1. Neuropharmacology 52: 244–252

77 Akirav I, Richter-Levin G (1999) Biphasic modulation of hippocampal plasticity by behavioral stress and basolateral amygdala stimulation in the rat. J Neurosci 19:10530–10535

78 Vouimba RM, Richter-Levin G (2013) Different patterns of amygdala priming differentially affect dentate gyrus plasticity and corticosterone, but not CA1 plasticity. Front Neural Circuits 7:80

79 Tran TT, Srivareerat M, Alhaider IA, Alkadhi KA (2011) Chronic psychosocial stress enhances long-term depression in a subthreshold amyloid-beta rat model of Alzheimer's disease. J Neurochem 119:408–416

80 Alkadhi KA, Tran TT (2014) Chronic psychosocial stress impairs early LTP but not late LTP in the dentate gyrus of at-risk rat model of Alzheimer's disease. Brain Res 1588:150–158

81 Gerges NZ, Stringer JL, Alkadhi KA (2001) Combination of hypothyroidism and stress abolishes early LTP in the CA1 but not dentate gyrus of hippocampus of adult rats. Brain Res 922:250–260

82 Alzoubi KH, Aleisa AM, Alkadhi KA (2005) Impairment of long-term potentiation in the CA1, but not dentate gyrus, of the hippocampus in obese Zucker rats: Role of calcineurin and phosphorylated CaMKII. J Mol Neurosci 27:337–346

83 Pavlides C, Ogawa S, Kimura A, McEwen BS (1996) Role of adrenal steroid mineralocorticoid and glucocorticoid receptors in long-term potentiation in the CA1 field of hippocampal slices. Brain Res 738:229–235

84 Xu L, Holscher C, Anwyl R, Rowan MJ (1998) Glucocorticoid receptor and protein/RNA synthesis-dependent mechanisms underlie the control of synaptic plasticity by stress. Proc Natl Acad Sci U S A 95:3204–3208

85 Vouimba RM, Muñoz C, Diamond DM (2006) Differential effects of predator stress and the antidepressant tianeptine on physiological plasticity in the hippocampus and basolateral amygdala. Stress 9:29–40

86 Bramham CR, Southard T, Ahlers ST, Sarvey JM (1998) Acute cold stress leading to elevated corticosterone neither enhances synaptic efficacy nor impairs LTP in the dentate gyrus of freely moving rats. Brain Res 789:245–255

87 Yamada K, McEwen BS, Pavlides C (2003) Site and time dependent effects of acute stress on hippocampal long-term potentiation in freely behaving rats. Exp Brain Res 152:52–59

88 Aleisa AM, Alzoubi KH, Gerges NZ, Alkadhi KA (2006) Nicotine blocks stress-induced impairment of spatial memory and LTP of the hippocampal CA1 region. Int J Neuropsychopharmacol 9:417–426

89 Dringenberg HC, Oliveira D, Habib D (2008) Predator (cat hair)-induced enhancement of hippocampal long-term potentiation in rats: Involvement of acetylcholine. Learn Mem 15: 112–116

90 Diamond DM, Bennett MC, Fleshner M, Rose GM (1992) Inverted-U relationship between the level of peripheral corticosterone and the magnitude of hippocampal primed burst potentiation. Hippocampus 2:421–430

91 Pavlides C, Watanabe Y, McEwen BS (1993) Effects of glucocorticoids on hippocampal long-term potentiation. Hippocampus 3: 183–192

92 Sui L, Ge SY, Ruan DY, Chen JT, Xu YZ, Wang M (2000a) Age-related impairment of long-term depression in area CA1 and dentate gyrus of rat hippocampus following developmental lead exposure in vitro. Neurotoxicol Teratol 22:381–387

93 Sui L, Ruan DY, Ge SY, Meng XM (2000b) Two components of long-term depression are impaired by chronic lead exposure in area CA1 and dentate gyrus of rat hippocampus in vitro. Neurotoxicol Teratol 22:741–749

94 Dietz B, Manahan-Vaughan D (2017) Hippocampal long-term depression is facilitated by the acquisition and updating of memory of spatial auditory content and requires mGlu5 activation. Neuropharmacology 115:30–41

95 Gerges NZ, Aleisa AM, Schwarz LA, Alkadhi KA (2003) Chronic psychosocial stress decreases calcineurin in the dentate gyrus: A possible mechanism for preservation of early LTP. Neuroscience 117:869–874

96. Alzoubi KH, Aleisa AM, Alkadhi KA (2007) Nicotine prevents disruption of the late phase LTP-related molecular cascade in adult-onset hypothyroidism. Hippocampus 17:654–664
97 Figueroa-Mendez R, Rivas-Arancibia S (2015) Vitamin C in health and disease: Its role in the metabolism of cells and redox state in the brain. Front Physiol 6:397
98 Ferreira NR, Lourenco CF, Barbosa RM, Laranjinha J (2015) Coupling of ascorbate and nitric oxide dynamics in vivo in the rat hippocampus upon glutamatergic neuronal stimulation: A novel functional interplay. Brain Res Bull 114:13–19
99 Suárez I, Bodega G, Fernández B (2002) Glutamine synthetase in brain: Effect of ammonia. Neurochem Int 41:123–142
100 Nakajima K, Kanamatsu T, Takezawa Y, Kohsaka S (2015) Up-regulation of glutamine synthesis in microglia activated with endotoxin. Neurosci Lett 591:99–104
101 White BC, Sullivan JM, DeGracia DJ, O'Neil BJ, Neumar RW, Grossman LI, Rafols JA, Krause GS (2000) Brain ischemia and reperfusion: Molecular mechanisms of neuronal injury. J Neurol Sci 179:1–33
102 Szatkowski M, Barbour B, Attwell D (1990) Nonvesicular release of glutamate from glial cells by reversed electrogenic glutamate uptake. Nature 348:443–446
103 Zhang M, Li WB, Liu YX, Liang CJ, Liu LZ, Cui X, Gong JX, Gong SJ et al (2011) High expression of GLT-1 in hippocampal CA3 and dentate gyrus subfields contributes to their inherent resistance to ischemia in rats. Neurochem Int 59:1019–1028
104 Setsuie R, Wada K (2007) Functions of UCH-L1 and its relation to neurodegenerative diseases. Neurochem Int 51:105–111
105 Jara JH, Frank DD, Özdinler PH (2013) Could dysregulation of UPS be a common underlying mechanism for cancer and neurodegeneration? Lessons from UCHL. Cell Biochem Biophys 67: 45–53
106 Ferguson SM, De Camilli P (2012) Dynamin, a membrane-remodelling GTPase. Nat Rev Mo Cell Biol 13:75–88
107 Gubellini P, Bisso GM, Ciofi-Luzzatto A, Fortuna S, Lorenzini P, Michalek H, Scarsella G (1997) Ubiquitin-mediated stress response in a rat model of brain transient ischemia/hypoxia. Neurochem Res 22:93–100
108 Lee CH, Won MH (2014) Increased dynamin-1 and -2 protein expression in the aged gerbil hippocampus. Cell Mol Neurobiol 34:791–796
109 Lynch MA, Bliss TV (1986) Noradrenaline modulates the release of [14C] glutamate from dentate but not from CA1/CA3 slices of rat hippocampus. Neuropharmacology 25:493–498
1110 Frey U, Matthies H, Reymann KG, Matthies H (1991) The effect of dopaminergic D1 receptor blockade during tetanization on the expression of long-term potentiation in the rat CA1 region in vitro. Neurosci Lett 129:111–114
111 Frey U, Schroeder H, Matthies H (1990) Dopaminergic antagonists prevent long-term maintenance of posttetanic LTP in the CA1 region of rat hippocampal slices. Brain Res 522:69–75
112 Otmakhova NA, Lisman JE (1996) D1/D5 dopamine receptor activation increases the magnitude of early long-term potentiation at CA1 hippocampal synapses. J Neurosci 16:7478–7486
113 Otmakhova NA, Lisman JE (1998) D1/D5 dopamine receptors inhibit depotentiation at CA1 synapses via cAMP-dependent mechanism. J Neurosci 18:1270–1279
114 Kulla A, Manahan-Vaughan D (2000) Depotentiation in the dentate gyrus of freely moving rats is modulated by D1/D5 dopamine receptors. Cereb Cortex 10:614–620
115 Knox LT, Jing Y, Fleete MS, Collie ND, Zhang H, Liu P (2011) Scopolamine impairs behavioural function and arginine metabolism in the rat dentate gyrus. Neuropharmacology 61:1452–1462
116 Caine SB, Geyer MA, Swerdlow NR (1992) Hippocampal modulation of acoustic startle and prepulse inhibition in the rat. Pharmacol Biochem Behav 43:1201–1208
117 Sato Y, Aoki M (1997) Regional differences in the depressant effects of midazolam on excitatory synaptic transmission in the rat hippocampus. Neurosci Lett 223:181–184
118 Sato Y, Fujito Y, Aoki M (1997) Differential effects of a benzodiazepine on synaptic transmissions in rat hippocampal neurons in vitro. Brain Res 773:98–107
119 Kobayashi S, Fujito Y, Matsuyama K, Aoki M (2004) Differential effects of midazolam on inhibitory postsynaptic currents in CA1 pyramidal cells and dentate gyrus granule cells of rat hippocampal slices. Brain Res 1003:176–182
120 Miller MW (1995) Generation of neurons in the rat dentate gyrus and hippocampus: Effects of prenatal and postnatal treatment with ethanol, alcohol. Clin Exp Res 19:1500–1509
121 Tran TD, Kelly SJ (2003) Critical periods for ethanol-induced cell loss in the hippocampal formation. Neurotoxicol Teratol 25:519–528
122 Zhao WF, Ruan DY, Xu YZ, Chen JT, Wang M, Ge SY (1999) The effects of chronic lead exposure on long-term depression in area CA1 and dentate gyrus of rat hippocampus in vitro. Brain Res 818: 153–159
123 Musumeci G, Castrogiovanni P, Castorina S, Imbesi R, Szychlinska MA, Scuderi S, Loreto C, Giunta S. Changes in serotonin (5-HT) and brain-derived neurotrophic factor (BDFN) expression in frontal cortex and hippocampus of aged rat treated with high tryptophan diet. Brain Res Bull 2015; 119(Pt A):12–18.
124 Hirota K, Roth SH (1997) The effects of sevoflurane on population spikes in CA1 and dentate gyrus of the rat hippocampus in vitro. Anesth Analg 85:426–230
124 Hasegawa Y, Ogiue-Ikeda M, Tanabe N, Kimoto T, Hojo Y, Yamazaki T, Kawato S (2013) Bisphenol A significantly modulates long-term depression in the hippocampus as observed by multi-electrode system. Neuro Endocrinol Lett 34:129–134
125 Aleisa AM, Helal G, Alhaider IA, Alzoubi KH, Srivareerat M, Tran TT, Al-Rejaie SS, Alkadhi KA (2011a) Acute nicotine treatment prevents REM sleep deprivation-induced learning and memory impairment in rat. Hippocampus 21:899–909
126 Aleisa AM, Alzoubi KH, Alkadhi KA (2011b) Post-learning REM sleep deprivation impairs long-term memory: Reversal by acute nicotine treatment. Neurosci Lett 499:28–31
127 Alhaider IA, Aleisa AM, Tran TT, Alzoubi KH, Alkadhi KA (2010) Chronic caffeine treatment prevents sleep deprivation-induced impairment of cognitive function and synaptic plasticity. Sleep 33:437–444
128 Zagaar M, Alhaider I, Dao A, Levine A, Alkarawi A, Alzubaidy M, Alkadhi K (2012) The beneficial effects of regular exercise on cognition in REM sleep deprivation: Behavioral, electrophysiological and molecular evidence. Neurobiol Dis 45:1153–1162
129 Zagaar M, Dao A, Alhaider I, Alkadhi K (2013) Regular treadmill exercise prevents sleep deprivation-induced disruption of synaptic plasticity and associated signaling cascade in the dentate gyrus. Mol Cell Neurosci 56:375–383
130 Raven F, Meerlo P, Van der Zee EA, Abel T, Havekes R. (2018) A brief period of sleep deprivation causes spine loss in the dentate gyrus of mice. Neurobiol Learn Mem. 2018 (Epub ahead of press)
131 Kirino T (1982) Delayed neuronal death in the gerbil hippocampus following ischemia. Brain Res 239:57–69
132 Pulsinelli WA, Brierley JB, Plum F (1982) Temporal profile of neuronal damage in a model of transient forebrain ischemia. Ann Neurol 111:491–498
133 Smith M, Auer R, Siesjo B (1986) The density and distribution of ischemic brain injury in the rat following 2–10 min forebrain ischemia. Acta Neuropathol 64:319–332
134 Schmidt-Kastner R, Hossmann KA (1988) Distribution of ischemic neuronal damage in the dorsal hippocampus of rat. Acta Neuropathol 76:411–421

135 Kadar T, Dachir S, Shukitt-Hale B, Levy A (1998) Sub-regional hippocampal vulnerability in various animal models leading to cognitive dysfunction. J Neural Transm (Vienna) 105:987–1004

136 Ouyang YB, Volobouéva LA, Xu LJ, Giffard RG (2007) Selective dysfunction of hippocampal CA1 astrocytes contributes to delayed neuronal damage after transient forebrain ischemia. J Neurosci 27: 4253–4260

137 Ouyang YB, Xu L, Liu S, Giffard RG (2014) Role of astrocytes in delayed neuronal death: GLT-1 and its novel regulation by microRNAs. Adv Neurobiol 11:171–188

138 Stary CM (2016) Exploring and exploiting unique properties of the hippocampal dentate gyrus for post-stroke therapy: Astrocytes link ischemic resistance with neurogenic potential. Neural Regen Res 11:1756–1757

139 Aitken EG, Schiff SJ (1986) Selective neuronal vulnerability to hypoxia in vitro. Neurosci Lett 67:92–96

140 Kass IS, Lipton P (1986) Calcium and long-term transmission damage following anoxia in dentate gyrus and CAI regions of the rat hippocampal slice. J Physiol Lond 378:313–334

141 Choi DW (1990) Cerebral hypoxia: Some new approaches and unanswered questions. J Neurosci 10:2493–2501

142 Mitani A, Yanase H, Sakai K, Wake Y, Kataoka K (1993) Origin of intracellular Ca^{2+} elevation induced by in vitro ischemia-like condition in hippocampal slices. Brain Res 601:103–110

143 Shimizu H, Mizuguchi A, Aoki M (1996) Differential responses between CA1 pyramidal cells and granule cells to ischemic insult in rat hippocampal slices. Neurosci Lett 203:195–198

144 Li Y, Zhu X, Ju S, Yan J, Wang D, Zhu Y, Zang F (2017) Detection of volume alterations in hippocampal subfields of rats under chronic unpredictable mild stress using 7T MRI: A follow-up study. J Magn Reson Imaging 46:1456–1463

145 Gerges NZ, Alzoubi KH, Park CR, Diamond MD, Alkadhi KA (2004) Adverse effect of the combination of hypothyroidism and chronic psychosocial stress on hippocampus-dependent memory in rats. Behav Brain Res 155(1):77–84

146 Alzoubi KH, Aleisa AM, Gerges NZ, Alkadhi KA (2006) Nicotine reverses adult-onset hypothyroidism-induced impairment of learning and memory: Behavioral and electrophysiological studies. J Neurosci Res 84:944–453

148 Alzoubi KH, Gerges NZ, Aleisa AM, Alkadhi KA (2009) Levothyroxin restores hypothyroidism-induced impairment of hippocampus-dependent learning and memory: Behavioral, electrophysiological, and molecular studies. Hippocampus 19:66–78

149 Sánchez-Huerta K, Pacheco-Rosado J, Gilbert ME (2015) Adult onset-hypothyroidism: Alterations in hippocampal field potentials in the dentate gyrus are largely associated with anaesthesia-induced hypothermia. J Neuroendocrinol 27:8–19

150 Fernandez-Lamo I, Montero-Pedrazuela A, Delgado-Garcia JM, Guadano-Ferraz A, Gruart A (2009) Effects of thyroid hormone replacement on associative learning and hippocampal synaptic plasticity in adult hypothyroid rats. Eur J Neurosci 30:679–692

151 Artis AS, Bitiktas S, Taskin E, Dolu N, Liman N, Suer C (2012) Experimental hypothyroidism delays field excitatory post-synaptic potentials and disrupts hippocampal long-term potentiation in the dentate gyrus of hippocampal formation and Y-maze performance in adult rats. J Neuroendocrinol 24:422–433

152 Kerchner GA, Deutsch GK, Zeineh M, Dougherty RF, Saranathan M, Rutt BK (2012) Hippocampal CA1 apical neuropil atrophy and memory performance in Alzheimer's disease. Neuroimage 63: 194–202

153 Dao AT, Zagaar MA, Levine AT, Salim S, Eriksen JL, Alkadhi KA (2013) Treadmill exercise prevents learning and memory impairment in Alzheimer's disease-like pathology. Curr Alzheimer Res 10:507–515

154 Hwang LL, Wang CH, Li TL, Chang SD, Lin LC, Chen CP, Chen CT, Liang KC et al (2010) Sex differences in high-fat diet-induced obesity, metabolic alterations and learning, and synaptic plasticity deficits in mice. Obesity (Silver Spring) 18:463–469

155 Porter D, Faivre E, Flatt PR, Hölscher C, Gault VA (2012) Actions of incretin metabolites on locomotor activity, cognitive function and in vivo hippocampal synaptic plasticity in high fat fed mice. Peptides 35:1–8

156 Lennox R, Porter DW, Flatt PR, Holscher C, Irwin N, Gault VA (2014) Comparison of the independent and combined effects of sub-chronic therapy with metformin and a stable GLP-1 receptor agonist on cognitive function, hippocampal synaptic plasticity and metabolic control in high-fat fed mice. Neuropharmacology 86: 22–30

157 Pathak NM, Pathak V, Lynch AM, Irwin N, Gault VA, Flatt PR (2015) Stable oxyntomodulin analogues exert positive effects on hippocampal neurogenesis and gene expression as well as improving glucose homeostasis in high fat fed mice. Mol Cell Endocrinol 412:95–103

158 Hao S, Dey A, Yu X, Stranahan AM (2016) Dietary obesity reversibly induces synaptic stripping by microglia and impairs hippocampal plasticity. Brain Behav Immun 51:230–239

159 Asadbegi M, Komaki A, Salehi I, Yaghmaei P, Ebrahim-Habibi A, Shahidi S, Sarihi A, Soleimani Asl S et al (2018) Effects of thymol on amyloid-β-induced impairments in hippocampal synaptic plasticity in rats fed a high-fat diet. Brain Res Bull 137:338–350

160 Foster TC (2002) Regulation of synaptic plasticity in memory and memory decline with aging. Prog Brain Res 138:283–303

161 Patrylo PR, Williamson A (2007) The effects of aging on dentate circuitry and function. Prog Brain Res 163:679–696

162 Rosenzweig ES, Barnes CA (2003) Impact of aging on hippocampal function: Plasticity, network dynamics, and cognition. Prog Neurobiol 69:143–179

163 Mattson MP, Wan R (2005) Beneficial effects of intermittent fasting and caloric restriction on the cardiovascular and cerebrovascular systems. J Nutr Biochem 16:129–137

164 Greene JG, Borges K, Dingledine R (2009) Quantitative transcriptional neuroanatomy of the rat hippocampus: Evidence for wide-ranging, pathway-specific heterogeneity among three principal cell layers. Hippocampus 19:253–264

165 Zeier Z, Madorsky I, Xu Y, Ogle WO, Notterpek L, Foster TC (2011) Gene expression in the hippocampus: Regionally specific effects of aging and caloric restriction. Mech Ageing Dev 132:8–19