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Regional Health and Function in the hippocampus: Evolutionary compromises for a critical brain region

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Abstract

The hippocampus is especially vulnerable to damage caused by metabolic dysregulation. However distinct sub-regions within the hippocampus differ by their relative susceptibility to such damage. Region CA1 pyramidal neurons are most sensitive to metabolic perturbations while region CA3 pyramidal neurons show more resistance, and these unique profiles of susceptibility are but one example that differentiates CA1/CA3 neurons. We present here a hypothesis that inextricably links the unique biochemistries of learning and memory in region CA1, to that of cell survival signaling, and in so doing, suggest an explanation for region CA1 susceptibility to metabolic dysfunction. Further, we propose a signaling mechanism to explain how both pathways can be simultaneously regulated. Critical to this process is the protein phosphatase PHLPP1. Finally we discuss the implications of this hypothesis and the inherent challenges it poses for treatment of neurological disorders resulting in reduced hippocampal function by increased neuron death.

I. A brief review of CA1 hippocampal synaptic connectivity and synaptic plasticity

The temporal lobe houses one of the most important brain regions for learning and memory—the hippocampus. The ability to form new memories and give context to the events that shape our lives depends upon normal hippocampal function. Anatomically it can be roughly separated into three distinct regions (Figure 1): Cornu Ammonis area 1 (CA1), Cornu Ammonis area 3 (CA3), and Dentate Gyrus (DG), and lesion of any sub-region results in memory deficits [1-3]. The studies show each region plays an important and distinct role in normal information processing.

Activity dependent changes in synaptic transmission at hippocampal CA3-CA1 synapses provide a model of memory. Recording electrodes placed in area CA1 neurons, while stimulating presynaptic neurons of area CA3, reveal a long-term increase in synaptic transmission following trains of high-frequency stimulation, termed long-term potentiation (LTP). Conversely, low-frequency stimulation results in a long-term decrease in synaptic transmission named long-term depression (LTD)[4]. These observations, relating neuronal activity to synaptic strength, are the foundation for what is termed synaptic plasticity, i.e., the

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concept that neurons can alter their degree of connectivity by modulating the strength of their synaptic communication.

Two ionotropic glutamate receptors are involved in the induction and expression, of LTP/LTD in area CA1. *N*-methyl *D*-aspartate (NMDA) receptors are ionotropic glutamate receptors on postsynaptic neurons and are critical to LTP/LTD induction in CA1 neurons. The combination of glutamate binding to the NMDA receptor and postsynaptic depolarization to remove a Mg^{2+} block of the ion channel results in increased Ca^{2+} influx. The degree of NMDA receptor activation and subsequent level Ca^{2+} influx, shifts the activity of Ca^{2+} sensitive kinases and phosphatases to increase or decrease the level of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors in the postsynaptic membrane [5,6]. AMPA receptors are another class of ionotropic glutamate receptors, and activated AMPA receptors increase Na^+/Ca^{2+} influx and the level of neuron depolarization. Consequently, a large rise in Ca^{2+} activates kinases to increase in the number of activated postsynaptic AMPA receptors, which corresponds to the increase in synaptic strength between neurons during LTP. In contrast, a modest rise in Ca^{2+} activates a phosphatase cascade which removes synaptic AMPA receptors resulting in the decrease in the synaptic strength of LTD. In summary, mechanisms of synaptic plasticity in region CA1 involve require activation of the NMDA receptor, leading to changes in kinase/phosphates signaling cascades to regulate the level of AMPA receptors in the membrane.

II. Regional differences in hippocampal vulnerability

Interestingly, the CA3 and CA1 hippocampal subregions exhibit differential susceptibility to metabolic diseases and stressors that increase with age. Area CA3 shows enhanced resistance to ischemic damage compared to area CA1 [7,8]. In addition to stroke, Alzheimer's disease pathology selectively targets area CA1 of the hippocampus. For example, studies in animals show that both beta-amyloid and tau selectively damage area CA1 of the hippocampus, yet spare area CA3[9,10]. In addition, brains from patients with Alzheimer's disease show greater neuron loss in area CA1[11]. Finally, type II diabetes is another example of a metabolic disease that can target area CA1 health and impair hippocampal function. Type II diabetes is associated with obesity, and arises from reduced insulin receptor sensitivity. This results in hyperglycemia, (intermittent) hypoglycemia, hyperinsulemia, neuropathy, and other debilitating comorbidities. Human studies show that the hippocampus is one of the earliest brain regions to be impaired by type II diabetes [12], and type II diabetes can increase the risk for Alzheimer's disease [13]. In addition, using organotypic hippocampal slice cultures, studies examining hippocampal vulnerability to hypoglycemia, a common problem in diabetes and associated with neuropathy, reveal select vulnerability of region CA1. The drug 2-deoxyglucose (2DG) induces hypoglycemia by inhibiting glycolysis. Either removing glucose from the culture media or adding 2-DG to the culture media, selectively damages area CA1 but not area CA3 in organotypic slices[14]. Together the evidence suggests that diseases that affect metabolic dysregulation can target area CA1 of the hippocampus while sparing area CA3. However, it remains unclear what mechanism(s) are responsible for regional differences in hippocampal vulnerability, and why such mechanism(s) exist.

III. A brief review of PI3 kinase/AKT cell survival signaling

The PI3 kinase pathway (Figure 2) is a robust and powerful cell survival signaling pathway. Insulin and growth factors such as insulin-like growth factor 1 (IGF-1), acting on membrane receptors, stimulate PI3 kinase. In turn PI3 kinase induces downstream phosphorylation and activation of the related survival protein kinases; serum and glucocorticoid- inducible kinase (SGK) and protein kinase B (AKT). AKT and SGK are thought to act on some of the same molecules (e.g. FOXO1/3a) to promote cell survival. On the other hand SGK is distinct from

AKT in its protein structure and phosphorylation of other target substrates, suggesting a unique role in neuronal signaling. In the case of AKT, activated PI3 kinase phosphorylates (activating) the downstream protein PIP₃ –dependent kinase 1(PDK1), which in turn phosphorylates protein kinase B (AKT) at a threonine 308 residue. Subsequently the kinase PDK2 can maximally activate AKT by phosphorylating the protein at a serine 473 residue. Conversely, protein phosphatase 2A (PP2A) and pleckstrin homology and leucine rich repeat protein phosphatase 1 (PHLPP1) inhibit AKT by dephosphorylation of Thr308 and Ser473, respectively[15,16]. Thus, AKT activity is regulated by phosphorylation at two sites, AKT308 and AKT473, and the extent of AKT phosphorylation is thought to determine cell survival signaling.

Recent studies from our laboratory show that the level of AKT survival signaling is unequal across hippocampal regions and is subject to change across the lifespan [17]. Specifically, phosphorylation of AKT473 is markedly higher in region CA3 pyramidal neurons compared to CA1. These differences occur both in cytoplasmic and nuclear fractions, although nuclear phosphorylated AKT473 shows the greatest difference. Furthermore, this regional difference is maintained from young adult to old age. Interestingly, opposite that observed for regional AKT473 levels, PHLPP1 levels were higher in region CA1 and lower in region CA3, suggesting a possible mechanism for reduced AKT473 levels in region CA1. A different picture emerges for phosphorylation of AKT308. First, cytoplasmic phosphorylated AKT308 does not exhibit the region-dependent differences that are evident for AKT473. Second, the level of phosphorylated AKT308 in the nucleus changes in opposite directions with age, decreasing in nuclei of CA1 neurons and increasing in the nuclei of CA3 neurons indicating that older animals exhibit regional differences in AKT survival signaling. The reduced nuclear AKT308 with advanced age may contribute to increased CA1 neuron vulnerability across the lifespan, compared to CA3 neurons. The observations suggest a mechanism for increased CA1 susceptibility to damage, however, raises the question, why should region CA1 be less privileged to AKT survival signaling?

IV. The Crossroads of PI3 kinase signaling and synaptic plasticity

Together the evidence suggests that AKT signaling is reduced across the lifespan in region CA1 compared to CA3, and suggests reduced AKT signaling may underlie the enhanced susceptibility of CA1 neurons to metabolic stress. The results imply that an increase in CA1 AKT activity might be a reasonable target for protecting the hippocampus from processes that lead to age-related memory deficits. However, evidence is mounting to indicate that the downstream effectors of PI3 kinase, SGK and AKT, have differential effects on synaptic plasticity and memory function and an increase in AKT activity may be detrimental to memory.

A number of studies suggest that, in area CA1 of the hippocampus, the upstream signaling pathways involving insulin and IGF-1, through PI3 kinase, alter mechanisms of learning and memory and activity of this pathway modulates synaptic plasticity. For example, using hippocampal slice culture preparations and hippocampal neuronal cell cultures, Izzo et al. (2002) and Man et al. (2003), respectively, showed that PI3 kinase was important for the induction of LTP[18,19]. In the latter article, the authors demonstrated that inhibition of PI3 kinase prevented NMDA-dependent insertion of AMPA receptors into the membrane. In agreement with these findings, Ramsey et al. (2005) showed that application of des-IGF-1 to hippocampal slices caused a 40% increase in excitatory postsynaptic potentials (EPSP's) at CA1 synapses, attributed to modulation of postsynaptic AMPA receptors [20]. The signaling pathway for synaptic plasticity, down stream of PI3 kinase, appears to differentially involve SGK and AKT. For example, Strutz-Seebohm et al. (2005) showed that SGK-2 and SGK-3 induced AMPA receptor insertion into the postsynaptic membrane in a PI3 kinase-dependent fashion [21]. Conversely, other researchers have provided evidence that induction of LTD

following metabotropic glutamate receptor activation involves a cascade from PI3 kinase through the phosphorylation and activation of AKT [22]. Further, studies in *Drosophila* neuromuscular junction synapses show deletion of AKT impairs LTD induction. This effect can be reversed by administering an AKT expressing transgene[23]. Alternatively, a review by Peineau (2008) suggests AKT may have a role to play in LTP induction via inhibition of GSK-3 β [24]. However, because SGK can also inhibit GSK-3 β [25], it is unclear whether SGK may be the dominant protein controlling GSK-3 β activity and LTP induction.

The activation of SGK and AKT may also differentially influence memory function. For example, von Herten et al. (2005) reported that memory consolidation and reconsolidation of a contextual fear association was correlated with upregulated SGK-3 and that fear learning was associated with upregulated SGK-1[26]. Tyan et al. (2008) showed an association between phosphorylated/activated SGK-1 in area CA1 and spatial learning and that activated SGK-1 was critical to the upregulation of zif268 [27], an immediate early gene associated with spatial learning and memory. Over-expression of a dominant-negative form of SGK-1 (SGK-1S422A) inhibited activation of SGK-1 after learning, and inhibited expression of zif268; together suggesting that SGK-1 played an important role in regulating the downstream mechanisms of memory.

Recent studies by Chao et al. (2007) illuminate some potential differences in how the downstream effectors of PI3 kinase, AKT and SGK-1, may differentially regulate hippocampal learning and memory. The authors over-expressed wild type and mutant forms of AKT and SGK-1 in the CA1 region of the rat hippocampus. Over-expression of a constitutively activated form of SGK-1 caused animals to perform better on a spatial memory task, whereas over-expression of a constitutively inactivate form of SGK-1 caused animals to performed much worse. On the other hand, over-expression of wild type AKT in area CA1 worsened spatial learning and memory, while over-expression of a constitutively inactivate form of AKT (unable to be phosphorylated specifically at Ser473) improved learning and memory[28]. Thus the data suggests phosphorylated AKTSer473 downregulates mechanisms of learning and memory in area CA1 of the hippocampus, whereas phosphorylated SGK-1 is important for and facilitates learning and memory.

V. The Hypothesis

We hypothesize that in CA1 pyramidal cells of the hippocampus, like other cells, the PI3 kinase pathway is involved in cell survival signaling through activation of downstream kinases including SGK and AKT. In addition to cell survival signaling, SGK and AKT are involved in synaptic plasticity and memory; activation of SGK potentiates mechanisms of learning and memory while AKT inhibits mechanisms of learning and memory. However, PI3 kinase activates both SGK and AKT at the same time. Therefore a mechanism must exist to temporarily disengage simultaneous activation of both kinases (i.e. activate SGK without simultaneous activation of AKT). We hypothesize that the recently discovered AKT phosphatase PHLPP1 may serve this purpose because PHLPP1 contains a specific membrane localization sequence also found in AKT but not SGK, and through which, PHLPP1 attenuates, via dephosphorylation, levels of activated AKT while permitting full activation of SGK at the membrane.

VI. Discussion: Mechanism and Implication of CA1 AKT Signaling

Research continues to seek out innovative strategies for improving hippocampal-dependent learning and memory and improving general hippocampal health with age and disease. Studies exploring how to improve hippocampal health primarily focus on two strategies. One option is to treat and reduce damage inducing stressors. For example, a major goal of Alzheimer's

disease research is to reduce the toxic beta-amyloid load that contributes to disease pathology. Alternatively, increasing neuronal defenses that protect against the toxic effects of beta-amyloid may help prevent neuronal death without altering the total beta-amyloid load. In this regard, drugs selectively targeting and activating the PI3 kinase/AKT pathway could increase the resistance of neurons to stressor-induced death to improve hippocampal health and function. Indeed, *in vitro* [29] and *in vivo* [30] studies show upregulating AKT activity will protect against cell death due to beta-amyloid exposure, and using AKT as a strategy to treat brain disease is an emerging area of research [31].

There are several reasons for choosing AKT as a therapeutic strategy. First, if not all, most known growth factors signal through this cell survival protein, and growth factors are well known to improve cellular health and upregulate anti-apoptotic mechanisms. Second, AKT induces cell survival in virtually every cell type; for which reason it also has direct involvement in the induction and progression of many cancer types. Finally, activation of AKT protects against many diverse stressors and cell death-inducing agents in the nervous system. Because neurodegenerative diseases commonly involve multiple dysregulated cellular pathways, AKT's ability to promote cell survival through a variety of actions (including inhibition of intrinsic apoptotic signaling, inhibition of extrinsic apoptotic signaling, and inhibition of necrosis by increasing energy supply) increases the likelihood that AKT-augmenting strategies would protect against a particular neuropathology regardless of whether the exact mechanism of cell death is known.

However recent studies investigating the role of PI3K/AKT in the hippocampus suggest that AKT-augmenting strategies to improve hippocampal health may entail risk. As mentioned previously, over-expression of AKT in the rat hippocampus impairs learning on a hippocampal-dependent spatial learning task, while mutation (and inhibition) of AKT at Ser473 improves learning. Further, one study reports increased levels of phosphorylated AKT473 in a mGluR/PI3 kinase/mTOR dependent form of LTD. Combined, these results implicate phosphorylated AKT473 as a negative regulator of synaptic strength, which might explain why area CA1 has reduced levels of phosphorylated AKT473 across the lifespan.

The hypothesis maintains that region CA1 of the hippocampus must have a way to activate SGK via PI3 kinase but without simultaneous activation of AKT. How might this be? To answer this question, we propose the mechanism outlined in (Figure 3). Central to the mechanism is the recently discovered AKT inhibitor PHLPP1, a phosphatase with two unique properties. PHLPP1 is a recently identified protein that dephosphorylates AKT specifically at the Ser473 site [15] to reduce AKT activity. Further, PHLPP1 phosphatase activity on AKT depends upon a conserved PDZ domain in AKT, and SGK also contains the same conserved PDZ domain. Therefore, though not yet tested, SGK likely is also a substrate for PHLPP1 as well. This highlights the importance of the second unique property of PHLPP1, i.e., to date PHLPP1 is the only known phosphatase that contains a PH domain. Recall, PH domains allow proteins to bind PIP₃ at the membrane, and PI3 kinase phosphorylates PIP₂ to PIP₃. This is critical because AKT, but not SGK, also contains a PH domain. Consequently, when activated, PI3 kinase increases levels of PIP₃, and PIP₃ would attract both AKT and PHLPP1 to the membrane where PHLPP1 would selectively dephosphorylate AKT at Ser473. However, because SGK does not have a PH domain, it would not contact PHLPP1 at the postsynaptic membrane and therefore would not be inhibited. In this way, neurons could selectively activate SGK without concomitantly activating AKT, and induce SGK-dependent mechanisms of LTP/learning and memory. Further, a potential negative feedback mechanism for PHLPP1's effects on AKT may be mediated by membrane localized calpain. Both calpain-I and calpain-II can cleave PHLPP1 [32]. Increased Ca²⁺ influx activates calpain-I [33]. A decrease in membrane localized PHLPP1, by calpain mediated cleavage, would allow increased AKT activity. Therefore the calpain-PHLPP1 axis may serve to modulate the AKT-SGK axis. One obvious prediction made

by this model suggests calpain can regulate AKT activation. Intriguingly, Tan (2006) showed inhibition of calpain I and calpain II in mouse embryonic fibroblasts prevents activation of AKT (as measured by AKTser473) in staurosporine and tumor necrosis factor α models of cell death, providing evidence of a direct link between calpain regulation and AKT regulation [34].

One might be compelled to conclude from our hypothesis that over-expression of PHLPP1 would improve memory. However, over-expression of PHLPP1 significantly impaired learning and memory as measured by a spatial memory task, and down regulation of hippocampal levels of over-expressed PHLPP1 by calpain-mediated degradation restored normal learning and memory. The authors further showed that PHLPP1 dephosphorylates/inhibits MAP kinase and CREB [32], proteins critical to the stabilization of LTP and memory consolidation[35]. Thus, if too much PHLPP1 is present, robust inhibition of MAPK/CREB signaling would overwhelm any beneficial effects from AKT inhibition.

What consequences does this hypothesis have on treatment strategies to improve hippocampal health with aging and disease? The implications are: 1) robust activation of growth factor pathways, though improving overall brain health, might actually impair learning and memory due to CA1 dysfunction; 2) strategies to reduce stressors in the hippocampus, such as reducing beta-amyloid load, may be more successful for hippocampal health rather than upregulating total PI3 kinase activity; 3) development of selective agonists for SGK-1, SGK-2, or SGK-3 may safely increase CA1 mechanisms of learning and memory with aging or disease; and 4) combinations of strategies 3 and 4 may provide for optimal health and function of the hippocampus. 5) Finally, any strategy to improve regional health and function in the hippocampus will simultaneously require careful patient evaluation with memory tests sensitive enough to differentiate specific forms of memory. Region CA1 and CA3 are both important for overall hippocampal function but individually serve unique and important roles in specific kinds of memory; CA3 may be more important for spatial memory while CA1 is more important for temporal memory processing[36]. Therefore detecting detrimental effects of overactivating AKT in the hippocampus may be less apparent if robust memory tests are used; however, tests which strongly probe CA1 function may reveal impairment.

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Figure 1.

Synaptic connectivity in the hippocampus. **A)** An example of hippocampal architecture. The image shows a hippocampal coronal section from a rat. Regions CA1, CA3, and DG are labeled in white. **B)** Schematic diagram showing regional synaptic connections within the hippocampus. **1)** Afferent axons of the perforant path enter into the hippocampus from the entorhinal cortex (E.C.), and synapse on granule neurons (circles) of the dentate gyrus (DG). **2)** DG neurons then send axons (i.e mossy fibers) to the large pyramidal neurons (Large Triangle) of area CA3. **3)** CA3 neurons send recurrent connections back on themselves and **4)** as well as projections to area CA1 (Schaffer Collaterals). **5)** Finally area CA1 neurons send efferent projections out of the hippocampus.

Figure 2.

Classic activation of AKT and SGK by growth factor dependent activation of PI3 kinase. Binding of growth factors (such as IGF-1) to receptor tyrosine kinases induce autophosphorylation of receptor subunit. Phosphorylated receptors attract cytoplasmic PI3 kinase to the membrane causing phosphorylation of membrane bound PIP₂. Phosphorylated PIP₂ increases membrane levels of PIP₃. Both PIP₃-dependent kinase 1(PDK1) and protein kinase B (AKT) bind PIP₃ at the membrane, and induce PDK1 to phosphorylate AKT at Thr308. Subsequently, AKT is also phosphorylated by PDK2 at Ser473, fully activating AKT. Similarly PIP₃ induces activation of the AKT related kinase SGK, however, without direct binding of SGK to PIP₃. Pro-survival kinase AKT and SGK can then phosphorylate target

substrates at the membrane, cytoplasm, and nucleus; including the pro-apoptotic nuclear transcription factor forkhead box 03a (FOXO3a). Phosphorylation of nuclear FOXO3a induces its cytoplasmic shuttling and degradation at the proteasome, thereby inhibiting upregulation of pro-apoptotic proteins regulated by FOXO3a.

Figure 3.

A proposed model of PHLPP1-dependent regulation of AKT/SGK mediated LTP in area CA1 hippocampal neurons. **1)** Glutamate is released from presynaptic neurons and binds to postsynaptic AMPA and NMDA receptors. Simultaneous, binding of IGF-1 binds receptors and causes autophosphorylation of receptor subunit. **2)** Phosphorylated IGF-1 receptors attract cytoplasmic PI3 kinase to the membrane. Membrane activated PI3 kinase phosphorylates membrane bound PIP₂ to PIP₃. **3)** PIP₃ activates both AKT and SGK, however only AKT binds PIP₃ via its PH domain. The protein phosphatase PHLPP1 also binds PIP₃ at the membrane and selectively dephosphorylates (thus inhibiting) AKT but not SGK. **4)** SGK upregulates mechanisms beneficial for memory formation. **5)** A modest rise in Ca²⁺ from NMDA receptor activity or mGluR mediated release of Ca²⁺ from intracellular stores results in activation of calpain. Calpain cleaves PHLPP1 and attenuates AKT's inhibition.