The central role of heat shock factor 1 in synaptic fidelity and memory consolidation

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Abstract Networks of neuronal synapses are the fundamental basis for making and retaining memory. Reduced synapse number and quality correlates with loss of memory in dementia. Heat shock factor 1 (HSF1), the major transcription factor regulating expression of heat shock genes, plays a central role in proteostasis, in establishing and sustaining synaptic fidelity and function, and in memory consolidation. Support for this thesis is based on these observations: (1) heat shock induces improvements in synapse integrity and memory consolidation; (2) synaptic depolarization activates HSF1; (3) activation of HSF1 alone (independent of the canonical heat shock response) augments formation of essential synaptic elements—neurotransmitters, vesicle transport, synaptic scaffolding proteins, lipid rafts, synaptic spines, and axodendritic synapses; (4) HSF1 coalesces and activates memory receptors in the post-synaptic dendritic spine; (5) huntingtin or α -synuclein accumulation lowers HSF1 while HSF1 lowers huntingtin and α -synuclein aggregation—a potential vicious cycle; and (6) HSF1 agonists (including physical activity) can improve cognitive function in dementia models. Thus, via direct gene

expression of synaptic elements, production of HSPs that assure high protein fidelity, and activation of other neuroprotective signaling pathways, HSF1 agonists could provide breakthrough therapy for dementia-associated disease.

Keywords HSF1 · Heat shock factor 1 · Memory · Synapse, heat shock · Heat shock proteins · Synapse · Synapsin, PSD95 · Synaptophysin · SAP97 · Celastrol · B₁₂ · Exercise · Hyperthermia · Fear · Emotion · Stress · Dementia · Alzheimer's · Neurodegenerative disease · TRP · Ethanol · Resveratrol · SIRT1 · GSK3 · Curcumin · Xenohormetic · Insulin · Diabetes · Calcium · Glutamate · NMDAR · AMPAR · HSP90 inhibitor · Consolidation · Fidelity · Neuron survival · Drug discovery · Therapy · Cognitive function · Scaffolding proteins · Lipid rafts · Synaptic spines · Integrin · Hippocampus · Amyloid · BDNF · Huntingtin · α -Synuclein · Parkinson's · Aggregation · Herbs · GGA · CaMKII · Calcium channel

Introduction

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“Life lessons learned through pain, you shall not do again.”

Grandmother Mimi

Through memory, organisms can learn to react appropriately to the environment in order to survive and thrive. The complexity of memory varies across eukaryotes. For example, the sea slug *Aplysia* has the capacity for long-term memory to avoid danger, while other species have memory systems that permit sophisticated forms of learning and information processing in the service of survival and reproduction (Bailey et

al. 2015). The fundamental anatomical basis for making and retaining memory lies in synapses that link neurons into networks. Synaptic junctions are formed from specialized membranes on the presynaptic side of neurons that convert electrical signals into the release of chemical neurotransmitters. These transmitters communicate with other cells in the network by binding to specific receptors that transform the message back to electrical signals in the postsynaptic cell. A decline in the number and quality of synapses in neuronal networks correlates with loss of memory in dementia disease states (Gong and Lippa 2010).

Background: synapse formation and maturation

Plasticity and stability of synaptic connections are determined by activity (Kittler and Moss 2001). For neurotransmission, depolarization of the synaptic membrane opens calcium-permeable ion channels. The increased presynaptic calcium triggers docking and fusion of the synaptic vesicles containing glutamate (or other neurotransmitters) to the presynaptic membrane and release of the transmitter into the synaptic cleft. Glutamate diffuses within the cleft and binds to glutamate receptors. The synapse is stabilized by activation of glutamate receptors important for memory: *N*-methyl-D-aspartate-type receptors (NMDARs) and amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPA). As Vaughn proposed in the synaptotrophic hypothesis decades ago: “whether a glutamate synapse is maintained, modified or dissolved is dependent on the changing molecular fabric of its junctional membranes” (Vaughn 1989). Thus, a well-maintained synapse permits memory consolidation. A schematic highlights the stages of the axodendritic synapse—see Fig. 1

Post-synaptic protein 95 (PSD95) is a multifunctional protein. PSD95 is an activity-dependent regulator of NMDAR (Lin et al. 2004; Sheng and Kim 2011). It provides a platform to align pre- and post-synaptic membranes, clusters post-synaptic receptors (including NMDAR, AMPAR), and coordinates the activation of post-synaptic receptors to signaling events in the post-synaptic neuron. Notably, PSD-95 overexpression in hippocampal slices increases AMPAR-mediated synaptic transmission, as occurs in long-term potentiation of memory (Sheng and Kim 2011; Chen et al. 2014).

On the presynaptic side of neurons, synapsin I and synaptophysin proteins are essential for vesicle formation, transport, and release (Chen et al. 2014). Synapsins are also regulatory proteins that are needed for synaptogenesis and synaptic plasticity and thus key components in establishing long-term memory (Bykhovskaia 2011). The action of synaptic proteins is key to the formation and maturation on both the pre and post sides of the synapse.

HSF1 promotes transcription of synaptic proteins: synapsin I, synaptophysin, post-synaptic density protein 95 (PSD95), and synapse-associated protein 97 (SAP97)

An elegant study by Chen and coworkers examined the effect of HSF1 activation by the HSP90 inhibitor 17-(allylamino) geldanamycin (17-AAG) on synaptic function in neurons challenged with soluble A β oligomers. HSP90 inhibitors have a non-intuitive property: they release HSF1 bound to HSP90 enabling it to activate gene expression. In Chen’s study, 17-AAG upregulated important pre- and post-synaptic proteins.

◀ **Fig. 1** Schematic of the growth of the axodendritic synapse. Synapsin and synaptophysin are essential for vesicle formation and release. PSD95 is essential in establishing a platform for the memory receptor, NMDA-R. Stages in the development of interneuronal synapses. **a** and **b** An axon growth cone approaches and interacts dynamically with a developing dendrite through a two-way filopodial communication. **c** The pre- and post-synaptic terminals form a morphologically unspecialized but functional contact. **d** Synaptic vesicles begin to accumulate at the presynaptic terminal, triggering neurotransmitter release and further synaptic differentiation. **e** Differentiation of the presynaptic terminal is followed by postsynaptic differentiation and by the accumulation of membrane components (such as PSD-95) at the postsynaptic side. **f** The recruitment of organizing molecules like PSD-95 at the postsynaptic specialization is followed by rapid neurotransmitter receptor accumulation at the site and the functional maturation of the synapse. A spine synapse is used to illustrate the sequence of events during synapse development, but functional glutamatergic synapses can form along the dendrite shaft as well as in spineless dendrites. Figure reproduced with permission of publisher (Cohen-Cory 2002)

Notably, 17-AAG enhanced expression of synapsin I and synaptophysin, which aid in vesicle transport, docking, and release at nerve terminals. At the post-synaptic density, 17-AAG increased the scaffolding protein PSD95 (Fig. 2). Using the Transcription Element Search System, multiple sites for HSF1-responsive elements (nGAAn and nTTCnGAAnnTTCn) were predicted in promoters of the synaptic genes. Overexpression of HSF1 induced PSD95 transcription. Blockade of HSF1 by either treatment with a specific inhibitor (KRIBB11) or knockdown by siRNA abolished 17-AAG induction of PSD95. Thus, while 17-AAG activated the stress response with increased HSP70, HSP40, and HSP27 expression, the selected synaptic proteins were directly enhanced by HSF1 (Chen et al. 2014).

Chen et al. also found that the addition of A β oligomers to cultured hippocampal neurons reduced dendritic spine density and blocked mushroom-like structure formation (Chen et al. 2014). Mushroom-like structures, on the post-synaptic spine, form the dome for glutamate receptors and are the site of synaptic transmission (Hotulainen and Hoogenraad 2010).

Fig. 2 17-AAG upregulates the transcriptional levels of PSD95, synapsin I, and synaptophysin, as determined by qRT-PCR. * $p < 0.05$ (Student's t test). $n = 3$. (Figure reprinted with permission of publisher (Chen et al. 2014))

Chen et al. found that 17-AAG restored spine density and mushroom-like structures in the A β oligomer-treated neurons. In vivo, 17-AAG administered to mice via intra-cerebroventricular injection prevented contextual memory loss induced by injection of A β oligomers. Levels of PSD95 and BDNF (a key regulator of synaptic transmission and plasticity) were restored by 17-AAG (Chen et al. 2014).

Similar to Chen et al.'s observations, Ortega and colleagues found that 17-AAG preserved learning and memory when administered prior to injection of amyloid beta₂₅₋₃₅ into the *Cornu Ammonis* region (CA1) of the hippocampus of rats. 17-AAG increased hippocampal immunolabeling of HSF1, HSP27, and HSP70 (Ortega et al. 2014).

Most recently, Thistrup et al. reported that treatment with a novel HSP90 inhibitor with high HSP70 induction capacity reversed synaptic impairments in the rTg4510 transgenic mouse model of Alzheimer's disease, which displays tau-mediated synaptic dysfunction. Thistrup and coworkers noted that HSP90 inhibition in both their study and Chen's 17-AAG study alleviated synaptic impairments well within 24 h and suggested that HSP90 inhibition may work independent of tau clearance (Thistrup et al. 2015). Unfortunately, the toxicity of conventional HSP90 inhibitors limits their role in the clinical setting (Zhou et al. 2013).

SAP97 is a scaffolding protein that stabilizes the synapse and drives dendritic growth (Zhang et al. 2015b). In a comprehensive study, Ting et al. (2011) examined HSF1-mediated upregulation of SAP97 in cultured atrial cardiomyocytes, a synaptic rich tissue. By using four different modalities to increase HSF1—heat shock, geranylgeranylacetone (GGA), HSF1 overexpression, or SIRT1 activation—Ting's group found that HSF1 directly induces transcription of *DLG1*, the gene encoding SAP97. Indeed, its promoter sequence contains heat shock elements from -919 to -740, as predicted by MOTIF-SEARCH. Thus, HSF1 is directly involved in SAP97 expression (Ting et al. 2011).

Heat shock enhances memory, synapse function, and neuron survival

Volado is a colloquialism in Chile for absent-minded or forgetful behavior. Appropriately, the Volado fly has a deficiency of the synaptic adhesion molecule, α -integrin, and provides an animal model for dementia. Grotewiel and coworkers found that heat shock corrected olfactory memory impairment in the Volado fly. Fifteen minutes of heat shock temporarily restored their memory for 3 h; after 24 h, the memory impairment returned. Heat shock improved α -integrin expression, which acts as a bridge between synaptic membranes and the extracellular matrix, inducing structural integrity and facilitating cell-to-cell information transfer (Grotewiel et al. 1998).

Nikitina and coworkers studied another fruit fly model of dementia, *agn^{ts3}*, which has a mutation of LIM k1 that is key to actin remodeling and associated with accumulation of β -amyloid in hippocampal neurons. Heat shock reduced β -amyloid and improved learning ability (Nikitina et al. 2014).

Pathways of HSF1 activation

HSF1 activation is not caused solely by protein misfolding or cellular stress. HSF1 also plays a role in physiologic events critical to intercellular communication. For example, at the neuromuscular junction, cholinergic neurotransmission induces a cascade of calcium signaling events that activate HSF1 in post-synaptic muscle cells (Silva et al. 2013). Similarly, in a remarkable *in vivo* study in non-heat-stressed *C. elegans*, stimulation of the worms' thermo-sensory neurons activated HSF1 in distal tissues (the pharyngeal muscles) (Tatum et al. 2015). Rho family GTPases like Rac 1 also activate HSF1 (Han et al. 2001; Gungor et al. 2014) and play a role in formation of the synaptic spine cytoskeleton (Evans et al. 2015). Glycogen synthase kinase-3 (GSK3) inhibition promotes activation of HSF1 by AKT activation (Bijur and Jope 2000), and is associated with synaptic functional integrity and improved cognitive ability (King et al. 2014). SIRT1 deacetylation of HSF1 activates HSF1, as is observed with resveratrol (Westerheide et al. 2009). In animal models of Alzheimer's disease, resveratrol also limits memory loss (Solberg et al. 2014).

As the synapse is a modified membrane, the same triggers for HSF1 activation in the membrane should apply at the synapse. The signaling cascades originating from the plasma membrane that activate HSF1 were recently reviewed by Török and colleagues (Török et al. 2014) (Fig. 3). Indeed, kinases, second messengers, and channel receptors (particularly TRP) that are active in membranes are also active in synapses: lipid rafts, calcium channels, calcium, CaMKII, MAPK, AKT, PKA, PKC, GSK3, mTOR, Rac1, ceramide, PLA₂, sphingosylphosphorylcholine, etc. Török and colleagues also proposed the membrane-sensor hypothesis and suggested that the changes of fluidity and microdomain organization of the plasma membrane are important drivers of different subsets of HSP expression compared to that observed upon classical heat shock. The evidence suggests the presence of alternative pathways induced by different stressors (Vigh et al. 2007; Balogh et al. 2010, 2011; Csoboz et al. 2013; Török et al. 2014).

Suzuki and colleagues (Suzuki and Yao 2013) contributed major insight into how CaMKII and synaptic lipid raft coalescence coordinate the formation of post-synaptic density and activation of memory receptors. Specifically, his group observed that either synaptic glutamate stimulation or ischemic stress thickens the post-synaptic density and induces long-

term memory potentiation. Suzuki attributes translocation of CaMKII into the postsynaptic density as the initiator of the postsynaptic thickening, which is accompanied by post-synaptic lipid raft consolidation. The thickening results from generation of PSD95 as well as the formation and stabilization of complexes composed of PSD95, CaMKII, lipid rafts, and glutamine memory receptors (Suzuki and Yao 2013). While Suzuki did not address HSF1, CaMKII activates HSF1, which plays a fundamental role in lipid raft formation (Nagy et al. 2007). Therefore, HSF1 appears to play a core role in the consolidation of memory complexes through generation of PSD and lipid rafts. This ultimately leads to coalescence and activation of memory receptors, synapse and dendrite stabilization, and long-term memory retention (Jiang et al. 2013).

HSF1 inducers and cognitive preservation

The best proof of principle of the importance of HSF1 in neurologic function is the multitude of HSF1 inducers that preserve cognitive competence. A wide range of HSF1 elicitors, via HSF1 activation or expression, share a remarkable ability to improve or maintain cognition, while many of the HSF1 inducers may have other beneficial properties, notably raising HSPs (Gombos et al. 2011; Haldimann et al. 2011; Neef et al. 2011; Crul et al. 2013). The following discussion focuses on HSF1 inducers and their role in nurturing brain tissues, whether through canonical or non-canonical pathways. But first we note that loss of HSF1 activity is associated with neurodegeneration (Kondo et al. 2013; Jiang et al. 2013; Verma et al. 2014). Most recently, α -synuclein, a protein associated with Parkinson's disease, has been found to accelerate HSF1 protein degradation, while HSF1 activation in turn limits α -synuclein accumulation (Kim et al. 2016). Similarly, accumulation of mutant huntingtin blocks HSF1 transcription, while HSF1 limits huntingtin aggregation (Das and Bhattacharyya 2015, 2016). Thus, low HSF1 activity from either elevated α -synuclein or elevated mutant huntingtin accumulation can lead to a vicious cycle that augments pathologic progression.

Exercise activates HSF1 in skeletal muscle (Locke et al. 1995). Exercise raises brain HSP70 and the neurotrophic factor, BDNF, and improves brain function and memory after traumatic brain injury in a rodent model (Zhao et al. 2014). Exercise also increases neuronal dendrite spine formation and synaptic proteins (Lin et al. 2012). In humans, observational and interventional studies found associations of exercise with beneficial cognitive effects in Alzheimer patients or elderly subjects (Rolland et al. 2000; Laurin et al. 2001; Shah et al. 2014; Vidoni et al. 2015).

A novel dihydropyridine, LA1011, developed in the Vigh-Penke laboratory, is a co-inducer of HSP27 and HSP70—

lipase, *GCS* glucosylceramide synthase, *GFR* growth factor receptor, *GlcCer* glucosylceramide, *GSK3* glycogen synthase kinase-3, *HSF1* heat shock factor 1, *P3* inositol triphosphate, *MAG* monoacylglycerol, *MAGL* monoacylglycerol, lipase, *MAPK* mitogen-activated protein kinase, *mTOR* target of rapamycin, *PI3K* phosphoinositol-3-kinase, *PIP2* phosphatidylinositol 4,5-bisphosphate, *PIP3* phosphatidylinositol-3,4,5-triphosphate, *PKA* protein kinase A, *PKC* protein kinase C, *PLA2* phospholipase A2, *PLC* phospholipase C, *PLD* phospholipase D, *SIP* sphingosine-1-phosphate, *SGT* glucosyltransferase, *SK1* sphingosine kinase 1, *SMase* sphingomyelinase, *SPC* sphingosylphosphorylcholine, *TRP* transient receptor potential channel. (Figure reprinted with permission of publisher (Török et al. 2014))

reduced amyloid accumulation in an Alzheimer mutant mouse model (overexpression human APP695sw mutation and presenilin-1 mutation M146L (Tg PS1/APPsw)) (Paris et al. 2010).

Ethanol ingestion raises HSF1 and can preserve cognitive function (Collins et al. 2010; Varodayan et al. 2011). Low chronic ethanol consumption is associated with a reduction in age-associated memory loss (Anstey et al. 2009). Pertinently, ethanol protected the hippocampal-entorhinal cortex from amyloid toxicity in an ex vivo model (cortical slice cultures from maturing rats); this neuroprotection correlated temporally with rises in HSPs (Belmadani et al. 2004). Collins' group observed that alcohol preconditioning increased synaptic PSD95 expression as well as NMDAR synaptic localization (Collins et al. 2010). Varodayan and coworkers confirmed ethanol's ability to activate HSF1 and trigger expression of synaptotagmin 1, a synaptic protein that (combined with calcium) initiates vesicle fusion to pre-synaptic membranes that results in neurotransmitter release (Varodayan et al. 2011).

Celastrol, a traditional Chinese herbal medicine, inhibits proteasome activity and may also stimulate SIRT1 to activate HSF1 and induce HSP expression (Walcott and Heikkila 2010; Sharma et al. 2015). Brown and associates recently reported in this journal the potential for celastrol as a viable therapy for neurodegenerative disease (Chow et al. 2014). Their study emphasized the ability of HSP induction by celastrol to protect the brain from misfolded, aggregation-prone proteins in diseases like Alzheimer's. Indeed, celastrol

Fig. 4 Effect of LA1011 treatments on Morris water maze performance. The fitted survival curves using the Cox proportional hazard model represents the probability those animals find the platform during a trial, capped at 90 s. Mice were tested on four consecutive days after the initial water maze trial—the effect of day has been modeled in. Wild type (*wt*), APPxPS1 transgenic (*tg*). We compared *wt* + saline vs. *wt* + LA1011 ($p = 0.047$), *wt* + saline vs. *tg* + saline ($p = 0.036$), and *tg* + saline vs. *tg* + LA1011 ($p = 0.001$) treatment groups using log-rank tests ($n = 8/\text{group}$). Reproduced with permission from the *Journal of Alzheimer's Disease* (Kasza et al. 2016)

GGA, mentioned above, is an anti-ulcer medication sold in Japan. Based on its ability to activate HSF1 and HSPs, Hoshino et al. demonstrated that 9 months of oral GGA administration to an Alzheimer mutant mouse model (APPsw) reduced amyloid accumulation in the brain and preserved neurons and cognitive ability (Hoshino et al. 2011).

Insulin signaling increases HSF1 activity by deactivating GSK3's suppression of HSF1 (Bijur and Jope 2000; Hooper and Hooper 2009). Insulin administration raises HSP levels in myocardial tissue (Li et al. 2004). Insulin receptors in the brain are dense in the hippocampus and cerebral cortex and are associated with enhanced synaptogenesis (Needleman and McAllister 2008). In an anesthesia-induced spatial learning and memory deficit mouse model, intranasal administration of insulin prior to sedation prevented memory loss and increased synaptic protein expression of synaptophysin, synapsin-1, and PSD95 (Zhang et al. 2016). Recent human data have demonstrated that nasal inhalation of insulin improves memory (Craft et al. 2012). Conversely, type 2 diabetes mellitus is associated with higher risk of dementia and Alzheimer's disease (Cooper et al. 2015).

Families of HSP-inducing xenohormetic substances with anti-dementia properties have been effective in delaying or treating dementia in animal models and some human clinical trials. The substances include polyphenols, terpenoids, and rosmarinic acid (Hooper et al. 2010; Hügel and Jackson 2014). Several of these agents activate HSF1 by SIRT1-mediated

deacetylation (Westerheide et al. 2009). Resveratrol, a SIRT1 activator, limits plaque formation in Alzheimer mutant mice (Solberg et al. 2014). A combination of adaptogens, *Eleutherococcus senticosus*, *Schisandra chinensis*, and *Rhodiola rosea*, raises HSP levels (Panossian et al. 2009) and improves memory and cognitive performance (Aslanyan et al. 2010). Curcumin activates HSF1 (Teiten et al. 2009) and augments memory function (Zhang et al. 2015a). Capsaicin activates calcium channels (TRPV) and thereby activates HSF1 (Bromberg et al. 2013) and improves cognitive function while blocking tau phosphorylation and β -amyloid accumulation in a diabetic-dementia animal model (Yang et al. 2015).

Vitamin B₁₂ deficiency is associated with dementia, while its supplementation improves memory ability. Interestingly, vitamin B₁₂ deficiency inhibits SIRT1 and thus blocks activation of HSF1. Vitamin B₁₂ supplementation, on the other hand, restores HSF1 and SIRT1 to normal levels (Ghemrawi et al. 2013).

Emotional and social experience can alter neurotransmitters and hormones that subsequently can induce HSF1 activity. In particular, serotonin, an HSF1 activator (Tatum et al. 2015), is associated with danger recognition (Christianson et al. 2010). Oxytocin levels surge during sexual encounters (Blaicher et al. 1999) and are also associated with activation of HSPs (Moghimi et al. 2014). It is intriguing to speculate that via HSF1 activation, emotional events could become more memorable.

Reflection

The studies presented above provide substantial evidence of the benefit of HSF1 activators in cognitive disorders. This benefit can occur through generation of HSPs, gene expression important for synaptic form and function, and activation of other neuroprotective signaling pathways. In the past, the biomarker of HSF1 activity has been determined by evidence of downstream HSP70 generation. Future studies should include biomarkers of the multiple pathways of HSF1 to better understand their relative contribution to cognitive enhancement/preservation.

We propose that HSF1 plays a key role in the organism's ability to recognize danger and other intense experiences with consequences for fitness. It is not surprising that we remember fearful events. Many of our most memorable memories are dangerous events, such as a car accident, fire in our home, insect sting, or snakebite. We believe that these events activate HSF1 and result in lasting memories that can protect us from injury over time. Through learning and memory, organisms can successfully respond to environmental stimuli and survive to reproduce.

It is not intuitive that seemingly unrelated events like heat shock or exercise can improve brain function in a fruit fly, mouse, or human. In reflection, the ancient Greek philosopher Thales' wisdom to cultivate "a sound mind in a healthy body" suggests a mind-body connection that is supported by these observations. Certainly, HSF1's role in synaptic generation and conservation embodies a tangible connection between neural circuitry and environmental events that can lead to adaptive behavior.

Translating the knowledge of molecular and cellular events of the synapse to successfully treat memory disorders in in vivo animal models may open major opportunities for drug discovery. Modalities that safely and effectively activate HSF1 are needed to prevent and treat neurodegenerative diseases. If efficacious, HSF1 inducers could alleviate the torment and suffering associated with these maladies.

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