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Emerging Non-canonical Roles of Heat Shock Transcription Factor 1 in Synaptic Gene Regulation in Combating Neurodegeneration

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ABSTRACT

Heat shock factor 1 (HSF1) is arguably the most important master regulator orchestrating every aspect of our cellular stress response in virtually all cells. Besides the classic role of HSF1 in transcriptional upregulation of the genes encoding for heat shock proteins (HSPs) during the heat shock response (HSR), numerous non-HSP-related target genes and functions have been identified, including multiple synaptic genes involved in brain functions of learning and memory. Herein, we will focus on reviewing the roles of HSF1 in synaptic regulation and in memory formation. Specifically, we will 1) revisit the *Hsf1*-null mouse genetic data and discuss the implication of HSF1 in neurodegeneration; 2) review evidence supporting HSF1's novel role in memory formation; 3) review the recently confirmed HSF1 direct gene targets concerning synaptic plasticity and memory formation; 4) discuss therapeutic considerations of HSF1-based strategies in treating cognitive decline. Although we will designate the majority of this review to the emerging non-canonical roles of HSF1 in regulating genes beyond the HSR process (i.e., non-HSP genes), we will also include recent conceptual advance in the area of HSF1 at the crossroad between cancer and neurodegeneration via countering amyloidogenesis. Lastly, we will briefly discuss how we may utilize the cutting-edge technology of multi-omics in the future to fill the current knowledge gaps in HSF1 biology in the mouse brain during aging and neurodegeneration.

Key words: heat shock response (HSR); transcription factors; HSF1 gene targets; BDNF; cellular proteostasis; chaperones; synaptic plasticity; learning and memory; neurodegeneration

List of abbreviations:

HSF1	Heat shock factor 1
HSR	Heat shock response
HSP	Heat shock proteins
HSEs	Heat shock elements
NDDs	Neurodegenerative diseases
BDNF	Brain derived neurotrophic factor
UPR	Unfolded protein response
UPS	Ubiquitin-proteosome system
LTP	Long-term potentiation
EET	Enriched environmental treatment

INTRODUCTION & BACKGROUND

The heat shock response (HSR) is a cellular response to diverse environmental and physiological stressors via the induction of genes encoding for a class of heat shock proteins (HSPs and molecular chaperones, proteases, and other proteins) that are essential for the protection and recovery from cellular damage [1–7]. HSR is the most ancient and evolutionarily conserved molecular and cellular process in all eukaryotic cells. Since its pioneering discovery by the Italian scientist Ferruccio Ritossa 60 years ago [8–10], the HSR has been widely studied in lower eukaryotic model organisms (e.g., yeast, Drosophila, and *C. Elegans*). Despite considerable mechanistic insights that have been obtained from studies in higher eukaryotes, our understanding of the HSR remains incomplete, in particular in mammals.

Mechanistically, the HSR is a universal transcriptional program orchestrated by heat shock transcription factors (HSFs) to induce immediate upregulation of those cytoprotective genes in response to various cellular stress [11,12]. To date, at least seven heat shock transcription factors have been identified in mammalian cells [13] with HSF1 being best characterized due to its essential role in activating genes in response to proteotoxic stress. A majority of these genes encode molecular chaperones, the major protein quality controllers with the capacity to unfold and refold misfolded protein substrates and facilitate their degradation [14]. Therefore, the HSR is fundamental to the maintenance of cellular proteome homeostasis. Many age-related diseases are characterized by aberrant synthesis, folding, and aggregation of proteins. Upregulation of individual HSPs (e.g., iHSP70) has been demonstrated to be beneficial in

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cytoprotection in numerous experimental models, including its well-established role in neuroprotection [15]. The focus of this review is on the upstream transcription factor HSF1 with special emphasis on its emerging roles in synaptic plasticity and learning memory.

Overview of the HSF1 biology

The ubiquitous HSF1 is constitutively expressed in most tissues and cell types in all living organisms. Based on the "Human Protein Atlas; https://www.proteinatlas.org/ENSG00000185122-HSF1), it is indicated to have low tissue specificity. During unstressed conditions, the mammalian HSF1 exists as a monomer and is repressed primarily in the cytosol [4]. Upon proteotoxic stress [16], HSF1 becomes de-repressed for activation. Following the de-repression, HSF1 undergoes several activating post-translational modifications (PTMs, phosphorylation in particular) [17,18] and forms a transcriptionally active trimer that accumulates in the nucleus, ensued by binding to heat shock elements (HSEs) located in the upstream regulatory promoter regions of the *Hsp* genes. These steps occur sequentially and are highly regulated events [6,7,11,19]. Besides the trimerization and nuclear translocation are the two prerequisite events reaching the best consensus, additional levels of regulation may be required for enabling DNA-binding that can be promoter-specific and/or cell type-specific (e.g., iHsp70), due to differences in chromatin architecture and epigenetic modifications. This hypothesis was supported by the evidence that a constitutively trimerized HSF1 mutant readily binds to the promoter of the interleukin-6 (IL-6) gene but not to those of the *Hsp*70 or *Hsp*27 [20].

HSF1 regulation

The DNA-binding and transcriptional capacity of HSF1 is suppressed at both the intramolecular level (e.g., PTMs) and the intermolecular level (via interacting with the molecular chaperones such as HSP70, HSP90, and TRiC/CCT [20–22], or via interacting with a negative regulator like heat shock factor binding protein 1 (HSBP1) [23]). According to the popular model in the field, in the absence of stress, HSF1 activity is mainly repressed by its binding to HSPs including HSC/HSP70 and HSP90, [4,6,24–27] - "the multiplex chaperone titration model" [28], which was contested by the other group [29]. The repression of the activation domain is also largely regulated by phosphorylation on residues within the regulatory domain [29,30]. Out of the 12 serine residues of HSF1 identified by mass spectrometry, phosphorylation of Ser303 and Ser307 has been shown to suppress HSF1 activity, and these two sites can be phosphorylated by multiple kinases [31,32]. Phosphorylation of HSF1 on Ser121 residue in the DNA binding domain by mitogen-activated protein kinase 2/MAPK2 or AMP-activated protein kinase/AMPK represses HSF1 activity [33,34]. In contrast, Ser230 and Ser326 present in the regulatory domain are the phosphorylation sites positively associated with HSF1 activation upon stress [35,36]. Ser230 site was found to be phosphorylated by several kinases as well; one is by the calcium calmodulin-dependent kinase II (CaMKII) in HeLa cells after heat shock. CaMKII is a kinase highly regulated by neuronal activity and thus is a critical player in the process of synaptic plasticity and memory [37]. It remains to be determined if the same CaMKII-induced modification on Ser 230 occurs during neuronal response upon elevated neuronal activity. On the other hand, HSF1 can be inactivated by acetylation on the Lys80 site and be activated and stabilized via SIRT1-mediated deacetylation [38] and possibly also by acetyltransferase EP300 [39]. It should be pointed out that all the identified regulatory mechanisms were largely studied in non-neuronal cellular models under heat shock. Both constitutive and inducible iHSP70 protein are highly enriched at synapses [40,41], and their roles in learning and memory have been comprehensively reviewed recently [42].

Overview of HSF1's roles in CNS diseases

HSF1 was reportedly expressed in neurons, astrocytes, and oligodendrocytes based on immunohistochemistry of developing mouse brain [43] and adult rat spinal cord tissue [44]. In principle, HSF1 is ubiquitously and constitutively expressed in all cell types in the central nervous system (CNS), perhaps at different subcellular distribution and expression levels. Given the principal role of HSF1 as the master controller of HSR, its loss of function predictably contributes to age-related diseases involving stress. Indeed, alterations in HSF1 function impact protein homeostasis and are strongly linked to diseases, such as neurodegenerative disorders (NDDs), metabolic diseases, and different types of cancers [45–49]. In particular, several major NDDs such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), and prion diseases are all associated with the accumulation of disease-specific misfolded proteins, and the formation of protein aggregates or inclusion bodies, resulting in neuronal dysfunction and cell death [50–52]. Many NDDs are characterized by altered proteostasis, which is largely dependent on the functional chaperones to clear the misfolded and aggregation-prone proteins [53–56], and thus are true examples of proteinopathies [57]. Recent genetic and mechanistic studies reveal shared pathological mechanisms including proteostasis collapse (e.g., defective stress granules and degradation pathways), dysfunctional mitochondrial homeostasis, and maladaptive innate immune responses [58], consistent with a new theory that NDDs are considered proteinopathy-driven immune disorders [59]. Of note, synaptic vulnerability and dysfunction are also common features across several NDDs, such as AD, PD and HD [60,61].

Aging is widely accepted as a major risk factor for NDDs, and is associated with reduced physiological cellular processes like proteostasis, in particular [62]. Proteostasis collapse has long been established as a hallmark of nematode aging [63]. A recent transcriptomic study reveals that proteostasis decline is also an intrinsic feature of human senescence [64]. Levels of the HSF1 protein and messenger RNA (mRNA) decline with age in mouse tissues examined, correlating with reduced HSR [65–67]. Given that HSF1 is arguably one of the most critical regulators in stress response in CNS, its loss of function can be a major factor contributing to neurodegeneration, an accelerated aging process. Indeed, aberrant HSF1 protein degradation upon proteotoxic stresses of misfolded proteins characteristics of tauopathy [68], PD [69], and HD [70] was widely reported, suggesting that HSF1 protein degradation represents a common mechanism underlying its loss-of function. Herein, we will focus on the emerging roles of HSF1 in regulating genes pertinent to synaptic plasticity, the fundamental process of mammal brain's ability to adapt to various changes to reorganize and modify neuronal connections which is crucial for learning and memory.

MATERIALS AND METHODS

We performed a comprehensive literature review to identify original publications concerning potentially important roles of HSF1 and HSR in synaptic functions and learning/memory, with special focus on those studies conducted in mammals (rodents and humans). The PubMed and PubMed Central were searched using the following key words: HSF1, Heat shock response/HSR, neuronal

HSR, transcription-dependent and -independent targets, HSP and non-HSP, genome-wide transcriptome, proteostasis, stress, memory, synaptic plasticity. Only the published original papers or highly quoted review articles were cited in this review, with the exceptions of the two former graduate students; theses, which are in the public domain. The data presented in this review were selected or summarized by the first and corresponding author. We used the weblink of https://knowledge.brain-map.org/ searching for the specific gene expression in developing mouse brain from the Allen Brain Atlas Transcriptomics Explorer.

Main text

HSF1-null mice develop typical signs of NDDs: At least three lines of *Hsf1*-null mouse models were generated by independent research groups two decades ago with the *Hsf1* gene globally ablated [71–73], all on mixed genetic backgrounds. Systemically, *Hsf1*-null mice display aberrant immune response [74], and are more vulnerable to environmental challenges such as heat and genotoxic stress [75–77]. Paradoxically, *Hsf1*-null mice are more resistant to oncogenesis [78–82]. More recently, HSF1's crucial roles in metabolic regulation [76,83–85] including mitochondrial function [86–89] have received much attention. In general, the multiple systemic phenotypes in *Hsf1*-null mice all support the classic title of HSF1 in controlling cellular stress response and proteostasis. One interesting aspect of HSF1 in immune regulation is disclosed by the initial findings of HSF1's roles in binding to the two most prominent pro-inflammatory cytokine genes (IL-1beta and IL-6), opening up their promoter chromatin structures and allowing repressive factors to suppress their gene expression [90–92]. There is a potential translational significance of the HSF1-mediated non-HSP gene expression involved in mediating a HSR in shaping the subsequent adaptive immune responses (i.e., cytokine storm) during the pathogenesis of Coronavirus infection (SARS-CoV-2) [93].

Several groups reported largely comparable phenotypes using these lines of *Hsf1*-null mice [94–96] as summarized in Table 1. Enlarged lateral ventricles, astrogliosis, demyelination, and neurodegeneration (hippocampus, in particular) were all detected at a very young age, starting from 1-2 months of age (1-2 M). Oxidized proteins were detected at 5 M, [97] but not in another report by nitrotyrosine staining [94]. Surprisingly, reactive microglia were detected only at mid-age (12 M), along with an increased accumulation of ubiquitinated proteins/high molecular-weight species [95]. Aberrant affective behaviors (reduced anxiety/social interaction, and increased depression-like behaviors) were reported in neonatal *Hsf1*-null mice, which could be rescued by constitutively expressed *Hsf1* gene [96]. Enlarged ventricle (so called ventriculomegaly) is the medical sign of hydrocephalus in humans, most often seen in aging and cognitively impaired individuals or schizophrenia patients [97,98], and typically indicating a buildup of fluid in the cavities (ventricles) deep within the brain (e.g., after stroke or acute brain injury). Interestingly, only the lateral ventricle was enlarged associated with prominent myelin loss, while the third ventricle was just slightly larger than normal and the size of the fourth ventricle was unaltered. The changes detected were not different between 1 to 3 month-old-null mice, indicating that the abnormalities found to occur either prenatally after embryonic day 18.5 or early postnatally before 1 month of age [94]. Based on the finding that "enlargement of cerebral ventricles as an early indicator of encephalomyelitis" in a study using an experimental model of the T-cell autoimmune disease of multiple sclerosis in mice [99], we speculate that the enlarged ventricle seen in young *Hsf1*-null mice may be a result of early brain inflammation. Indeed, markedly increased astrogliosis was found around the lateral ventricles [95]. Under normal conditions, astrocytes maintain CNS homeostasis to support the survival and information processing functions of neurons [100]. In aging brains, ventriculomegaly is often seen to be associated with gliosis where the ependymal cells are replaced with dense patches of astrocytes [97]. In *Hsf1*-null mice, massive astrogliosis occurred selectively in the two major regions in which demyelination was detected at a young age (2 M): in the cervical region of spinal cord and the corpus callosum (CC, the largest white matter tract) region [95]. It is therefore plausible that the enlarged ventricle, demyelination and the astrogliosis are the inter-related events in mechanisms, forming a vicious cycle in the *Hsf1*-null mice that warrants further investigation. Taken together, these findings strongly indicate that loss of HSF1 function directly contributes to neurodegeneration.

HSF1 is required for learning memory: In addition to NDD-relevant brain pathologies, the hippocampal formation was also reported to be severely impaired in *Hsf1*-null mice at neonatal age [96].

Table 1. Reported CNS phenotypes from HSF-deficient mice.

Age (M)	$HSF1^{-/-}$	References	Genet. Background
Embryonic E18.5	Not detected	Xiao et al 1999 [74]	Sv129xBalb/c [71]
1–3	Enlarged lateral ventricles	Santos 2004 [94]	Sv129 [71]
		Homma 2007 [95]	129Sv/Ev-C57BL/6 [72]
2	Demyelination (corpus callosum)	Homma 2007 [95]	129Sv/Ev-C57BL/6 [72]
1–2	Astrogliosis (hippocampus, striatum cortex, cerebellum, spinal cord)	Santos 2004 [94]	Sv129 [71]
		Homma 2007 [95]	129Sv/Ev-C57BL/6 [72]
3	Impaired hippocampal spinogenesis and neurogenesis	Uchida 2011 [96]	ICR [73]
3	Neurodegeneration (caudate putamen, external capsule and corpus callosum)	Uchida 2011 [96]	ICR [73]
12	Accumulated ubiquitinated proteins	Homma 2007 [95]	129Sv/Ev-C57BL/6 [72]
Neonatal	Impaired afferent behaviors (reduced anxiety and socialization, increased depression-like behavior)	Uchida 2011 [96]	ICR [73]
6–7	Impaired working memory (T maze)	Zhu 2008 [104]	Sv129xBalb/c [71]
	$HSF1^{+/-}$		
12–24	Aggregated insoluble α-synuclein and tau	Kim 2016, 2017 [68,69]	C57BL/6-129Sv [71]
12	Increased anxiety	Kim thesis 2017 [103]	C57BL/6-129Sv [71]
4–25	Impaired working, spatial memory (short- and long-term working memory)	Wang 2017 [101]	C57BL/6-129Sv [71]
		Kim thesis 2017 [103]	C57BL/6-129S [71]

Furthermore, impaired working and contextual memory were reported in heterozygous *Hsf1* mice at a young age (4-5 M), and compromised long-term memory only at a very old age of 23-25 months [101–103]. These behavioral data collected from the *Hsf1*-null mice [102–104] strongly suggest that HSF1 is involved in the process of learning, both short and long-term forms of memory. Before we review the direct evidence supporting the importance of HSF1 in learning and memory, we provide a anatomical human and mouse brains showing the hippocampal and frontal cortex, the two regions most critical for long-term learning and memory in Figure 1.

Direct evidence supporting the importance of HSF1 in learning and memory was derived from the studies using pharmacological and genetic (AAV-shRNA) approaches in the contextual fear conditioning [101,105], the most widely used paradigm in rodents to study the hippocampus-dependent association memory [106–108]. Since HSF1 downregulation via AAV-shRNA-*Hsf1* (intracerebroventricularly, icv) did not affect fear acquisition (short-term memory) during the ~8 min of footshock (FS) training, but reduced fear retention after 24-72 h (Figure 2A), indicating that HSF1 is required for memory retention, but not acquisition. Furthermore, boosting HSF1 activation via a CNS-permeable HSP90 inhibitor completely rescued the contextual fear memory in an acute model of icv injected soluble oligomeric Aβ (AβOs); the latter was found to only impair hippocampus-dependent contextual memory without affecting amygdala-mediated tone response [105]. An HSF1-dependent mechanism was confirmed by an HSF1 DNA-binding inhibitor, KRIBB11 [109]: the most significant abrogating effect was observed when the inhibitor compound was administered at 1 h post-training, and to a lesser degree at 3 and 6 h post-training [101,102]. This result indicated that HSF1 is required for the initial stage of memory storage or retrieval, which requires robust gene transcription, and that HSF1 likely directly regulate these transcriptional activating events.

HSF1 in spine, synaptic plasticity and memory

Dendritic spines are the specialized and highly dynamic structures on the dendrites of neurons where the excitatory synaptic contacts take place in the brain [110]. Both dendrites and dendritic spines play pivotal roles in brain connectivity and are well-accepted to form the structural basis of the long-term synaptic plasticity related to the cognitive processes (e.g., learning and memory). Both internal and external stimuli can induce changes in dendritic spine morphology and the density on the order of minutes. It is now clear that the structural plasticity of dendritic spines is related to the changes in synaptic functional characteristics, and correlates with learning and memory, and other cognitive processes. This has been studied in great detail in several AD mouse models: the loss of dendritic spines directly correlates with the loss of synaptic function, and synaptic failure is an immediate cause of cognitive decline and memory dysfunction [112]. Postsynaptic dendritic spines play an important role in learning and memory [113]: the size of a dendritic spine positively correlates with the size of its postsynaptic density (PSD), the number of glutamate receptors, and synaptic strength [114–115]. Postsynaptic spines are usually classified into three groups according to their morphological structure: mushroom spines, thin spines, and stubby spines. It has been postulated that the mushroom spines are stable "memory spines" that make functionally stronger synapses that are responsible for memory storage [116,117], and the mushroom spines have been found to be selectively destabilized in AD, despite unclear mechanisms underlying this cellular process [118–120]. Impaired calcium signaling is believed to be one major cause [121,122].

Compelling evidence indicates that Aβ, especially the soluble AβOs, selectively targets synapses and disrupts their structures and functions [123–125], primarily via NMDA receptor-mediated calcium influx [126–128]. PSD95 is the major PSD scaffolding protein at excitatory synapses (along with the CaMKII, the two major post-synaptic components of PSD) [129]. It is crucial for synapse maturation and plasticity [115], which can be diminished by AβOs [130,131], correlating with cognitive decline [132]. In the studies reported by Wang et al [101], a CNS-permeable HSP90 inhibitor compound, which is predicted to release HSF1, leading to its activation in the nucleus to activate its target genes based on the classic model of HSP90-HSF1 interaction [29,133–135], not only induced multiple HSPs (iHSP70, HSP27, and HSP 40) but also several synaptic proteins (synapsin I, synaptophysin, and PSD95) in primary neurons and in the mouse brains (hippocampus, in particular). The effect appears to be specific to certain synaptic genes and proteins because of the expression of two other PDZ-containing scaffolding proteins, SNAP25 and SAP97, as well as presynaptic Rab3a and the most abundant postsynaptic CaMKII protein was not changed [105]. More importantly, this HSP90 Inhibitor also rescued synaptic damage induced by soluble Aβ oligomers as evidenced by the restored colocalized synapsin I and PSD95 clusters, indicating active synapses, and the increased mushroom spines (Figure 2B), which corroborated with the enhanced *in vivo* spine formation and strength as monitored by two-photon microscopic live imaging [101]. Lastly, the inhibitor treatment promoted *in vivo* long-term potentiation (LTP): a single administration of a HSP90 inhibitor 30 min before high-frequency stimulation (HFS) was also found to enhance *in vivo* LTP recorded from rat medial perforant path-dentate granule cell synapses, the most severely defective in AD, as evidenced by both the increased amplitude of PS and the

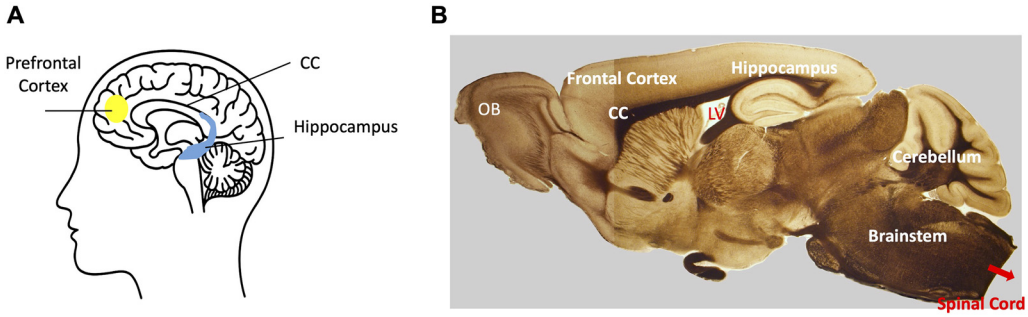

Figure 1. (A) Schematic diagram of human brain showing the hippocampus, prefrontal cortex, and corpus callosum (CC). (B) Microscopic image of sagittal section of a mouse brain (7 months of age): two images were combined manually from the same section. OB: Olfactory bulbs; LV: lateral ventricle.

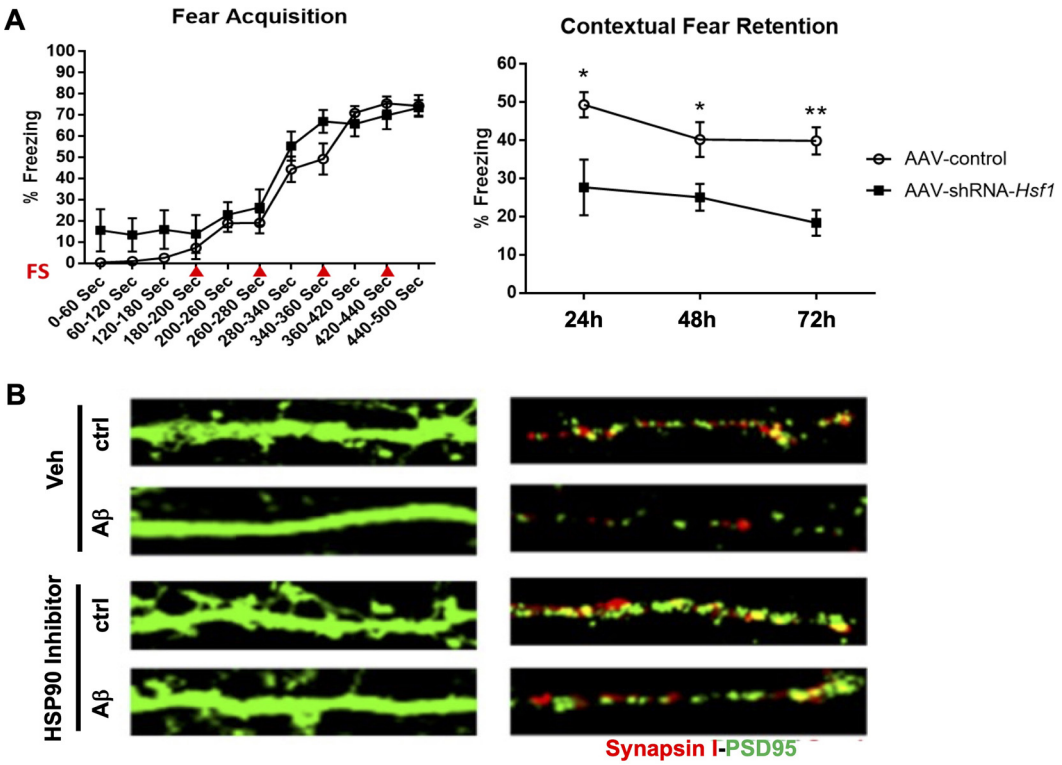

Figure 2. (A) HSF1 knockdown impairs memory retention indicated by % freezing time at 24, 48, 72 h but not fear acquisition during the training. We conducted fear contextual tests 14 days after mice were injected with AAV-shRNA-*Hsf1* (> 10^10 pfu, icv) or a control vehicle to knockdown HSF1 [102]. Freezing time (%) during fear acquisition and contextual fear acquisition and retention in the contextual fear conditioning test. N = 11-14. One-way ANOVA with Tukey's post hoc test, ctrl (control) vs AAV-shRNA-*Hsf1*. *P < 0.05; **P < 0.01. FS: footshock; red arrowheads indicate the timing of FS. (B) Effects of a CNS-permeable HSP90 inhibitor on synaptic morphology and active synaptic clusters in primary neurons by confocal microscopy 24 h after Aβ treatment (left panels: fluorescently labeled neuronal dendrites; right panels: immunocytochemistry). Veh: vehicle; Ctrl: control. Please see reference 102 for quantification graphs.

slope of EPSP [105]. Similar results were reported from a separate study on rescuing LTP deficits in young rTg4510 (tau Tg) mice [136]. The inhibitor treatment also enhanced the coherence of oscillatory activity, another measure of neuronal network functionality [137–139]; reduced frequency power and coherence correlate with memory loss [140–143]. The coherence of local field potential (LFP) activity within the hippocampal CA1 region and between CA1 and the prefrontal cortex for beta (12 - 30Hz), gamma (30 -100Hz), and higher frequency (190 - 200 Hz) oscillations were all enhanced by the HSP90 inhibitor treatment in mice even at very old age (18 M) [101]. Lastly, the HSP90 inhibitor was neuroprotective (e.g., on CA1 neurons in particular) and rescued Aβ-induced short-term and long-term memory (e.g., fear contextual memory and spatial working memory in water maze) [101], which was corroborated by an independent study using an acute rat model of injecting $A\beta_{25-35}$ to the CA1 region [144]. Of note, all the afore-described beneficial effects from the HSP90 inhibitor were abolished by HSF1 inhibition either via AAV-shRNA or the HSF1 inhibitor, indicating an HSF1-dependent mechanism [101].

HSF1 directly regulates synaptic genes in the mouse brain

De novo gene transcription during LTP and synaptic plasticity: In mammals, LTP is an electrophysiological measure of synaptic strength that correlates with synaptic spine morphology and density, which forms the foundation of memory [113–116]. *De novo* gene transcription plays a crucial role in regulating synaptic plasticity and LTP within the brain. Specifically, while the initial phase of LTP relies on post-translational modifications of existing proteins, the late and enduring phase necessitates new gene transcription and protein synthesis to maintain the long-lasting changes in synaptic strength associated with learning and memory [145–147].

In addition to its classic role of activating heat shock genes encoding for HSPs, evidence is emerging in HSF1's roles beyond the HSR, such as in activating genes involved in synaptic functions. Uchida et al [96] demonstrated a direct role of HSF1 in binding and activating the two genes *(ST8SiaII and ST8SiaIV)* encoding for the two polysialyltransferases responsible for the polysialic acid (PSA) biosynthesis. Because these polysialyltransferases and the PSA-neural cell adhesion molecule (NCAM) expression are known to be required for hippocampal formation, synaptic plasticity, memory formation, and anxiety behavior, the authors speculated that their findings explain the impaired hippocampal formation and depression-like behaviors in *Hsf1*-null mice at neonatal age. It would be interesting to follow up the studies to see if the same mechanistic defect continues throughout adulthood and even into old age. Nevertheless, this was the first report on a bonafide CNS target gene of HSF1 directly involved in hippocampal formation concerning synaptic plasticity.

Years later, Chen et al., [105] reported that HSF1 also directly regulated a specific panel of synapse-related genes including immediate early genes/IEGs (*Fos* and *Arc*), synapsin I (*Syn I*), PSD95 (*Dlg4*), synaptophysin (*Syp*), and brain-derived neurotrophic factor

BDNF (*Bdnf*) in the context of soluble AβOs models in a primary neuronal model of AD concerning soluble Aβ challenge. Direct binding and transcriptional activation of the *Dlg4* gene encoding for PSD95 was also recently confirmed by chromatin immunoprecipitation (ChIP-PCR) by an independent group, which represents a crucial mechanism accounting for the impairment and loss of the thalamostriatal excitatory synapses in both cellular and mouse models of HD [148]. The C57BL/6 mouse hippocampus is found to undergo major alterations in gene expression after contextual fear conditioning [149]. The *Bdnf* is one IEG induced rapidly during contextual learning training selectively in the CA region of the hippocampus [106]. Interestingly, HSF1 displays a strikingly similar gene expression pattern to that of the *Bdnf* gene in the brain, particularly high in the hippocampus and cortex, but not in the cerebellum (Figure 3A). Marked induction of most of the *Bdnf* genes from the purified synaptosomes of mouse brain upon treatment was reported with an Hsp90 inhibitor or directly overexpressed HSF1 via AAV [101], indicating a potentially crucial role of HSF1 in upregulating *Bdnf* gene. Below, we will focus on this novel HSF1-BDNF axis.

BDNF is the major neuronal growth factor in the brain, critical for neuronal growth and survival, neuroprotection, synaptic plasticity, and learning/memory [150–156]. BDNF levels have been reported to be reduced in aging brains [155], in AD [156,157], in PD [107,108], in HD [158], and in many other CNS disorders such as depression [159], and schizophrenia [160]. Increasing *Bdnf* expression is a potential therapeutic strategy to ameliorate neuronal damage to prevent and treat CNS disorders [161,162]. BDNF expression is controlled by 9 *Bdnf* promoters (I-IX) in both rodents and humans; each promoter drives transcription of a small exon, which is spliced to the common protein-coding exon [163,164]. Interestingly, most of the *Bdnf* promoters, except promoters II and VII, contain heat shock elements (HSEs), the HSF1 binding sites, predicted by the analyses with JASPAR (https://jaspar.elixir.no/) [165].

is HSF1 also an activity-dependent transcription factor? It is well-established that neuronal activity plays a pivotal role in synaptic plasticity largely through the actions of neurotrophins such as BDNF. Neuronal activity regulates the transcription of the *Bdnf* gene (promoter I and IV, in particular) [166,167], the transport of BDNF mRNA and protein into dendrites, and the secretion of BDNF protein to support the required long-lasting changes in the structure and function of the synapses [168]. This process is primarily mediated via the transcriptional activation from the promoters containing the cAMP response element (CRE) by the transcription factor CREB, the prototype of the activity-dependent transcription factor [169–175]. CREB acts fast as a first-line factor already bound to some of its target genes (e. g., IEGs) [176–179]. Several activity-dependent transcription factors (e.g., MEF2, Npas4, and SRF) are also important for the synaptic plasticity underlying long-term memory [147,178]. Of note, multiple HSEs are present in both of the activity-dependent *Bdnf* promoters I (3 elements) and IV (4 elements), some of which are closely located with the CREB binding site (CRE), as shown in Figure 3B [165], implicating HSF1 being another activity-dependent transcription factor.

The hippocampus-dependent contextual fear memory [180] requires *de novo* gene expression and protein synthesis via a Ca^{2+}/cAMP-CREB-BDNF pathway [166,178,181]. Footshock (FS, 0.2 mA x 2) administration to young wild type C57BL/6 mice rapidly induced nuclear translocation of HSF1 into the hippocampal CA1 pyramidal neurons peaking at 1 hr, which corresponded with selectively induced HSF1 binding to the *Bdnf* promoters I and IV after FS, as detected by immunohistochemistry and ChIP-PCR, respectively. FS upregulates mRNA driven by *Bdnf* promoter I and IV in the hippocampus, confirmed by quantitative qPCR [165]. Of note, these promoter regions were also detected when immunoprecipitated with a phosphorylated (p)CREB antibody, indicating that HSF1 and active pCREB

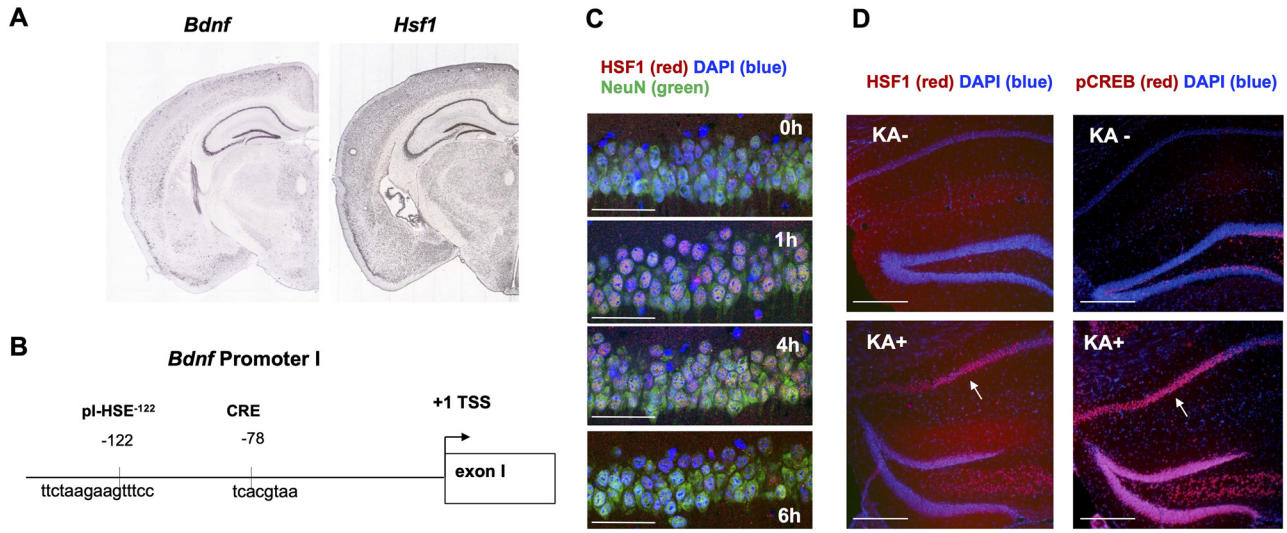

Figure 3. HSF1-BDNF axis.

(**A**) Schematic diagram showing the ChIP-PCR-confirmed HSF1 binding site, HSE, and the CREB binding site, CRE, which are located adjacently in the *Bdnf* promoter 1. (**B**) High expression levels of mRNAs of *Bdnf* and *Hsf1* genes in the hippocampus and cortex in young adult mice, depicted in the Allen Brain Atlas Transcriptomics Explorer. (**C**) HSF1 nuclear translocation in the CA1 of the hippocampus, peaking at 1 hr after kainic acid treatment. Immunohistochemistry was conducted with anti-HSF1 (red), anti-NeuN (green, neuronal marker), and DAPI (blue, nuclei maker) at 0, 1, 4, and 6 h after administration of kainic acid (24 mg/kg, i.p.). Scale bar, 50 μm. (D) Co-nuclear translocation of HSF1 and phosphorylated (p)-CREB at the CA1 region of the hippocampus 1 hr after kainic acid treatment. Scale bar, 250 μm. HSF1: Heat shock factor 1. CREB: cAMP-responsive element-binding protein. CA: NeuN: Neuronal nuclear protein. DAPI: 4′,6-diamidino-2-phenylindole. Figure 3C and 3D: Franks et al., 2023 [165], reused with permission.

co-regulate these promoters 1 h after footshock [165]. These results suggest the activity-induced interplay between HSF1 and the activated pCREB.

Similar results were reported by using a different acute stress model of kainate acid (KA), a glutamate kainate receptor agonist [165]. KA induces seizures and neuronal death when used at a high dose, primarily within the hippocampus CA1 area by excitotoxicity [182]. I.p. injection of KA to young adult mice induced HSF1 nuclear translocation peaking at 1 h (Figure 3C) and its binding to multiple *Bdnf* promoters in the hippocampus, together with pCREB [169]. Interestingly, the HSF1 binding patterns on the promoters differed by KA and footshock, suggesting that HSF1 and pCREB orchestrate to render fine-tuned promoter control depending on the types of stress. Further studies using ChIPseq together with functional validation experiments will be required to draw a solid conclusion. Of note, neuronal activity-dependent increased calcium levels were reported to lead to activated CaMKII and PKC, both reportedly phosphorylate and modulate on the HSF1 trans-activational activity: CaMKII sites on Ser 230 (active) [36] and the PKC site on Ser303/307 (repressive) [183] in the context of LTP. Additional experimental paradigms may be used to directly address the important mechanistic question of whether HSF1's role in synaptic plasticity depends on its transcriptional activation of genes that are induced by neuronal activity. Rigorous experimental evidence is also required to determine if HSF1 is another principal transcription factor for memory, given that there are a few activity-dependent transcription factors (e.g., CREB, MEF2, Npas4, and SRF) known to be crucial for synaptic plasticity. Indeed, the genome-wide gene regulation by HSF1 in the CNS in response to different types of stress and its interplay with other transcription factors represents a severe knowledge gap in terms of stress-induced impacts on synaptic plasticity.

Summary of the additional HSF1 gene targets in CNS by recent ChIP-PCR, ChIPseq, and RNAseq studies

Over the last two decades, there have been numerous non-HSP gene targets emerged, disclosing the pivotal roles of HSF1 in diverse stress response processes besides HSR and aging. These include autophagy, apoptosis, multidrug resistance, non-coding RNA transcription, chromatin remodeling, and immune response, which are excellently reviewed [184]. A follow-up bioinformatic study has generated a most comprehensive HSF1 target gene database [185], revealing that those genes involved in aging and protein quality control in proteostasis are most evolutionally conserved from vertebrates to non-vertebrates. These are the chaperone genes, cellular stress responsive pathway genes (UPR, autophagy, oxidative stress), and genes in aging (e.g., insulin/IGF1 and mTOR pathways, ribosome biogenesis and chromatin remodeling) and glucose metabolism. However, the mouse and human databases were based on the gene data collected from a few cell lines for different cell types: oocytes, spermatocytes, and hepatocytes from mice and three cancer cell lines derived from humans. Of great interest, a few shared gene clusters in immune response and circadian have general implications aging and age-related diseases.

Up to date, compared to the gene database collected from lower eukaryotes [21,186–189], genome-wide transcriptomic data were relatively rare from mouse brains, except for the ChIPseq and RNAseq data collected from the cellular models of HD mice: comprehensive transcriptomic analysis reveals that genes related to HSR in proteostasis (e.g., *DNAJB1, HSPA1B,* and *HSPB1*), as well as the mitochondrial related genes, were the most affected clusters selectively downregulated in the medium spiny neurons (MSNs) at symptomatic disease stage of HD patients' postmortem brains [190]. The interplay between HSF1 with another master metabolic transcription regulator PGC-1α in mitochondrial function was studied in HD models [87,191]. Paradoxically, the earlier data based on ChIPseq [192] of the HSF1 targets most affected by stress are not directly associated with proteostasis, but with cytoskeletal binding, focal adhesion, and GTPase activity. There are sporadic reports on CNS-related gene targets as summarized in Table 2. Of particular interest is transthyretin (TTR) because of its potent neuroprotective roles in stroke and AD [193,194]. TTR serves as a major scavenger of Aβ peptides, and celastrol can enhance the binding of HSF1 to the TTR gene promoter [195]. TTR aggregates are responsible for many systemic amyloidosis such as familial amyloidotic polyneuropathy and cardiomyopathy. Differences in TTR levels have been found in several neuropathologies [196]. In addition, the excitatory glutamate transporter gene (*SLC1A2, GLT1,* or *EAAT2*) with predicted HSE sites present in its promoter is also a potential direct gene target of HSF1 [197,198], awaiting to be confirmed by ChIP-PCR binding assays. Similarly, the gene encoding for SAP97 (*Dlg1*), another scaffolding protein at synapses, has not been confirmed as a direct gene target of HSF1, despite predicted HSE sites and confirmed the regulatory role of this gene reported in cultured cardiomyocyte cell line [199]. Further analysis based on RNAseq will hopefully identify more synaptic genes as novel HSF1 targets from CNS, preferably in a brain region and cell-type specific manner using the current advanced single cell omics approaches.

Therapeutic considerations of boosting HSF1 during neurodegeneration

Clinical trials in symptomatic patients of neurodegenerative proteinopathies using therapies directed toward initiating trigger events such as Aβ and tau for AD have yielded little success, especially when used in advanced stages of the disease rather than as prophylactics [200]. This prompts new potential strategies to identify common features of the downstream degenerative cascade such as HSR. For over two decades, the induction of molecular chaperones has been actively pursued by both academics and pharmaceuticals as a therapeutic strategy for treating age-related diseases such as NDDs both experimentally and pharmaceutically, including the development of small molecular HSF1 inducers or blockers [201–204]. Various approaches to inducing HSF1 have been thoroughly reviewed [205]. Below we provide a mechanistic update on a few most-studied compound categories, and voice for the safest physiological approach to exercise.

HSP90 inhibitors: Heat shock protein 90 (HSP90) is one major molecular chaperone protein ubiquitously expressed throughout all tissues in the body [16]. Like HSP70, it is also richly localized in synaptic compartments [40,41], and its major client proteins have been implicated in both cancer and neurodegeneration (e.g., HSF1 and AKT). Thus, pharmacologically feasible HSP90 inhibitors were under active

Table 2. ChIP-confirmed HSF1's non-HSP target genes in mouse CNS.

Gene	Encoded Protein	Functions	References
St8siall	Sialyltransferases II	PSA-NCAM	Uchida 2011 [96]
St8siaIV	Sialyltransferases IV	Hippocampal formation	
TTR	Transthyretin	Neuroprotection	Wang 2014 [195]
Dlg4	PSD95	Synaptic integrity, strength	Chen 2014 [105]
			Zarate 2021 [148]
Bdnf	BDNF	Neurotrophin	Sakata, Liao [165]

development a decade ago; over 300 clinical trials on cancer [202]. They have been studied extensively in experimental conditions of various age-related diseases [32,206]. In most studies in NDDs, the rationale has been premised on the presumed functions of HSP90 inhibitors in the induction of cytoprotective HSPs to facilitate the degradation of pathological proteins via HSF1 activation and HSR. The majority of the published data on HSP90 inhibitors were generated from *in vitro* studies, while *in vivo* success has been limited [134,207–211]. Two major hurdles to therapeutic use of HSP90 inhibitors are systemic toxicity and limited CNS permeability. As reported previously [101] that chronic treatment of symptomatic AD mice with a proprietary CNS-permeable HSP90 inhibitor compound (OS-20) offered synaptic protection via a HSF1-dependent gene transcription and alleviated cognitive decline without noticeable systemic toxicity. Although the HSR was induced in mouse forebrains (hippocampal CA1, in particular), there was no benefit from the OS-20 treatment in reducing amyloid pathology [101]. Given the same compound reportedly did not significantly reduce aggregated proteins and improve survival in rodent models of ALS [211], we concluded that the HSR elicited by HSP90 inhibitors may not be sufficient to clear misfolded proteins in mouse brains, a view shared by the others [212].

Riluzole: Riluzole is currently used to treat amyotrophic lateral sclerosis (FDA approval in December 1995), and is in clinical trials for several other CNS disorders including traumatic spinal cord injury/SCI [213,214], HD [215], and AD [https://www.alzforum.org/therapeutics/riluzole]. While its full mechanism of action is unclear, it has been widely presumed to target neurons and reduce glutamate-mediated excitotoxicity via modulating glutamate release by blocking the overactivation of sodium channels [216,217], and via modulating postsynaptic glutamate receptor signaling. Its anti-inflammatory effect has also been reported by suppressing astrocytosis in PD models [218]. Glutamate-mediated toxicity has been implicated in AD. In two AD mouse models, riluzole administration, either before or during amyloid accumulation, prevented memory decline [219,220]. Riluzole was reported to reduce tau pathology and improve memory performance in TauP301L-expressing mice [221]. In rodent models, riluzole reportedly prevented age-related changes in gene expression similar to those seen in AD, including synaptic and mitochondrial gene pathways [198,199]. Congruent with the report that riluzole can increase the monomeric form of HSF1 via protein stabilization to amplify the HSR in cultured neuronal models [222], riluzole provided neuroprotection partially through a mechanism of HSF1-dependent regulation of glutamate transporter 1 (GLT1/EAAT2) [198]. Expression of the same glutamate transporter gene has been reported to be corrected by chronic riluzole treatments in AD rats [198]. So far, the pilot phase II clinical trial of riluzole in mild AD patients was recently completed, using neuroimaging as biomarkers [https://www.alzforum.org/therapeutics/riluzole], showing improved brain glucose metabolism [223]. It remains to be determined if the selectively affected synaptic genes in AD brain [224] would be corrected from the riluzole therapy in patients.

Celastrol: Oral celastrol, a major component of traditional Chinese herbal medicine, is a neuroprotective agent with anti-inflammatory and antioxidant properties, and is thus under active development for the applications of treating NDDs [225–228]. It was initially reported to inhibit proteasome activity and upregulates HSPs presumably through HSF1 [229], an HSR-dependent mechanism [230]. Paradoxically, the proteasome inhibitor MG132 was also reported to activate HSF1 to induce HSR [231,232], and celastrol lost its neuroprotective effects under conditions of UPS inhibition in a rodent PD model [233]. Therefore the mechanism of action of celastrol on proteostasis is unclear; in one report [234], celastrol worked synergistically with HSP90 inhibitors to target cancer proteostasis. Nevertheless, it remains as an active compound prototype for drug development. Currently, the major challenge of its toxicological profile, and the formulation, (e.g., solubility, bioavailability, and dosage issues), limits its clinical applications [228].

Exercise: Physical exercise can improve overall brain function and prevent/slow down cognitive decline in the elderly, in particular those with early-stage AD [235–243]. It is well established that physical exercise can enhance hippocampus-dependent forms of learning and memory in laboratory animals, commensurate with increases in hippocampal neural plasticity via enhancing neurogenesis and LTP [244–251]. Enriched environmental treatment (EET) has been widely used in research, which cosists of physical exercise, mental stimulation, and social interaction [245], and is well established for its neurotrophic effects [245,252,253]. Exercise-based EET reduces amyloid load and improves memory performance in familial AD mouse models [254–256]. It is speculated that EET protects the brain against AD largely by inducing BDNF expression to enhance synaptic plasticity and reduce neuronal vulnerability to oxidative stress [257,258]. Our prior studies have demonstrated that EET in early life is particularly effective in reversing BDNF deficiency and modulating neurotransmitter genes, which can persist into later life [259–261]. EET also induces many other genes in the brain [262,263]. Interestingly, early-life EET affects the DNA methylation landscape in the aged mouse hippocampus [264], while epigenetic changes such as DNA methylation and histone acetylation are the hallmarks of cellular aging [62]. Epigenetic changes affect transcriptional controls in the hippocampus [265], and the plasticity of neuronal circuits [266]. EET also induces increased chromatin accessibility and insulation, targeting synapse-associated genes in cortical tissues [267]. However, the major transcription factor(s) that mediate the EET gene effects remain unclear (except for CREB). Because HSF1 binds to *Bdnf* promoters and likely to neurotransmitter genes (e. g., glutamate transporter 1/GLT1/EAAT2), we speculate that early-life EET exerts its beneficial effects possibly through an HSF1-dependent transcriptional mechanism. Although increased HSPs, such as HSP70, have been reported in rodent and human brains after exercise [268,269], and activated HSF1/HSR in skeletal muscles and hearts [270–273], activated HSF1 in CNS has been unstudied [274]. Interestingly, exercise increased HSP72 expression in circulating exosomes and improved multiple metabolic parameters [275,276], and cold-heat therapies are being considered for treating AD and PD [277].

Cancer vs NDDs: HSF1 inducers or inhibitors?

Given its crucial role in regulating the stress-inducible *HSP* gene expression, HSF1 inducers or activators have been implicated in treating CNS diseases, including NDDs. On the contrary, an unexpected notion is the multifaceted pro-oncogenic role of HSF1 [69,271], suggesting that cancerous cells are enduring chronic proteotoxic stress [278]. Accordingly, cancerous cells become dependent on HSF1 for their growth and survival even in the absence of environmental stress, a phenomenon referred to as "HSF1 addiction of cancer" [279]. Of note, HSF1 is dispensable for non-cancerous cells under normal conditions. Furthermore, HSF1 is often overexpressed

in human cancers and correlated with poor prognosis [280,281]. Collectively, a large body of evidence has strongly suggested HSF1 as a promising anti-cancer therapeutic target.

Whereas NDDs and cancer are two seemingly unrelated pathologies, intriguingly, they do share certain features, one of which is proteomic instability. As an indicator of severe proteomic instability, amyloid aggregates are intimately associated with NDDs in humans, particularly in AD [282,283]. Despite its evident implication in NDDs, it remains largely unknown whether amyloidogenesis also occurs in human cancers. Of great interest, it was shown that HSF1 represses amyloidogenesis in cancer cells; and, importantly, amyloidogenesis is tumor suppressive [284]. These findings not only illuminate the new phenomenon of "tumor-associated amyloidogenesis" but also uncover a previously unrecognized mechanism underlying the pro-oncogenic role of HSF1.

Then, how does HSF1 repress amyloidogenesis? Contrary to the widely presumed mechanism, namely induction of HSP expression, our recent study using tissue overgrowth models, driven by oncogenic AKT signaling, uncovered that HSF1 acts as a direct anti-amyloid factor [285]. HSF1, unexpectedly, physically interacts with soluble AβOs. Numerous studies in NDDs have indicated that soluble AβOs, the intermediates of insoluble amyloid fibril assembly, are highly toxic to synapses [285]. By binding to AβOs, HSF1 impedes the assembly of amyloid fibrils (AFs); more importantly, it neutralizes AβOs and thereby protects the essential mitochondrial chaperone HSP60 from the attack by AβOs. In the absence of HSF1, AβOs cause the misfolding, degradation, as well as aggregation of HSP60, leading to mitochondrial proteomic instability and, ultimately, causing apoptosis and mitophagy. Moreover, heightened protein translation owing to AKT hyperactivation is causally related to amyloidogenesis. Taken together, these findings suggest amyloidogenesis as a checkpoint mechanism that constrains uncontrolled growth and preserves tissue homeostasis, consistent with its emerging tumor-suppressing role [285].

Surprisingly, the very same molecular mechanism seems to be conserved in human AD. Proximity ligation assays unequivocally detected AβOs-HSP60 interactions in human AD brains, but not in age-controlled normal brains. In human AD brain lysates, AβOs were found to interact with both HSF1 and HSP60, suggesting that at this late stage of the disease AβOs already overwhelmed HSF1 and started attacking HSP60. Furthermore, adding recombinant HSF1 proteins into those brain lysates largely disrupted AβOs-HSP60 interactions; instead, AβOs interacted with recombinant HSF1 proteins. Resembling the finding in the brain overgrowth model, HSP60 proteins were Lys48 polyubiquitinated and diminished in human AD brain lysates. Similar changes were also found in HSF1 proteins, revealing deficiencies of both HSP60 and HSF1 in human AD brains. These changes in both HSP60 and HSF1 are congruent with the detrimental impacts resulting from their direct interactions with AβOs.

The direct anti-amyloid effects of HSF1 were demonstrated in *in vitro* $A\beta_{42}$ fibrillation assays [285]. A panel of recombinant HSPs, just like the negative control Glutathione-S-transferase (GST), did not impede the formation of $A\beta_{42}$ fibrils; by stark contrast, recombinant HSF1 proteins did even at a 1:1 molar ratio. At a 1:4 molar ratio, HSF1 proteins nearly completely blocked the $A\beta_{42}$ fibrillation, an effect further visualized by transmission electron microscopy. Distinct from its impacts on amyloid fibrils, HSF1 proteins stabilized but not abolished AβOs, suggesting that HSF1 specifically binds to AβOs rather than $A\beta_{42}$ monomers. In accordance with its direct anti-amyloid effects, lentiviral overexpression of a transcription-deficient HSF1 mutant, which lacks the C-terminal transactivation domain, was able to block the attack on endogenous HSP60 by transfected $A\beta_{42}$ peptides in cultured primary human neurons, thereby averting the $A\beta_{42}$-induced neurotoxicity. As expected, these HSF1 mutants themselves interacted with $A\beta_{42}$ in neurons.

In sum, tissue overgrowth, cancer, and NDDs all converge on amyloidogenesis. By countering amyloidogenesis, HSF1 enables tissue overgrowth and cancer but antagonizes neurodegeneration. Thus, the anti-amyloid action of HSF1 may have therapeutic potential for both cancer and NDDs.

Current knowledge gaps and challenges of targeting HSF1 in NDDs

Revisiting the concept of blunted neuronal HSR: Neuronal HSR is generally accepted to be intrinsically blunted, a statement largely based on the relatively weak response measured by *Hsp70* induction in cultured rat or mouse neurons compared to other cell types (astrocyte) after heat shock treatments [286–289]. The relative HSR has also been more studied in several mouse models of HD and ALS with prominent non-cell autonomous disease mechanisms, revealing differential roles of neurons and astrocytes in response to mis-aggregated proteotoxic stress as detailed in a recent review [212]. However, the HSR in the brains of other NDDs was relatively unstudied.

Detecting neuronal HSR in vivo: It should be noted that, over the last three decades, the "gold standard" for measuring HSF1 transcriptional activity has been determined by the promoter binding assays of *Hsp70* (e.g., Luciferase-reporter, EMSA, and ChIP). The results only reflect HSF1 regulation on one *Hsp* gene, albeit the most important one for the HSR. The initial findings from three decades ago showing promising neuroprotective HSR against glutamate-induced excitotoxicity (i.e., *Hsp70* mRNA and 72/83-kDa HSP) in cultured primary neurons pre-treated by heat shock [290,291] should be revisited using *in vivo* paradigms to determine HSF1's potential prominent role in this process. Using a fluorescent *Hsp70* reporter mouse [292], differential induction of the iHSP70 expression was detected *in vivo* after injecting mice with a CNS-permeable HSP90 inhibitor [101]. As shown by both Western blotting analysis and using the fluorescent reporter mice (Figure 4A and B). Indeed, the iHSP70 response was weaker in the hippocampus than in the liver, a phenomena reported in in vitro comparison between primary neuronal culture with non-neuronal cell lines [293]. Of note, the *in vivo* induction of iHSP70 response was detected most notably in the hippocampal CA1 (CA1-a, in particular) [294], a subregion critical for cognitive learning and memory.

Paradoxically, several reports from Bates' group using multiple semi-quantitative measures indicate inconsistent results. suggest competent neuronal HSR throughout an entire aging process in mouse brain in response to heat shock or HSP90 inhibition [295] as well as in MSNs compared to that of astrocytes and oligodendrocytes [296]. On the other hand, the HSR was reportedly impaired in the mouse brain of HD [297] which involved both HSF1-dependent and -independent mechanisms [298]. Heat shock and other stresses likely induce different levels of HSPs and HSR depending on cell types. The regional and cell-type specific HSR should be further characterized in the future in mouse brains using various diseased models for comparison.

In reshaping chromatin structural landscape and in epigenetic regulation: The same Bates' group also first reported altered chromatin architecture in a mouse model of HD, as the result of progressively impaired HSR [207]. Epigenetic regulation of gene expression

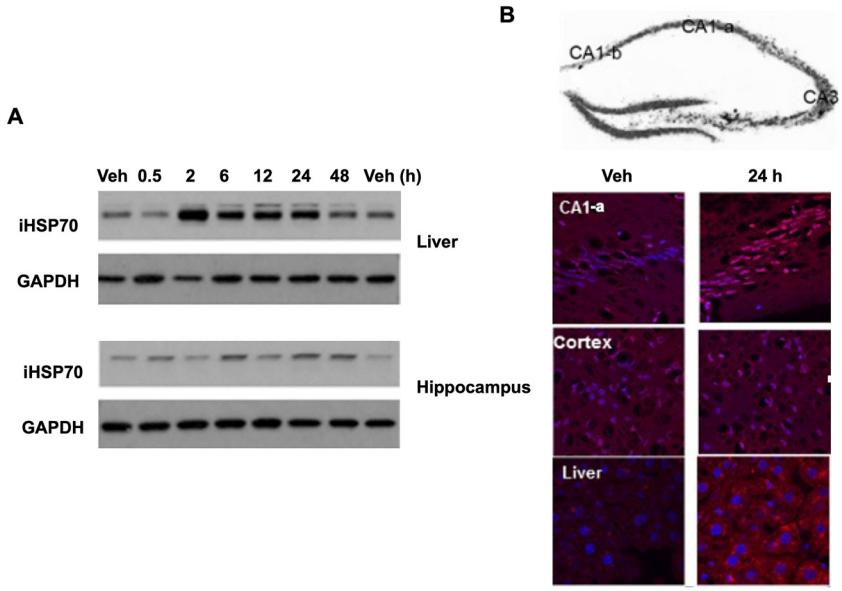

Figure 4. (A) Western blots of iHSP70 induction from mouse tissue after a single i.p. injection of a CNS-permeable HSP90 inhibitor. (B) Confocal microscopic images of the mouse brain sections taken from the HSP70-reporter mice at 24 h after injecting (i. p.) the CNS-permeable HSP90 inhibitor [294]. Data presented in this Figure were published in Wang et al., 2017 [101, 294], and are reorganized and reused with permission.

has been recognized as a crucial mechanism in both physiological and pathological brain processes [299], underlying stress-mediated alteration of the brain [296] concerning cognition [300]. Epigenetic mechanisms, including DNA methylation and histone modifications, altered chromatin structure, and the accessibility of DNA, have been increasingly reported in aging and cognitively declined brains [301]. Furthermore, small non-coding RNA (e.g., microRNA/miRNA) bind to messenger RNA (mRNA) to regulate translation which can be dysregulated during aging and NDDs. It was recently reported that HSF1 fails to bind to the *hsp70* promoter in cortical neurons during heat shock and, and the *hsp70* promoter is less accessible in neurons compared to non-neuronal cells due to histone deacetylases repression [293]. Based on these findings, we speculate that neurons, particularly in the aging brain, are more vulnerable than other cell types to disruptions in epigenetic regulation. Furthermore, the disrupted epigenetic regulation likely involves dysregulated and dysfunctional HSF1 which can lead to impaired neuronal function, cognitive decline, and increased susceptibility to neurological disorders [302]. This is a plausible hypothesis awaiting to be proven.

A major obstacle to treating NDDs is our lack of fuller understanding of the molecular mechanisms underlying the selective neuronal vulnerability in each disease. Vulnerability is a complex feature and likely results from multiple genes altered in the selectively affected neurons, in addition to the particular neuronal and glial environment surrounding these neurons. Using cell-type specific profiling techniques, and systems-level functional genomics, researchers from The Rockefeller University headed by the late Paul Greengard has identified 7 specific brain regions conserved between mouse and human vulnerable to AD neuropathology, as well as the conserved resistant neuronal types [303]. These regions are most relevant to the "stressed synapses", a concept proposed by the team led by the late Bruce McEwen [304]. Those findings justify the high relevance of our future research focusing on the hippocampal CA3-CA1, entorhinal cortex, and Dentate Gyrus (DG) in the context of AD-relevant synaptic failure. Although the glutamatergic pyramidal neurons of the hippocampus are highly vulnerable to damage in both age-related cognitive decline and in AD [305], other cell types, including neuronal subtypes should also be included in our future studies. Given the crucial roles of HSF1 and the co-chaperones/HSPs in harnessing the synaptic proteostasis [41,306], we believe that it is imperative to fully evaluate the HSF1 transcriptional activity based on genome-wide approaches (e.g., ChIPseq and RNAseq) in future studies. So far, research on *in vivo* CNS screening of HD disease-related human and murine genes is ahead of other NDDs, linking gene pathways of genome stability, including DNA maintenance and mitochondrial functions as well as proteostasis [307–309]. Results from these studies shall greatly facilitate new HD therapeutic target pathways.

CONCLUSIONS AND PERSPECTIVES

Chaperones are crucial in the process of maintaining cellular proteostasis. HSPs are of paramount importance in synaptic proteostasis, and thus in maintaining synaptic fidelity and plasticity [41,205]. As the master regulator of chaperone gene transcription, HSF1's roles in these two processes are fundamental for brain CNS health, and are highly implicated in NDDs. This was supported by strong CNS phenotypes displayed in multiple lines of *Hsf1*-null mice.

Despite numerous reports on the potent neuroprotective actions of iHSP70 and activated HSF1 via HSP90 inhibitors in degrading misfolded protein aggregates during NDDs, the success is largely limited to *in vitro* cultured cellular models. Lacking *in vivo* success is largely due to intrinsically blunted neuronal HSR which can be a fundamental mechanism underlying neurodegeneration. The recently emerged compelling evidence for HSF1 as a critical transcription factor for a number of non-*Hsp* genes directly involved in synaptic plasticity (e.g., immediate early genes/IEGs, *Dlg4* and *Bdnf*) underscores the paramount importance of this master stress responsive transcription factor in regulating synaptic plasticity via orchestration of gene expression with the principle CREB.

As illustrated in the graphical abstract (Figure 5), while HSF1's roles in the direct regulation of several synapse-related genes are

emerging, our journey of understanding the multifaceted roles of HSF1 in the CNS has just begun, especially concerning the process of normal aging and NDDs (accelerated aging). Currently, the lack of a comprehensive characterization of HSF1 in aging mouse brains and in the brains of NDDs, along with neuronal HSR response compared to other cell type contributions in a brain region-specific manner in response to various stressors represents a severe knowledge gap; genome-wide synaptic transcriptomes await to be determined in mouse brains in various acute and chronic stress models (e.g., NDDs models). A fuller in-depth mechanistic understanding of the HSF1-mediated neuroprotection also requires further studies using deep omics approaches to mouse brain tissue (e.g., single-cell scRNAseq and proteomics). In addition, how HSF1 is dysregulated during aging and neurodegeneration in mouse brains requires further characterization using systems biology approaches, at both gene and protein levels, in a region- and cell type-specific manner. Recent advances in several cutting-edge technologies render opportunities and feasibility for new findings [310–313]. Lastly, using advanced mouse genetics of brain cell type-specific knock-out of *Hsf1* mice can facilitate further clarification of the potential contributing epigenetic regulation to the neuronal HSR in different diseased settings in the future.

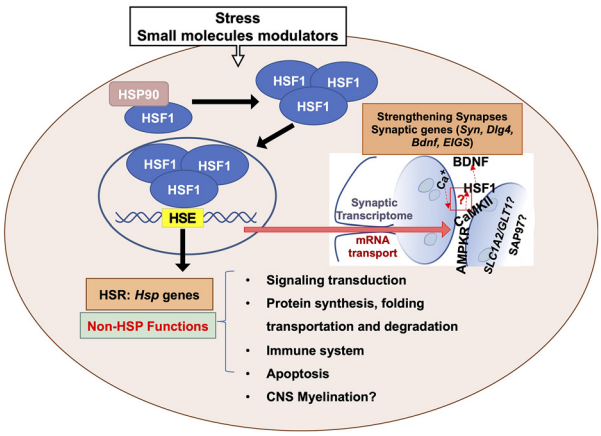

Figure 5. Graphical Abstract.

AUTHOR CONTRIBUTIONS

Conceptualization, methodology, software, validation, formal analysis, investigation, resources, and data curation: F. F. L., generated the structural framework and wrote the manuscript with K. S. and C. K. D. contributed partially to the writing: K. S. contributed to the BDNF and synaptic plasticity, and the section of exercise/EET, and C-K D contributed to the section of cancer and NDDs. All authors read and approved the final manuscript.

Project administration and funding acquisition, F. F. L. All authors have read and agreed to the published version of the manuscript.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

DECLARATIONS

Not applicable.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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