Title
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Publication Date
2020

DOI
10.1016/j.neulet.2019.134642

Peer reviewed

Neuroscience Letters 715 (2020) 134642

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Review article

Heat shock protein signaling in brain ischemia and injury

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ARTICLE INFO

Keywords:
Heat shock protein 70
Cerebral ischemic stroke
Traumatic brain injury
Neuroprotection
Pharmacological induction

ABSTRACT

Heat shock proteins (HSPs) are chaperones that catalyze the refolding of denatured proteins. In addition to their ability to prevent protein denaturation and aggregation, the HSPs have also been shown to modulate many signaling pathways. Among HSPs, the inducible 70 kDa HSP (HSP70) has especially been shown to improve neurological outcome in experimental models of brain ischemia and injury. HSP70 can modulate various aspects of the programmed cell death pathways and inflammation. This review will focus on potential mechanisms of the neuroprotective effects of HSP70 in stroke and brain trauma models. We also comment on potential ways in which HSP70 could be translated into clinical therapies.

1. Introduction

The brain undergoes a stress response after cerebral ischemia (CI) and traumatic brain injury (TBI). One of the most highly upregulated stress proteins are the heat shock proteins (HSPs). These proteins were so named, as they were noted to be highly induced by heat stress. They are a family of proteins identified by their molecular weight, and possess chaperone functions for which they have been described to assist in protein folding, protein degradation and other related activities. Under conditions of cell stress or injury, these actions protect the cell by preventing the aggregation of damaged proteins and promote the assembly of nascent proteins. HSP70, in concert with its co-chaperone HSP40, is a key HSP family member involved in the degradation of damaged proteins [1]. In acute brain injury models, many studies have reported that in addition to typical chaperone functions, HSP70 interrupted multiple cell death pathways, such as classical apoptosis, necrosis, and inflammation [2,3]. HSP70 has now been shown to interrupt several of these pathways and ultimately leads to improvements in neurological outcome [4]. We will discuss the mechanism of HSP70 neuroprotection in brain injury along with potential pharmacological means of applying HSP70 at the clinical level.

2. Heat shock proteins

At the onset of brain injury, synthesis of most cellular proteins is downregulated. However, there is a small class of proteins which are actually upregulated and have collectively been referred to as stress proteins. HSPs are named in accordance with their molecular mass. The constitutive HSPs perform cellular housekeeping functions and include HSP90, HSP40 and HSP70 [5]. Inducible forms include inducible HSP70 has also been referred to as HSP70i or HSP72, but here we will refer to it as HSP70. Inducible HSPs are upregulated in response to cell stress, including thermal, ischemic and traumatic stresses to the tissue. While previously debated whether their upregulation reflected cell stress, or actively represented a cytoprotective mechanism, work over the past few decades now indicate that HSPs represent the latter [6]

In the brain and in cultures of brain cells, heat and ischemic stress have been shown by several labs to trigger robust induction of HSP70 [7]. As such, HSP70 has been the most widely studied stress protein in terms of its neuroprotective properties. HSP70 interacts with hydrophobic peptide segments of unstructured proteins in an ATP-dependent manner. HSP70 also contains a C-terminal substrate-binding domain which identifies unstructured polypeptide segments, and an N-terminal ATPase domain which assists in protein folding, alternating between an ATP-bound open state with low substrate affinity and an ADP-bound closed state with high substrate affinity [8]. In studies of CI, HSP70 was first observed to be induced in brain regions that were relatively resistant to ischemic insults. Thus, the notion of a 'molecular penumbra' was introduced, and raised questions as to whether this expression was an epiphenomenon of the injury, or an active participant in cell survival [9]. By showing that specifically increasing HSP70, several labs have shown that Hsp70 protects the brain and brain cells against

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https://doi.org/10.1016/j.neulet.2019.134642
Received 18 July 2019; Received in revised form 16 November 2019; Accepted 19 November 2019
Available online 20 November 2019
0304-3940/ Published by Elsevier B.V.

experimental brain insults including CI and TBI [4,10–13]. Conversely, downregulation of HSP70 results in the opposite. Consistent with its chaperone functions, induction of HSP70 has also been shown to reduce protein aggregation and the development of intracellular inclusions, while preventing the redistribution of ubiquitin [14,15]. HSP70 has also been shown to mediate cytoprotection by interfering and regulating apoptotic and immune pathways.

3. Heat Shock Protein 70 induction and the unfolded protein response

HSP70 induction occurs though the activity of heat shock factor 1 (HSF1), which is a transcription factor that binds to HSP70's 5'promoter region, as well as that of all HSP genes [16]. HSPs are normally located intracellularly and are bound to HSF1 under homeostatic conditions [17]. When the cell experiences stress, such as trauma, ischemia, and other denaturing stimuli which lead to unfolded proteins, HSPs dissociate from HSF, thus allowing HSPs to bind denatured or aggregated proteins. HSPs are also capable of binding other proteins involved in cell death pathways. Following such stresses, dissociated HSF translocates to the nucleus where it is phosphorylated by protein kinase C, and forms activated trimers. These trimers then bind to heat shock elements (HSEs), which are DNA sequence motifs present within the heat shock gene and are recognized by HSFs. Once HSFs bind to HSEs, more synthesis of HSP70 protein occurs [16]. HSP90 acts as an inhibitor of HSP70 induction, as HSP90 is normally bound to HSF1 in the resting state. During the stress response, HSP90 dissociates from HSF1, thus liberating it to bind HSEs with subsequent upregulation of HSP70 [18].

HSP70 protein, once synthesized in high quantities following the initial stress response, acts in concert with HSP40, HSP90 and ATP to restore denatured proteins to their property tertiary architecture. These proteins form a complex which binds denatured proteins and, through chaperone functions, lead to their repair and refolding. This occurs through several cycles whereby the chaperone complex attempts to refold the protein. HSP70 acts indirectly through its cochaperones CHIP (C-terminus of HSP70/HSC70 interacting protein) and BAG-1 (Bcl-2–associated athanogene-1) [19]. CHIP is a ubiquitin ligase that interacts with HSP70 and sequesters and ubiquitinates unfolded proteins, followed by their degradation [20]. CHIP may also enhance HSP70 induction under conditions of cell stress, thus maintaining protein homeostasis by regulating chaperone levels [21]. BAG-1 is another HSP70 cochaperone involved in protein degradation. CHIP and BAG-1 interact directly, and their co-expression increases protein degradation [22]. Therefore, these proteins act together to shift chaperone activity from protein folding to protein degradation. [23–25]. Hsp90 also plays a role in protein degradation, although its actions are opposite those of HSP70, where HSP90 seems to inhibit substrate ubiquitination and degradation [26,27].

4. HSP70 in CI and TBI

HSP70 induction has been shown to confer neuroprotection against many acute brain insults, of which we will largely focus on CI and TBI. HSP70 upregulation has been achieved in experimental studies through the use of genetic models that either overexpress or are deficient in HSP70. HSP70 can also be manipulated via viral vector-mediated HSP70 overexpression, siRNA-mediated downregulation or induction via the application of sublethal heat stress. Many experimental studies have now established that HSP70 induction led to neuroprotection in variety of acute neurological injuries.

Cessation or reduction of cerebral blood flow followed by reperfusion of neural tissue initiates an array of signaling pathways, including excitotoxicity to apoptosis, all of which ultimately lead to cellular damage and death. Under non stressful, homeostatic conditions, very little inducible HSP70 is present; however, it is robustly increased following injury, and is perhaps the most highly induced proteins expressed in response to such stress. Early studies showed a correlation between HSP70 overexpression and neuroprotection. In experimental stroke models, initial HSP70 induction was observed within neurons of the penumbra [9], or brain regions immediately adjacent to the infarct, and thought to be likely to survive CI. This was followed by HSP70 induction within astrocytes and microglia as well as endothelial cells of the cerebral vasculature [9], cell types which have been thought to be more resistant to CI compared to neurons. Thus, HSP70 was thought to play a role in protecting cells from ischemic insults compared to cells and brain regions where HSP70 expression was lower or absent. On the other hand, critics of this model have argued that HSP70 may simply be a marker of stressed cells with nothing to do with saving the cell from a likely death. However, when HSP70 was overexpressed in neurons and astrocytes using viral vectors, HSP70 overexpressing neurons and astrocytes were more resistant to ischemic and ischemia-like insults [8]. Similarly, transgenic mice that overexpressed HSP70 in the brain had better neurological outcomes following experimental CI and TBI compared to wildtype mice. Conversely, HSP70 deficiency worsened outcome in similar models [10,28]. Further, three different studies in wildtype animals were given HSP70 protein in an attempt to boost brain levels [29–31], and in each of these studies, animal subjected to stroke and treated with HSP70 had better functional and histological outcomes.

With many similarities to CI, TBI causes mechanical damage to brain cells and their vessels. This mechanical damage triggers cell death cascades which takes place over the ensuring hours or days [32–34]. TBI pathophysiology has substantial overlap with that seen in stroke, including oxidative stress, excitotoxicity, neuroinflammation and edema. In TBI models, several studies showed a neuroprotective effect of HSP70. Our lab reported that transgenic mice overexpressing HSP70 and subjected to experimental TBI via controlled cortical impact (CCI), had better neurological outcomes compared to wildtype controls [4]. Conversely, HSP70 deficient mice had worse outcomes compared to both wildtype and HSP70 transgenic mice. Further, HSP70 overexpression not only led to smaller lesions sizes and better neurological function, it also reduced the extent of brain hemorrhage and blood brain barrier (BBB) disruption. The reduction in BBB damage and hemorrhage correlated to suppression of MMP-2 and -9 [4,35]. A related study in a model of neurodegeneration similarly showed that HSP110 or HSP70 deficient mice had worse outcomes compared to wildtype, while treatment with HSP70/HSP110 inducers Celastrol and BGP-15 improved neurological outcome [36]. HSP70 overexpression also protected against brain contusion, edema, neuronal apoptosis, and neurological motor deficits in a rodent hemorrhagic shock model with carotid occlusion [37].

Not all studies showed beneficial effects of HSP70 in acute neurological injury models. An early study from our laboratory showed no effect of HSP70 overexpression in a transgenic mouse model of stroke, although it did protect astrocytes derived from the same mouse strain [38]. It should be noted that this particular HSP70 transgenic model had somewhat lower levels of HSP70 overexpression (approximately 2.5 times higher than wildtype controls) compared to other transgenic models where HSP70 overexpression was at least ten fold higher [39,40]. HSP70 has also not been shown to improve outcomes in other neurological conditions such as the synucleinopathies which are thought to cause Parksinson's disease and related conditions [41,42]. Further, as elaborated in more detail below, extracellular HSP70 has the potential to worsen outcomes from stroke, as it is known to act on the pro-inflammatory Toll-like receptor-4 (TLR4). In fact, in a related model of retinal ischemia-reperfusion injury, extracellular HSP70 was identified as a factor which promoted inflammation-induced retinal neuron death [43]. Thus, the beneficial properties of HSP70 may be limited by the levels to which it can be increased, the nature of the insult or disease as well as the compartment in which it acts.

HSPs have also been shown to interfere with specific cell death pathways, of which programmed cell death (apoptosis) and

inflammation have been the best studied. The precise mechanism by which HSPs modulate these pathways is unclear, but may simply bind stressed or stress-associated proteins in an indiscriminate and parallel manner, as these actions occur within similar time frames and similar brain regions. The following sections will review how HSPs have been shown to modulate these pathways.

5. Heat shock protein 70 interrupts several cell death signaling pathways

In addition to its classic chaperone functions related to protein folding and aggregation, HSP70 has been shown to directly interfere with multiple cell death pathways. After brain injury, apoptotic or programmed cell death has been observed in parallel with necrosis. In CI, the best studied pathways include the intrinsic apoptotic pathway, which occurs within the cell's mitochondria [44], and the extrinsic pathway, which is initiated by ligand interactions at surface receptors [45]. In CI and TBI, apoptosis occurs following reactive oxygen species signaling, death receptor ligation, genomic damage, protease activation and others. Many studies have now documented that HSP70 directly or indirectly interferes with both pathways.

The intrinsic apoptotic pathway originates from mitochondrial stress/damage due to the acute brain insult. Following brain injury, mitochondria release cytochrome c, which combines with caspase-9 to form the apoptosome, followed by activation of executor caspases causing apoptotic death. Apoptosis may also proceed through a caspase-independent pathway which is initiated when injured mitochondria release apoptosis inducing factor (AIF). The Bcl-2 family members differentially affect this pathway through direct interaction with cytochrome c and AIF release. Bcl-2 family members include three subgroups: the anti-apoptotic proteins (Bcl-2, Bcl-XL, and Bcl-w), the pro-apoptotic proteins (Bax and Bak), and the BH3-only proteins (Bad, Bid, Bim, Noxa, and PUMA). Bcl-2 family members participate in both deaths promoting and death salvaging activities. BH3-only proteins lead to brain cell death following ischemic insults through interactions with other Bcl-2 proteins [46]. HSP70 interferes at multiple points within the intrinsic apoptotic pathway. It interacts with several proteins of the apoptosis cascade, both upstream [47,48] and downstream of the mitochondria [49]. In experimental stroke, HSP70 interrupts cytochrome c translocation from the mitochondria to the cytosol [35,50] and AIF translocation from the mitochondria to the nucleus. In a cell free system, HSP70 interfered with recruitment of procaspase-9 and apoptosis protease activating factor-1 (Apaf-1) into the apoptosome [51]. HSP70 similarly prevented mitochondrial release of another pro-apoptotic protein, Smac/DIABLO [52]. The mitochondrial HSPs, HSP70, HSP75 and mortalin assistants which function by maintaining mitochondrial membrane potential, preserve mitochondrial function and protein import [53]. In a model of HSP70 protection in astrocytes, HSP70 was also correlated to higher ATP levels [54] along with reduced oxidative stress and preserved mitochondrial membrane potentials [55] and glutathione [56,1]. In a related study of myocardial ischemia, overexpression of HSP70 was found to reduce oxidative stress by increasing mitochondrial manganese superoxide dismutase (SOD2) [57].

Bcl-2 is central to preventing intrinsic apoptosis, as it blocks mitochondrial release of cytochrome c and AIF. HSP70 increases levels of Bcl-2 in some disease models, including ischemic neurons [17]. Some investigators have proposed that the balance between Bcl-2's pro- and anti-apoptotic members determines whether cells undergo apoptosis or survival [58]. Thus, it is conceivable that HSP70 overexpression could decrease apoptosis upstream of mitochondria via increased Bcl-2 levels. As such, HSP70 has been shown to reduce heat shock-induced apoptosis by blocking translocation of pro-apoptotic Bax from the cytosol to the mitochondrial where it aids in forming the mitochondrial transition pore (MTP) [48], and the MTP is opposed by anti-apoptotic Bcl-2. Incorporation of Apaf-1 into the apoptosome is required for caspase-9 activation, and HSP70 has been shown to interfere with this [51], although this has not been consistently demonstrated [47].

The extrinsic apoptotic pathway, which relies on the engagement of receptors located on the cell's surface, is also referred to as the "death receptor pathway". Ligation of these so-called death receptors leads to caspase-8 and caspase-10 activation, which triggers a cascade that ultimately leads to activation of effector caspases, particularly caspase-3 [59]. Several such death receptors have been identified, but the most widely studied in brain ischemia and injury include tumor necrosis factor receptor (TNFR) and Fas (also known as CD95). These receptors are bound by their respective ligands TNF (and related TNF family molecules) and fas ligand (FASL) [60]. FasL initiates apoptosis by binding to Fas, followed by the recruitment of its adaptor protein Fas-associated death domain protein (FADD). FADD then binds procaspase-8 at its death effector domain thus forming a 4 molecule complex that is referred to as a death-inducing signaling complex (DISC). The DISC leads to activation of procaspase-8 to caspase-8 followed by activation of caspase−10, which in turn activates effector caspase-3 [61].

HSP70 has also been shown to interact with this extrinsic death receptor pathway at several levels. It can prevent receptor-mediated apoptosis through its ability to bind death receptors TNF-related apoptosis-inducing ligand-I (TRAIL-RI, also known as death receptor-4 DR4) and TRAIL-RII (also known as DR5). When TRAIL-RI and TRAIL-RII are bound by its ligand TRAIL, TNF-related apoptosis occurs, but HSP70 has been shown to interrupt receptor binding as well as DISC formation [62,63]. Downstream of DISC formation and caspase 8 activation, HSP70 can prevent apoptosis by inhibiting BID activation [64]. Recently, it has been shown that dynamin, a GTPase involved in endocytosis, can also traffic Fas via the endoplasmic reticulum to the cell's surface [65]. Once expressed on the cell surface, Fas can trigger apoptosis when bound by its ligand FasL. We recently showed that HSP70 may prevent movement of Fas from the cytosol to the cell surface by interacting with both dynamin and Fas, and that overexpression of HSP70 as well as dynamin inhibition improved neurological outcome in CI [10]. Thus, HSP70 appears to affect both apoptotic pathways at multiple points in the cascades.

6. Heat shock protein 70 modulates inflammation

Inflammation follows both CI and TBI, and begins with activation of the brain's immune cell, or microglia. This is soon followed by an influx of circulating leukocytes into the injured brain [66–68]. Once activated, these immune cells elaborate several cytotoxic agents such as reactive species, cytokines, glutamate and proteases, all of which have been implicated in exacerbating cell death [69]. Following brain injury, HSP70 has been shown to regulate inflammation via pro- and anti-inflammatory mechanisms depending on its location within or outside of the cell. When HSP70 is intracellular, it seems to inhibit immune responses, whereas extracellularly, it seems to potentiate them.

Its anti-inflammatory activities include its ability to inhibit transcription and translation of immune molecules. HSP70 has been shown to interact with and inhibit activation of the pro-inflammatory transcription factor nuclear factor-kappaB (NF-kB) and its target genes. It has also been shown to prevent processing of matrix metalloproteinases (MMPs) to their active form. Intracellular overexpression of HSP70 by genetic manipulation or induction by heat stress has been shown to reduce production of nitric oxide and expression of inducible nitric oxide synthase (iNOS) while decreasing NF-kB activation [70]. Heat stress, which induces HSP70, has also been correlated to decreased secretion of proinflammatory cytokine TNF-α and reduced generation of reactive oxygen species (ROS). HSP70 induced in macrophages has similarly been shown to inhibit responsiveness to inflammatory cytokines TNF-α and interleukin (IL)-1, IL-10 and IL-12 [71,3,72]. In line with these observations, HSP70 induction in a model of intracerebral hemorrhage decreased TNF-α expression, preserved blood brain barrier (BBB), reduced brain edema, and improved neurological function [73].

HSP70 induction by heat stress in phagocytes also inhibited NADPH

oxidase (NOX) activity in neutrophils with subsequent reduction of superoxide. It also enhanced expression of superoxide dismutase (SOD), an endogenous superoxide scavenger. In a similar model of heat stress [74], HSP70 induction inhibited phosphorylation of inflammatory transcription factors or their partner molecules IkB, JNK and p38. HSP70 induction also blunted the ability of DNA to bind transcription factors, such as NF-kB, activator portien-1 and signal transducer and activator of transcription factor 1 (STAT-1), and led to the down-regulation of several pro-inflammatory genes [75]. Other studies have also shown that prior-heat stress leads to the inhibition of the inflammatory response, and this inhibition was associated with upregulation of HSP70 and decreased nuclear NF-kB translocation [76,77]. HSP70 was shown to interact with inhibitor of kB (IkB) by preventing its phosphorylation, thus inhibiting NF-kB by preventing its dissociation from it [78]. Other studies have shown that HSP70 inhibits NF-kB by directly binding it and its regulatory proteins in stroke and neuroinflammation models [40,79]. How HSP70 inhibits NF-kB may depend on the nature of the stimulus. When pro-inflammatory cytokine TNF-α was used to induce cell death, HSP70 directly inhibited the IkB kinase (IKK), the kinase which phosphorylates and activates IkB [80]. However, in a stroke model, HSP70 directly associated with NF-kB and IkB, and prevented IkB phosphorylation by IKK in an indirect manner [40]. In both studies, NF-kB inhibition by HSP70 led to downstream reduction in both transcription and translation of NF-kB's target genes, and led to neuroprotection. One such gene inhibited by HSP70 and also regulated by NF-kB is MMP-9. Cultured astrocytes overexpressing HSP70 exposed to ischemia-like insults had reduced MMP-9 mRNA, and is consistent with the notion that HSP70 regulates inflammation at the transcriptional level [81]. However, HSP70 overexpressed in astrocytes also decreased MMP-2 expression, which is not regulated by NF-kB [81]. MMP-2 is known to be regulated by STAT-1 [82], which HSP70 and heat stress are also known to inhibit [75,83]. HSP70 also seems to act at the post translational level where it was found to inhibit processing of MMPs to their active forms. Another report further linked HSP70 to neuroprotection via the micro RNA miR-122 [84]. In this study, a beneficial effect of miR-122 was observed in experimental stroke, and this depended on HSP70's ability to inhibit NF-kB. Thus, HSP70 can interrupt inflammatory signaling and inflammatory molecules at multiple levels.

Extracellular HSP70 has also been shown to modulate immune responses, but in a manner opposite to intracellular HSP70 [85]. In the extracellular environment, HSP70 appears to potentiate at immune responses. In models of adaptive immunity, exogenous administration of HSP70 in culture or immunization of mice was shown to potentiate T-cell responses indicating that HSP70 acts as an immune adjuvant [86] [87]. Extracellular HSP70 can also interact with the receptors on macrophages and dendritic cells, and aid in antigen presentation [88]. In addition to adaptive immune activities, extracellular HSP70 has also been shown to participate in innate immune activities. It has been shown to interact with microglia and macrophages through Toll-like receptors (TLRs). Some work has shown that HSP70 can bind TLRs and activate NF-kB [89]. HSP60 and HSP90 have also been shown to interact with TLR2 and TLR4 [90]. However, some of this latter work may have resulted from preparations of recombinant HSPs containing low levels of endotoxin, which can also TLR4 [91]. However, there are no published works of extracellular HSPs in CI or TBI.

7. Pharmacological therapy of heat shock protein 70 in brain injury

While many laboratory studies of neuroprotection by HSP70 have largely used genetic manipulation to upregulate the protein, pharmacological means of inducing HSP70 would have wider translational relevance. A few studies have explored the pharmacological induction of HSP70 in focal and global CI models [92,93] and experimental TBI [94,92,93]. The majority of approaches used Hsp90 inhibitors, which, by liberating HSF, upregulated HSP70. The most studied of these has been geldanamycin (GA), which has been shown to both induce HSP70 in the brain and lead to better neurological outcomes from experimental stroke. However, GA has since been found to be less than ideal for clinical translation due to hepatoxicity [95]. As such, GA analogue 17-allylamino-17-demethoxygeldanamycin (17-AAG) has been shown to have similar HSP90 inhibitory functions with less toxicity. 17-AAG has been studied in clinical trials through IV administration for cancer therapy [95,96]. Work from our group has shown that when 17-AAG is given parenterally, it causes HSP70 induction in the brain, and leads to similar beneficial effects in experimental TBI as seen in HSP70 overexpressing mice. 17-(2-dimethylaminoethyl) amino-17-demethoxygeldanamycin (17-DMAG), also a GA derivative, is thought to have wider tissue distribution, and was studied in an experimental stroke model where it was shown to improve neurological outcome through HSP70 induction. The beneficial effect was also correlated to reduced inflammation through inhibition of microglial activation and phosphorylation NF-kB's inhibitor protein IkB [97].

Other HSP70-inducing compounds include the purine-based compounds, the resorcinols. While this class has been studied for cancer treatment, and a few have moved to clinical trial, none have been studied in brain injury models to date [96,16]. A few studies have been carried out in stroke models with another HSP70 inducer, geranylgeranylacetone (GGA), previously studied for treatment of gastric ulcers. Administration of GGA in experimental stroke showed similar beneficial effects and this was associated with an anti-inflammatory effect through up-regulation of HSP70 by inducing protein kinase C [98,99]. In a TBI model, pretreatment with GGA similarly led to a neuroprotective effect by reducing neuronal apoptosis and inhibiting microglial activation [100]. As GGA may be the best tolerated of the HSP70 inducing drugs, this approach may be the most promising as far as translating a treatment to patients suffering stroke or TBI.

While most pharmacological approaches that have been studied in humans for other indications have focused on HSP90 inhibitors to upregulate HSP70, there are other approaches that deserve investigation. Other partners in the HSP pathways have the potential to be targeted. For example, small molecules to act as HSF mimics could be used to pharmacologically upregulate HSP70, rather than relying on sufficient endogenous HSFs to stimulate HSP70 production. A limitation to current HSP90 inhibitors and other means of inducing HSP70 as it pertains to acute neurological diseases is that generation of HSP70 protein may take hours to produce, and it is well known that very early intervention increases the likelihood of a good outcome. Administering recombinant HSP70 protein itself would circumvent this time sensitive problem. In fact, a few preclinical studies of stroke delivered HSP70 protein by conjugating it to carrier molecules to facilitate brain penetration after parenteral administration [29–31]. In one report, HSP70 was conjugated to the brain penetrating HIV TAT protein [29], while in another, HSP70 was conjugated a fragment of an anti-DNA antibody (mAb 3E10 or Fv) which is thought to penetrate cell membranes [30]. Other areas of investigation in the treatment of stroke and brain trauma include targeting the chronic phases of injury, and include employing cell based treatments. One issue surrounding cell based therapies such as stem cells, is that the transferred cells seem to die or disappear after administration. Thus, one possibility may be to generate stem cells that overexpress HSPs in order to improve their survival.

8. Conclusions

HSPs, particularly HSP70, has been shown to directly engage in multiple mechanisms of neuroprotection in experimental models of acute brain injury. HSPs appear to have multifaceted mechanisms of protection by interfering with several aspects of acute brain injury. Several compounds have now been shown to pharmacologically induce HSP70 in the brain, and suggests that this may be a viable approach with potential for clinical translation. As recent advances in acute

stroke treatment include revascularization strategies, there may be renewed interest in neuroprotection as adjunctive agents in at least stroke patients. Thus, it seems that clinical studies should be the next step.

Acknowledgments

This research was supported by grants from the National Institutes of Health (RO1 NS106441, R03 NS101246), and the Veteran's Merit Award (I01 BX000589) to MAY, Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by Ministry of Education (NRF-2016R1D1A1B03933017) JYK, Grants to MAY was administered by the Northern California Institute for Research and Education, and supported by resources of the Veterans Affairs Medical Center, San Francisco, California.

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