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Review Article

Acupuncture-induced HSP70 upregulation in neuroprotection: mitochondrial and anti-apoptotic mechanisms

Hejun Wen[1], San Tian[1], Xiao Han[1], Qiuyu Xiao[1], Hong Zhang[2]

[1]Acupuncture and Tuina School, Chengdu University of Traditional Chinese Medicine, Chengdu 610000, Sichuan, China; [2]Department of Rehabilitation Medicine, Jiangwan Hospital of Hongkou District, Shanghai 200081, China

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Abstract: Heat shock protein 70 (HSP70) represents a major stress-inducible chaperone, holding considerable significance in regulating the proteostasis, mitochondrial homeostasis, and apoptosis in the injured nervous system. Acupuncture has shown neuroprotective effects in multiple models of neurological diseases, yet the role of HSP70 as a mechanistic link between acupuncture stimulation and neuronal protection has not been systematically clarified. To this end, current evidence on acupuncture-induced HSP70 regulation is hereby summarized, and its potential contribution to neuroprotection is accordingly discussed, with particular emphasis on mitochondrial preservation and anti-apoptotic signaling. Available studies suggest that acupuncture-associated HSP70 upregulation is linked to enhanced cellular stress adaptation, reduced oxidative injury, stabilization of Bcl-2 family-dependent mitochondrial integrity, inhibition of cytochrome c release and apoptosome formation, and suppression of downstream caspase activation. In addition to these intracellular effects, emerging evidence also uncovers the involvement of HSP70 in neuroinflammatory regulation and neuron-glia communication, suggesting its broader role in shaping the injured neural microenvironment. However, current evidence remains largely associative, leaving several key issues unresolved, including questions of causal necessity, cell-specific regulation, intercellular trafficking, and neuroimmune integration. Overall, HSP70 may represent a promising integrative mediator of acupuncture-induced neuroprotection, yet its precise mechanistic function still warrants further experimental validation.

Keywords: Heat shock protein 70, acupuncture, neuroprotection, mitochondria, apoptosis, neuroinflammation

Introduction

Neuronal apoptosis and defective post-injury repair constitute key pathological features across numerous neurological disorders, including ischemic stroke, spinal cord injury, and neurodegenerative diseases [1]. Cellular adaptation to these pathological stresses is critically regulated by heat shock proteins (HSPs), which maintain proteostasis and promote survival under damaging conditions [2-4]. Among them, HSP70, rapidly induced by oxidative and ischemic stress and exerting broad cytoprotective effects, has gained increasing attention [5]. Existing evidence indicates that HSP70 can stabilize mitochondrial homeostasis, interfere with caspase-related apoptotic signaling, and support axonal recovery. All these imply its central position in neuronal stress resistance and post-injury repair [6-10].

Acupuncture has shown promising neuroprotective effects in multiple models of neurological injury [11]. Beyond improving neural repair and attenuating apoptosis, acupuncture has been reported to modulate neuroendocrine-immune interactions while activating intracellular signaling pathways such as PI3K/Akt and MAPK [12-14]. However, these mechanistic observations remain fragmented, and the role of HSP70 as a potential mediator linking acupuncture stimulation to neuronal survival has not been sufficiently integrated.

Given the intimate relationship between mitochondrial dysfunction and intrinsic apoptosis,

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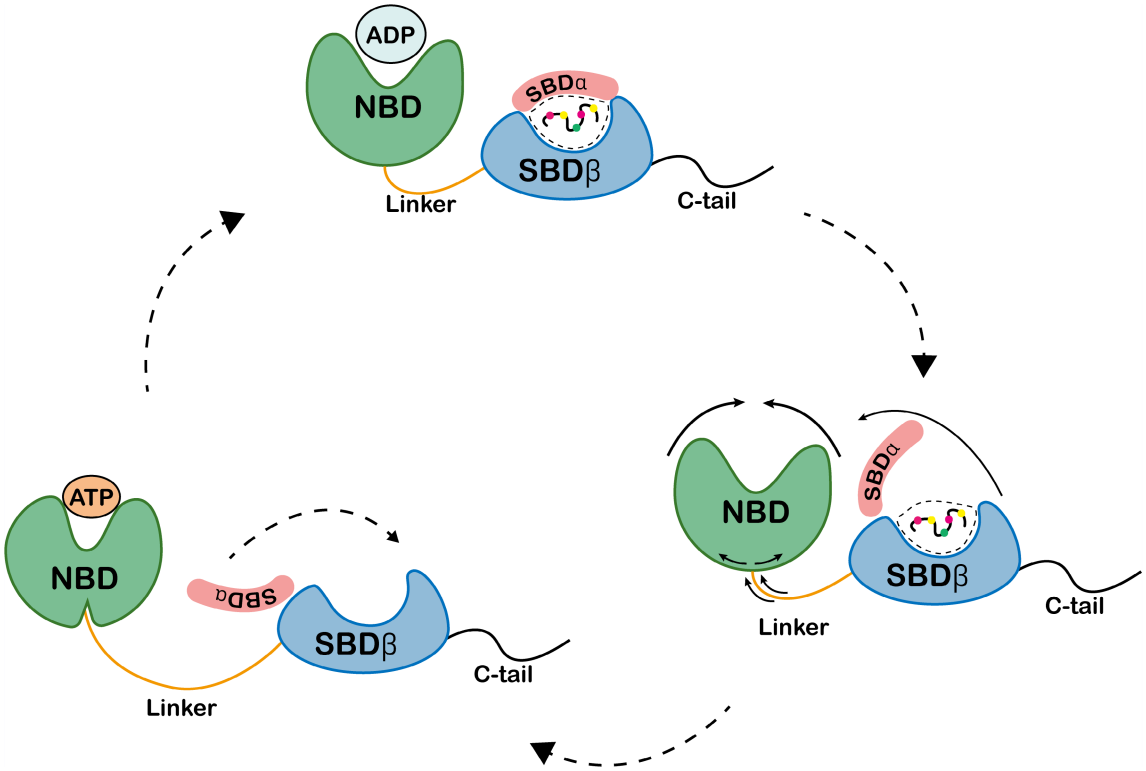

Figure 1. ATP-dependent allosteric cycle of HSP70. HSP70 undergoes conformational transitions during its ATPase cycle. In the ATP-bound state, NBD adopts an open conformation, promoting linker docking and a low-affinity substrate-binding state of the SBDβ. ATP hydrolysis induces closure of the SBDα lid, resulting in high-affinity substrate binding. Following ADP release, the SBD reopens, allowing substrate dissociation and resetting the chaperone cycle. This ATP-driven cycle enables HSP70 to maintain proteostasis by preventing protein misfolding.

HSP70 may function as a plausible mechanistic bridge between acupuncture and neuroprotection [15]. Nevertheless, it remains poorly defined how much acupuncture-triggered HSP70 upregulation actually contributes to mitochondrial preservation and apoptosis inhibition. Consequently, this review examines current evidence on acupuncture-induced HSP70 regulation and discusses the potential involvement of HSP70 in neuroprotection through interconnected mitochondrial and anti-apoptotic mechanisms in neural injury models.

Structure and functions of HSP70

HSP70 is a highly conserved molecular chaperone that plays essential roles in protein quality control, cellular stress tolerance, and survival. The HSP70 family includes multiple isoforms distributed across distinct subcellular compartments, including the cytosol, endoplasmic reticulum, and mitochondria, where they perform overlapping yet context-dependent functions [16]. Structurally, canonical HSP70 proteins consist of an N-terminal nucleotide-binding domain (NBD, ~44 kDa), a conserved interdomain linker, and a C-terminal substrate-binding domain (SBD), which contains a β-sheet-rich substrate-binding pocket and an α-helical lid domain [17].

ATP binding and hydrolysis drive nucleotide-dependent conformational changes and allosteric coupling between the NBD and SBD. In the ATP-bound state, HSP70 assumes a more open conformation characterized by reduced substrate affinity, facilitating rapid substrate binding and release. ATP hydrolysis to ADP promotes lid closure over the substrate-binding pocket, thus strengthening and stabilizing substrate interaction [18]. These conformational transitions are fundamental to the chaperone cycle of HSP70. **Figure 1** illustrates the allosteric transitions of HSP70.

The SBD (~25 kDa) comprises a β-sheet-rich SBDβ subdomain and an α-helical SBDα lid, which together regulate substrate specificity,

binding stability, and residence duration [19]. The C-terminal region further confers isoform-specific properties, including differences in client recognition, subcellular localization, and co-chaperone interactions [20]. Conformational fluctuations of the lid domain govern substrate entry into the binding cleft, enabling HSP70 to engage a broad range of unfolded or misfolded peptide motifs [21-23]. HSP70 recognizes non-native polypeptides, prevents protein aggregation, facilitates refolding or triage for degradation, and thus maintains proteostasis [16, 24]. These functions are particularly important in neurons, which are highly vulnerable to proteostatic disruption owing to their long lifespan, high metabolic demand, and susceptibility to oxidative stress.

The HSP70 cycle is under stringent regulation by co-chaperones. J-domain proteins of the HSP40 family stimulate ATP hydrolysis and recruit client proteins to HSP70 [25, 26]. By contrast, the BAG family proteins and HSPBP1 act as nucleotide exchange factors (NEFs), promoting ADP release and ATP rebinding to accelerate substrate cycling and influence client fate [24, 27]. HSP110 family proteins likewise serve as nucleotide exchange factors for cytoplasmic HSP70 and contribute to the formation of large chaperone complexes that sustain protein quality control during acute proteotoxic stress [28, 29]. The composition and activity of these co-chaperone systems are context-dependent, varying according to substrate load, stress intensity, and subcellular environment. In addition, post-translational modifications and isoform-specific sequence variations can modulate ATPase activity, client binding, intracellular localization, and chaperone stability, thus fine-tuning HSP70 functions [16, 30]. Recent structural and computational studies verify a dynamic and heterogeneous mode of client engagement, consistent with a "fuzzy binding" model rather than a single static interaction interface [19, 31].

In the nervous system, HSP70 undergoes rapid upregulation in response to acute pathological stressors, including oxidative stress, excitotoxicity, and mitochondrial dysfunction, thus promoting neuronal resilience [32-34]. As a key neuroprotective factor, HSP70 suppresses protein aggregation, assists protein folding, and limits stress-induced apoptosis [35]. Dysregulation of HSP70 and its co-chaperone network has been implicated in multiple neurological disorders, including Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and ischemic neuronal injury [35-37]. Therapeutic strategies under investigation include upregulating HSP70 expression, tuning co-chaperone activity, pharmacologically targeting allosteric regulation of the HSP70 cycle, and exploring combinatorial regimens aimed at selectively strengthening HSP70-dependent proteostasis [37, 38].

Neuronal apoptosis and its regulatory mechanisms

Apoptosis is an energy-dependent form of programmed cell death under strict genetic control, which is essential for tissue homeostasis by removing damaged, impaired, or redundant cells [39, 40]. In the nervous system, apoptosis assumes both physiological and pathological roles. Under physiological conditions, apoptosis contributes to neuronal development, circuit refinement, and the removal of supernumerary or damaged cells [41, 42]. Conversely, excessive or dysregulated apoptosis results in irreversible neuronal loss in a wide range of neurological disorders, including ischemic stroke, Alzheimer's disease, and Parkinson's disease [43-45]. Due to their high metabolic demand, long lifespan, and limited regenerative capacity, neurons are especially prone to apoptotic injury [46], making it important to elucidate the molecular mechanisms of neuronal apoptosis for understanding disease progression and identifying potential neuroprotective strategies.

Apoptotic signaling is generally classified into two major pathways: the intrinsic (mitochondria-dependent) pathway and the extrinsic (death receptor-mediated) pathway. While initiated by distinct upstream signals, both pathways converge on the activation of executioner caspases, including caspase-3, -6, and -7, which dismantle cellular architecture and execute apoptotic cell death [47]. In neurons, the intrinsic pathway is particularly vital, as ischemia, excitotoxicity, oxidative stress, and calcium dysregulation frequently converge on mitochondrial dysfunction [48]. Conversely, the extrinsic pathway is closely linked to neuroinflammatory signaling, particularly in the pres-

ence of cytokines and death ligands released by activated glial cells [49].

Intrinsic (mitochondria-dependent) apoptotic pathway

The intrinsic pathway is triggered by intracellular stressors commonly observed in neural injury, including DNA damage, oxidative stress, calcium overload, and endoplasmic reticulum stress [50, 51]. A central event in this pathway is mitochondrial outer membrane permeabilization (MOMP), which triggers the release of pro-apoptotic factors such as cytochrome c and Smac/DIABLO from the mitochondrial intermembrane space into the cytosol [52, 53]. Cytosolic cytochrome c binds to apoptotic protease activating factor-1 (Apaf-1), promoting apoptosome formation and the activation of caspase-9. This initiates a cascade that activates effector caspases including caspase 3 and caspase 7, ultimately executing apoptotic cell death [47, 54].

Neurons' susceptibility to intrinsic apoptosis is strongly influenced by the balance among Bcl-2 family proteins [55]. Increased activation of pro-apoptotic proteins such as Bax and reduced expression or function of anti-apoptotic proteins such as Bcl-2 have been reported in cerebral ischemia, spinal cord injury, and neurodegenerative diseases [56, 57]. Following MOMP, cytochrome c promotes apoptosome assembly, whereas Smac/DIABLO antagonizes XIAP and other inhibitor of apoptosis proteins (IAPs), thus relieving caspase suppression [58]. Dependent on oxidative phosphorylation, neurons are particularly sensitive to mitochondrial injury, creating a vicious cycle in which mitochondrial dysfunction amplifies apoptotic signaling, while apoptotic signaling further exacerbates mitochondrial damage [59, 60].

Extrinsic (death receptor-mediated) apoptotic pathway

The extrinsic pathway is initiated by the activation of cell-surface death receptors, particularly members of the TNF receptor superfamily, including Fas (CD95), TNFR1, and the TRAIL receptors DR4 and DR5 [61, 62]. These receptors are expressed by neurons and glial cells in the central nervous system and are closely linked to inflammatory signaling [63, 64]. Upon ligand binding by FasL, TNF-α, or TRAIL, the receptors trimerize and recruit the adaptor protein FADD and pro-caspase-8 to form the death-inducing signaling complex (DISC) [65, 66]. Subsequently, pro-caspase-8 is activated by autocatalytic cleavage, thereby initiating the downstream caspase cascade and apoptotic execution [67, 68].

The intrinsic and extrinsic pathways are functionally connected through Bid, a BH3-only member of the Bcl-2 family. Activated caspase-8 cleaves Bid to generate truncated Bid (tBid), which translocates to mitochondria and promotes Bax/Bak-dependent mitochondrial permeabilization [69]. In this way, extrinsic death receptor signaling amplifies the intrinsic apoptotic pathway. This crosstalk is particularly evident in ischemic and inflammatory conditions where glia-derived TNF-α or FasL can activate death receptor signaling while simultaneously enhancing mitochondrial vulnerability, thereby accelerating neuronal death [70, 71]. TNFR1 signaling is often regarded as a double-edged pathway. One branch activates NF-κB-dependent survival and inflammatory programs, whereas the other promotes caspase-8 activation and apoptotic cell death [72].

Overall, neuronal apoptosis arises from the integrated activation of both intrinsic and extrinsic signaling pathways, which converge on executioner caspases and ultimately give rise to irreversible neuronal damage. The intrinsic pathway is particularly relevant to ischemia, oxidative stress, calcium overload, and mitochondrial dysfunction, while the extrinsic pathway is closely associated with neuroinflammatory signaling. Given that excessive apoptosis is a hallmark pathological feature in many central nervous system diseases, regulatory molecules targeting both apoptotic pathways have attracted substantial research attention. In this context, HSP70 has emerged as a potentially important neuroprotective factor, as it may preserve mitochondrial integrity, interfere with apoptosome-related signaling, and limit death receptor-associated apoptotic activation. Collectively, these observations provide a mechanistic rationale for examining the contribution of HSP70's acupuncture-mediated regulation to neuroprotection in neural injury.

Integration of apoptotic pathways and relevance to neuroprotection

In the injured nervous system, neuronal apoptosis rarely results from the isolated activation of a single pathway; instead, mitochondrial dysfunction, oxidative stress, inflammatory signaling, and death receptor activation often occur simultaneously and interact with one another, creating a self-amplifying pro-death environment [73]. Under these conditions, the distinction between intrinsic and extrinsic apoptosis remains mechanistically useful, yet the two pathways are better understood as interconnected components of a broader injury response. This very interplay holds critical implications for neuroprotection. In multiple neurological disorders, limiting neuronal death may depend not only on suppressing downstream caspase activation, but also on stabilizing mitochondrial function, reducing inflammatory amplification, and preserving intracellular stress tolerance [74, 75]. Molecules acting at the interface of these processes are therefore of particular interest, as they may simultaneously affect several levels of the apoptotic cascade.

In this respect, HSP70 is of notable relevance because its protective roles are not limited to protein folding alone. Under stress conditions, HSP70 has been implicated in the maintenance of mitochondrial integrity, the regulation of apoptosome-associated signaling, and the attenuation of death receptor-related apoptosis [33]. Such actions suggest that HSP70 may contribute to neuronal survival by buffering the convergence of multiple injurious signals rather than by acting exclusively on a single apoptotic event. This integrative role may be especially important in pathological settings characterized by the coexistence of mitochondrial damage and inflammatory signaling, as is often the case in ischemic and neurodegenerative injury.

Viewed in this way, neuroprotection is not simply a matter of blocking apoptosis at its endpoint, but an issue of modulating the stress networks that drive neurons toward irreversible death. This facilitates a useful framework for considering how interventions that regulate HSP70 might influence neuronal fate under pathological conditions.

Role of HSP70 in regulating apoptosis

HSP70 regulates apoptosis at multiple levels and exerts potent cytoprotective effects. As a molecular chaperone, HSP70 inhibits Bax translocation to the outer mitochondrial membrane, limits cytochrome c release, and thereby attenuates apoptosome assembly and downstream caspase activation [33, 76]. Additionally, HSP70 has been reported to interact with Apaf-1, thereby suppressing procaspase-9 activation, while also suppressing the activation of executioner caspases such as caspase-3 and caspase-7 [77]. HSP70 also attenuates AIF-mediated nuclear damage and modulates upstream stress pathways including death receptor signaling, protein kinase R (PKR), and lysosomal membrane permeabilization [78-80]. Taken together, these properties allow HSP70 to suppress both mitochondrial and receptor-mediated apoptotic signaling at multiple stages (**Figure 2**).

Conversely, loss or inhibition of HSP70 increases cellular susceptibility to apoptosis. This is accompanied by an increased Bax/Bcl-2 ratio, elevated cytosolic cytochrome c levels, and enhanced cleavage of caspase-3 and PARP1 [81]. Within the nervous system, the cytoprotective properties of HSP70 assume critical significance under pathological conditions such as ischemic injury, neurodegenerative diseases, and traumatic injury. Enhanced expression of HSP70 has been consistently linked to enhanced neuronal survival outcomes.

HSP70 in the intrinsic pathway

Within the intrinsic apoptotic pathway, HSP70 acts at multiple stages surrounding MOMP to limit death signaling. At the level of Bcl-2 family regulation, HSP70 stabilizes anti-apoptotic Bcl-2 while suppressing mitochondria-dependent apoptotic signaling [82]. HSP70 may also cooperate with anti-apoptotic proteins such as Bcl-2 and Bcl-XL to reinforce their pro-survival functions [83]. Under severe stress, Bax is activated and translocates to the mitochondrial outer membrane to drive MOMP, and HSP70 counteracts this process by inhibiting Bax translocation and oligomerization, thus limiting cytochrome c release [82, 84, 85]. In addition, HSP70 can directly interact with Apaf-1 and interfere with apoptosome assembly [86]. Me-

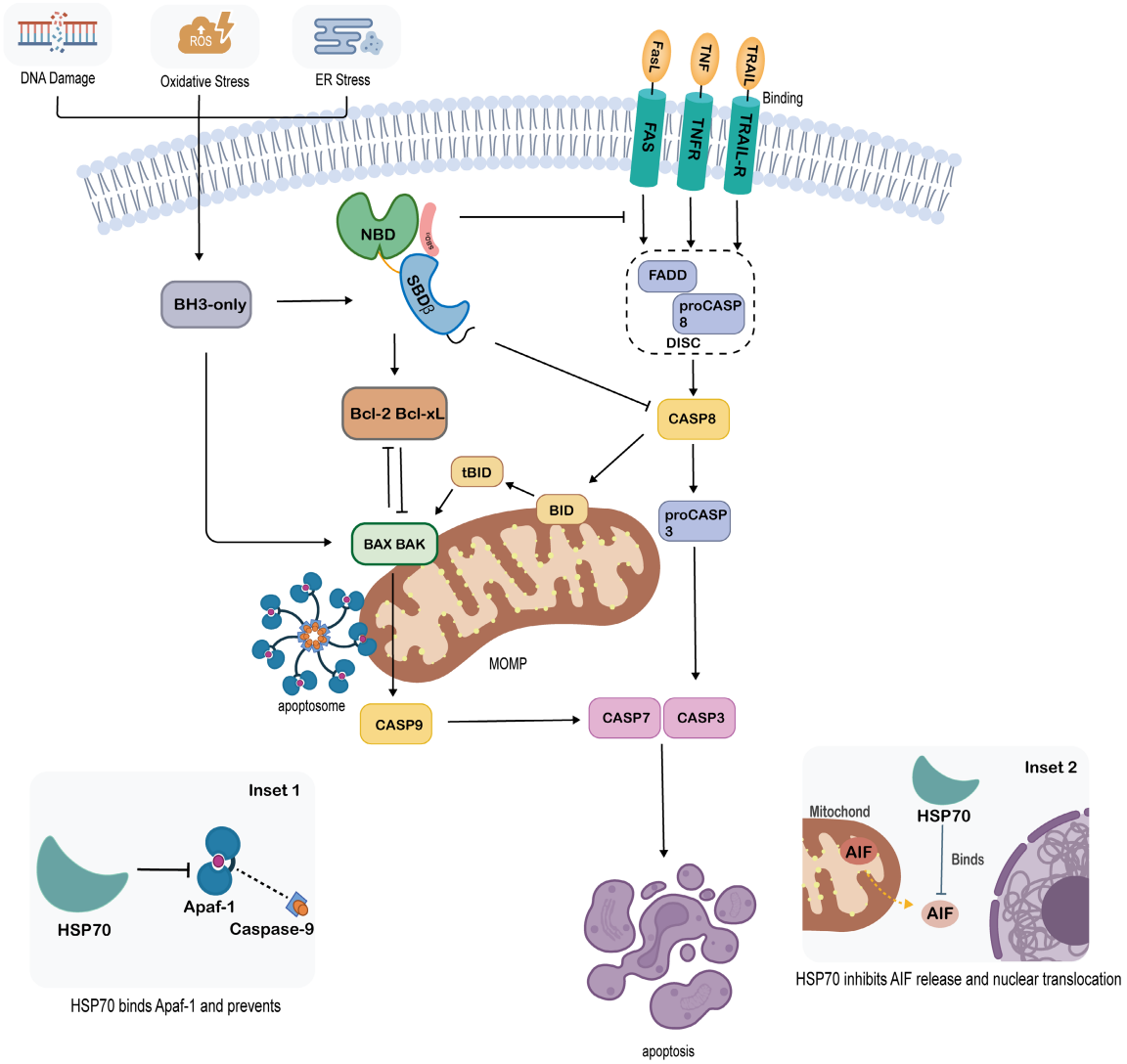

Figure 2. Anti-apoptotic mechanisms of HSP70 in intrinsic and extrinsic apoptotic pathways. HSP70 interferes with multiple checkpoints of apoptosis. In the intrinsic pathway, HSP70 stabilizes Bcl-2 family proteins, inhibits Bax/Bak activation, prevents MOMP, and reduces cytochrome c release. HSP70 also binds Apaf-1 (Inset 1), thereby inhibiting apoptosome formation and caspase-9 activation. In the extrinsic pathway, HSP70 suppresses DISC formation, inhibits caspase-8 activation, and limits tBID-mediated mitochondrial amplification. In addition, HSP70 prevents AIF nuclear translocation (Inset 2), thereby attenuating caspase-independent cell death.

chanistically, the ATPase domain of HSP70 is indispensable for mediating its interactions with pro-apoptotic factors including Bax, thereby modulating the structural integrity of the mitochondrial membrane [87]. Through these coordinated actions, HSP70 preserves mitochondrial integrity and prevents the amplification of apoptotic signaling. These effects are particularly critical in neurons highly dependent on mitochondrial function and especially vulnerable to oxidative stress and energy failure [88].

HSP70 in the extrinsic pathway

HSP70 acts as an important modulator of the extrinsic apoptotic pathway. It can negatively regulate Fas at the protein level, thereby modulating Fas-related signaling [89]. Meanwhile, HSP70 suppresses Fas-mediated apoptosis by inhibiting caspase-8 activation, with a concomitant reduction in downstream caspase-3 activity [90]. In the TRAIL branch, HSP70 resists Apo-2L/TRAIL-induced apoptosis by associating with death receptors DR4 and DR5 and

blocking recruitment of FADD and caspase-8 to the DISC, inhibiting DISC assembly and downstream apoptotic signaling [91]. More broadly, it dampens proteolytic signaling associated with receptor-mediated cell death [92].

Beyond receptor-proximal regulation, HSP70-associated molecules may also participate in TNFR-related death signaling under specific conditions. An HSP70-containing complex interacts with TNFR1 while inducing TNFR1-dependent cytotoxic signaling in tumor cells [93]. In addition, by binding IKKγ and impairing NF-κB-dependent survival signaling, HSP70 modulates TNF-associated downstream signaling, thus shifting the balance toward TNF-mediated apoptosis [94]. Importantly, it integrates intracellular and extracellular stress signals to restrain both major apoptotic pathways. Upon activation, caspase-8 cleaves Bid to generate truncated Bid (tBid). This fragment translocates to mitochondria and promotes mitochondrial outer membrane permeabilization, establishing a functional connection between death receptor signaling and the intrinsic apoptotic machinery [95-97]. Such a Bid-dependent crosstalk is critical, as it amplifies receptor-mediated apoptotic signaling through mitochondrial dysfunction, enhanced cytochrome c release, and downstream caspase activation [98-100]. By preserving mitochondrial integrity and restraining this Bid/tBid-mediated amplification loop, HSP70 limits the propagation of extrinsic apoptotic signals into the intrinsic pathway [91, 101]. In certain type II cells, however, it may also modulate TRAIL sensitivity in a context-dependent manner by upregulating TRAIL-R1 and TRAIL-R2 through a p53-associated mechanism [102].

Aberrant Fas and TNFR signaling can promote neuroinflammation and neuronal degeneration. In animal models of cerebral ischemia and spinal cord injury, elevated HSP70 levels are associated with a lower Bax/Bcl-2 ratio, reduced cleavage of caspase-3 and caspase-8, and fewer TUNEL-positive neurons, supporting its anti-apoptotic and neuroprotective effects [89, 90, 103].

Acupuncture regulation of HSP70 in neuroprotection

In neurological disorders, acupuncture is increasingly recognized as a neuroprotective intervention. Among molecular mediators implicated in this process, HSP70 appears to be a key stress-responsive effector [80, 104]. As a core component of the cellular stress response, it contributes to proteostasis, preserves mitochondrial integrity and function, and limits apoptosis triggered by ischemia, oxidative stress, inflammation, and excitotoxicity [105, 106]. Experimental studies further indicate that acupuncture increases HSP70 expression in ischemia-affected brain regions, including the hippocampus and cerebral cortex, and that this HSP70 upregulation may improve neuronal tolerance to ischemic stress [107-110].

Mechanistically, the neuroprotective effects of acupuncture appear to converge on HSP70 through two closely related processes. First, acupuncture enhances stress adaptation through neuroendocrine regulation and activation of molecular chaperone responses [111], thereby favoring HSP70-associated resistance to oxidative and inflammatory injury [33]. Second, acupuncture may strengthen HSP70-associated mitochondrial protection by stabilizing Bcl-2-related survival signaling, limiting mitochondrial membrane permeabilization, and suppressing apoptotic signaling [112, 113]. Collectively, these findings establish a mechanistic framework for interpreting the regulation of HSP70 by acupuncture in relation to neuronal survival and injury-related cellular responses.

Acupuncture-induced HSP70 upregulation and stress adaptation in neural injury

HSP70 is a major stress-responsive molecular chaperone involved in neuroprotection. In the injured central nervous system featuring limited regenerative capacity, inducible HSP70 facilitates the preservation of proteostasis, limit protein aggregation, and support neuronal survival under ischemic, oxidative, and inflammatory stress conditions [104, 114]. Experimental studies indicate that acupuncture can upregulate HSP70 expression in injured or stress-sensitive brain tissue, and this induction is found to be generally associated with enhanced cellular stress adaptation, neuroprotection, and functional recovery under conditions such as cerebral ischemia/reperfusion injury [108-110, 115]. Far from being a nonspecific stress response alone, this response appears to reflect an adaptive program through

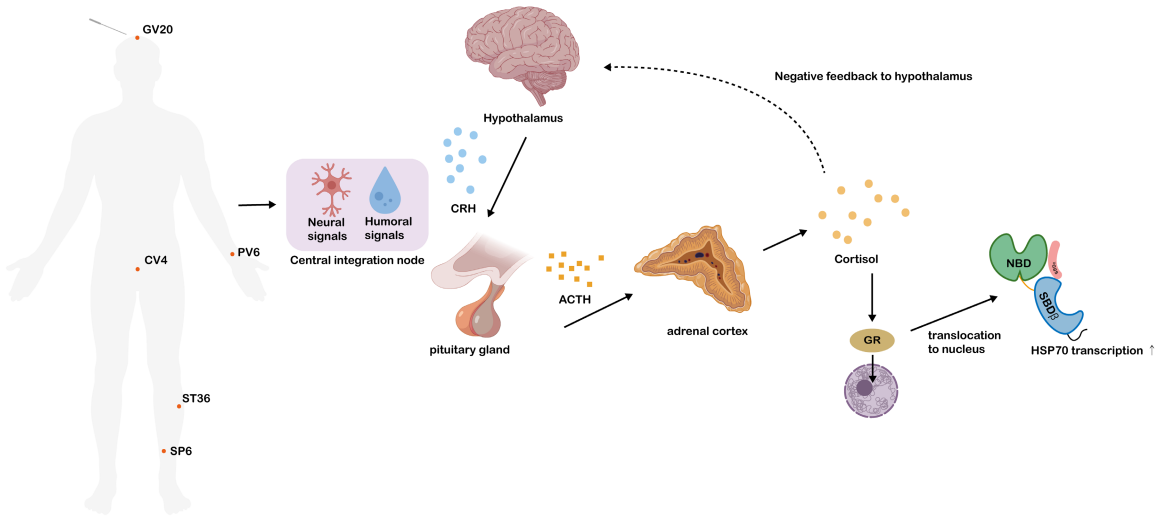

Figure 3. Acupuncture-mediated activation of the HPA axis and glucocorticoid receptor-dependent induction of HSP70. Acupuncture stimulation at acupoints (e.g., GV20, CV4, ST36, SP6) engages neural and humoral pathways that converge on the hypothalamus. HPA corticotropin-releasing hormone axis promotes CRH release, ACTH secretion from the pituitary, and induces cortisol production in the adrenal cortex. Cortisol binds to glucocorticoid receptors (GR), leading to GR nuclear translocation and upregulation of HSP70 transcription. This pathway links peripheral acupuncture stimulation to central stress adaptation and cytoprotective responses.

which peripheral somatic stimulation engages central stress-defense mechanisms.

A critical component of this adaptive response may involve neuroendocrine regulation through the hypothalamic-pituitary-adrenal (HPA) axis. Prolonged stress disrupts HPA negative feedback, while acupuncture may facilitate stress adaptation not only through HSP70-related cytoprotection but also through restoration of glucocorticoid receptor (GR)-dependent HPA-axis negative feedback, including increased GR expression in the hippocampus and hypothalamic PVN as well as reduced corticotropin-releasing hormone (CRH)/stimulates adrenocorticotropic hormone (ACTH) overactivation [116, 117]. This observation is mechanistically relevant as GR folding, ligand responsiveness, and maturation depend on the HSP70 chaperone cycle and its cooperation with HSP90 [118]. Thus, acupuncture-induced HSP70 upregulation may promote stress adaptation not only by increasing the pool of available molecular chaperones, but also by supporting GR-dependent neuroendocrine homeostasis. Consistent with this view, electroacupuncture has also been demonstrated to concomitantly increase HSP72 expression and ACTH release. This supports the notion that acupuncture can engage both heat-shock-related cytoprotection and HPA-axis neuroendocrine activation as coordinated components of an adaptive stress response [110, 119]. The neuroendocrine mechanism linking acupuncture stimulation to HSP70 upregulation via the HPA axis is illustrated in **Figure 3**.

Regional induction of HSP70 following acupuncture is particularly pronounced in models of ischemic and excitotoxic brain injury. In cerebral ischemia-reperfusion models, electroacupuncture at GV26, PC9, and GV16 has been reported to further enhance HSP70 expression in the hippocampus, increase SOD activity, and reduce the MDA content in brain tissues. This suggests a potential association between HSP70 induction and protection against ischemia-reperfusion injury [109]. In middle cerebral artery occlusion models, electroacupuncture likewise increases HSP70 expression in ischemic cortical and hippocampal regions and is associated with reduced DNA fragmentation, lower PARP activation, and less apoptosis [108, 120]. At the systems level, these findings suggest that acupuncture-induced HSP70 is not merely a marker of cellular stress, but may actively mediate regional adaptive responses to stress and early inflammatory remodeling following neural injury. This interpretation is further supported by observa-

tions that upon peripheral acupuncture stimulation, TRPV1-related somatosensory signaling may contribute to remote HSP70 induction in central stress-responsive regions [110, 121]. While current evidence does not yet define the precise cell-specific origin of induced HSP70, available data support the view that acupuncture-evoked HSP70 upregulation is closely linked to adaptive stress resistance in the injured nervous system.

HSP70-associated mitochondrial protection and anti-apoptotic signaling after acupuncture

Neurons are characterized by their high energy demand, dependence on oxidative phosphorylation, and limited regenerative capacity, rendering them particularly vulnerable to mitochondrial dysfunction. In ischemia, excitotoxicity, and inflammatory injury, mitochondria-dependent apoptosis is rapidly activated and contributes substantially to neuronal loss in stroke, neurodegenerative disorders, traumatic brain injury, and spinal cord injury. Key events in this process encompass MOMP, pathological opening of the mitochondrial permeability transition pore (mPTP), and release of cytochrome c and apoptosis-inducing factor (AIF), which jointly govern the fate of stressed neurons toward either recovery or irreversible cell death. In this context, available evidence suggests that acupuncture-associated HSP70 upregulation is linked to reduced neuronal apoptosis and improved mitochondrial resilience [103, 115].

A primary mechanism underlying the cytoprotective action of HSP70 involves the stabilization of Bcl-2 family-dependent mitochondrial homeostasis. HSP70 is known to preserve anti-apoptotic Bcl-2 signaling while limiting Bax activation, mitochondrial translocation, and oligomerization, thus restraining MOMP and cytochrome c release [74-76, 87]. In cerebral ischemia models, electroacupuncture increases HSP70 and Bcl-2 expression in hippocampal and cortical neurons, while reducing Bax levels. These variations are accompanied by lower cytochrome c release and reduced caspase-3 activation [108-110]. In parallel, acupuncture improves oxidative balance by enhancing superoxide dismutase activity, reducing malondialdehyde accumulation, and preserving mitochondrial membrane potential in ischemic brain tissue [107]. These findings indicate that acupuncture-evoked HSP70 upregulation is closely associated with early mitochondrial stabilization, suppression of oxidative injury, and attenuation of intrinsic apoptotic signaling. Supportive evidence from non-acupuncture models further reinforces this interpretation: elevated HSP70 expression limits cytochrome c release, maintains mitochondrial transmembrane potential, and improves cell survival under oxidative stress. Conversely, reduced HSP70 levels correspond with Bax activation, membrane potential collapse, and apoptotic cell death [74-76, 82, 87, 119].

Beyond these early events, acupuncture-associated HSP70 induction may also exert broader beneficial effects on mitochondrial quality control and cellular antioxidant systems. In ischemic and degenerative models, increased HSP70 expression is accompanied by improved mitochondrial morphology, reduced oxidative damage, and enhanced resistance of neurons to metabolic stress [94, 95, 99, 105]. For instance, electroacupuncture increases spinal cord HSP70 expression in amyotrophic lateral sclerosis models and is associated with reduced oxidative injury and delayed functional decline [115]. Other acupuncture-responsive antioxidant pathways, including thioredoxin-1 and HIF-1α-related adaptive signaling, may cooperate with HSP70-associated cytoprotection rather than functioning as independent protective mechanisms [100, 101]. Likewise, emerging evidence that acupuncture modulates mitochondrial quality control and mitophagy suggests an additional layer that reinforces HSP70-linked mitochondrial preservation, yet direct causal evidence for HSP70 dependence in these pathways remains limited [102, 115, 116].

At later stages of the intrinsic apoptotic cascade, HSP70-associated protection may extend to inhibition of mPTP opening, restraint of AIF translocation, and suppression of apoptosome-dependent caspase activation. Pathological opening of the mPTP causes rapid dissipation of mitochondrial membrane potential, swelling of mitochondria, rupture of the outer membrane, and release of cytochrome c and AIF; once translocated to the nucleus, AIF induces large-scale DNA fragmentation through a caspase-independent mechanism particular-

ly relevant in severe ischemia-reperfusion injury [92, 102]. In myocardial ischemia-reperfusion models, electroacupuncture pretreatment inhibits FXR/SHP signaling, upregulates HSP70, and reduces AIF translocation [122], supporting the possibility that HSP70 contributes to controlling mPTP-dependent death pathways. In central nervous system ischemia models, acupuncture preserves mitochondrial membrane potential, mitigates mitochondrial swelling, reduces cytosolic release of pro-apoptotic factors, and attenuates caspase-9 and caspase-3 activation [92, 98, 103, 107]. Mechanistically, this pattern is consistent with the established anti-apoptotic functions of HSP70, including interference with Apaf-1-dependent apoptosome assembly and inhibition of downstream caspase activation [92, 120]. Additional acupuncture studies have demonstrated reduced Bax, caspase-9, caspase-3, and TUNEL positivity after preconditioning, which further support the view that acupuncture-evoked HSP70 may restrain apoptosis both upstream at the mitochondrial level and downstream at the level of apoptosome and effector caspases [116, 117, 121]. Taken together, current evidence supports a model wherein acupuncture-associated HSP70 induction stabilizes mitochondria, mitigates oxidative injury, and suppresses both caspase-dependent and caspase-independent apoptotic execution, thus facilitating neuronal survival following stress.

Neuroinflammatory and cellular contexts of acupuncture-induced HSP70 regulation

Beyond its intracellular anti-apoptotic functions, HSP70 also regulates the neuroinflammatory processes and cellular interactions within the central nervous system [123]. As a chaperokine, extracellular HSP70 serves as both a molecular chaperone and a signaling regulator, interacting with cell surface receptors including TLR4 and RAGE to activate diverse pathways that modulate neuroinflammation and glial cell communication [124-126]. Accumulating evidence suggests that the neuroprotective effects of acupuncture-induced HSP70 are not solely attributable to intracellular mechanisms, but also involve complex interactions among neurons, glial cells, and the immune microenvironment [127-129].

Among these cellular components, microglia play a pivotal regulatory role by engaging in complex crosstalk with neurons, astrocytes, oligodendrocytes, and infiltrating immune cells. They secrete pro-inflammatory mediators and chemokines that actively remodel the neuroinflammatory microenvironment following neural injury [130, 131]. Activated microglia can adopt distinct phenotypes, broadly categorized as pro-inflammatory (M1-like) and anti-inflammatory (M2-like) states, each exerting differential effects on neuronal survival [132]. An imbalance between these phenotypic states is closely linked to neurodegenerative processes. HSP70 has been reported to suppress pro-inflammatory signaling pathways and may promote a shift toward a more neuroprotective microglial phenotype [133, 134]. In addition to microglia, astrocytes contribute to neuronal protection by maintaining metabolic support, regulating extracellular homeostasis, and modulating inflammatory responses [135]. Acupuncture-induced HSP70 expression in astrocytes may further enhance these supportive functions while attenuating inflammatory stress within the neural microenvironment [136-138].

Beyond its cell-autonomous effects, accumulating evidence suggests that HSP70 may also play a role in intercellular communication within the central nervous system [15]. It can be released into the extracellular space through non-classical secretion pathways, including exosome-mediated transport [139]. Specifically, astrocyte-derived exosomes containing HSP70 are internalized by neurons, leading to enhanced neuronal stress tolerance and survival [140]. However, it remains unclear whether acupuncture-induced HSP70 is transferred between glial cells and neurons through such mechanisms. Additional studies are required to determine whether HSP70-mediated neuron-glia communication contributes to the overall neuroprotective effects of acupuncture.

At the systems level, these intracellular and intercellular mechanisms converge to form a coordinated protective network. HSP70 preserves mitochondrial integrity, restricts mitochondrial permeability transition, reduces AIF release, and suppresses apoptosome formation and caspase activation. These effects are further reinforced by the modulation of neuro-

inflammatory responses and cellular interactions, thus inhibiting the amplification of oxidative stress and apoptotic signaling. Taken together, HSP70 functions as a pivotal mediator that bridges acupuncture-induced signals with mitochondrial preservation, inflammation control, and neuronal survival.

Discussion

While growing evidence associates acupuncture-induced HSP70 expression with attenuated neuronal damage and apoptosis, current studies remain constrained by several notable limitations that hinder mechanistic interpretation. The major unresolved issues can be broadly grouped into three areas: causal inference, cell-specific regulation, and systems-level neuroimmune integration. First, most available studies show an association between HSP70 upregulation and improved outcomes, yet they fail to establish whether HSP70 is mechanistically required for acupuncture-induced neuroprotection. In particular, loss-of-function experiments and cell-specific intervention studies remain scarce in acupuncture models, making it challenging to distinguish whether HSP70 is a true effector or merely a stress-associated marker. Second, current evidence lacks sufficient cell-specific resolution to clarify the location, timing, and mechanism of HSP70 induction following acupuncture stimulation. While HSP70 upregulation has been reported in both neurons and glial cells, it is still unclear whether these responses occur synchronously, differ in magnitude, or reflect distinct functional roles in neuronal protection and inflammatory regulation. These observations suggest that HSP70 is unlikely to act as a purely intracellular anti-apoptotic molecule, but may instead function in a cell-context-dependent manner across varying neural cell populations. Third, the intercellular trafficking and extracellular signaling of HSP70 within the injured nervous system remain poorly defined. A particularly important unresolved question is whether acupuncture-induced HSP70 can be transferred between glial cells and neurons through extracellular vesicles, including exosome-mediated pathways. It also remains uncertain whether HSP70 contributes to broader neuroimmune regulation following acupuncture, including blood-brain barrier stability [141], peripheral immune-cell recruitment [142], and T-cell-associated inflammatory responses [143].

Whether the immunomodulatory properties of HSP70 induced by acupuncture are restricted solely to microglial modulation or also participate in shaping adaptive immune responses still awaits further clarification. One possible explanation is that HSP70 may influence not only microglial polarization, but also the local neuroinflammatory environment, indirectly affecting processes such as the Th17/Treg balance [144]. Another outstanding question is whether varying acupuncture parameters produce distinct temporal or quantitative patterns of HSP70 induction. Importantly, parameter-dependent variations in HSP70 induction may help account for the inconsistent effects of acupuncture on microglial activation, cytokine profiles, and peripheral immune-cell responses across experimental settings. Future studies should therefore prioritize systematic comparisons of stimulation modality, frequency, intensity, treatment timing, and acupoint selection, while simultaneously assessing cell-specific HSP70 induction, intercellular signaling, and downstream inflammatory outcomes. Resolving these limitations will be essential not only to establish whether HSP70 is mechanistically indispensable for the neuroprotective effects of acupuncture, but also to clarify its role as a central hub coordinating mitochondrial protection, glial regulation, and neuroimmune adaptation.

Disclosure of conflict of interest

None.

Address correspondence to: Hong Zhang, Department of Rehabilitation Medicine, Jiangwan Hospital of Hongkou District, Shanghai 200081, China. E-mail: freoiter@outlook.com

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