

Heat shock protein 70 in Alzheimer's disease and other dementias: A possible alternative therapeutic

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Abstract

Alzheimer's disease (AD) is considered a global health issue with a high social burden due to the level of disability it causes in those who suffer from it. In the absence of a therapeutic alternative for this disease, we will follow one of the biochemical pathways involved in the development of AD, which is related to molecular chaperones. The molecules are responsible for eliminating toxins and misfolded proteins at the cerebral level. These chaperones are a set of proteins from the heat shock proteins (HSPs) family, which, among their functions, help maintain homeostasis and protect cells against stress. Various authors have described the activity of HSPs in different neurodegenerative diseases, highlighting the activity of heat shock protein 70 (HSP70) in the presence of aberrant proteins characteristic of neurodegeneration, such as amyloid- β (A β) and tau. The role of HSP70 in AD and other dementias lies in its mechanism, which, along with other proteins from the HSP family, has the capacity to eliminate A β aggregates by promoting catalytic pathways. In this review, we explore the biological role of the HSP70 protein in AD and other dementias and its potential therapeutic use

Keywords

Alzheimer's disease, amyloid- β , amyloid- β protein precursor, heat shock protein 70, heat shock proteins, hyperphosphorylated tau protein

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Introduction

Dementia is a term used to encompass a group of symptoms that affect thinking skills, limiting people from performing their everyday activities. There are many factors that condition its development. Currently, approximately 55 million people worldwide suffer from some form of dementia, with Alzheimer's disease (AD) being the most prevalent with approximately 70%,¹ representing an economic impact both worldwide and for healthcare systems.²

Cognitive functions are modulated by synapse processes that involve different pathways responsible for releasing chemical substances that allow the connection between neurons, thus enabling neurocognitive abilities. In the case of dementia, there are anatomical changes at the brain level that interrupt these processes. Thus, vascular dementia is the result of one or more cerebral vascular lesions, of any etiology, that cause brain tissue to be injured, also causing difficulties in motor function,

especially in walking and loss of balance. This type of dementia occurs in approximately 5% to 10% of individuals with dementia.^{3–5} However, it is more common to find it as

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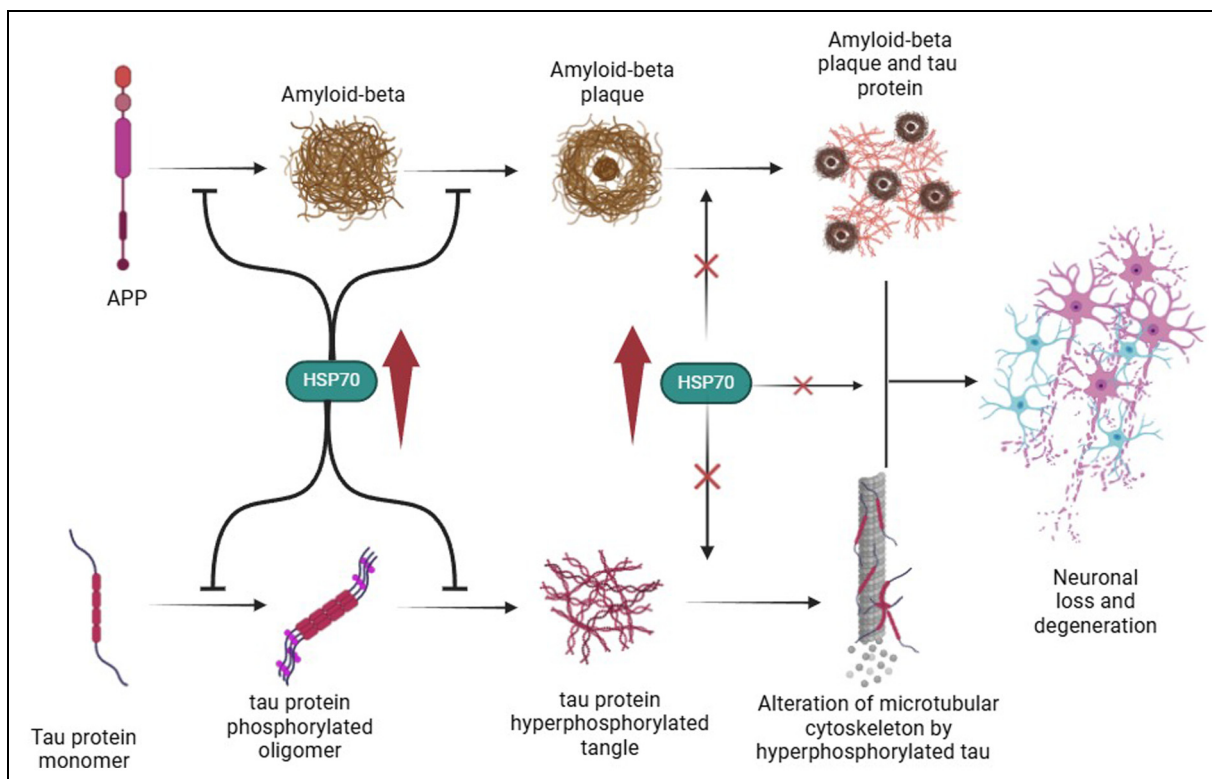


Figure 1. Participation of HSP70 on Alzheimer's disease. HSP70 has the ability to prevent neuronal loss and/or neurodegeneration by inhibiting the oligomerization of A β PP and/or the phosphorylation of tau protein. It has also been proposed that HSP70, in the presence of A β oligomers, increases its expression by interfering with the homeostasis of these oligomers and preventing their aggregation on neuronal structures. Created with BioRender.com.

a mixed pathology, showing at the brain level both changes in cerebrovascular disease and AD.

AD is a neurodegenerative disease that requires many years for changes in the brain to affect people who suffer from it and to start having problems with memory and language.⁶ Among the changes observed in the brain are an excessive accumulation of the protein fragment amyloid- β (A β) outside of neurons and an abnormal form of the strands of the tau inside neurons, as well as a notable neuronal damage that ends up damaging brain tissue,⁷ such as consequence of the interruption of chemical signals that maintain cognitive functionality.

In vivo findings have shown the toxicity of A β , resulting in the cell death of neurons deactivated with tau, indicating that tau is essential for neurodegeneration and cytotoxicity induced by A β .⁸ However, despite these studies, the results are still limited, not allowing us to identify all the biochemical pathways involved.

The appearance of A β and hyperphosphorylated tau,⁹ has also been implicated in neuroinflammation mechanisms that involve different neuronal action pathways mediated for innate immunity^{10–12}; A β aggregates can activate pro-inflammatory reactions by causing damage to neurons, leading to ischemia or hypoxia^{13–15}; Thus, neuronal damage in dementia is a consequence of the stress to which neuronal

cells are subjected as a consequence of the misfolding of the tau protein, which generates toxic products and accumulation of A β plaques.^{11,16–18}

Thus, the heat shock proteins (HSPs) known as molecular chaperones HSP60, HSP70, and HSP90, play an important role since they allow cells to protect themselves against stressors. These biomolecules are a series of highly conserved proteins whose functions include maintaining cellular homeostasis,¹⁹ and they also allow the regulation of protein folding both inside and outside the cells, and participate in other cellular mechanisms such as the translocation and degradation of proteins and cellular degradation.^{20–22}

Considering these biochemical mechanisms involved in the development of dementia, which involve incorrect protein folding and tau phosphorylation processes to avoid neuronal toxicity, molecular chaperones could represent an alternative in the search for new therapeutic targets for a disease for which there is no real cure to date. Therefore, this review focuses on describing the relationship between dementia as an entity and HSPs, with emphasis on HSP70 for its role in regulating tau stability and its phosphorylation dynamics as well as its ability to inhibit oligomerization and aggregation of both A β and tau proteins to identify its possible clinical application.

Role of HSP70 and in dementia

Dementia is a complex disease with a high prevalence among older adults; it is said that approximately 25% of people over 55 years of age have a history of dementia being the major cause of disability and dependency among elderly people.²³ The changes observed at the microscope level show the presence of plaques and neurofibrillary tangles (NFTs), and may be present in other types of dementia such as mixed dementia plaques are extracellular A β peptide, whereas the intracellular NFTs mainly are composed of hyperphosphorylated forms of the microtubule-associated tau protein²⁴ as well as the defective cleavage of amyloid- β protein precursor (A β PP) and the consequent A β plaque formation giving rise to a downstream cascade that leads to tau pathology.²⁵

A β PP is a transmembrane protein with extracellular and intracellular domain and a hydrophobic transmembrane domain. Its participation in neurite outgrowth, synaptic plasticity, and cell survival has also been noted and it interacts with other receptors to maintain intracellular calcium homeostasis.^{26,27}

A β PP can be cleaved by a combination of different secretases complexes, following two pathways the amyloidogenic A β PP processing in which α - and γ -secretases participate and the amyloidogenic processing of A β PP in which the β -secretase participates instead of α -secretase producing mainly A β ₁₋₄₀ and, to a lesser extent, the most amyloidogenic A β ₁₋₄₂.²⁸

These are some of the proteins involved in the accumulation of A β /tau. However, to date no mechanisms have been established that would allow them to be influenced to modify this process. The protein HSP70 plays an important role in this process due to its ability to inhibit oligomerization and aggregation of both A β and tau and its ability to maintain homeostasis.²⁹

HSP70 is a family of 17 members that can be induced by stress or expressed constitutively, as in the case of Hsc70, which is responsible for assisting in protein folding. The HSP70 chaperone can collaborate with both the HSP40 and HSP90 chaperones in various cellular compartments actively participating in cellular apoptosis processes.³⁰ It has been reported that in AD the levels of HSP70 are altered, in postmortem brain tissue these levels have been reported increased, which suggests that HSP70 is present in these areas with the intention of solubilizing protein aggregates to prevent cellular damage.³¹

On the other hand, it has also been pointed out that among the functions of these chaperones is helping proteins to acquire their conformation, so in neurodegenerative diseases such as dementia, where an incorrect packing of one or more proteins is observed. The HSP70 chaperone plays an important role allowing regulating the assembly of newly generated polypeptides, refolding of aberrant proteins or targeting them for elimination.^{29,32}

Biological role of HSP70 in dementia

Some studies have shown in animal models how the variation in HSP70 levels conditions the degradation of the A β protein in microglial cells.³³ HSP70 has also been shown to decrease the number of oligomers through the refolding of misfolded proteins.³⁴ On the other hand, the HSP70 chaperone has also been associated with a reduction in the levels of the tau in different in vivo models. HSP70 binds to tau, prevents its aggregation and facilitates its degradation by means of E3 ubiquitin ligase. On the contrary, the inhibition of HSP70 can hinder the proper folding of the molecule, facilitating its cellular degradation.³⁵

HSP70 also interacts with other chaperones such as HSP40, enhancing their activity and affecting the catalytic activity of polypeptides mediated by adenosine triphosphate (ATP), protecting neurons from stress.³⁶ Thus we can say that in this mechanism the role of HSP70 is rather passive and repetitive, allowing to maintain the concentrations of substrate in optimal conditions to avoid native folding and substrate splitting, the energy of ATP is used in both processes.

HSP70 interferes with the homeostasis of A β aggregates. Soluble A β oligomers, which become toxic in their oligomeric form, tend to form fibrils that eventually aggregate into stable β -sheet plaques³⁷; several authors have demonstrated that abundant expression of HSP70 effectively prevents the accumulation of A β in neurons in AD mice models, as can be seen in Table 1. This is achieved through HSP70's stimulation of cytokines such as TGF-B1 and insulin-degrading enzyme (IDE),³⁸ stimulation of microglia and astrocytes for the enzymatic elimination of A β , and suppression of A β production by preventing its assembly upon recognizing its aggregated form.³⁹⁻⁴⁵ It is well known that A β plays a fundamental role in the histopathology and progression of AD, so it can be deduced that HSP70 plays an important role in AD progression by directly interacting with A β proteostasis, as be seen in Figure 1. Specifically, HSP70 is a potent inhibitor of apoptosis.⁴⁶

HSP70 consists of a characteristic structure composed of three domains: N-terminal, substrate-binding domain, and C-terminal⁵⁰; due to this characteristic, it can recognize hydrophobic amino acid sequences that have been recently synthesized by ribosomes. In AD, HSP70 has the specific function of stabilizing proteins, which gives it a neuroprotective role,³⁸ various studies have reported a direct correlation between HSP70 dysfunction and the deposits of A β and NFTs.⁴⁷

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Table 1. HSP70 models in various neurodegenerative diseases and their results.

Disease	Model	Results	Route of administration & dosage	Conclusions
Alzheimer's Disease	Adult male transgenic 5XFAD and non-transgenic mice	-Regulation of genes involved in antigen presentation. -Increase in cellular reactivity -Reduction of A β plaques.	2 μ g/mouse In 4 μ l intranasal Injection	Regulation of multiple antigen presentation processing genes mediated by HSP70 in old TG 5XFAD animals, it is suggested that HSP70 has therapeutic application in neurodegenerative diseases such as AD by activating adaptive immunity. ⁴⁷
Alzheimer's Disease	Neuroblastoma cells N2A	-Decrease in A β oligomerization -Reduction of A β toxicity	125 μ g / 3 mL Direct insertion into the medium	The authors suggest an important mechanism of HSP70 in the cytotoxicity given by A β effect in AD. ⁴⁸
Alzheimer's Disease	Adult males of NMRI mice and transgenic 5XFAD mice	-Prevent memory deterioration -HSP70 treatment reduces the accumulation of A β peptides in mouse brain -Improves neuronal morphology and neuronal survival in mouse brain	2 μ g/mouse In 4 μ l Intranasal injection	HSP70 treatment protects memory in 5XFAD and OBX mice. HSP70 has been shown to be an important neuroprotector in Alzheimer's disease. ⁴⁹

5XFAD: Familiar Alzheimer's disease transgenic mouse model with 5 AD linked mutations (3 mutations in APP695 (I716 V, Kn670N/M671L, V717I) and 2 mutations in PSEN1 (M146L, L286 V)).

N2A: mouse neuroblastoma cell line.

NMRI: Naval Medical Research Institute outbred mouse model.

This is achieved through HSP70's stimulation of cytokines such as TGF-B1 and IDE,³⁸ stimulation of microglia and astrocytes for the enzymatic elimination of A β , and suppression of A β production by preventing its assembly upon recognizing its aggregated form.^{39–45} It is well known that A β plays a fundamental role in the histopathology and progression of AD, so it can be deduced that HSP70 plays an important role in AD progression by directly interacting with A β proteostasis. Specifically, HSP70 is a potent inhibitor of apoptosis.⁴⁶

Biological role of HSP70 in other dementias

While most studies on late-onset dementias have focused specifically on AD, it has been discovered that AD shares pathophysiological characteristics with vascular dementia and mixed dementia⁵¹; In animal tissue models, it has been suggested that areas with hypoperfusion, ischemic damage, or trauma-induced lesions show the presence of A β PP,⁵² which may suggest that patients with vascular dementia have A β accumulations similar to the aggregates observed in AD. Evidence has been found that ischemic events lead to an increase in AD markers^{53,54}, age plays an important role in cerebral vascularization, as it can contribute to the development of small vessel disease, causing

white matter lesions or other vascular alterations,^{55–58} in the elderly, these events occur early, which may promote the expression of A β characteristic of AD.

In the case of mixed dementia, it is composed of a combination of AD with vascular-origin lesions or vascular dementia⁵⁹; given the evidence that both AD and vascular dementia involve active participation of HSP70 in the presence of A β aggregate markers, it can be inferred that HSP70 plays an important neuroprotective role in mixed dementia, given this relationship and previous evidence on the etiology of mixed dementia.^{60,61}

Therapeutic advances

Molecular chaperones have been extensively studied for their direct neuroprotective role in neurodegenerative diseases. Based on this, various studies have explored the potential of activating or inhibiting these highly specialized proteins to develop drugs targeting molecular chaperones.⁶² Understanding the biochemical composition of HSPs and the epigenetic factors that modulate different HSPs has led to innovative strategies for a variety of diseases that depend on aberrant proteins in their progression, such as chronic degenerative diseases.⁶³ The main goal is to modulate HSPs expression with clinically useful drugs that

interact with the HSP of interest without affecting other HSPs involved in normal daily activities.

Among the reported advances, the development of HSP90 inhibitors has been approved by the FDA as a cancer treatment^{63–65} which could lead to the approval of these same molecules for the treatment of AD; however, there is extensive research into developing new molecules targeting other HSPs, such as HSP40, HSP60, HSP70, and small molecule HSPs.^{66–69}

HSP70 as a therapeutic target

The specific mechanism of HSP70 involves its ability to form complexes with other HSP-type proteins and ATP to target specific proteins.⁷⁰ It has been demonstrated that the inhibition of HSP70 through HSP70 ATPase modulators significantly reduces tau levels. Similarly, the same study suggests that a combination of HSP90 and HSP70 inhibition could be a promising pharmacological target for treating AD, specifically targeting reactive tau protein species.⁷¹ Other studies have suggested that HSP70 can be used not only as a potential therapeutic target in AD but also for modulating the heat shock factor 1 (HSF-1) transcription factor, which increases the expression of HSP70 and other HSPs. Various molecules, such as carbenoxolone and arimoclomol, have become strong candidates for modulating HSP70 expression,^{72,73} These molecules have been tested in animal models focused on Parkinson's disease, AD, and amyotrophic lateral sclerosis^{74–76}; while these drugs have reached preclinical trials with promising results, a long road remains to prove their effectiveness, especially in human models. Studies have also been conducted using HSP70 directly in animal models, as shown in Table 1.

Discussion

Dementia represents a complex pathophysiological process that conditions the functionality of the person who suffers from it due to the loss of cognitive functions, limiting their quality of life. These pathologies have been linked to the accumulation of A β and tau protein that causes synaptic loss because of imbalances in homeostasis.

Although there has been progress in identifying the mechanisms involved and the related biochemical pathways, there is still no specific treatment for these pathologies, so there is still a pressing need to develop and assess effective treatment strategies, as well as predict the treatment response. Therefore, given the cellular mechanisms in which the HSP70 protein and its co-chaperones are involved, they constitute an alternative due to their capacity to modulate the folding of proteins at the brain level and their degradation and elimination.

In this review, the HSP70 protein was analyzed as a potential therapeutic target associated with AD and other dementias. HSP70 is a crucial molecular chaperone in

cells that protects them from misfolded or denatured proteins and fulfills protein degradation functions when necessary. In the context of AD and other late-onset dementias, we found that the role of HSP70 is fundamental both in the onset and progression of the disease.

The neuroprotective activity of HSP70 has been demonstrated in various chronic neurodegenerative diseases, such as Parkinson's disease, Huntington's disease, and conditions involving aberrant proteins that cause neuronal stress.^{77–79} Numerous studies have shown that HSP70 prevents the formation of toxic A β aggregates, NFTs of tau and promotes their elimination through various mechanisms, culminating in proteolysis mediated by autophagy or the proteasome. Additionally, HSP70 has indirect neuroprotective effects⁴⁵ due to its role as a modulator of the cellular stress response, including vascular and inflammatory effects, as seen in vascular dementia and mixed dementia. It is suggested that HSP70 may offer neuroprotective effects against cellular stress derived from vascular processes or mixed events, potentially reducing cell death and promoting neuronal survival in this context.

Although the vast majority of studies supporting this hypothesis are primarily animal models, there are genetic models and protein measurements that substantiate this theory with direct evidence in humans. However, these are still in the early stages of experimental investigation. In some animal models, exogenous intranasal administration delivery⁸⁰ has shown promising results in AD models, suggesting the potential for developing drugs and molecules that can cross the blood-brain barrier (BBB). It is noteworthy that the specific mechanisms involved in transporting HSP70 across the BBB are not well understood but involve receptors, neuronal terminals, vascular spaces, and/or specific lymphatic channels.⁸¹ This model demonstrated improvements in characteristic dementia symptoms and a reduction in A β plaques.⁸⁰

A β PP is also recognized by HSP70, which prevents the formation of A β monomers. Similarly, A β PP is expressed under conditions of tissue damage, such as in small vessel disease, as previously mentioned. This supports the theory of HSP70's role in dementias not correlated with aberrant proteins, as in the case of AD, but rather significantly related to the deterioration of brain cells and the neurovascular system. This reinforces the important role of HSP70 as a neuroprotector in late-onset dementias, positioning it as a promising therapeutic target by influencing various mechanisms among the different late-onset dementias that are likely highly interconnected.

Conclusions

The emergence of aberrant proteins is a common theme in neurodegenerative diseases. The formation of A β and tau aggregates in AD, as well as regions with tissue damage due to ischemia, positions HSP70 as an interesting

candidate for mitigating the toxicity of these proteins. New therapies based on HSP70 could be proposed for use in AD and other late-onset dementias. Among the results obtained from various studies are the modulation of HSF-1 to over-express HSP70, HSP90 inhibitors, and/or the combination of these mechanisms to prevent early pathological events caused by A β , its precursors, or tau.^{82,83} While there is evidence from various studies of HSP70's fundamental role in the pathophysiology of dementias, there is very little evidence in in vivo models due to the limitations applied to these types of investigations.⁴⁷ It would be interesting to consider whether a single agent aimed at increasing HSP70 expression has the desired effectiveness given its mechanism with the disease, or if various targeted agents complement the effect of HSP70. Addressing these and other questions related to dementias not only offers the opportunity to correctly intervene in this disease but also provides the opportunity to delve into other chronic-degenerative diseases and reveal the importance of HSPs in the neurodegenerative process. Research on HSP70 in neurodegeneration is ongoing and promising for future clinical use.

The study and understanding of HSP70 still have a long way to go. The field of study on HSP70 in chronic neurodegenerative diseases represents an area of opportunity full of new possibilities. The new knowledge about HSP70 and its pathways of action reveals its therapeutic potential for the benefit of human health. This review opens new doors in the quest to find new therapeutic avenues for better treatment of these diseases in their various contexts.

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Statements and declarations

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References

- 2024 Alzheimer's disease facts and figures. *Alzheimers Dement* 2024; 20: 3708–3821.
- Cao Q, Tan CC, Xu W, et al. The prevalence of dementia: a systematic review and meta-analysis. *J Alzheimers Dis* 2020; 73: 1157–1166.
- Magallón-Zertuche V, Garrido-Dzib AG, Salazar-González E, et al. A systematic review and meta-analysis on the prevalence of mild cognitive impairment and dementia in Mexico. *Dement Geriatr Cogn Disord* 2024; 53: 274–288.
- Chang-Wong E and Chang-Chui H. Vascular cognitive impairment and dementia. *Continuum (Minneapolis)* 2022; 28: 750–780.
- Iadecola C. The pathobiology of vascular dementia. *Neuron* 2013; 80: 844–866.
- Kapasi A, DeCarli C and Schneider JA. Impact of multiple pathologies on the threshold for clinically overt dementia. *Acta Neuropathol* 2017; 134: 171–186.
- De Sanctis P, Mahoney JR, Wagner J, et al. Linking dementia pathology and alteration in brain activation to complex daily functional decline during the preclinical dementia stages: protocol for a prospective observational cohort study. *JMIR Res Protoc* 2024; 13: e56726.
- King ME, Kan HM, Baas PW, et al. Tau-dependent microtubule disassembly initiated by prefibrillar beta-amyloid. *J Cell Biol* 2006; 175: 541–546.
- Scheltens P, De Strooper B, Kivipelto M, et al. Alzheimer's disease. *Lancet* 2021; 397: 1577–1590.
- Leng F and Edison P. Neuroinflammation and microglial activation in Alzheimer disease: where do we go from here? *Nat Rev Neurol* 2021; 17: 157–172.
- Onyango IG, Jauregui GV, Čarná M, et al. Neuroinflammation in Alzheimer's disease. *Biomedicines* 2021; 9: 24.
- Thakur S, Dhapola R, Sarma P, et al. Neuroinflammation in Alzheimer's disease: current progress in molecular signaling and therapeutics. *Inflammation* 2023; 46: 1–17.
- Agudelo SF, Corrales NZ and Suárez JAS. Rol del óxido nítrico en la hipótesis vascular de la enfermedad de Alzheimer. *Rev Méd Sinerg* 2021; 6: 692–692.
- Tirado R, Pampin B, Gallego Gómez R, et al. Proteína precursora del beta-amiloide (β -App) y daño axonal difuso tras un traumatismo craneoencefálico: un punto de vista forense. *Med Legal Costa Rica* 2022; 39: 37–50.
- Pascual B, Funk Q, Zanotti-Fregonara P, et al. Neuroinflammation is highest in areas of disease progression in semantic dementia. *Brain* 2021; 144: 1565–1575.

16. Granger KT and Barnett JH. Postoperative cognitive dysfunction: an acute approach for the development of novel treatments for neuroinflammation. *Discov Today* 2021; 26: 1111–1114.
17. Ahmad MA, Kareem O, Khushtar M, et al. Neuroinflammation: a potential risk for dementia. *Int J Mol Sci* 2022; 23: 16.
18. Yang X, Cai P, Liu Q, et al. Novel 8-hydroxyquinoline derivatives targeting beta-amyloid aggregation, metal chelation and oxidative stress against Alzheimer's disease. *Bioorg Med Chem* 2018; 26: 3191–3201.
19. Deocaris CC, Kaul SC and Wadhwa R. The versatile stress protein mortalin as a chaperone therapeutic agent. *Protein Pept Lett* 2009; 16: 517–529.
20. Rosenzweig R, Nillegoda NB, Mayer MP, et al. The Hsp70 chaperone network. *Nat Rev Mol Cell Biol* 2019; 20: 665–680.
21. Cyr DM and Ramos CH. Specification of Hsp70 function by Hsp40 co-chaperones. *Subcell Biochem* 2023; 101: 127–139.
22. Ciesielski SJ, Young C, Ciesielska EJ, et al. The Hsp70 and JDP proteins: structure-function perspective on molecular chaperone activity. *Enzymes* 2023; 54: 221–245.
23. Loy CT, Schofield PR, Turner AM, et al. Genetics of dementia. *Lancet* 2014; 383: 828–840.
24. Ingelsson M and Hyman BT. Disordered proteins in dementia. *Ann Med* 2002; 34: 259–271.
25. Orobets KS and Karamyshev AL. Amyloid precursor protein and Alzheimer's disease. *Annu Rev Neurosci* 2023; 24: 14794.
26. Roda AR, Serra-Mir G, Montoliu-Gaya L, et al. Amyloid-beta peptide and tau protein crosstalk in Alzheimer's disease. *Neural Regen Res* 2022; 17: 1666–1674.
27. Rice HC, Malmazet D, Schreurs A, et al. Secreted amyloid-beta precursor protein functions as a GABA(B)R1a ligand to modulate synaptic transmission. *Science* 2019; 363: eaao4827.
28. Esquerda-Canals G, Marti-Clua J, Roda AR, et al. An intracellular amyloid-beta/AbetaPP epitope correlates with neurodegeneration in those neuronal populations early involved in Alzheimer's disease. *J Alzheimers Dis* 2017; 59: 1079–1096.
29. Koren J, Jinwal UK, Lee DC, et al. Chaperone signalling complexes in Alzheimer's disease. *J Cell Mol Med* 2009; 13: 619–630.
30. Zhang XY, Yu JC, Chen WT, et al. Identification of HSP70 gene family members in *Fritillaria cirrhosa* and expression analysis in different tissues under high temperature stress. *Zhongguo Zhong Yao Zhi* 2024; 49: 2422–2433.
31. Taylor JP, Hardy J and Fischbeck KH. Toxic proteins in neurodegenerative disease. *Science* 2002; 296: 1991–1995.
32. Batko J, Antosz K, Miskow W, et al. Chaperones-A new class of potential therapeutic targets in Alzheimer's disease. *Int J Mol Sci* 2024; 25: 3401.
33. Yamashima T, Mochly-Rosen D, Wakatsuki S, et al. Cleavage of Hsp70.1 causes lysosomal cell death under stress conditions. *Front Mol Biosci* 2024; 11: 1378656.
34. Belenichev IF, Aliyeva OG, Popazova OO, et al. Involvement of heat shock proteins HSP70 in the mechanisms of endogenous neuroprotection: the prospect of using HSP70 modulators. *Front Cell Neurosci* 2023; 17: 1131683.
35. Jeyachandran S, Chellapandian H, Park K, et al. A review on the involvement of heat shock proteins (extrinsic chaperones) in response to stress conditions in aquatic organisms. *Antioxidants (Basel)* 2023; 12: 1444.
36. Omid A, Nazifi S, Rasekh M, et al. Heat-shock proteins, oxidative stress, and antioxidants in one-humped camels. *Trop Anim Health Prod* 2023; 56: 29.
37. Rodríguez AEE and Signoret VCZ. Papel de la agregación del péptido Beta amiloide en la enfermedad de Alzheimer. *Rev Educ Bioquím* 2017; 36: 2–11.
38. Wang H, Tan MS, Lu RC, et al. Heat shock proteins at the crossroads between cancer and Alzheimer's disease. *Biomed Res Int* 2014; 2014: 239164.
39. Evans CG, Wisén S and Gestwicki JE. Heat shock proteins 70 and 90 inhibit early stages of amyloid β -(1–42) aggregation in vitro. *J Biol Chem* 2006; 281: 33182–33191.
40. Magrané J, Smith RC, Walsh K, et al. Heat shock protein 70 participates in the neuroprotective response to intracellularly expressed β -amyloid in neurons. *J Neurosci* 2004; 24: 1700–1706.
41. Hoshino T, Murao N, Namba T, et al. Suppression of Alzheimer's disease-related phenotypes by expression of heat shock protein 70 in mice. *J Neurosci* 2011; 31: 5225–5234.
42. Calderwood SK, Mambula SS and Gray PJ Jr. Extracellular heat shock proteins in cell signaling. *FEBS Lett* 2007; 581: 3689–3694.
43. Muchowski PJ and Wacker JL. Modulation of neurodegeneration by molecular chaperones. *Nat Rev Neurosci* 2005; 6: 11–22.
44. Venediktov AA, Bushueva OY, Kudryavtseva VA, et al. Closest horizons of Hsp70 engagement to manage neurodegeneration. *Front Mol Neurosci* 2023; 16: 1230436.
45. Zatsepina OG, Evgen'ev MB and Garbuz DG. Role of a heat shock transcription factor and the major heat shock protein Hsp70 in memory formation and neuroprotection. *Cells* 2021; 10: 1638.
46. Kim JY, Han Y, Lee JE, et al. The 70-kDa heat shock protein (Hsp70) as a therapeutic target for stroke. *Expert Opin Ther Targets* 2018; 22: 191–199.
47. Bobkova NV, Garbuz DG, Nesterova I, et al. Therapeutic effect of exogenous hsp70 in mouse models of Alzheimer's disease. *J Alzheimers Dis* 2014; 38: 425–435.
48. Rivera I, Capone R, Cauvi DM, et al. Modulation of Alzheimer's amyloid β peptide oligomerization and toxicity by extracellular Hsp70. *Cell Stress Chaperones* 2018; 23: 269–279.
49. Evgen'ev M, Bobkova N, Krasnov G, et al. The effect of human HSP70 administration on a mouse model of Alzheimer's disease strongly depends on transgenicity and age. *J Alzheimers Dis* 2019; 67: 1391–1404.
50. Sharma D and Masison DC. Hsp70 structure, function, regulation and influence on yeast prions. *Protein Pept Lett* 2009; 16: 571–581.
51. Alva G and Potkin SG. Alzheimer disease and other dementias. *Clin Geriatr Med* 2003; 19: 763–776.

52. Kalaria RN, Bhatti SU, Palatinsky EA, et al. Accumulation of the β amyloid precursor protein at sites of ischemic injury in rat brain. *Neuroreport* 1993; 4: 211–214.
53. Kalaria RJ. Similarities between Alzheimer's disease and vascular dementia. *J Neurol Sci* 2002; 203: 29–34.
54. Kester MI, Goos JD, Teunissen CE, et al. Associations between cerebral small-vessel disease and Alzheimer disease pathology as measured by cerebrospinal fluid biomarkers. *JAMA Neurol* 2014; 71: 855–862.
55. Cai Z, Wang C, He W, et al. Cerebral small vessel disease and Alzheimer's disease. *Clin Interv Aging* 2015; 10: 1695–1704.
56. Kalaria RN and Sepulveda-Falla D. Cerebral small vessel disease in sporadic and familial Alzheimer disease. *Am J Pathol* 2021; 191: 1888–1905.
57. Liu Y, Braidy N, Poljak A, et al. Cerebral small vessel disease and the risk of Alzheimer's disease: a systematic review. *Ageing Res* 2018; 47: 41–48.
58. Paolini Paoletti F, Simoni S, Parnetti L, et al. The contribution of small vessel disease to neurodegeneration: focus on Alzheimer's disease, Parkinson's disease and multiple sclerosis. *Int J Mol Sci* 2021; 22: 4958.
59. Jellinger K and Attems J. Neuropathological evaluation of mixed dementia. *J Neurol Sci* 2007; 257: 80–87.
60. Jellinger KA. The enigma of mixed dementia. *Alzheimer Dement* 2007; 3: 40–53.
61. Korczyn AD. Mixed dementia—the most common cause of dementia. *Ann N Y Acad Sci* 2002; 977: 129–134.
62. Taldone T, Ochiana SO, Patel PD, et al. Selective targeting of the stress chaperome as a therapeutic strategy. *Trends Pharmacol Sci* 2014; 35: 592–603.
63. Xiao Y and Liu Y. Recent advances in the discovery of novel HSP90 inhibitors: an update from 2014. *Curr Drug Targets* 2020; 21: 302–317.
64. Jhaveri K, Taldone T, Modi S, et al. Advances in the clinical development of heat shock protein 90 (Hsp90) inhibitors in cancers. *Biochim Biophys Acta* 2012; 1823: 742–755.
65. D'Andrea AD. Mechanisms of PARP inhibitor sensitivity and resistance. *DNA Repair (Amst)* 2018; 71: 172–176.
66. Khalil AA, Kabapy NF, Deraz SF, et al. Heat shock proteins in oncology: diagnostic biomarkers or therapeutic targets? *Biochim Biophys Acta* 2011; 1816: 89–104.
67. Maloney A and Workman P. HSP90 As a new therapeutic target for cancer therapy: the story unfolds. *Expert Opin Biol Ther* 2002; 2: 3–24.
68. Vidyasagar A, Wilson NA and Djamali A. Heat shock protein 27 (HSP27): biomarker of disease and therapeutic target. *Fibrogenesis Tissue Repair* 2012; 5: 7.
69. Rappa F, Farina F, Zummo G, et al. HSP-molecular chaperones in cancer biogenesis and tumor therapy: an overview. *Anticancer Res* 2012; 32: 5139–5150.
70. Woo JA, Liu T, Zhao X, et al. Enhanced tau pathology via RanBP9 and Hsp90/Hsc70 chaperone complexes. *Hum Mol Genet* 2017; 26: 3973–3988.
71. Jinwal UK, Koren J, Leary O, et al. Hsp70 ATPase modulators as therapeutics for Alzheimer's and other neurodegenerative diseases. *Mol Cell Pharmacol* 2010; 2: 43–46.
72. Lanka V, Wieland S, Barber J, et al. Arimoclomol: a potential therapy under development for ALS. *Expert Opin Investig Drugs* 2009; 18: 1907–1918.
73. Cudkowicz ME, Shefner JM, Simpson E, et al. Arimoclomol at dosages up to 300mg/day is well tolerated and safe in amyotrophic lateral sclerosis. *Muscle Nerve* 2008; 38: 837–844.
74. Malik B, Nirmalanathan N, Gray AL, et al. Co-induction of the heat shock response ameliorates disease progression in a mouse model of human spinal and bulbar muscular atrophy: implications for therapy. *Brain* 2013; 136: 926–943.
75. Cleren C, Calingasan NY, Chen J, et al. Celastrol protects against MPTP- and 3-nitropropionic acid-induced neurotoxicity. *J Neurochem* 2005; 94: 995–1004.
76. Inden M, Kitamura Y, Takeuchi H, et al. Neurodegeneration of mouse nigrostriatal dopaminergic system induced by repeated oral administration of rotenone is prevented by 4-phenylbutyrate, a chemical chaperone. *J Neurochem* 2007; 101: 1491–1504.
77. Meriin AB and Sherman MY. Role of molecular chaperones in neurodegenerative disorders. *Int J Hyperthermia* 2005; 21: 403–419.
78. Cummings CJ, Sun Y, Opal P, et al. Over-expression of inducible HSP70 chaperone suppresses neuropathology and improves motor function in SCA1 mice. *Hum Mol Genet* 2001; 10: 1511–1518.
79. Adachi H, Katsuno M, Waza M, et al. Heat shock proteins in neurodegenerative diseases: pathogenic roles and therapeutic implications. *Int J Hyperthermia* 2009; 25: 647–654.
80. Ekimova IV, Nitsinskaya LE, Romanova IV, et al. Exogenous protein Hsp70/Hsc70 can penetrate into brain structures and attenuate the severity of chemically-induced seizures. *J Neurochem* 2010; 115: 1035–1044.
81. Hanson LR and Frey WH 2nd. Intranasal delivery bypasses the blood-brain barrier to target therapeutic agents to the central nervous system and treat neurodegenerative disease. *BMC Neurosci* 2008; 9: S5.
82. Kurop MK, Huyen CM, Kelly JH, et al. The heat shock response and small molecule regulators. *Eur J Med Chem* 2021; 226: 113846.
83. Yang F, Wang Y, Yan D, et al. Binding mechanism of inhibitors to heat shock protein 90 investigated by multiple independent molecular dynamics simulations and prediction of binding free energy. *Molecules* 2023; 28: 4792.