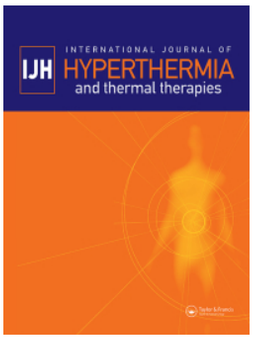

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Inducers and co-inducers of molecular chaperones

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Abstract
Molecular chaperones, which are mostly heat- or stress-induced proteins (HSPs), not only regulate various cellular functions such as protein folding, refolding of partially denatured proteins, protein transport across membranes, cytoskeletal organization, degradation of disabled proteins, and apoptosis, but also act as cytoprotective factors against deleterious environmental stresses. Recent studies indicated that moderate overexpression of molecular chaperones could confer cells and tissues stress tolerance and provide beneficial effects on various pathological states associated with protein misfolding and protein aggregation. Mild heat shock, transfection of HSP genes, and some chemical compounds are the major means of overexpression of molecular chaperones. In this review, we summarize recent studies of chemical compounds that could induce or enhance the expression of molecular chaperones or HSPs.

Keywords: *Heat shock proteins, molecular chaperones, chaperone inducers and co-inducers*

Introduction

It is generally accepted that heat shock proteins (HSPs) have basic and indispensable functions in the life cycle of proteins as molecular chaperones [1], as well as play a role in protecting cells from environmental deleterious stresses [2]. Molecular chaperones are also able to inhibit the aggregation of partially denatured proteins and refold them as demonstrated in *in vitro* and *in vivo* studies [3, 4]. Therefore, molecular chaperones are considered to be endogenous cytoprotective factors, lifeguards or guardians of proteome [5, 6].

Many lines of study indicate that molecular chaperones provide the organism with beneficial functions at both the cellular and tissue levels. For example, the induction of molecular chaperones in animals by whole body hyperthermia or by gene transfer could protect the brain and heart from tissue injury induced by ischemia [7, 8]. A moderate over-expression of molecular chaperones resulted in extended life spans in the nematode and fruit fly [9, 10]. Also, molecular chaperones could suppress the aggregate formation

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of mutant proteins that cause neurodegenerative diseases, such as spinocerebellar ataxia 1 (SCA1) [11], spinal and bulbar muscular atrophy (SBMA) [12], familial amyotrophic lateral sclerosis (FALS) [13] and Huntington's disease [14]. Although the substrates of the molecular chaperones are usually normal or wild-type proteins, molecular chaperones could also deal with mutant proteins in some cases; that is, they can help even mutant proteins fold correctly and maintain normal function by inhibiting non-productive folding pathways [15, 16]. It should be very useful and beneficial to find non-toxic chaperone inducers for the prevention and treatment of various pathological states, such as stress ulcers and ischemia-induced injuries, as well as diseases associated with protein misfolding and protein aggregation. Here, current information on small molecules that could enhance the expression of HSPs or molecular chaperones are summarized (see Table I). A chaperone inducer is a compound that can activate heat shock transcription factors (HSFs) and induce

Table I. Summary of chaperone inducers and co-inducers.

Compounds	Inducer or co-inducer	Concentrations required for the induction of HSPs	Solvent*	Reference
NSAIDs				
Sodium salicylate	Inducer and co-inducer	45–60 mM	PBS	Ishihara et al. 2003
Indomethacin	Inducer and co-inducer	500–750 μM	DMSO	[21]
Aspirin	Inducer and co-inducer	400 μM	PBS	[20]
Hsp90 inhibitors				
Geldanamycin	Inducer	20–400 nM	DMSO	[26]
Radicicol	Inducer	5 μM	ethanol	[24]
Herbimycin-A	Inducer	1–2 μM	DMSO	[27]
Arachidonic acid	Inducer and co-inducer	20 μM	Ethanol	[28]
Prostaglandins (PGs)				
PGA1	Inducer	10–20 μM	Ethanol	[30]
PGJ2	Inducer	10–20 μM	Ethanol	[29]
2-Cyclopentene-1-one	Inducer	500–1000 μM	DMSO	[33]
Proteasome inhibitors				
MG132	Inducer	10 μM	DMSO	[34]
Lactacystin	Inducer	10 μM	DMSO	[34]
Serine protease inhibitors				
DCIC	Inducer	5–20 μM	DMSO	[35]
TLCK	Inducer	100–300 μM	PBS	[35]
TPCK	Inducer	50–100 μM	Ethanol	[35]
Anti-ulcer drugs				
Geranylgeranylacetone (GGA)	Inducer and co-inducer	1 μM	Ethanol	[36]
Rebamipide	Inducer	100–500 μM	DMSO	[40]
Carbenoxolone	Inducer	10–500 μM	PBS	[41]
Polaprezinc (zinc L-carnosine)	Inducer	10–200 μM	PBS	[42]
Herbal medicines				
Paeoniflorin	Inducer and co-inducer	10–150 μM	PBS	[51]
Glycyrrhizin	Co-inducer	10–100 μM	PBS	[51]
Celastrol	Inducer and co-inducer	2–7 μM	DMSO	[50]
Dihydrocelastrol	Inducer and co-inducer	8 μM	DMSO	[50]
Dihydrocelastrol diacetate	Inducer and co-inducer	3 μM	DMSO	[50]
Bimoclomol (BRLP-42)	Co-inducer	1–10 μM	PBS	[43]
Curcumin	Co-inducer	3–10 μM	DMSO	[49]

*PBS: phosphate buffered saline (soluble in water); DMSO: dimethyl sulphoxide.

HSPs by itself. HSF1 is the primary stress-inducible transcription factor that senses and responds to a variety of physiological and environmental stress conditions. The process of HSF1 activation involves multiple steps, including translocation into the nucleus, oligomerization from monomer to trimer, acquisition of DNA-binding activity and phosphorylation [17]. In contrast, a chaperone co-inducer is a substance that cannot induce HSPs by itself, but can enhance HSP induction in combination with other mild stresses. A chaperone co-inducer also has the ability to lower the temperature threshold of the heat shock response.

Chaperone inducers and co-inducers

It is well known that various substances that perturb protein structure such as ethanol, amino acid analogues and heavy metals induce HSPs or molecular chaperones. These substances, however, cannot be used for medical applications because of their toxicity.

Non-steroidal anti-inflammatory drugs (NSAIDs)

Previously, non-steroidal anti-inflammatory drugs (NSAIDs), such as sodium salicylate [18], indomethacin [19] and aspirin [20] have been shown to decrease the temperature threshold of the heat shock response or induce HSPs through the activation of HSF1. NSAIDs are considered to be very useful for protecting cells against diverse forms of stress, because the same drug can inhibit inflammation and induce cytoprotective molecular chaperones [17]. Pre-treatment with these NSAIDs confers cytoprotection [18] and suppresses the protein aggregation and apoptosis caused by an expanded polyglutamine tract [21]. The concentration of sodium salicylate required for the induction of HSPs, however, appears to be too high for clinical application (45–60 mM) [17, 21].

Hsp90 inhibitors

According to the HSF1 cycle model, HSF1 is usually bound to a molecular chaperone complex containing Hsp90, Hsp70, Hsp40 and other co-chaperones and exists in an inactive state. Once cells are exposed to a stressful condition that perturbs the protein structure and causes protein denaturation, molecular chaperones are released from HSF1 and recruited to the site of the denatured proteins, then HSF1 is activated [22]. Geldanamycin, radicicol and herbimycin A, which are known as Hsp90 inhibitors, are able to activate the heat shock response and induce HSPs [23–25]. These compounds are shown to bind to Hsp90 and disrupting the chaperone complex and, consequently, releasing the inactive HSF1, which in turn leads to the activation of HSF1 and the expression of HSPs. Treatment of mammalian cells with geldanamycin could inhibit the aggregation of huntingtin exon 1 protein containing a polyglutamine tract in the pathological range (51 glutamines) [26]. Radicicol, a macrocyclic anti-fungal antibiotic isolated from an herbal remedy, and herbimycin A, a benzoquinoid ansamycin antibiotic that inactivates p-60$^{v\text{-}src}$ tyrosine kinase, are also shown to induce HSPs and to confer cytoprotection in rat cardiomyocytes [24, 27].

Arachidonic acid and prostaglandins

Cell and tissue injuries activate the inflammatory response through the actions of arachidonic acid and its metabolites. Exposure to arachidonic acid resulted in the

induction of heat shock gene transcription via acquisition of DNA binding activity and phosphorylation of HSF1 [28]. Prostaglandins (PGs) are a class of naturally occurring cyclic 20-carbon fatty acids that are synthesized from polyunsaturated fatty acid pre-cursors. The type A and J prostaglandins (PGA_1, PGA_2 and PGJ_2), which are potent growth inhibitors, could activate HSF1 and induce HSPs [29, 30]. Treatment with PGA_1 or PGJ_2 renders cells thermotolerant [31, 32]. Induction of HSPs by PGs requires the presence of a reactive α,β-unsaturated carbonyl group in the cyclopentane ring (cyclopenteneone). This cyclopentenone ring itself, 2-cyclopentene-1-one, is able to activate HSF1 and enhance the expression of HSP genes [33].

Proteasome inhibitors and serine protease inhibitors

Proteasome inhibitors such as hemin, MG132 and lactacystin could activate HSF2 (not HSF1) and augment the expression of the same set of HSPs as HSF1 [34]. Also, serine protease inhibitors (TPCK, TLCK and DCIC) are capable of stimulating HSF1 activation and enhancing the expression of HSPs [35]. These inhibitors of protein degradation might cause the accumulation of mis-folded and disabled proteins or disturb intra-cellular protein homeostasis, which in turn might elicit the stress response.

Anti-ulcer drugs

Geranylgeranylacetone (GGA), an acrylic isoprenoid, is clinically used as an anti-ulcer drug and could induce HSPs through HSF1 activation in gastric mucosal cells [36]. Pre-treatment of animals with GGA markedly suppressed ischemia-reperfusion injury of the liver, small intestine and heart [37]. When orally administered, GGA enhanced the induction of HSPs in the rat liver in combination with heat shock and protected the liver from injury caused by ischemia-reperfusion [38]. GGA itself, however, could not induce HSPs in cultured rat hepatocytes [39]. Therefore, the positive effect of GGA on the induction of HSPs might be cell-type specific. Thus, GGA might work as a chaperone inducer or a co-inducer. Other anti-ulcer drugs such as rebamipide [40], carbenoxolone [41] and polaprezinc (zinc L-carnosine) [42] have been shown to induce HSPs, but these have not been extensively examined.

Others

Bimoclomol, a hydroxylamine derivative, is a co-inducer of HSPs. Bimoclomol itself has no HSP-inducing activity, but when cells are heat shocked in the presence of bimoclomol, HSPs are induced at higher levels than by heat shock alone [43]. Bimoclomol, however, has been shown to have protective activities against various forms of stresses at the levels of cell, tissue or organism [44]. Bimoclomol is shown to bind directly to HSF1 and induce a prolonged binding of HSF1 to HSE [45]. It has been reported in experimental animal models that bimoclomol has potential therapeutic use in the treatment of diabetic peripheral neuropathy [46], cardiac dysfunction [47] and cerebrovascular disorders [48].

Curcumin, a major component of turmeric, a seasoning commonly used in Indian food, is a potent stimulator of the heat shock response [49]. Curcumin itself could not induce HSPs, but when cells were heated at a mild temperature in the presence of curcumin, the expression level of HSPs was much higher than that induced by heat shock alone. Thus, curcumin seems to be a chaperone co-inducer.

Herbal medicines

Celastrol is a member of the triterpenoid compounds derived from the *Celastraceae* family of plants. Extracts of these plants have been used in traditional Chinese medicine for the treatment of fever, chills, inflammation and rheumatoid arthritis. Celastrol and its derivatives (dihydrocelastrol and dihydrocelastrol diacetate) could activate HSF1 and induce HSPs at micro-molar concentrations [50]. Also, a sub-optimal concentration of celastrol and mild heat shock had a synergistic effect on the induction of HSPs. Pre-treatment of cells with celastrol could render them stress-resistant. Therefore, celastrol might be called both a chaperone inducer and a chaperone co-inducer.

Recently, it was found that paeoniflorin, one of the major constituents of a herbal medicine derived from *Paeonia lactiflora* Pall, could induce HSPs by itself through the activation of HSF1 [51]. Also, thermotolerance was induced by the treatment with paeoniflorin. Paeoniflorin had no toxic effect at concentrations as high as 200 μM. Another compound, glycyrrhizin, a main constituent of the hydrophilic fraction of licorice (*Glycyrrhiza glabra*) extracts, had an enhancing effect on the HSP induction by heat shock, but could not induce HSPs by itself. Thus, paeoniflorin might be termed a chaperone inducer and glycyrrhizin a chaperone co-inducer. Peony extracts and their constituents, such as paeoniflorin, have been shown to have various biological and bio-modulating activities including improvement of memory, anti-oxidant activity, anti-epileptic activity, anti-mutagenic properties and anti-hyperglycemia. Glycyrrhizin is also known to have a wide range of pharmacological actions, such as anti-viral, anti-carcinogenic, anti-allergic and anti-inflammatory activities. Although the molecular mechanisms of these pharmacological functions of paeoniflorin and glycyrrhizin are not yet fully understood, these activities might be ascribed in part to their positive effect on the induction of molecular chaperones. A recent study, however, indicated that much higher concentrations of paeoniflorin (0.5–1.0 mM) could induce apoptosis in some type of cells [52].

In the preliminary experiments, treatment of the nematode *C. elegans* with a combination of heat shock and paeoniflorin resulted in a significant increase in their life span by as much as 20–30%. Recent studies indicate that an anti-convulsant drug, named ethsuximide, could extend the life span of *C. elegans* [53]. Therefore, non-toxic chaperone inducers might be useful for the study of ageing and senescence. Also, the effect of paeoniflorin on tumour cell growth was examined. When B16 melanoma cells were transplanted into C57BL mice, most mice died within 30–40 days. In contrast, intra-peritoneal administration of paeoniflorin every 2 days suppressed the growth of tumour cells and all mice were still alive at 40 days after the transplantation of tumour cells (Figure 1).

Conclusions

Molecular chaperones have beneficial functions to inhibit protein denaturation, assist in the refolding and degradation of denatured proteins and suppress the accumulation of disabled proteins in the cell. Therefore, it is of value to search for non-toxic chaperone inducers and co-inducers among natural compounds and herbal medicines for the prevention and treatment of various pathological states including stress ulcers, ischemia-induced injuries, neurodegenerative diseases, transplantation surgery, cancer and ageing. Some chaperone inducers have already been examined for the prevention of protein aggregation expanded polyglutamine tract in cell culture models [21, 26] and tested for the protection against neurodegeneration in a hemi-Parkinsonian animal model [54]. Since most of the chaperone inducers and co-inducers summarized in this review have

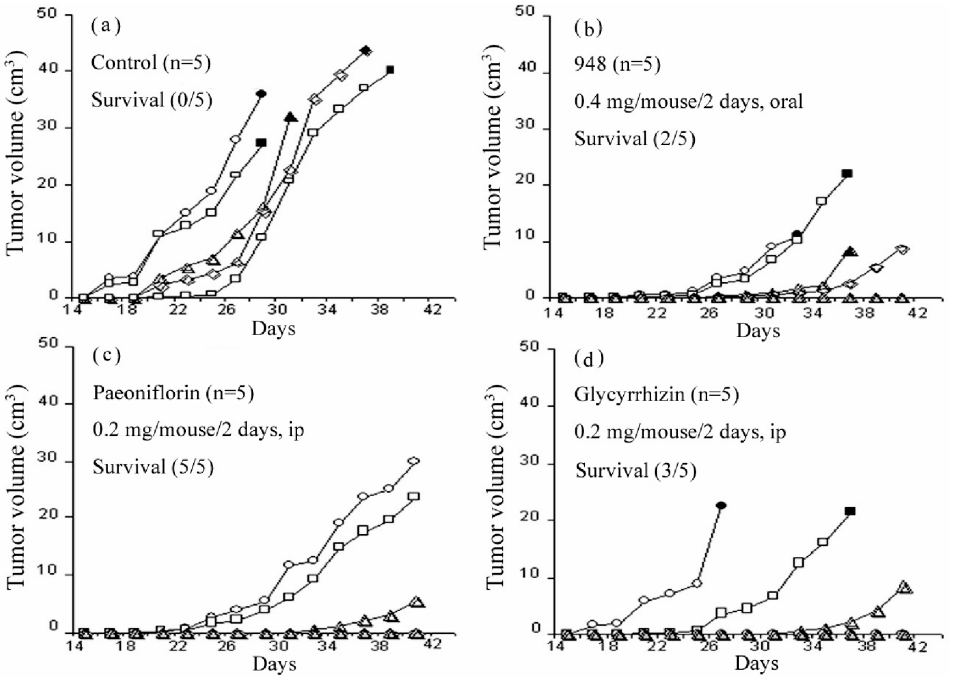

Figure 1. Effect of paeoniflorin and other herbal medicines on tumour growth *in vivo*. B16 melanoma cells (1×10^6 cells) were transplanted subcutaneously into the right thigh of C57BL/6J mice on 0 day. (*a*) Non-treated control mouse. (*b*) Mixture of herbal medicines (948, see [51]). (*c*) Paeoniflorin. (*d*) Glycyrrhizin. These herbal medicines at the indicated amounts were administered intraperitoneally every 2 days. Tumour volumes were measured every 2 days at 14 days or later after the transplantation of tumour cells. One line represents one individual. Filled symbols indicate the death of animals.

bioactive and biomodulating activities, clinical use of these compounds must proceed very carefully with respect to possible side effects.

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