

# Implications of heat shock/stress proteins for medicine and disease

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**Abstract:** Heat shock/stress proteins (HSPs) are crucial for maintenance of cellular homeostasis during normal cell growth and for survival during and after various cellular stresses. The HSP70 family functions as molecular chaperones and reduces stress-induced denaturation and aggregation of intracellular proteins. In addition to the chaperoning activities, HSP70 has been suggested to exert its protective action by protecting mitochondria and by interfering with the stress-induced apoptotic program. The biochemical and functional properties of HSPs observed in cultured cells may be relevant to organs and tissues in whole animals. The activation of the hypothalamic-pituitary-adrenal axis and the sympathetic nerve system elicits the stress response in selected peripheral tissues; the HSP70 expression in the vasculature and stomach increases resistance against hemodynamic stress and stress-induced mucosal damage, respectively. Gastric mucosa pretreated with mild irritants acquires a tolerance against subsequent mucosal-damaging insults. This phenomenon is known as “adaptive cytoprotection”. Transient ischemia also induces ischemic tolerance in the brain and heart, which is called “ischemic preconditioning”. The heat shock response is believed to contribute to the acquisition of the tolerance. The therapeutic applications of chaperone inducers that induce HSPs without any toxic effect are also introduced. *J. Med. Invest.* 44 : 137-147, 1998

**Key Words:** heat shock/stress proteins, physiologic stress, stress ulcer, ischemic tolerance, chaperone inducers

## INTRODUCTION

The heat shock response, first observed in *Drosophila melanogaster* over thirty years ago (1), is now recognized to represent a universally conserved cellular defense program. The heat shock response is mediated by the increased expression of genes encoding a group of proteins referred to as the heat shock proteins (HSPs) or stress proteins. Over the last 30 years, the heat shock response has been observed in cells from all organisms; from bacteria to human. In addition to heat shock, a variety of metabolic insults, including heavy metals, amino acid analogs, oxidants, and different metabolic poisons, also elicits the response. Stress proteins are highly conserved with respect to their primary structure, mode of regulation, and biochemical function (2, 3). HSP expression is not limited to cells undergoing acute stress, and several members of HSP families are constitutively expressed. Many stress proteins maintain cellular homeostasis by acting as molec-

ular chaperones (4-6). Molecular chaperones have been defined as proteins that bind to and stabilize an otherwise unstable conformer of another protein. By controlling binding and release, they participate in the folding and assembly of nascent and unfolded peptides and facilitate protein transport to a particular subcellular compartment and disposal by degradation (7). Stress proteins are classified into families according to their apparent molecular weights and respective inducers. Major stress proteins expressed in mammalian cells are listed in Table 1.

Stress proteins are crucial for the maintenance of cell integrity during normal cell growth as well as during pathophysiological conditions. Most of our knowledge concerning the homeostatic role of stress proteins has come from studies using cultured cells. The best example of the acquisition of tolerance by stress proteins is illustrated by the phenomenon of “acquired thermotolerance”. Cells subjected to a sublethal heat shock treatment or other insults, if they are provided an appropriate recovery period, are able to survive a second lethal stressor. Although much less is known about their expression in vivo, HSPs are acutely induced in intact animals in response to various metabolic insults, such as ischemia/reperfusion

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Table 1. Major stress proteins expressed in mammalian cells

Name	Size (kDa)	Location	Remarks
ORP150	150	Endoplasmic reticulum	Hypoxia inducible
HSP 104/110	104/110	Cytosol/nucleus	Required to survive severe stress molecular chaperone (?)
HSP90	90	Cytosol/nucleus	Part of steroid hormone receptor complex ; chaperon for protein kinases (?)
Grp78 (Bip)	78	Endoplasmic reticulum	Constitutively expressed molecular chaperone
Grp75	75	Mitochondria	Constitutively expressed molecular chaperone
HSC70	73	Cytosol/nucleus	Constitutively expressed molecular chaperone
HSP70	72	Cytosol/nucleus	Highly stress inducible
HSP60	60	Mitochondria	Molecular chaperone (chaperonin)
TCP-1	60	Cytosol	chaperonin related to HSP60
HSP56	56	Cytosol	Part of steroid hormone receptor ; binds FK506
HSP47	47	Endoplasmic reticulum	Collagen chaperone
HSP40 (Hdj 1)	40	Cytosol/nucleus	Cofactor for HSP70
Small HSPs	20-30	Cytosol/nucleus	Proposed regulator of actin ; proposed molecular chaperone
HSP10	10	Mitochondria	Cofactor for HSP60
Ubiquitin	8	Cytosol/nucleus	Involved in protein degradation by proteasome

or inflammation, as well as whole body hyperthermia (8-10). Are the biochemical and functional properties of the heat shock response/proteins observed in cultured cells relevant to organs and tissues in the whole animal? In order to address this issue, in this review, we will focus on the HSP expression in vivo and on the clinical implications of the heat shock response/stress proteins. Because of space limitations, we will not describe the structure of stress proteins. In this regard, please refer to the recent reviews and references therein (2-7).

## INDUCTION OF HEAT SHOCK RESPONSE IN VITRO

The expression of stress proteins is not only induced by elevated temperature, but also by several environmental stresses described above. Many of these agents/treatments share the common property of affecting the proper conformation of proteins. Consequently, the intracellular accumulation of unfolded or misfolded "abnormal" protein may be a common signal (11), but other mediators, including classical second messengers, such as intracellular free

calcium, protein kinases, or alterations in DNA, have also been suggested to induce stress proteins (12, 13).

The stress response in mammalian cells is usually considered to be transcriptionally regulated by the activation of a pre-existing pool of the heat shock transcription factor (HSF), which binds to the heat shock promoter element (HSE) that is composed of at least three pentanucleotide modules (nGAAn) arranged as a contiguous inverted repeat (14). The HSF family includes HSF1, HSF2, HSF3, and HSF4 in higher eukaryotes (15-19). HSF1 is identified as the mediator of stress-induced transcription of heat shock genes (17, 20, 21). HSF2 has been suggested to be important for controlling the activities of heat shock gene expression in normal or unstressed cells (21). The precise physiological roles of HSF 3 and HSF 4 are not completely elucidated (18, 19).

HSF1 is present in normal, unstressed cells as a monomer. HSFs have two highly conserved regions: an NH<sub>2</sub>-terminal DNA-binding domain of 100 amino acids and an adjacent trimerization domain containing three leucine zippers. In higher eukaryotes, there is a fourth leucine zipper domain near the COOH-terminus that appears to interact directly

with the more NH<sub>2</sub>-terminal leucine zipper array to prevent trimerization and to mask the nuclear localization signal in resting cells (22). As illustrated in Fig.1, upon exposure to stress, it rapidly trimerizes, acquires DNA-binding activity, is transported into the nucleus, and becomes transcriptionally competent (23, 24). It has been suggested that the acquisition of DNA-binding activity by HSF1 is independent of inducible phosphorylation, but acquisition of transcriptional activation is linked to inducible serine phosphorylation (25). The redox regulation is also suggested to be involved in the transcriptional activation of heat shock genes (26, 27).

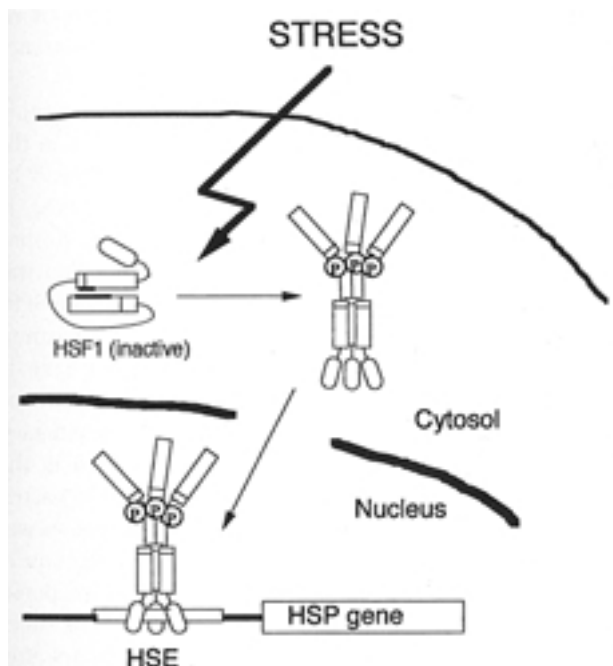


Fig.1. Model of HSF1 activation. In resting cells, HSF1 is present in the cytosol as a monomer. Stress induces trimerization, acquisition of HSF1-DNA binding activity, and nuclear translocation. Stress-inducible serine phosphorylation is required for transcriptional activation.

## HOW STRESS PROTEINS PROTECT CELLS AGAINST DAMAGE UNDER STRESSFUL CONDITIONS

Members of the HSP70 protein family include: HSC70 (a constitutive HSP70), present within the cytoplasm and nucleus; grp75, mitochondrial HSP70; grp78(Bip), a resident of the endoplasmic reticulum. In addition, under conditions of stress, another form of the highly stress-inducible HSP70 (simply referred to here as HSP70) is synthesized at high levels. This stress-inducible HSP70 plays a critical role in the induction of resistance to various metabolic insults (28, 29). The HSP70 protein family functions as molecular chaperones in refolding of denatured polypeptide (4-7). In fact, overproduction of HSP70 was shown to reduce stress-induced denaturation and aggregation of certain proteins (30, 31), leading to the common assumption that refolding and antiaggregating activities of HSP70 determine its role in protection against stresses (32, 33). However, under some conditions, the protective action of

HSP70 appears to be unrelated to its chaperoning action. TNF- $\alpha$ -induced apoptosis can be prevented by overexpression of HSP70 (34). This can be explained by the notion that overproduction of HSP70 interferes with the apoptotic program by suppressing the activation of JNK (35-38). Thus, the protective action of HSP70 in some circumstances may, at least in part, involve direct interference with the apoptotic program, although the molecular basis of this action is still unknown.

There is growing evidence that HSPs play an essential role in protecting cells against oxidative injury (39). Oxidative injury participates in a variety of pathological conditions, such as inflammation and ischemia/reperfusion injury. During inflammation, oxygen free radicals are generated by the phagocytic cells (polymorphonuclear leukocytes, monocytes-macrophages) infiltrating the inflamed tissues. Oxygen free radicals are also produced by a xanthine-xanthine oxidase system. Ischemia causes a decrease in ATP level related to uncoupling of oxidative phosphorylation, leading to the accumulation of xanthine and hypoxanthine. These substrates are normally metabolized by xanthine dehydrogenase. However, during ischemia and when the level of intracellular free calcium is elevated, the dehydrogenase reverts to xanthine oxidase. During reperfusion, xanthine and hypoxanthine are metabolized by xanthine oxidase, generating large amounts of superoxide anion. Oxygen free radicals are potent activators for HSP expression, and at the same time, overproduction of HSP70 protects cells against oxidative injury (39). For example, during activation, macrophages induce HSP70, to protect themselves against autooxidative damage associated with the enhanced respiratory burst activity (40).

Protective effects of HSP against oxygen radical-induced cellular damage may be targeted to any of the following: membranes (lipid peroxidation), proteins, DNA, and mitochondria. The protective effects of HSP70 against lipid peroxidation and DNA damage have been reviewed (41). Recently, Polla et al. suggested that mitochondria are selective targets for the protective effects of heat shock against oxidative injury (42). They demonstrated that overproduction of HSP70 by heat shock prevented hydrogen peroxide-induced decline of mitochondrial permeability transition and swelling of mitochondria, which are suggested to make the "decision to die" in the effector phase of the apoptotic process (43). Consequently, mitochondria may represent a key organella in the choice of necrosis (amplification of inflammation) or apoptosis (limitation of inflammation). Therefore, HSP70 may protect cells against oxidant-induced apoptosis. Thus, HSP overexpression may protect multiple cellular compartments and induce resistance of the cell against damage caused by various metabolic insults.

## INDUCTION OF STRESS PROTEINS IN RESPONSE TO PHYSIOLOGICAL STRESS

The ability to preserve homeostasis under stressful conditions is a requisite for survival of all organisms in an everchanging environment. At the cellular level, the stress

response is well characterized to be mediated by the rapid expression of heat shock genes. However, relatively little information is available on HSP induction in vivo and on its roles in normal as well as pathological conditions. Holbrook and colleagues have demonstrated in the rat that expression of the major HSP, HSP70, is induced in vivo in response to a variety of stresses, including mild elevations in body temperature ( $>1.5$  °C), ether anesthesia, surgery, and restraint stress (8, 44-46). They found that the response was present in the adrenal gland and vasculature and absent in all other tissues examined (44, 46). Restraint causes the rapid expression of HSP70 mRNA with a peak at 30-60 min after starting the stress. The induction of HSP70 transcript is followed by an elevation in HSP70 protein, with maximum expression occurring between 3 and 6 hours after restraint (46).

The restraint-induced HSP70 expression is, at least in part, regulated by neuroendocrine mechanisms. Stress induces the secretion of corticotropin-releasing hormone (CRH) from the hypothalamus, which in turn results in secretion of adrenocorticotrophic hormone (ACTH) from the anterior pituitary gland. ACTH then stimulates the adrenal cortex, increasing both the synthesis and release of glucocorticoids into the peripheral circulation. CRF also activates the sympathetic nerve center in the brain stem, resulting in the synthesis and release of catecholamines from both peripheral ganglia and the adrenal medulla. Hypophysectomy abolished the response of the adrenal cortex, and the addition of ACTH restored specific expression in the hypophysectomized rats, suggesting that ACTH mediates the adrenal response (47).

In contrast to the adrenal response, elevated HSP70 mRNA was observed in the aorta of hypophysectomized animals after restraint regardless of the presence or absence of ACTH or dexamethasone. A specific  $\alpha_1$  adrenergic-blocking agent, prazosin, virtually eliminated the induction of HSP70 in the vasculature, while the  $\beta$  adrenergic receptor antagonist, propranolol, had a lesser effect (46). Furthermore, the specific  $\alpha_1$  adrenergic agonist, phenylephrine, induced the expression of HSP70 in the aorta, suggesting that the vascular response to restraint is dependent on activation of the sympathetic nervous system, especially via  $\alpha_1$  adrenergic receptor (48). The physiological meaning of HSP induction in the vasculature is not completely understood. However, recent evidence suggests that the response plays an important role in protection of arteries against hemodynamic stress. Acute hypertension caused by treatment with various hypertensive agents, including phenylephrine, angiotensin II, and vasopressin, induces HSP gene expression in rat arterial wall (49, 50). Another interesting finding is that the rat strain with a genetic hypertensive background (SHR, spontaneously hypertensive rat) shows enhanced heat shock response in the aorta (51). Alternatively, overexpression of HSP70 prevents endotoxin-induced hypotension (52). Thus, HSP70 in the vasculature appears to induce resistance against hemodynamic stress.

## STRESS PROTEINS IN THE STOMACH

The stomach is frequently exposed to hot food, ethanol, and oxidants generated from ingested food, cigarette smoke, and *Helicobacter pylori*-associated inflammation. Gastric surface epithelial cells are the first line of defense against these irritants. Primary cultures of gastric surface epithelial cells from guinea pig fundic glands exhibit a typical heat shock response (27, 53). In order to study the physiological roles of stress proteins in the stomach, we focused on the HSP induction in the stomach after exposure of rats to restraint and water-immersion stress. This stress causes severe ulceration in the stomach; therefore, it is an excellent model for revealing the importance of stress proteins in gastric mucosal cytoprotection.

Restraint and water-immersion stress caused rapid expression of HSP90, HSC70, and HSP70 mRNAs in the hypothalamus, and these expressions were followed by inductions of the respective HSP proteins. However, in this case, HSP90 was more remarkably induced than HSP70. When the stress-induced HSP90 expression was examined in various brain regions, the elevation of HSP90 induction was observed selectively in the hypothalamus, hippocampus, and amygdala, all of which participate in mediating stress responses (Fig.2). The restraint and water-immersion stress activates the hypothalamic-pituitary-adrenal axis, and HSP70 induction was observed in the adrenal gland. The stress rapidly activated HSF1 in gastric mucosa within 15 min, and HSP70 mRNA expression was detected with a peak at 30 min, followed by induction of HSP70 protein (Fig.3). The gastric mucosal response preceded the formation of gastric mucosal lesion, since macroscopic ulceration was first detected at 2 hours after

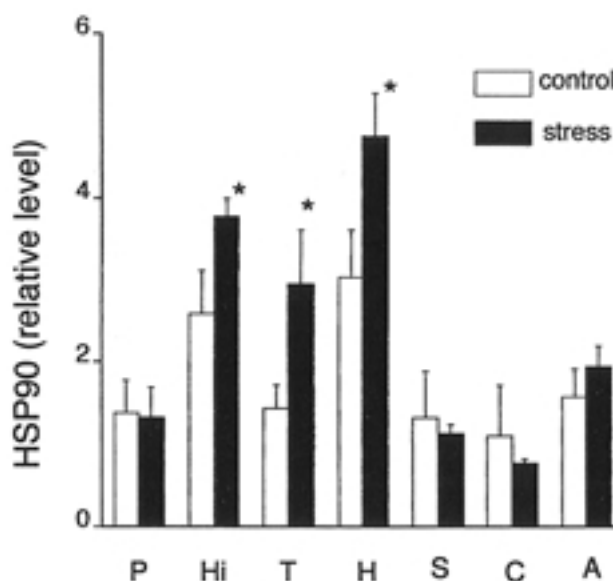


Fig.2. Accumulation of HSP 90 in rat brain regions after exposure to restraint and water-immersion stress. Before and after exposure of rats to restraint and water-immersion stress for 2 h, tissue proteins were extracted from A, amygdala; Hi, hippocampus; S, striatum; T, thalamus; H, hypothalamus; C, cortex; and P, pyriform cortex. The HSP level was measured by immunoblot analysis with a polyclonal anti-HSP90 antibody. Values are the mean  $\pm$  SD from 3 animals. \* $P < 0.05$  by Student's  $t$ -test, compared with unstressed rats.

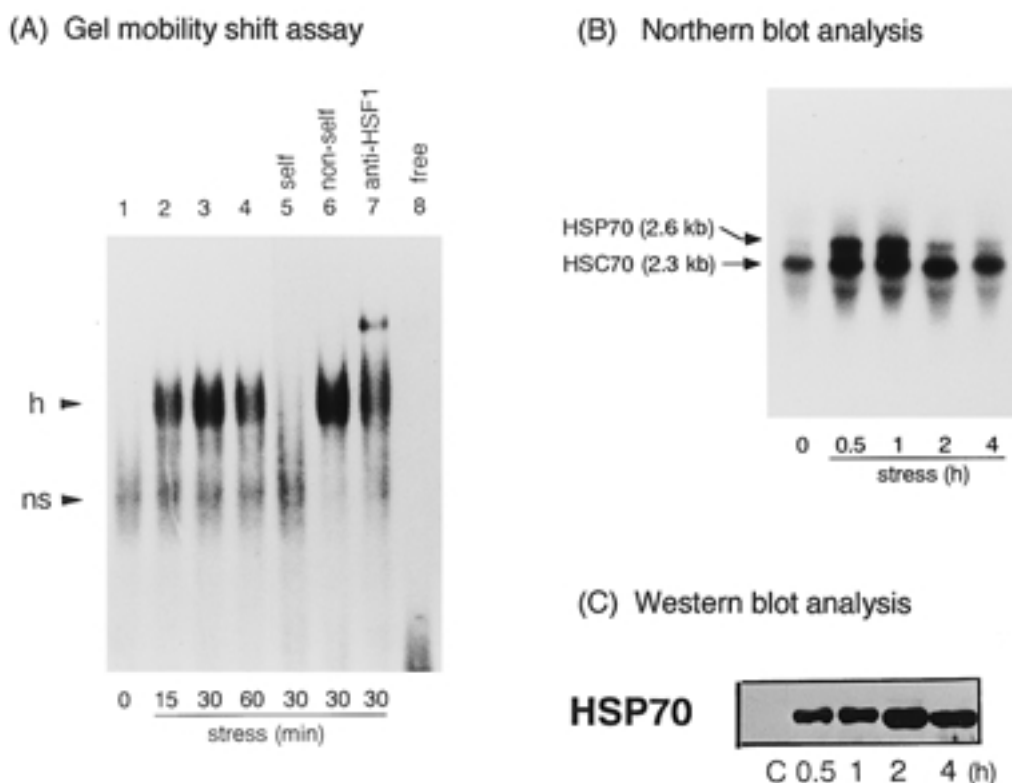


Fig.3. Activation of HSF1 and expression of HSP70 mRNA and protein in gastric mucosa of rats exposed to restraint and water-immersion stress. (A) Before and after exposure to restraint and water-immersion stress for the indicated times, total cellular protein was extracted from gastric mucosa, and gel mobility shift assay was performed with [ $^{32}$ P]HSE oligonucleotide. Lane 5 (marked self) and lane 6 (marked non-self) contained a 50-fold molar excess of unlabeled HSE oligonucleotide and the AP-1 oligonucleotide, respectively. Lane 7 shows the supershift experiment with an antibody against HSF 1. Interaction shown by "h" was specific HSE-binding activity. "ns", nonspecific interaction. (B) Total RNA was extracted from gastric mucosa of the rats and subjected to Northern hybridization with a cDNA probe for human HSP70. (C) The HSP70 protein level in the gastric mucosa was measured by immunoblot analysis with a polyclonal antibody against HSP70.

starting the stress.

In order to better understand the role of HSP expression in gastric mucosa, we exposed three experimental models; protein-malnourished rats, adrenalectomized rats, and vagotomized rats, to restraint and water-immersion stress (Fig.4). Rats fed a low-protein diet had a markedly reduced stress-induced HSP70 mRNA expression in the hypothalamus, adrenal gland, and stomach. The stress ulcer formation was enhanced in these animals. Although the HSP70 mRNA expression in the hypothalamus was rather enhanced in the adrenalectomized rats, bilateral adrenalectomy completely blocked the stress signal from the hypothalamus to the stomach, and the stress response was absent in the stomach, causing the most severe damage in the stomach. In contrast, subdiaphragmatic vagotomy almost completely prevented the stress ulcer formation. In this case, the HSP induction was markedly enhanced; HSP70 mRNA expression was accelerated and remained elevated for more than 4 hours (Fig.4). Thus, the extent of HSP induction was inversely correlated to the severity of gastric mucosal damage. We also found that the HSP expression in gastric mucosa was regulated by the activation of HSF1. These results strongly suggest that the gastric mucosal response is mediated by the activations of hypothalamic-pituitary-adrenal axis and sympathetic nerve system, and that HSPs,

especially HSP70, induce resistance of gastric mucosa against stress-induced mucosal damage. Thus, HSPs play a fundamental protective role in gastric mucosa under stressful conditions.

## STRESS PROTEINS IN THE CENTRAL NERVOUS SYSTEM AND HEART

Transient ischemia induces HSPs within certain regions of the brain, and it is of particular interest that the ability of a neuronal population to survive an ischemic trauma appeared to be correlated with increased expression of HSPs (9). The induction of the stress-inducible HSP70 after transient ischemia was most pronounced in the dentate granule cells and the hippocampal CA3 cells, where neuronal cells exhibit the highest survivability following the ischemic trauma. In contrast, HSP70 induction is minimal in those regions, like the hippocampal CA1 region, that appeared to be most sensitive to the ischemic episode (54). In addition to ischemia, stress protein induction has been observed in various pathological conditions such as trauma, epilepsy, elevated body temperature, neurodegenerative diseases, excitatory amino acids such as glutamate, and drug administration (for reviews see 55 and 56). Certain neuronal cells pretreated with mild heat

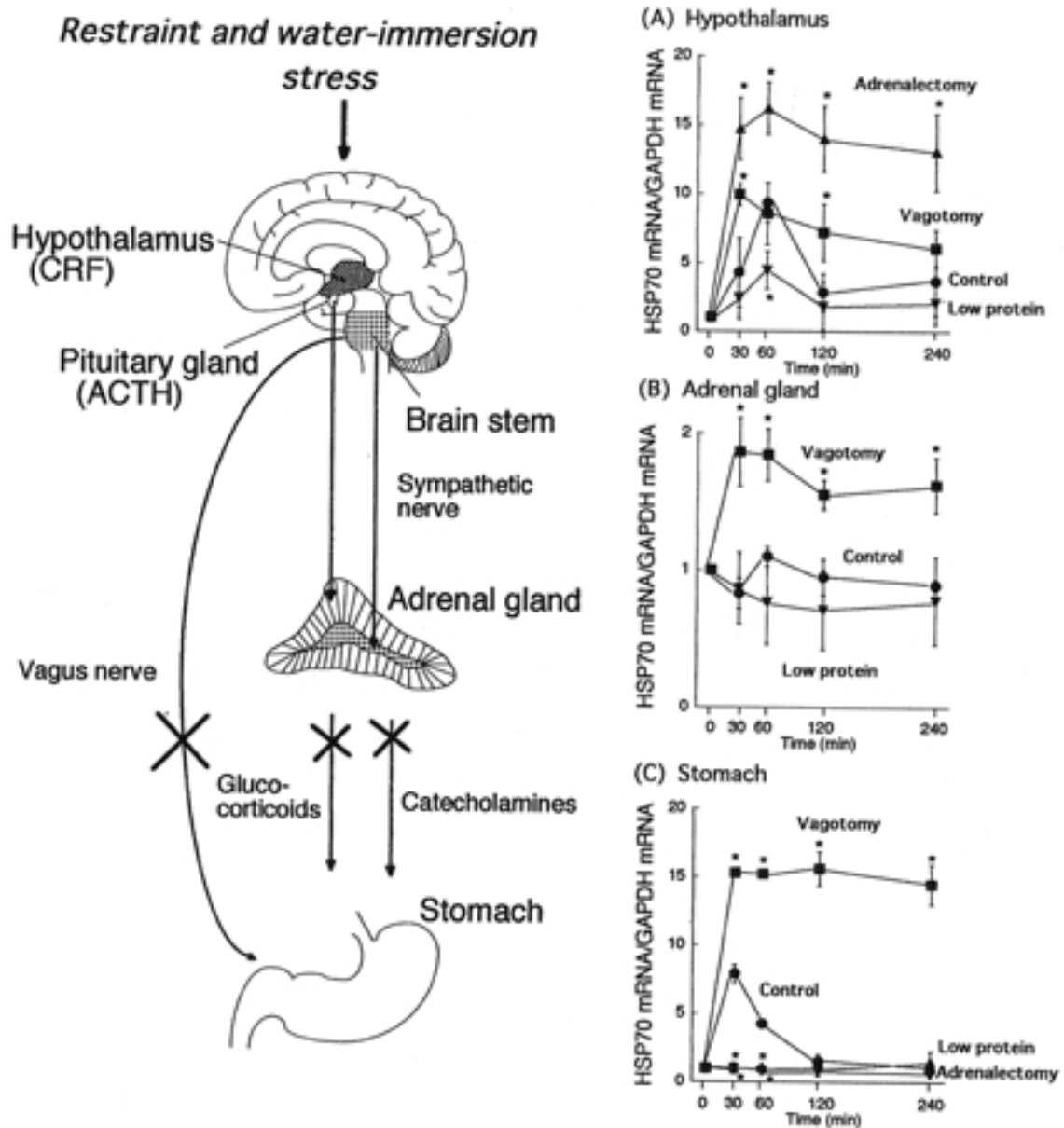


Fig.4. Expression of HSP70 mRNA in the hypothalamus, adrenal gland, and gastric mucosa of rats exposed to restraint and water-immersion stress. Control rats fed a 20% casein diet (●) or rats fed a 5% casein diet (○) for 3 weeks were exposed to restraint and water-immersion stress. Rats fed a 20% casein diet received bilateral adrenalectomy (□) or truncal vagotomy (△), and then they were enforced with the same stress one week after the operation. Before and after exposure to the stress for the indicated times, total RNA was extracted from the hypothalamus (A), adrenal gland (B), and gastric mucosa (C), and the HSP70 mRNA level was measured by Northern blot analysis, as described in the legend to Fig.3. The HSP70 mRNA level was quantified by densitometric analysis and standardized by the mRNA level of glyceraldehyde-3-phosphate dehydrogenase.

shock or sublethal ischemia acquire a tolerance against subsequent lethal ischemic stress. Stress proteins are believed to contribute to the acquisition of this tolerance (57-60). Recently, Kuwabara et al. identified a novel stress protein, the 150-kDa oxygen-regulated protein (ORP150), which is selectively induced in astrocytes exposed to hypoxia. This ORP is also expected to induce ischemic tolerance of astroglia (61).

In the heart, induction of stress response has been observed under physiological stresses, such as ischemia (10, 62, 63), trauma (64), hemodynamic overload (65, 66), and exercise (67), as well as hyperthermia (68). Induction of HSPs by pretreatment with heat shock or transient

ischemia has been shown to be correlated with improvement of functional recovery (69-71) and reduction of infarct size (68, 72, 73). These protective roles were demonstrated in transgenic mouse overexpressing HSP70 in the heart (74-76).

In the brain and heart, the acquisition of ischemic tolerance, which is sometimes referred to as "ischemic preconditioning" is an attractive phenomenon for physicians. The factors that induce the tolerance would be potential targets for treatment and prevention of cerebrovascular diseases and myocardial infarction. Stress proteins are believed to play an important role in the ischemic preconditioning.

### IMPLICATIONS OF CHAPERONE INDUCER FOR MEDICINE AND DISEASE

When cells are under sudden stress from heat, toxins, or disease-causing microorganisms, cellular proteins often lose their proper shape (i. e. aggregation), and HSP numbers quickly double (usually 10% of the protein mass of a cell). These HSPs rush to rescue the injured protein, repairing damage by binding to them and helping to fold them properly again (4-7). HSPs also bind to irreversibly damaged protein, helping to facilitate their degradation through the ubiquitin-proteasome pathway of proteolysis or lysosomal proteolysis (for reviews see 77 and 78). A large body of information supports that many HSPs work as molecular chaperones and are crucial for the maintenance of cell integrity during normal growth as well as during pathophysiological conditions. Therefore, it would be of great therapeutic benefit to discover compounds that induce HSPs without any toxic effect.

Biorex Research & Development Co., Hungary, has introduced a group of drugs in development that works by triggering the production of stress proteins. One hydroxylamine derivative (called Bimoclolmol) that was originally developed to prevent microangiopathy in diabetes patients is now under Phase II clinical trials. Biorex is already testing similar drugs for stroke and atherosclerosis. Bimoclolmol does not directly induce HSP70, but it amplifies the induction when cells are exposed to stressful conditions (79). There are numerous compounds that trigger the HSP induction; however, in most cases, they produce harmful conditions. We introduced a non-toxic chaperone inducer for the first time (80). Geranylgeranylacetone (GGA), an acyclic polyisoprenoid, is an antiulcer drug developed in Japan and has been widely used for more than 13 years. This drug rapidly induces resistance of gastric mucosal cells to irritants within 30 min *in vivo* and *in vitro*. We demonstrated that GGA can directly activate HSF1 and transiently cause transcriptional activation of heat shock protein genes to a lesser extent in both cultured gastric epithelial cells and rat gastric mucosa (80). This compound also enhances heat shock response of gastric mucosa of rats exposed to restraint and water-immersion stress and suppresses stress ulcer formation (Fig.5). GGA has been widely used as an antiulcer drug with a previously unrealized action that induces HSPs without any toxic effect. Nontoxic chaperone inducers may have potential therapeutic benefits for treatment and prevention of several diseases, such as ischemia/reperfusion injury, trauma, inflammation, infection, stress ulcer, and organ transplantation (Fig.6).

In addition to studies on the protective effects of stress proteins on ischemia/reperfusion injury in the brain and heart, there are several on-going projects that target stress proteins. For example, the capacity of HSPs as chaperones might prevent the accumulation of deadly plaques in neurodegenerative ailments such as Alzheimer's disease. Linqest has shown that stress proteins regulate another closely watched class of proteins, prions, which are prone to improper folding. Malformed prions is believed to cause

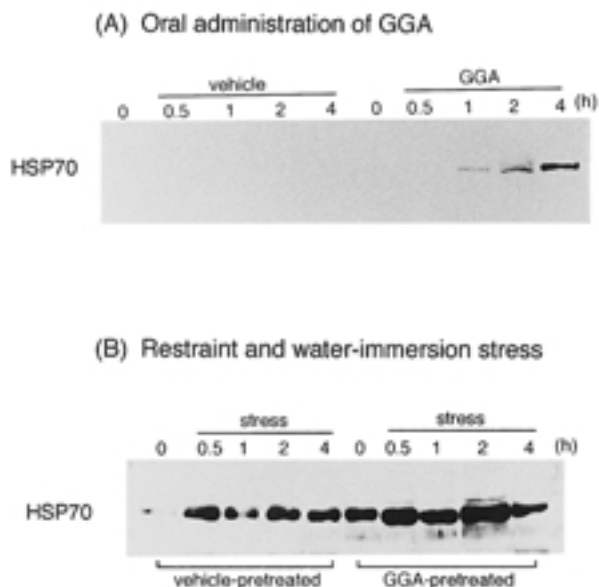


Fig.5. Effects of geranylgeranylacetone (GGA) on HSP70 induction in rat gastric mucosa. Gastric mucosa was collected from rats at the indicated times after intragastric administration of GGA or vehicle (A). Gastric mucosa was also isolated after exposing rats, pretreated with GGA or vehicle for 2 h, to restraint and water-immersion stress (B). Tissue proteins were extracted from gastric mucosa and subjected to immunoblot analysis with an antibody against HSP70.

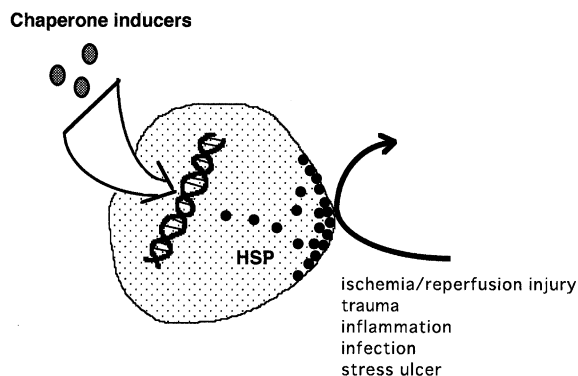


Fig.6. Therapeutic implications of chaperone inducers.

mad cow disease as well as human Creutzfeldt-Jakob disease (81).

Now immunologists are also using stress proteins to develop vaccines for AIDS and other infectious diseases and for treatment of cancer. Stress proteins themselves (HSP65 and HSP70) are potent stimuli of the immune system (for reviews see 82-84). The immune responses raised against pathogen HSPs appear to be essential in protective immunity. HSPs are highly conserved in all organisms and the molecular mimicry may lead to auto-immune reactions in the host (83). HSPs may participate in the processing and/or presentation of exogenous antigens. A possible involvement of HSPs in the antigen presentation is suggested by the structural similarities between major histocompatibility complex (MHC) class 1 and structural models of HSP70 (4). It has been suggested that tumor cells express HSP70 and HSP90 on the cell mem-

brane. HSC70 has been suggested to be a transformation-associated antigen and a target for anti-tumor immunity (85). Immunization with HSP-peptide complexes elicits potent T cell response against the chaperoned peptides and hence against the cells from which the HSPs are purified, as seen in studies with cancers (86). Since HSPs are potent immune-system stimuli, they could be used in vaccines as generic immune-system boosters, or adjuvants for treatment of cancer as well as infectious diseases.

## CONCLUSION

The stress response represents a highly conserved defense program by which cells adapt to abrupt and adverse changes in their environment. Through the study of the structure/function of the stress proteins, especially those which function as molecular chaperones, the molecular basis for the acquisition and maintenance of protein conformation in the cell is now recognized. At the same time, there is increasing evidence that stress proteins play a crucial role in the protection of organs and tissues against injuries from surgery, ischemia/reperfusion, inflammation, or organ transplantation. Considering the potent cytoprotective action of stress proteins, nontoxic chaperone inducers may be of great therapeutic benefit as a new generation of drugs for the treatment of diseases.

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