

Commentary

Loss of Defense Against Stress: Diabetes and Heat Shock Proteins

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HYPOTHESIS

WE PROPOSE THAT DIABETES produces a vulnerable condition with impaired defenses against stress, resulting in widespread unprotected organ systems. More specifically, the ultimate natural history of diabetes and its complications is determined by the net effect of diabetes-induced inflammation, oxidation, and glycation, as well as an induced deficiency of heat shock factor-1 (HSF-1) that subsequently reduces the stress proteins that HSF-1 stimulates—heat shock proteins (Hsps) 60, 70, and 90. (Hsp 70 is also termed Hsp 72.) Furthermore, we speculate that reduced HSF-1 and Hsp levels are the result of an insulin resistance–diabetes-induced loss of membrane fluidity. The hypothesis is based on the following observations: (1) HSF-1 and Hsp levels are low in animal models of diabetes, in human subjects with diabetes, and in people with just insulin resistance. (2) Low Hsp levels lead to cells and tissues that are susceptible to injury with shortened viability. (3) Medications and lifestyles that raise Hsp levels improve diabetes complications and slow the progression of diabetes.

WHAT ARE Hsps?

Hsps are “cellular lifeguards” that have anti-oxidant effects and anti-inflammatory action, aid in folding and refolding proteins, protect cellular nuclear and lipid membranes from injury, and inhibit apoptosis. They are a diverse group of proteins classified by similar function rather than structure, which is to protect cells from injury by preventing protein damage and aggregation. Three of the most abundant Hsps are produced when HSF-1 is activated by a perceived cellular stress, such as oxidation of cellular elements, unfolding of proteins, or increased membrane fluidity—a signal to the cell that it is “melting.” Activated HSF-1 acts as a transcription factor to initiate Hsp expression. In general, Hsps “condition” the cell and therefore the tissue, organ, or organism to stress, thus promoting robustness. Baseline Hsp 70 levels are relatively low but rise promptly in response to stress. Hsp 60 levels similarly rise in response to stress but also play a major role in mitochondrial preservation, being considered a “mitochondrial lifeguard.”¹ Recently it has been noted that mitochondrial dysfunction may be a primary abnormality contributing to the pathogenesis of type 2 diabetes.²

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Modulation of HSF-1 and Hsps has significant impact on organ viability and longevity. Exercise and caloric restriction increase Hsps, while aging reduces Hsps. Transgenic animals that overexpress Hsp 70 or Hsp 60 are resistant to ischemic damage and neurodegenerative insults.¹ Recently, HSF-1 activity has been demonstrated to be a major modulator of aging; increased HSF-1 activity extends life span, while reduced HSF-1 activity lowers life span.³ Clinically, higher serum levels of Hsp 70 measured immediately after severe trauma correlate with improved survival.⁴

Hsp LEVELS ARE LOW IN DIABETES

In the rat model of streptozotocin-induced type 1 diabetes, HSF-1 activation and the Hsp 70 level are low in liver, heart, and skeletal muscle. Additionally, the suppression of Hsp 70 levels by diabetes correlates with generalized increase in tissue inflammation. Furthermore, in that study diabetes blunted the normal HSF-1 and Hsp 70 induction by endurance exercise.⁵ Hsp 60 levels in the heart of rats with streptozotocin-induced diabetes are low.⁶ In a small study of patients with type 1 diabetes with neuropathy, Hsp 72 expression in peripheral leukocytes was extremely low in nine of 16 patients compared with a healthy control population.⁷

In the fatty Zucker rat, the animal model for type 2 diabetes, the Hsp 60 level is markedly lower in the myocardium and adipose tissue.⁶ Additionally, premature apoptosis of the beta cell precipitates the development of diabetes in the Zucker rat⁸—low levels of Hsps in the Zucker would promote apoptosis. Recent studies of individuals with type 2 diabetes demonstrate reduced skeletal muscle Hsp 70 expression correlates with degree of insulin resistance.^{9,10} The study by Kurucz et al.⁹ examined identical twins—one with and the other without type 2 diabetes. The twins without diabetes had lower Hsp 70 expression than healthy control subjects but not as low as their twin with diabetes.⁹ In the study by Bruce et al.,¹⁰ insulin administration during a euglycemic clamp is associated with a rise in Hsp 70 expression. The same research group demon-

strated that glucose administration blocks the normal exercise rise in Hsp 70 level.¹¹ Finally, studying the genetic expression of people with and without diabetes showed lower Hsp 70 expression in the skeletal muscle of subjects with diabetes. That study found that Hsp 70 expression negatively correlates with fasting glucose levels.¹²

INFLAMMATION

Because diabetes is a disease with increased inflammation, oxidation, and glycation, one would have predicted that in response levels of Hsps would be protectively high in diabetes. Yet, data in animal and human diabetes find low Hsp expression. Thus, the paradoxically lower levels of Hsps accentuate the damage incurred by diabetes insults, leaving organs that are vulnerable and prone to fail.

Importantly, intracellular Hsps have an anti-inflammatory action on cells by blocking nuclear factor- κ B (NF- κ B) activation.¹³ In diabetes, protein kinase C activation of NF- κ B is a primary pathway leading to diabetes-induced cytokine gene expression.¹⁴ Thus, low Hsp levels in diabetes will augment the activity of NF- κ B and accentuate inflammation.

MEMBRANE FLUIDITY

Membrane fluidity may play a role in increasing HSF-1 and Hsp expression, and, conversely, membrane stiffness may reduce the cellular Hsp response. Diabetes and insulin resistance are associated with stiffer, less fluid membranes, which is thought to be a result of glycation, oxidative stress, and insulin deficiency.¹⁵ Heat itself makes membranes more fluid. In fact our particular interest in Hsps began when we studied the effects of daily hot water immersion in patients with type 2 diabetes. We observed improved glycemic control and reduced neuropathic symptoms.¹⁶ Interestingly, heat shock itself preserves pancreatic beta cells in tissue culture.¹⁷

Figure 1 schematically demonstrates the cascade of events that ultimately lead to progressive organ damage in diabetes.

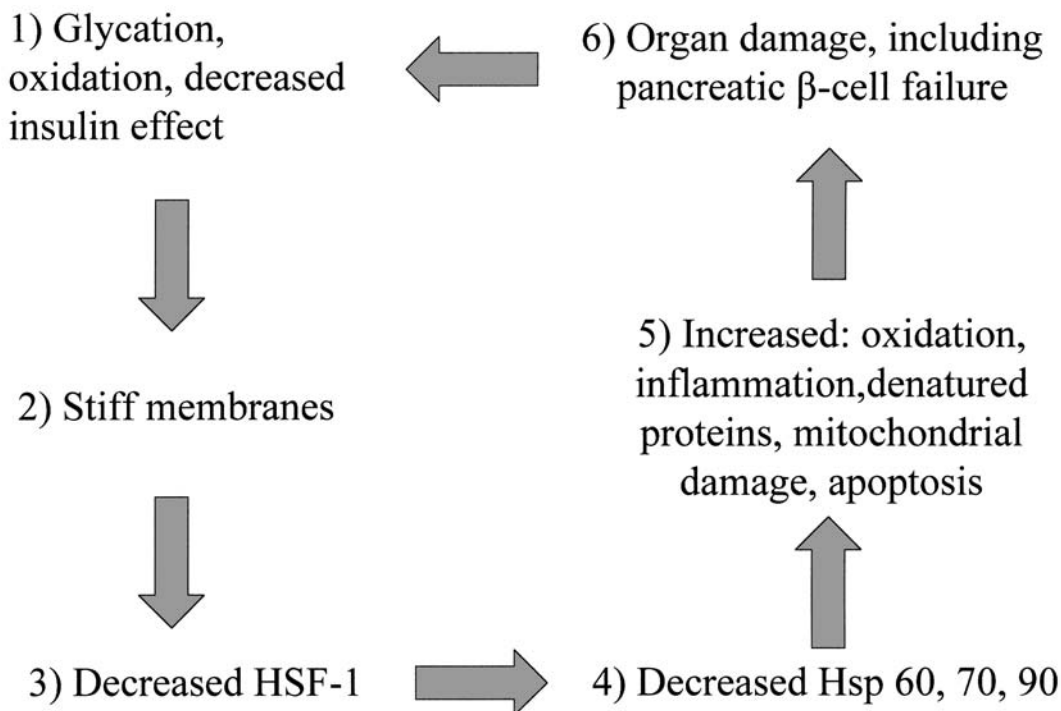


FIG. 1. Diabetes mellitus and Hsps.

RAISING HSP LEVELS

So, can drugs raise Hsp levels? Bimoclolmol is an experimental drug that increases membrane fluidity and extends the activity of HSF-1, and thus raises Hsp 70 levels. In animal models of diabetes, bimoclolmol improves wound healing, reduces diabetes complications, reduces tissue damage to vascular occlusion, and improves insulin sensitivity.¹⁸ Other conditions or drugs that increase membrane fluidity and are associated with improved outcomes are exercise, hexamethylglutaryl (HMG)-CoA reductase inhibitors,¹⁹ carvedilol,²⁰ pentoxifyllin,²¹ and lipoic acid. In fact, in the study referred to earlier in patients with type 1 diabetes with neuropathy, lipoic acid administration was associated with normalization of the low Hsp 72 level in six of the nine patients with low leukocyte Hsp 72 levels. Normalization of their Hsp 72 was associated with clinical improvement in their neuropathy.⁷

Exercise,⁵ carvedilol,²² and thiazolidinediones increase Hsps. In fact, the rise in Hsp 70 level, in response to thiazolidinediones, correlates with the anti-inflammatory action of thiazolidinediones on pancreatic beta cells.²³ Clinically, thiazolidinediones appear to preserve pancreatic beta-cell function.²⁴ Additionally, nitric oxide is

a potent stimulus for Hsp expression. Drugs that restore endothelial nitric oxide release, such as beta-adrenergic blockers, HMG-CoA reductase inhibitors, angiotensin converting enzyme inhibitors, and thiazolidinediones are associated with excellent results in clinical trials of diabetes.²⁵ Pertinently, near-infrared light therapy releases nitric oxide in blood vessels and improves diabetic neuropathy.^{26,27}

Finally, giving Hsps orally or intravenously is relatively impractical because Hsps are primarily intracellular molecules. However, liposomal delivery of Hsp 72 into renal tubular cells blocks activation, NF- κ B tumor necrosis factor, and subsequent ischemia-induced apoptosis.²⁸ Interestingly, many of the drugs or conditions that may raise levels of Hsps also block NF- κ B (i.e., exercise,²⁹ statins,³⁰ carvedilol,³¹ and pentoxifyllin³²).

TESTING THE HYPOTHESIS

Both animal and clinical studies can be used to test our hypothesis:

1. Using animal models of diabetes (the NOD mouse for type 1 diabetes and the Zucker

fatty rat for type 2 diabetes), one could produce overexpressing transgenic Hsp 60 and/or Hsp 70 animals and observe how these animals compare with non-transgenic ones in their development of diabetes and its complications. We would expect a marked delay in the development of diabetes and its complications in the overexpressing animals.

2. In the clinical setting one could examine whether Hsp 70, Hsp 60, or HSF-1 activation predicts the time to development of diabetes from a prediabetic condition like impaired glucose tolerance, or whether stress protein levels in people with diabetes predict the progression of complications and outcomes (blindness, renal failure, myocardial infarction, stroke, amputation, mortality, etc.).
3. Finally, using medications that raise Hsp levels, one could intervene in patients with impaired glucose tolerance and in patients with diabetes and observe whether pharmacologic induction of Hsp levels improves complications and outcomes.

CONCLUSIONS

By understanding the importance of the acquired low Hsp levels in diabetes, we can potentially modify the natural history of the disease. The low Hsps condition produces organs and tissues that are vulnerable to the assault of inflammation, oxidation, and glycation due to diabetes. Furthermore, low Hsp levels augment cytokine expression and thus inflammation. Finding and instituting medications and lifestyles that raise levels of Hsps will improve our ability to manage this progressive disease.

NOTE ADDED IN PROOF

As this paper was going to press Chen published data demonstrating in the streptozotocin induced diabetic rat that reduced myocardial Hsp60 was the result of lack of insulin effect-not hyperglycemia itself.³³ Furthermore, credit should be given to Vigh et al. for, in 1998, they hypothesized that membrane fluidity may control the expression of heat shock proteins.³⁴

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