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PERSPECTIVE AND REFLECTION ARTICLE

The importance of the cellular stress response in the pathogenesis and treatment of type 2 diabetes

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Abbreviations

Akt	Protein kinase B
AMPK	5′ AMP-activated protein kinase
apo A1	Apo-lipoprotein A1
ER	Endoplasmic reticulum
GLUT4	Glucose transporter type 4
GM3	Monosialodihexosylganglioside
HSF1	Heat shock factor 1
HSP	Heat shock protein
iHSP	Intracellular heat shock proteins
IRS	Insulin receptor substrate
mTOR	Mammalian target of rapamycin
pIKK-β	Inhibitor of nuclear factor kappa-B kinase subunit beta
pJNK	Phosphorylated c-Jun N-terminal kinase
PGC1-α	Peroxisome proliferator-activated receptor gamma coactivator 1-alpha
pps	Pulses per second
t2DM	Type 2 diabetes mellitus
V	Volts

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What if we had a new paradigm to explain the metabolic syndrome and type 2 diabetes? What if our focus on the importance of glucotoxicity, lipotoxicity, and inflammation could be addressed in a new perspective of a disease that so threatens global health? We propose that loss of cellular stress response in insulin responsive tissues is the near seminal event that disrupts metabolic homeostasis, leading to a cascade of pathological outcomes. As a valid paradigm, it necessarily would occur very early in the disease process and be a fundamental factor in the pathological features of the disease—namely, obesity, inflammation, beta-cell malfunction, insulin resistance, dyslipidemia, mitochondrial dysfunction, and organ vulnerability. Importantly, correcting the defect through a variety of means would restore metabolic homeo-dynamics and improve functioning of diverse organ systems adversely affected by type 2 diabetes mellitus (liver, muscle, kidney, heart, brain, and beta-cell). Conversely, inducing the defect would induce the disease. Indeed, defects in the stress response occur prior to the development of glucose intolerance, and restoration of the stress response aids in the resolution of all of the abnormalities associated with the metabolic syndrome and t2DM—yielding more robust organelles, organs, and, ultimately, organisms. Herein, we propose that impaired

Hsp activity is a near seminal event in the pathogenesis of t2DM—tipping the balance from health into disease.

Background: exercise, hyperthermia, and diabetes

Lifestyle modification is a primary intervention improving all of the major features of the disease: glycemia, dyslipidemia, obesity, and hypertension. Indeed, the Diabetes Prevention Program found that lifestyle modification to be more effective than drug therapy (Diabetes Prevention Program Research Group et al. 2009). We hypothesized that attempting to mimic the physiological effects of exercise by warming the body might duplicate the beneficial effects of exercise on glycemic control in t2DM. We reasoned that skeletal muscle is the major organ that consumes glucose in response to insulin and predicted that simply warming muscle would improve glucose indices. Indeed, when we treated traditionally managed t2DM with partial submersion in a hot tub for 30 min, 6 out of 7 days/week for 3 weeks. The results exceeded our expectations with improvements in fasting glucose, a 1 % drop in HbA1, a trend toward weight loss, and relief of neuropathic symptoms (Hooper 1999). The neuropathic improvement suggested that heat did more than just improve blood flow to muscles; therefore, we explored cellular mechanisms that surround the heat response and found a vast literature outside of clinical medicine concerning heat shock proteins (HSPs). A Hungarian colleague, Kurucz, reflected on the hot tub study and then examined messenger RNA (mRNA) of heat shock protein70 (Hsp 70) in skeletal muscle of patients with t2DM, subjects with glucose intolerance, and euglycemic identical twins of subjects with glucose intolerance. All subjects, including the euglycemic twins, had lower muscle mHsp70 than control subjects and the levels positively correlated with insulin sensitivity (Kurucz et al. 2002). Subsequently, as we will discuss below, nearly all of the pathological features of t2DM and its complications can be treated by induction of HSPs—ranging from whole body hyperthermia, to genetic modification, to pharmacological agents.

What are Hsps?

Hsps are almost as old as life itself, 2.6 billion years old, and remarkably evolutionarily conserved. Even plant Hsp70 remains 70 % homologous with human Hsp70(Hooper et al. 2010). The heat shock protein molecular chaperones protect cells and their organelles from succumbing to stressful insults, whether from heat, cold, oxidation, free radicals, toxins, or hypoxia. They guard protein integrity by aiding in protein folding, preventing aggregation, or degrading nonfunctional proteins from the cytoplasm. They are often anti-inflammatory inside the cell but can be pro-inflammatory outside the cell, acting as a danger signal that alerts the body to foreign threats. They preserve surface membranes, mitochondria, endoplasmic reticulum, and nuclear fidelity, and participate in intracellular transport. Hsps aid in wound healing, ischemia–reperfusion injury, and sepsis survival (Chen et al. 2007).

Hsp levels in diabetes

In both types of diabetes, iHSP levels [(iHsp70 (iHsp72, HSPA1A), iHsp27, and hemeoxygenase (iHsp 32)] and their response to stress are low in tissues that are insulin sensitive, particularly skeletal muscle, the heart, liver, and monocytes (Kurucz et al. 2002; Atalay et al. 2004a; Bruce et al. 2003; Nakhjavani et al. 2012; Rodrigues-Krause et al. 2012; McClung et al. 2008; Kavanagh et al. 2009; Figueredo et al. 1996). The fall in iHSPs is likely a consequence of the deactivation of the major regulator of iHSPs, HSF1 (Kavanagh et al. 2009, 2011; Atalay et al. 2004b). Within skeletal muscle types, HSP expression is associated with oxidative capacity. Slow twitch fibers (highly oxidative) have higher HSP expression levels, lower activation of inflammatory cytokines, and better insulin signaling compared to fast twitch fibers (Gupte et al. 2008). Moreover, diabetics have a decreased amount of slow twitch fibers and correlated to the severity of insulin resistance (Stuart et al. 2013). Further debilitating the function of Hsp70 is its glycation, which blocks its protein refolding ability (Bathaie et al. 2010). Loss of insulin signaling itself promotes deactivation of HSF1 via an inhibitory phosphorylation of HSF1 by glycogen synthase kinase 3-β (GSK-3β). A low Hsp state then promotes increased activation of inflammatory cytokines, c-Jun N-terminal kinase (JNK) and IkappaB kinase (pIKK-β), which phosphorylate serine 307 of IRS1 and further interfere with insulin signaling. Thus, a vicious cycle is created in which inflammation-induced insulin resistance leads to lower Hsps and further inflammation (Hooper and Hooper 2009). iHSP levels are inversely correlated with glucose disposal rate, insulin resistance, inflammatory cytokines, GLUT4 levels, and mitochondrial function (Bruce et al. 2003). The HSP response is delayed and diminished in diabetic wound healing (McMurtry et al. 1999). Finally, not all studies have found low iHsps in diabetes (Ugurlucan et al. 2010). Not infrequently, these studies were in drug-induced, streptozotocin, diabetes, and the acute stress of the sudden diabetic state could raise the levels initially and with time fall to lower levels (Bathaie et al. 2010).

Low levels of iHsps contribute to an impaired stress response in a disease disrupted by protein glycation and oxidation, free radical formation, protein aggregation, and inflammation, and may be a clue to the etiology of the disease itself for it sets up for disruption of homeostasis and induction of

pathology. On the other hand, appropriately serum extracellular HSPs are higher than normal in t2DM and rise further with longer duration of t2DM, higher glycemia, and inflammation (Nakhjavani et al. 2010, 2012).

Obesity and t2DM are associated with ER stress. Hsp72 directly binds to IRE1α and enhances IRE1α-XBP1 signaling at the ER and thus improves adaptation to ER stress and cell survival (Gupta et al. 2010). Furthermore, reduction of ER stress with agents that augment ER chaperones is associated with amelioration of obesity and diabetes (Lee et al. 2003, 2011).

HSF1 directly stimulates expression of the tight junction protein, occluding (Dokladny et al. 2008). Diabetes induces defects in intestinal tight junctions that lead to a chronic endotoxemia and exacerbate systemic inflammation (Geurts et al. 2013). Impaired HSF1 activity in t2DM may contribute to the gut endotoxemia. Tight junction defects also contribute to renal and retinal pathology in diabetes (Hara et al. 2009; Silva et al. 2013), again perhaps exacerbated by a low HSF1 state.

Aging, diabetes, and Hsps

t2DM is an age-related disease that reduces longevity and in many ways accelerates many of the features associated with aging. HSPs are thought to play a fundamental role in longevity and aging (Murshid et al. 2013). Cytoplasmic Hsp70 levels have been examined across many different species, and higher levels confer longer maximum life spans (Rincon et al. 2005; Salway et al. 2011). For example, in invertebrates, overexpression of HSP70 confers a more than 40 % extension in lifespan (Yokoyama et al. 2002). In *Caenorhabditis elegans*, the transcription factor that regulates Hsps, HSF, is required for daf-2 mutants to express their longevity phenotype. These mutants have reduced insulin-like growth factor receptor function and double the expected lifespan (Hsu et al. 2003). Aging is generally associated with lower iHSPs; however, in our long-term studies of non-human primates, we found that development of insulin resistance via a high fat diet conferred lower iHsps, not age itself (Kavanagh et al. 2007, 2012).

Interestingly, neurodegenerative diseases like Parkinson's and Alzheimer's diseases have a higher prevalence in patients with t2DM (Garcia-Lara et al. 2010; Hu et al. 2007). These diseases share a common loss of insulin signaling in brain and in the t2DM pancreatic beta cell with amyloid precursor accumulation and aggregation (Hooper and Hooper 2005; Frame and Zheleva 2006). Insulin sensitivity as a central aging mechanism is supported by the longest lived mouse models, which have high insulin sensitivity through genetic modification of growth hormone biology (Brown-Borg and Bartke 2012). While iHSPs have not been measured in neurons or beta cells in vivo, loss of insulin signaling likely reduces iHSPs in these tissues, resulting in abnormal protein accumulation and function. Administering insulin and Hsp70 can reduce amyloid accumulation in the brain (Tang et al. 2013; Huang et al. 2014; Bobkova et al. 2013).

Like aging, t2DM accelerates the loss of genome-protecting telomeres (Garagnani et al. 2013; Balasubramanyam et al. 2007) because preservation of telomeres is dependent on a functioning cell stress response (Strub et al. 2008). Disruption of Hsps by t2DM could accelerate aging (Pandita et al. 2004; Tzanetakou et al. 2012). Not surprisingly, telomere shortness and t2DM are both tied to malignant transformation (Ornish et al. 2013). Finally, aging and diabetes are both associated with fluidity reduction and micro-domain (Arnak et al. 2008; Vigh et al. 2007a). These changes in membrane organization can nullify healthy membrane-perturbing signaling and attenuating the heat shock response leading to a vicious cycle whereby aging reduces Hsp induction, which promotes aging through reduced cell survival and accumulation of oxidized proteins (Horvath and Vigh 2010; Vigh et al. 2007b; Török et al. 2013).

Hsp induction—importance of the membrane

We were intrigued how membrane composition could modulate the stress response and act as a temperature and/or stress sensor to activate the cellular stress response. We found evidence for a direct correlation between membrane fluidization and the Hsp response in mammalian cells. The thermal shift of membrane fluidity induced by heat was duplicated by membrane fluidizers (like benzyl alcohol and heptanol). The formation of isofluid membrane states in response to the chemical agents increased the expression of Hsp70 at physiological temperatures. Importantly, we demonstrated that the activation of Hsp expression by membrane fluidizers was not induced by a protein-unfolding signal (Balogh et al. 2013).

Saturated fats from animals are solid, while most unsaturated plant or marine origin fats are liquid at room temperature. Intuitively, it is not surprising that there is an association between type of dietary fats consumed, membrane fatty acid composition, and the development of diabetes (Weijers 2012). Less obvious is the notion that endurance exercise alone can change the membrane fatty acid content with a reduction of saturated fat and increased membrane fluidity (Marini et al. 2011). Conversely, patients with t2DM have higher saturated/cis-unsaturated fatty acid ratio in their membranes (resulting in lower membrane fluidity)(Weijers 2012). A high oleic acid intake normalizes the saturated/unsaturated fatty acid ratio, resets the proper membrane fluidity, and improves glycemia (Perona et al. 2007). Consumption of trans unsaturated fats, whose structure and effects on the membrane structure are closer to those of saturated fats, is also associated with diabetes and other health problems (Kavanagh et al. 2007; Bhardwaj et al. 2011). On the basis of the membrane sensor hypothesis, we speculate that a diet rich in cis-unsaturated fatty acids can be useful in the treatment of diabetes by

remodeling membranes and thus upregulating Hsp70 (Vigh et al. 2007b; Balogh et al. 2013; Török et al. 2013).

Our present interest focuses on better defining a heat receptor and understanding the acute changes in membrane fluidity induced by its activation. Evidence is now gathering that a membrane calcium channel transient receptor potential vanilloid (TRPV), can react to heat and the herb capsaicin and produce a calcium influx into the cell resulting in activation of HSF-1 and thus the cellular stress response (Bromberg et al. 2013). Interestingly, capsaicin ingestion can improve mitochondrial biogenesis, improve exercise performance, block fat-induced insulin resistance, and protect against ischemic events (Luo et al. 2012; Xu et al. 2011). Perhaps, it is no surprise that knock out of TRP channels leads to a t2DM phenotype (Zhu et al. 2011).

Finally, in addition to the general lipid dietary approach, single membrane lipid or lipid molecular species can also be important. The ganglioside GM3 blocks insulin signaling, causing a dissociation of the insulin receptor and caveolin-1 complex in the surface membrane microdomains (rafts) (Kabayama et al. 2007). Thus, a novel therapeutic intervention aimed at normalizing the elevated level of GM3 through inhibiting GM3 synthase could prove beneficial for the treatment of t2DM.

Exercise, diabetes, and Hsps

Exercise offers great potential for improving the complications associated with obesity and diabetes. Exercise can maintain optimal blood glucose, lipid, and blood pressure profiles, which prevent or delay chronic complication of diabetes (American Diabetes Association 2010; Eriksson 1999; Zanuso et al. 2010; Ostergard et al. 2006). Acute and chronic exercise induces mechanical and cellular changes that affect metabolism and organ structure. Acute bouts, depending on intensity of exercise, can result in structural damage to tissues that lead to an adaptive response of tissue repair. Repeated acute bouts lead to enhanced cardiovascular and skeletal muscle functioning (Harber et al. 2012; Gollnick et al. 1972; Hamilton and Booth 2000). Moreover, endurance exercise training increases skeletal muscle mitochondrial enzyme activity (Holloway et al. 2006; Dudley et al. 1982; Gollnick et al. 1973; Holloszy 1975) and respiratory control via oxidative phosphorylation (Holloszy 1967), which improves fatigue resistance (Conlee and Fisher 1979) by modifying fiber type characteristics (Gollnick et al. 1973). Exercise induces metabolic adaptations include increased insulin sensitivity and muscle glycogen content (Manabe et al. 2013) and improved fatty acid oxidation and synthesis of acid cycle enzymes (Harber et al. 2012). Repeated exercise bouts will enhance cardiovascular function such as increasing the absolute and relative left ventricular mass (Longhurst et al. 1981; Wernstedt et al. 2002) as well as vascular density in skeletal muscles (Lash and Bohlen 1992), while physical inactivity deconditions the skeletal muscle and cardiovascular system.

While the etiology of t2DM is not well understood, evidence suggests that progressive insulin resistance is associated with damaged pancreatic β-cell function (Alonso-Magdalena et al. 2011; Sheng and Yang 2008; Hooper 1999). These impairments may be the cause of physical inactivity and increase calorie intake due to lipotoxicity and excess fatty acids accumulation, and resulting in a chronic pro-inflammatory state (Eckel et al. 2005; Sheng and Yang 2008; Furuhashi et al. 2011). This has been supported in obese insulin type 2 diabetics and the descendants of patients with t2DM having a defective mitochondrial oxidative phosphorylation capacity and increased triglycerides and lipids in skeletal muscle (Eckel et al. 2005). Elevated lipid metabolites (ceremide and diacyglycerol) can directly activate inflammatory pathways (i.e., JNK, nuclear factor-κB, and IKK) (Copps and White 2012; Tanti et al. 2012). Moreover, an increase in inflammatory proteins impairs the insulin receptor substrate in t2DM and disrupts the downstream signal for the translocation of GLUT4 protein from the vesicles to the cell membrane, thus impairing glucose transport (Eckel et al. 2005; Hotamisligil 2005; Ozcan et al. 2004).

An acute bout of exercise improves whole-body insulin sensitivity and glucose tolerance (Wojtaszewski et al. 2002; Sakamoto and Goodyear 2002) 24–48 h after the bout (Hawley and Lessard 2008; Zierath 2002; Schneider et al. 1984). The precise mechanisms are not well understood; however, muscle contraction leads to an insulin independent effect via activation of 5′ adenosine monophosphate-activated protein kinase (AMPK) that likewise cause the translocation of GLUT4 to the cell membrane as well as increases GLUT4 gene expression (Daugaard and Richter 2001; Zisman et al. 2000; Hussey et al. 2012; Lehnen et al. 2011; Holloszy 2008; O'Gorman et al. 2006; Kraniou et al. 2006; Holmes and Dohm 2004; Daugaard et al. 2000), thereby improving glucose tolerance and insulin sensitivity (Chen et al. 2003; Richter et al. 2004; Frosig et al. 2004). AMPK is a key regulator of skeletal muscle metabolism and gene expression and is believed to be an important signaling molecule for adaptations caused by exercise training (Russell et al. 2014; Richter and Hargreaves 2013). Furthermore, exercise is known to have an anti-inflammatory effect with reduce pro-inflammatory cytokines in obese and diabetic humans (Belotto et al. 2010; TeixeiradeLemos et al. 2009; Petersen and Pedersen 2006; Gielen et al. 2003). Moreover, acute exercise reduces JNK activity and restores insulin sensitivity by modulating IRS (pSER) in humans (Pauli et al. 2010; Kiraly et al. 2010; Teixeira-Lemos et al. 2011) rat models (Kiraly et al. 2010; Ropelle et al. 2006; Berdichevsky et al. 2010), and cell cultures (Berdichevsky et al. 2010). Hsp72 functions as a natural inhibitory protein of JNK (Park et al. 2001; Volloch et al. 2000)

and improvements attribute to limiting inflammatory kinase disruption of insulin signaling (Gabai et al. 1997).

Muscle mitochondrial function in diabetes mellitus is impaired with fiber-type-specific defects in insulin signal transduction for glucose transport (Song et al. 1999). Specifically, GLUT4 is reduced in type I muscle fibers of type 2 diabetic patients (Gaster et al. 2001; Tanner et al. 2002). These impairments are associated with a low aerobic exercise capacity in obese type 2 diabetics (Kadoglou et al. 2009; Leite et al. 2009). Physical inactivity causes a deconditioning effect and a diminished capacity of skeletal muscle and the cardiovascular system, as observed in bed rest studies (Ringholm et al. 2011; Adami et al. 2013; Brocca et al. 2012). Moreover, in healthy populations, 2 weeks of inactivity can likewise impair peripheral insulin sensitivity and cardiovascular fitness (Olsen et al. 2008). This deconditioned effect may be associated with a decreased HSPs expression and HSF1 gene, which is observed in obese type 2 diabetic humans (Rodrigues-Krause et al. 2012).

Exercise will increase iHsps in response to a varied stress response such as muscle contraction (Liu and Steinacker 2001), ischemia (Bushell et al. 2002; Lepore et al. 2000; Liu et al. 2002), metabolism (Ndisang 2014), oxidative stress (Fittipaldi et al. 2014), and glycogen depletion (Febbraio and Koukoulas 2000; Khassaf et al. 2001). Moreover, the extent of such changes is dependent on training status, intensity, duration, mode, damaging/nondamaging, and fiber recruitment (see reviews: Liu and Steinacker 2001; Morton et al. 2009). Animal studies have shown that acute exercise increases iHsp70 in tissues such as skeletal muscle, lymphocytes, spleen, heart, brain, and liver (Lollo et al. 2013; Touchberry et al. 2012; Salo et al. 1991; Pahlavani et al. 1995; Mikami et al. 2004; Campisi et al. 2003). Interestingly, high-intensity exercise of short duration raises iHsps as effectively as longer duration exercise and produces similar positive metabolic effects on skeletal muscle (Bartlett et al. 2012). Moreover, resistance exercise, which can cause significant muscle damage, has demonstrated that mammalian target of rapamycin (mTOR) signaling is important for inducing hypertrophy (Farnfield et al. 2012; Apro et al. 2013). Recently, mTOR has been implicated as a key protein for the activation of HSF1 in cell cultures (Chou et al. 2012). Exercise induced heat shock proteins have been extensively studied in cardiac tissues and are thought to serve as a cardio protective role for ischemia–reperfusion injury. In fact, a single exercise bout will increase iHsp70 in large and small vessels (Milne et al. 2012) and myocytes and improved ischemia recovery and reduce infarct size (Dillmann and Mestril 1995; Mestril et al. 1994a, b; Nishizawa et al. 1996). Similarly, a cross-tolerance response (Whitley et al. 1999), such that an exposure to one stress (exercise) can protect against other stresses (i.e., hypoxia and or ischemia) or cross-talk (Vigh et al. 2007b), may also occur in skeletal muscle.

In conclusion, we believe that exercise can play a major role in enhancing the endogenous defense system against mechanical and metabolic muscle damage, which has the potential for cross-talk mechanisms for improving insulin signaling and reducing inflammatory induced insulin resistance. Ultimately, exercise can provide a model for developing new therapeutic options to overcome or limit the metabolic impairments of t2DM.

Hyperthermia, diabetes, and Hsps

While a tradition of treating diabetes with healing hot waters has thrived for centuries, particularly in Eurasia, only in the past decade have we invested scientific attention to understand the therapeutic effects of hyperthermia in treating diabetes. Table 1 highlights the results of studies examining hyperthermia and/or other nonpharmaceutical HSP induction methods in animal models of diabetes. One striking observation is how a brief heat shock—as short as 15 min and as infrequent as once a week—results in remarkable improvements in the metabolic state. A variety of techniques have been used to induce hyperthermia—hot water immersion, warm electric blanket, sauna, and infrared box. Mild, direct electrical current stimulation has also been used to augment heat-induced rises in HSPs. Relevantly, whole-body hyperthermia raises baseline iHSPs (Shinohara et al. 2006; Singleton and Wischmeyer 2006). Provocatively (but not recommended by us), it has been observed that low-dose gamma radiation, known to raise HSPs (Seo et al. 2006), applied to diabetic genotype animals over a lifetime is associated with longer lifespan and less renal disease than nonirradiated animals(Nomura et al. 2011).

As noted in Table 1, hyperthermic and nonpharmaceutical Hsp induction studies demonstrate multiple physiological improvements: notably increased GLUT4 transport and AMPK activation, improved adipokine profile, and reduced C-reactive protein, triglycerides, low-density lipoprotein (LDL), advanced glycosylation end product (AGE) formation, body weight, abdominal fat, liver fat, and blood pressure. Lastly, heat shock has been shown to protect from loss of organ function (liver, kidney, pancreatic beta cell, and peripheral nerves). The uniform amelioration of so many of the pathological features associated with t2DM with Hsp induction through nonpharmacologic methods reflects the fundamental role in the initiation and progression of the disease.

Herein, we will review, beyond our initial hot tub therapy study (Hooper 1999), the hyperthermia-metabolic syndrome studies as they differ considerably from the animal model studied, the tissues examined, and the method of Hsp induction. In collaboration with Febbraio and colleagues, we studied Hsp inducers in a fat diet mice model of t2DM. Fifteen minutes of weekly increasing body temperature to 41.5 °C via a warm blanket resulted in a transient rise in Hsp72 in skeletal

Table 1 Hyperthermia and/or other nonpharmaceutical HSP induction methods and therapies for diabetes/metabolic syndrome

Species and metabolic state or model	Heat or stress applied, intensity, duration frequency	Therapeutic result
Type 2 diabetes patients (Hooper 1999)	Hot tub: oral temperature rose 0.8 °C, 30 min, for 3 weeks, 6 out of 7 days/week	1 % fall in HbA1 1.3 mmol/l, weight loss trend, symptoms of neuropathy improved
Obese subjects (Biro et al. 2003)	Sauna: rectal temperature rose 1.0 °C, 15 min at 60 °C, daily, 2 weeks	Fasting blood sugar fell 0.3 mmol/l, weight loss 0.3 kg, BP fell 4 mmHg systolic and 5 mmHg diastolic
Obese subjects' ex vivo monocytes (Simar et al. 2004)	Cells incubated for 2 h at 42 °C	Decreases in pJNK, pIKK-β, and inhibitory serine IRS-1 phosphorylation
Type 2 diabetes patients (Beever 2010)	Sauna: far-infrared, 20 min, 3 times/week for 3 months	Increased quality of life: reduced stress, fatigue, increased health perception, and social functioning
Fat fed mice—model of t2DM (Chung et al. 2008)	Warming blanket: rectal temperature 41.5 °C for 15 min, weekly, 16 weeks	Prevented fat induction of fasting glucose, glucose intolerance, hyperinsulinemia, insulin resistance, and pJNK
Fat fed rats (Gupte et al. 2009a)	Hot water immersion: rectal temperature 41.0 °C for 20 min, weekly, 3 months	Improved glucose tolerance, insulin-stimulated glucose uptake, increased insulin signaling in slow twitch skeletal muscle, decreased pJNK, pIKK-β, increased mitochondrial enzyme levels
Aged insulin resistant rats 24 months old (Gupte et al. 2011)	Warming blanket: rectal temperature of 41–41.5 °C for 20 min, tested 24 h later	Increase in insulin-stimulated glucose uptake in slow twitch skeletal muscle
Aged insulin resistant rats 24 months old, in vitro soleus muscle (Gupte et al. 2011)	Incubated: 30 min at 42 °C	Inhibited anisomycin-induced activation of JNK: effect blocked by specific Hsp72 inhibitor
L-6 rat skeletal muscle cell line treated with tumor necrosis factor alpha to induce insulin resistance (Gupte et al. 2011)	Incubated: 43 °C for 20 min, tested 24 h later	Preserved ATP-coupled oxygen consumption, and fatty acid oxidation, i.e., enhanced mitochondrial function
db/db mice (Kokura et al. 2007)	Far infrared light: rectal temperature of 38 °C for 30 min, 3 times/week, 3 months	Improved glycemia, triglycerides, free fatty acid levels, urinary protein excretion, histological kidney damage, GLUT4 expression
db/db mice and fat mice (Morino et al. 2008)	Heat and mild electric stimulation: 42 °C electrodes and 12 V direct current (55 pps of 0.1 ms duration), 2 times/week for 12–15 weeks	Improved glycemic, reduced insulin levels, reduced liver and body fat, decreased size of adipocytes
HepG2 cells in high glucose medium (Morino-Koga et al. 2013)	Incubation at 42 °C and MES for 10 min	Increased activating phosphorylation IRS and Akt, increased accumulation of insulin on lipid rafts
db/db mice (Kondo et al. 2012)	Heat and mild electric stimulation: 42 °C electrodes and 12 V direct current (55 pps of 0.1 ms duration), 2 times/week for 12–15 weeks	Reduced beta cell apoptosis and ER stress, increased insulin response to glucose challenge, reduced cytokine activation
Low-dose streptozotocin rat(Bathaie et al. 2010)	Hot water immersion: rectal temperature 41.0 °C for 20 min, 3 times/week, 5 months	Lowered fasting glucose, Hb A1c AGE, triglycerides, low-density lipoprotein cholesterol, increased high-density lipoprotein cholesterol, and insulin secretion

muscle, liver, and adipose tissue over a 24-h period. After 16 weeks, heat therapy prevented fat induction of fasting glucose, glucose intolerance, hyperinsulinemia, insulin resistance, and phosphorylation of JNK (Chung et al. 2008). Gupte, Geiger, and coworkers studied fat fed male Wister rats by weekly immersion for 20 min in hot water to raise rectal temperature in a range of 41–41.5 °C for 12 weeks. The heat treatment did not alter body weight, but it did reduce epididymal fat accumulation compared to control fat fed animals. While fasting glucose levels were not altered by the diet, heat treatment, compared to fat fed control animals, reduced insulin levels, improved glucose clearance, improved mitochondrial function, increased insulin-stimulated glucose in both fast and slow twitch muscles, increased insulin signaling with activating phosphorylation of IRS and Akt, augmented GLUT4 translocation, and reduced JNK activation (which was blocked by Hsp72 inhibitor, KNK437), reduced activation of pIKK-β in fast twitch EDL muscle but not in slow twitch soleus muscle. Heat treatment phosphorylated Hsp25 in EDL muscle and restored low Hsp60 in the mitochondria. A single bout of heat treatment in a nonfat fed rat, 41 °C for 20 min, resulted in a rise in insulin stimulated glucose uptake

24 h after the heat shock. Finally, the authors studied the effect of heat (43 °C for 20 min) in vitro L6 muscles and found at 24 h improved oxygen consumption and fatty acid oxidation compared to sham-treated muscle (Gupte et al. 2009a). In a separate study by the same authors, a single bout of heat, 41 °C for 20 min, improved insulin-stimulated glucose uptake in aging Fisher 344 rats in slow twitch soleus muscle 24 h after the heat shock. In vitro heat treatment, 42 °C for 30 min, of soleus muscle applied to 3-month and older 24 month soleus muscles increased expression of Hsp72 and inhibited anisomycin-induced activation of JNK. Inhibition of Hsp72 transcription with KNK437 blocked the ability of heat treatment to reduce JNK activation, which suggests that heat treatment's ability to inhibit JNK activation in skeletal muscle is dependent on increased Hsp72 expression (Gupte et al. 2011).

Kokura and coworkers studied the rodent model of t2DM, db/db mice, treated three times per week for 12 weeks with rectal temperature of 38 °C for 30 min using far infrared light therapy. Heat treatment decreased fasting blood glucose, insulin, and triglycerides levels, and improved glucose tolerance and GLUT4 mRNA in muscle as compared with untreated db/db mice. The rise in urinary albumin and histological kidney damage observed in the db/db mice was inhibited by heat therapy (Kokura et al. 2007).

Kai, Kondo, and colleagues have developed a method that combines heat and mild electrical stimulation that maximizes Hsp72 expression in tissues. In their study, they heated fat fed mice to 42 °C in a warming box and applied electrodes with a 12-V direct current (55 pps of 0.1 ms duration), two times/week for 12–15 weeks. They observed lower fasting glucose, insulin and tumor necrosis factor alpha levels, but raised adiponectin levels, and improved glucose tolerance. Despite the same level of activity and calorie consumption, the treated animals had less liver and body fat, and weighed less with a change in the diet induced t2DM phenotype (see Fig. 1). At 15 weeks, fat cell size decreased and brown fat increased, as did uncoupling protein. The treated animals demonstrated improved insulin signaling in the liver (IRS phosphorylation, Akt activation), lower JNK activation, and higher Hsp72 expression. When Hsp 72 was knocked down with small interfering RNA, insulin signaling, and reduction in JNK activation by the treatment were blocked (Morino et al. 2008). When the same researchers used heat and electrical stimulation applied to db/db mice for 12 weeks, compared to sham treatment, insulin secretion was improved in response to a glucose challenge. Levels of HSP72, insulin, pancreatic duodenal homeobox-1, glucose transporter type 2, and insulin receptor substrate-2 were up regulated in the pancreatic islets of treated mice. On the other hand, JNK phosphorylation, nuclear translocation of forkhead box class O-1, and nuclear factor-κB p65 were reduced. Apoptotic signals, ER stress, and oxidative stress markers were attenuated. Thus, the therapy preserved beta cell function in addition to improving insulin signaling and body composition (Kondo et al. 2012). Finally, the same research group directed their attention to insulin-resistant liver cells, HepG2 cells in high glucose medium, by applying heat at 42 °C and MES for 10 min. The treatment activated the insulin receptor and improved insulin signaling in the absence of insulin by accumulating insulin receptors within lipid rafts (Morino-Koga et al. 2013).

Bathaie and colleagues studied streptozotocin-induced diabetic rats, which are the not ideal animal model to study t2DM, but can add insight into impact of hypoinsulinemia and hyperglycemia and long-term pathological impact. Rats were immersed in a circulating water bath (42 °C for 30 min) to obtain a core body temperature of 41 °C and repeated three times a week for 5 months. The treated diabetic rats compared to untreated animals had improvement in lipid profile [lower cholesterol, triglycerides, and higher density lipoprotein (HDL) cholesterol), better antioxidant capacity, insulin secretion, normalization of serum Hsp70 level and a decrease in AGE formation. The effect on fasting glucose was minimal. Glycated Hsp70 lost its chaperoning ability to reactivate the denatured luciferase. While fewer rats died in the intervention group, the reduction was not statistically significant (Bathaie et al. 2010).

Regarding the limited human studies, Biro and coworkers studied subjects with lifestyle-related diseases (12 % diabetes, 32 % hypertension, 60 % smoking, and 36 % obesity), which might be considered subjects with metabolic syndrome; however, the authors did not use that term. Patients were seated in a far-infrared sauna for 15 min, followed by a warm blanket for 30 min. The treatment raised the body temperature by 1.0 °C. Two weeks of therapy significantly reduced fasting glucose (99 to 94 mg/dl), body weight, and systolic and diastolic blood pressure, while serum lipids remained unchanged (Biro et al. 2003). In a study of insulin-resistant obese subjects with body mass index (BMI)>30 kg/m^2, compared to thinner, insulin-sensitive subjects with average BMIs of 21 kg/m^2 fasting blood was collected and incubated for 2 h ex vivo at 42 °C. Monocytes were separated and tested for insulin signaling and inflammatory markers. At baseline, obese subjects had increased phosphorylation and thus activation of JNK and pIKK-β with increased inhibitory serine phosphorylation of IRS-1 and reduced GLUT4 response to insulin. In response to the hyperthermia, monocyte iHsp25 and iHsp27 rose less in the obese group than in the thin cohort. The heat lowered phosphorylation of JNK and pIKK-β and reduced serine IRS-1 in the obese group. GLUT4 response to insulin after the heat challenge was not retested (Simar et al. 2012).

A study of t2DM patients who were treated with far infrared therapy three times a week for 3 months examined the psychosocial impact of the intervention. Heat therapy was

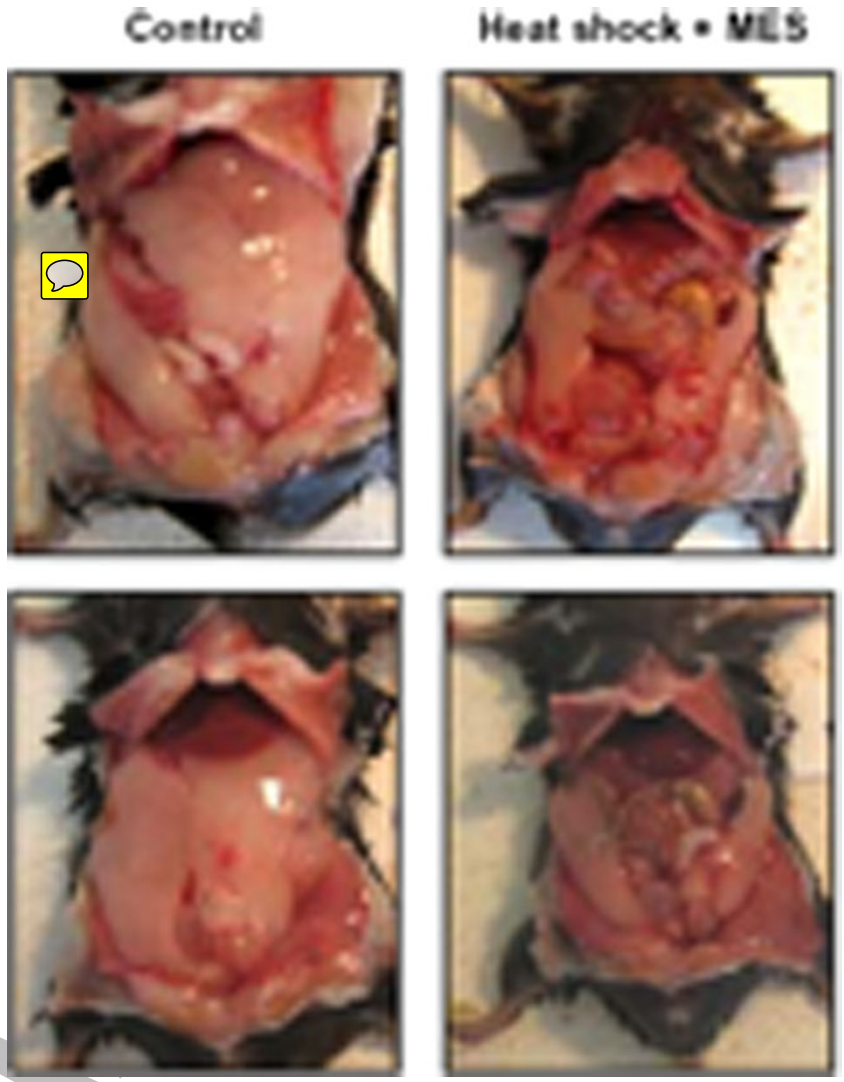

Fig. 1 Ventral aspect of high fat-fed mice sham-treated (control) or treated with heat shock and mild electrical stimulation [42 °C electrodes and 12 V direct current (55 pps of 0.1 ms duration) 10 min, two times per week] after 15 weeks of treatment with exposed peritoneal cavity, showing decrease in visible adipose tissues in treated mice. The diet induced t2DM phenotype is normalized by therapy [from open access journal, Plos1 (Morino et al. 2008)]. Similarly, but not shown here, heme oxygenase stimulation with cobalt protoporphyrin in the Zucker fat rat alters the t2DM phenotype to a thin, smaller rat (Nicolai et al. 2009)

associated with increased quality of life: reduced stress, fatigue, increased health perception, and social functioning (Beever 2010). Clearly, larger, clinical interventional hyperthermia studies are needed in humans.

Induction of Hsps with bioactive compounds and diabetes therapy

Background

In 1997, we showed that the cyto-protective properties of an Hsp inducer (bimoclomol) improved diabetic wound healing and cardiac ischemia (Vígh et al. 1997). Soon afterward, bimoclomol demonstrated amelioration of diabetic neuropathy, retinopathy, and nephropathy. Subsequently, we found that bimoclomol and other hydroximic acids modified membrane lipid domains where thermally or chemically induced perturbation of lipid phase is sensed and transduced into a cellular signal, leading to enhanced activation of heat shock genes (Török et al. 2003). Later, we were able to replicate the therapeutic effects of hyperthermia on t2DM with an Hsp coinducer (BGP 15) by blocking fat fed induction of t2DM in rodents—improving insulin signaling, lowering fasting glucose levels, and reducing cytokine levels. Overexpressing the Hsp72 gene prevented fat feeding-induced impairments in insulin signaling via reduced cytokine release (Chung et al. 2008).

Overview of bioactive inducers

The diverse compounds that raise Hsps and improve many of the pathologies associated with t2DM. These compounds vary widely in their structure and mechanism of Hsp induction and, like hyperthermia, their effects are diverse and consistently metabolically restorative. Table 2 summarizes the agents and their biological effects in t2DM subjects and t2DM animal models. While some of the agents are impractical for

Table 2 HSPs inducers: therapeutic effect on diabetes/metabolic syndrome

HSP inducer	Therapeutic result
Hydroximic acids (Crul et al. 2013)	Improves glycemia, insulin signaling, anti-inflammatory, mitochondria generation renal, and nerve protection; blocks weight gain to antipsychotic medications; ischemia protection; improves diabetic wound healing; reduces liver fat; improves dyslipidemia
Gerenylgerenylacetone (Kavanagh et al. 2011)	Improves glycemia, insulin signaling, anti-inflammatory
Alpha-lipoic acid (Gupte et al. 2009b)	Improves glycemia, insulin signaling, anti-inflammatory
Xenohormetic plant compounds(4)-cucumin (Sahin et al. 2012; Maradana et al. 2013), carvacrol (Cho et al. 2012; Wieten et al. 2010), resveratrol (Han et al. 2012; Ito-Nagahata et al. 2013), metformin (Tsuei and Martinus 2012), astaxanthine (Lee et al. 2010; Yuan et al. 2011), naringin (Sharma et al. 2011), rhodiola (Wang et al. 2012; Panossian et al. 2009), capsaicin (Luo et al. 2012; Joo et al. 2010)	Improves glycemia, insulin signaling, and anti-inflammatory; reduce fatty liver; improves exercise performance; reduces fatigue; preserves kidney function; reduces diabetes-related cancer risk; improves endothelial function; extends life span of nematode
Hemeoxygenase inducers (Li et al. 2008)	Improves glycemia, insulin signaling, anti-inflammatory
Hsp90 inhibitors (Lee et al. 2013; Farmer et al. 2012)	Improves glycemia, insulin signaling, anti-inflammatory
Chemical chaperones (Kars et al. 2010; Raciti et al. 2010)	Improves glycemia, insulin signaling, anti-inflammatory
GLP agonist (Cunha et al. 2009)	Protects islets cells
Hsp27 (Dai et al. 2009) and Hsp72 (Chung et al. 2008) gene overexpression	Improves glycemia, improves insulin signaling, reduces inflammatory cytokines, reduces body fat, preserves beta cells

therapeutic use in t2DM, many are nontoxic and effective when administered orally. Relevantly, some of these compounds also enhance exercise endurance and, in some cases, longevity.

Hydroximic acids This group of compounds, and BGP15 in particular, has received the most research as potentially therapeutic HSP inducers in diabetes. As coinducers of Hsps, they augment HSP induction through enhancing membrane fluidization, acting as raft stabilizers (Gombos et al. 2011) and thereby activating specific "heat sensors" in the membranes (Brameshuber et al. 2010; Török et al. 2013), which initiate a cascade of events resulting in HSF1 activation, IRS laden lipid raft formation, GLUT4 translocation, Akt phosphorylation, mTOR activation, glucose uptake, AMPK activation, SIRT1-like deacetylation, mitochondrial preservation, and reduced JNK activation (see Fig. 2). Relevantly, Rac1 inhibitors almost completely block the hsp-coinducer effect of BGP-15. Beyond improvements in metabolic homeostasis, this group of drugs demonstrate potential efficacy in treating complications of diabetes and providing renal, eye, kidney, nerve, endothelial function, and heart protection. Finally, animal disease models of previously untreatable diseases like muscular dystrophy and ALS respond to this class of drugs. Problems with drug tolerability and/or toxicity have not been identified in either animal or human trials (Crul et al. 2013).

Xenohormetic plant substances Plants and animals share common cellular survival stress responses, as well as common metabolic energy producing organelles, like mitochondria. Stressed plants synthesize bioactive compounds that can confer stress tolerance and longevity to an animal that consumes them by priming and augmenting the animal's HSP response. Indeed, many of the xenohormetic substances associated with ancient traditional diets and/or herbal medicines raise HSPs, improve insulin action, and enhance fitness. Perhaps the most effective drug used today in diabetes, metformin, is a xenohormetic plant compound that increases membrane fluidity, raises Hsps, restores metabolic homeostasis, reduces cancer risk, and reduces diabetic mortality (Hooper et al. 2010; Tsuei and Martinus 2012; Nunn et al. 2010; Muller et al. 1997; Wiernsperger 1999; Holman et al. 2008).

Geranylgeranylacetone Geranylgeranylacetone (GGA) is an antiulcer medication that is widely available in Japan and has been studied as a potential therapeutic agent in many maladies (colitis, ischemia, retinal detachment, infection, etc.). GGA is thought to prolong HSF1 activation (Kavanagh et al. 2011).

Alpha-lipoic acid Alpha-lipoic acid is a cofactor in oxidative metabolism and has a wide application as an over-the-counter product to aid in weight loss, wound healing, and neuropathy (Gupte et al. 2009b).

Hsp90 inhibitors Hsp90 represses HSF1 and, therefore, selective Hsp90 inhibitors activate HSF1-dependent transcription. This class of drugs raises Hsp 70 and improves insulin signaling, preserves diabetic islet cells, and reduces diabetic neuropathy. Unfortunately, the inhibition of Hsp 90 increases the toxicity of this class of compounds (Lee et al. 2013; Farmer et al. 2012).

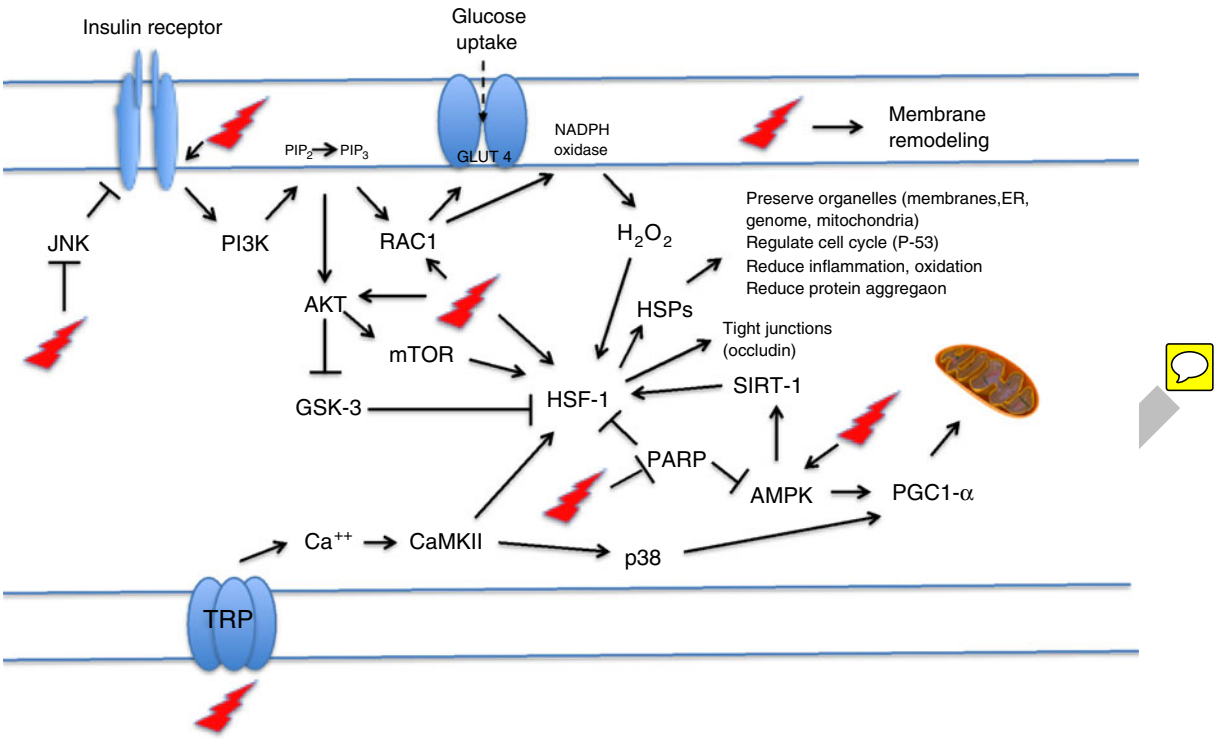

Fig. 2 Exercise, heat shock, and the multitarget, membrane-interacting HSP inducers (like hydroximic acid derivatives) can activate many of the same metabolic pathways. These activators increase insulin receptor autophosphorylation, block JNK's inhibitory phosphorylation of insulin receptor, increase Akt phosphorylation, activate mTOR, activate ras-related C3 botulinum toxin substrate 1 (RAC1), increase GLUT4 translocation and increase glucose uptake, increase second messenger H_2O_2, remodel membranes, increase AMPK, decrease HSF-1 acetylation, deactivates glycogen synthase kinase (GSK) inhibition of HSF-1, increase activation of HSF-1, inhibit poly ADP ribose polymerase (PARP), increase mitochondrial biogenesis and function, increase HSPs that restores stress resilience and organ survival—beta-cell, heart, liver kidney, retina, skin, etc., increase occludin expression and tight junction barrier function, activate the heat sensor transient receptor potential (TRP) that releases calcium as a second messenger to ultimately activate HSF1 and PGC1-α to increase mitochondrial function and synthesis (Dokladny et al. 2008; Crul et al. 2013; Török et al. 2013)

Hemeoxygenase inducers The Hsp heme oxygenase acts as an antioxidant and apoptosis blocker via its byproducts bilirubin/biliverdin and carbon monoxide. Induction of this Hsp changes the whole phenotype of diabetic animal models with marked reduction in adiposity and increases in adiponectin and insulin sensitivity (Li et al. 2008). The hemeoxygenase inducer L-4F is an apo-lipoprotein A1 mimetic, which reverses the obese mouse phenotype. As an aside, one of the defining criteria of the metabolic syndrome is low apo A1 (the major apo-lipoprotein of HDL). This raises the question: Does a low apo A1 level itself promote a lower HSP state associated with the t2DM (Marino et al. 2012)?

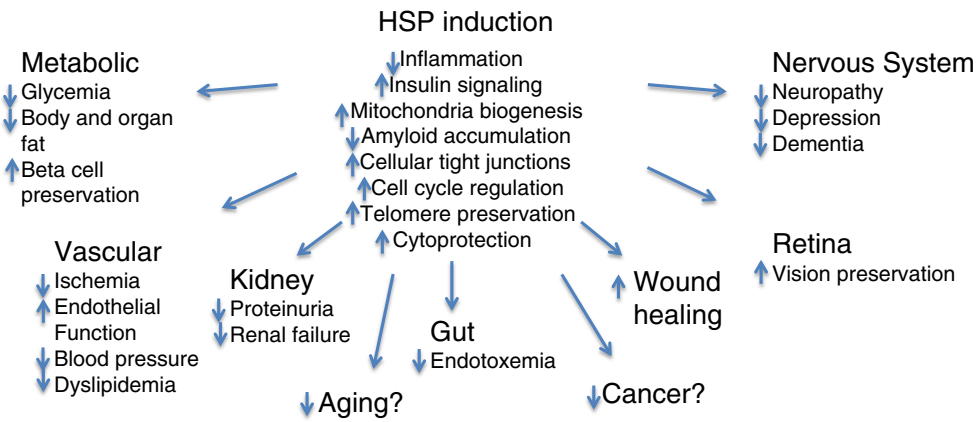

Fig. 3 HSP induction addresses the diverse pathological complications of t2DM

Chemical chaperones Chemical chaperones are similar to HSPs in their ability to facilitate protein folding. Two have been studied in humans, 4-phenylbuteric acid and tuaroursodeoxycholic acid (a bile salt), which were shown to reduce ER stress, stabilize mitochondria, and improve insulin signaling (Kars et al. 2010; Raciti et al. 2010).

Glucagon-like peptide agonist A glucagon-like peptide agonist increases ER chaperone BiP (Grp78), reduces ER stress, and improves islets cell culture survival from an FFA challenge (Cunha et al. 2009).

Common metabolic pathways of exercise, heat, and Hsp inducers

The stress of exercise results in a physiological response assuring survival by activating key metabolic events directed at a temporary reduction in anabolism (fat, glycogen, and protein synthesis) and a focus on generation of ATP. Exercise, heat shock, and many of the Hsp inducers on a cellular level activate AMPK, mTOR, PGC1-α, and SIRT1, particularly in skeletal muscle and liver. The net biological effect is increased fat oxidation, oxidative energy production, and mitochondrial biogenesis (Hooper et al. 2010; Reznick and Shulman 2006; Gurd 2011). With exercise conditioning stress tolerance is enhanced, muscle mass is gained, while inflammation and visceral fat mass are reduced. Heat shock and HSP inducers activate the same pathways and can improve exercise tolerance (Panossian et al. 2009).

Hsp induction addresses all of the diverse pathological features associated with t2DM

We view t2DM as a systemic multiorgan inflammatory disease and suggest that we think of it as "systemic diabetes mellitus" (Hooper 2005). The organ systems affected by t2DM are diverse and the disease itself is associated with comorbid diseases like cancer, dementia, and cardiovascular disease. Other seemingly unrelated inflammatory diseases like asthma and rheumatoid arthritis are associated with t2DM (Dandona et al. 2013; Graeber et al. 2013). Certainly, an age-related disease like t2DM that promotes early aging can contribute to major destructive pathologies.

Improving the cellular stress response via heat shock protein induction can play a core role in treating t2DM its complications. By addressing a fundamental defect that is so key to enhancing cellular resilience and survival, Hsp induction is able to promote pleotropic beneficial effects on diverse pathologies associated with t2DM (Fig. 3).

Reflections

Does the loss of the cellular stress response lie near the core of the pathogenesis of t2DM and the metabolic syndrome? Does a low muscle iHSP state occur years before the metabolic abnormalities appear? Has a sedentary lifestyle with ready access to calories led to an unfit, unconditioned phenotype? Should we begin to think of the syndrome as the "unconditioned syndrome"? We are intrigued that Tobin and coworkers have observed that space flight and zero gravity lab experiments lead to a diabetogenic state with increased inflammation, insulin resistance, and loss of muscle mass (Tobin et al. 2002). Our tissues have evolved over eons to survive a rigorous environment with regular pulses of stress and inflammation and are not prepared to thrive in a sedentary and calorically excessive lifestyle. iHSP induction can ensure that stressors positively influence survival and fitness. This new lifestyle is almost as alien as living in outer space.

New directions

Therapeutic interventions for t2DM focusing on diet and exercise are appropriate. For some individuals, intermittent bouts of intense exercise or fasting may result a better therapeutic impact to recover metabolic homeostasis than lifestyle changes that the body becomes complacent to. Restoration of the cellular stress response via modalities of heat shock and/or medicinal products is warranted. Mimicking exercise opens viable avenues to treat t2DM and its comorbidities.

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