

Heat Shock Gene Dysregulation and Inactivation of Drug Therapy

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COLUMN ARTICLE

In the current global epidemic for chronic disease the incidence of obesity and diabetes has been associated with non-alcoholic fatty liver disease (NAFLD) and insulin resistance in the developing and developed world and may rise to between 30 - 40% of the global population by the year 2050 [1,2]. Drug therapy to delay the complications of obesity and diabetes has escalated with the use of chronic disease medications [3] such as cholesterol lowering drugs, vascular drugs, appetite drugs and Alzheimer's disease drugs that assist in neuron-synapse connections. NAFLD interferes with the hepatic pharmacodynamics of various drugs with increased blood and brain drug levels that are side effects to chronic diseases. The success of the use of these chronic disease medications may require nutritional interventions that accelerate drug metabolism [4,5] and improve insulin resistance and endocrine therapy associated with the delay in the pathogenesis of NAFLD.

Hepatic pharmacokinetics associated with blood and brain drug levels require the activation of the calorie sensitive gene Sirtuin 1 (Sirt 1) to prevent circadian rhythm imbalances that interfere with brain interactions with hepatic drug metabolism [2,6-8]. Sirt 1 is now referred to as the heat shock gene [9-11] with its critical role in the metabolism of heat shock proteins (HSPs) such as HSP 60, 70 and 90 [12]. Sirt 1 is involved in suprachiasmatic nucleus regulation [2,6] with relevance to core brain temperature

control in man and cattle [7,8]. Sirt 1 is downregulated by excessive heat/cold, high calorie diets and oxidative stress associated with increases in HSP 70 levels [12-14]. Sirt 1 deacetylates heat shock factor 1 (HSF1) that is important to the expression of heat shock proteins (Figure 1) with relevance to interactions with amyloid beta for metabolism in the brain and liver [15].

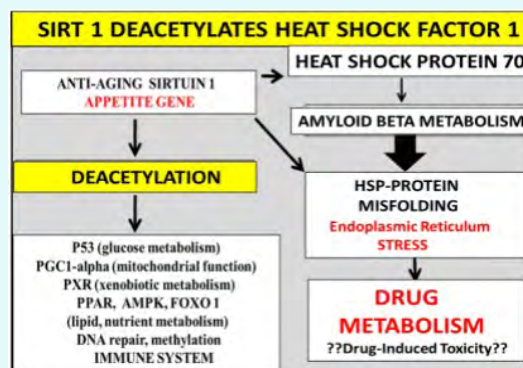


Figure 1: Overnutrition is involved with the downregulation of the calorie sensitive gene Sirt1 and inactivation of HSF1 deacetylation. Sirt 1 is connected to nutrient, protein, lipid and drug metabolism [6]. Sirt 1 repression is involved with primary HSP-amyloid beta misfolding with the induction of ER stress and intersects with defective drug metabolism and drug toxicity. Harmful temperature regulation inactivates the heat shock gene Sirt 1-HSF-1 interactions with interference of brain and liver drug pharmacokinetics.

Sirt 1 is involved with regulation of HSF1 for HSP synthesis and mammalian target of rapamycin (mTOR) important to body temperature regulation [16,17]. Sirt 1 as a deacetylase is important to the transcriptional regulation of nutrients, lipids and drugs [6] with Sirt 1 connections for body temperature regulation, HSP and drug metabolism [4,5]. Connections between mTOR1 for protein quality control and ER stress [18] that involve HSF1 implicate Sirt 1 to be important to HSP-amyloid beta misfolding [15] involved in ER stress related mitophagy and insulin resistance [5]. Downregulation of Sirt 1 induces temperature dysregulation and ER related programmed cell death [19] associated with the inactivation of endocrine system in man [20,21]. Temperature regulation of HSF1 is closely linked to nutrient sensing insulin/IGF-1 signalling, organ development and growth [22,23].

The events of the heat shock gene Sirt 1 dysregulation (stress, heat/cold disorders, overnutrition) may be the primary defect in the HSP misfolded protein induction of ER stress related to mitophagy/programmed cell death. Previous or new drugs may be the innocent bystander in drug induced ER stress toxicity [24-27] and may need to be re-interpreted with relevance to drug induced ER stress in cells. Pharmacological modulation of HSF1 [28-30] with relevance to Sirt 1 dysregulation may need to be reassessed with relevance to stress induced damage. Heat therapy has been used in obesity and diabetes [31] and heat therapy intervals need to be carefully determined to prevent inactivation of Sirt 1 and the induction of misfolded HSPs with relevance to hepatic ER stress and inactivation of drug and cholesterol metabolism.

CONCLUSION

Drug and endocrine therapy to delay the complications of obesity and diabetes has escalated with the use of chronic disease medications to improve therapy in the presence of ER stress induced mitophagy. Nutrient assessment in diabetes has increased to activate the heat shock gene Sirt 1 and to prevent ER stress that may be the critical to the prevention of drug induced toxicity, ER stress and mitophagy. Heat therapy may lead to inactivation of the heat shock

gene Sirt 1 with inactivation of various critical drug and endocrine therapies essential for multiple organ dysfunction syndrome.

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Keywords: *Heat Shock Gene; Pharmacokinetics; Temperature; Chronic Disease; Sirtuin 1; Heat Shock Protein; Nutrient; Heat Shock Factor 1; Drug; Endoplasmic Reticulum Stress*

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