GAVIN PUBLISHERS

Biomedical Discoveries

Alkhatib AJ. Biomed Discoveries: BMDC-103.
DOI: 10.29011/ BMDC-103. 100003

Research Article

The Progression of a Disease Depends on Downregulation of Heat Shock Protein 70 (HSP70) And Upregulation of Inducible Nitric Oxide Synthase (iNOS): A New Medical Hypothesis

Ahed J. Alkhatib*

Department of Legal Medicine, Toxicology of Forensic Science and Toxicology, School of Medicine, Jordan University of Science and Technology, Jordan

***Corresponding author:** Ahed J. Alkhatib, Department of Legal Medicine, Toxicology of Forensic Science and Toxicology, School of Medicine, Jordan University of Science and Technology, Jordan. Tel: +962795905145; Email: ahed.alkhatib64@yahoo.com

Citation: Alkhatib AJ (2018) The Progression of a Disease Depends on Downregulation of Heat Shock Protein 70 (HSP70) And Upregulation of Inducible Nitric Oxide Synthase (iNOS): A New Medical Hypothesis. Biomed Discoveries: BMDC-103. DOI: 10.29011/ BMDC-103. 100003

Received Date: 09 December, 2017; **Accepted Date:** 24 January 2018, 2018; **Published Date:** 30 January, 2018

Abstract

Introduction: A disease is usually accompanied by upregulation the expression of Heat Shock Proteins (HSP) which act as chaperons to offer some cellular protection to overcome pathologic processes. Other molecular mechanisms are also accompanied by diseases including the upregulation of Inducible Nitric Oxide Synthase (iNOS) which acts to widen the spectrum of disease including oxidative stress through increasing the production of free radicals.

Objectives: To investigate for what extent the upregulation of HSP70 will continue offering cellular protection with the disease progression; and if the expression of iNOS will change as the disease progresses.

Methodology: To test this hypothesis, we conducted several studies over 10 years including diabetes, Parkinson disease, and the protective effects of herbal treatments including *Urtica pilulifera.*

Results: The expression of HSP70 was downregulated through our studies significantly compared with control groups. Several studies reported different findings. When the methodology of these studies was reviewed, the levels of HSP70 were measured following the conduction of the experiments. In this regard, we agree with these studies. In other words, the upregulation of HSP70 offers cellular protection against cellular changes including oxidative stress, but with the progression of a disease, it seems that the ability of producing more HSP70 becomes limited. Our studies assessed the expression of HSP70 after the end of the experiment, at least one month, and showed that its expression was downregulated. The expression of iNOS is upregulated as disease progresses, and our studies showed its upregulation till the ends of our experiments. It is possible to have another hypothesis, if iNOS acts directly to suppress the expression of HSP70, but our studies in this level can't prove that. Using experimental model, we induced diabetic model and treated diabetic group with *Urtica pilulifera* and metformin and found that in both treatments, HSP70 was upregulated, and iNOS was downregulated. This implies that the disease progression may follow the net immunoreactivity of these two biomarkers which implies an epigenetic model.

Conclusion: The expression of both biomarkers HSP70 and iNOS helps in determining, at least partially, the progression of diseases.

Keywords: Chaperone; Disease; Downregulation; Expression; HSP70; iNOS; Progression; Upregulation

Introduction

This study presents our previous works in addition to exploring the literature about the progression of disease. We have studied various diseases and different organs and reached to our conclusion in building our new medical hypothesis. Accumulated data derived from our studies indicated that the balance between the expression of the two main players (iNOS and HSP70) is disturbed, and consequently a disease may progress. We will present our previous studies in this article in details. Ekmekcioglu et al. [1] stated that the expression of inducible NO synthase (iNOS/NOS2) can predict poor outcome in multiple cancers, and it has also been associated with several inflammatory conditions. We have conducted a study to explore the impact of the co-expression of iNOS and HSP70 in brains of diabetic rats. Diabetes type 1 was induced in rats and immune histochemical analysis for both iNOS and Hsp70 in the brain tissues was carried out. The results pointed to three points: diabetes significantly increased the expression of iNOS in brain compared with control (p=0.000), diabetes decreased the expression of HSP70 significantly in brain tissue of diabetic rat compared with control (p=0.000), and it was interestingly to find the most effects of expression, particularly iNOS to occur in gray matter (Figure 1) [2].

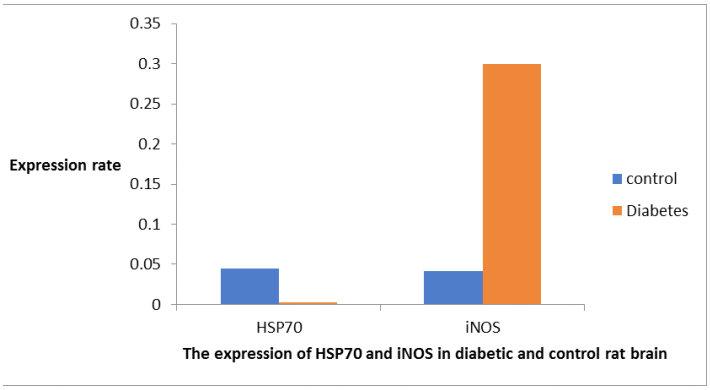

Figure 1: Expression of HSP70 and iNOS in rat brain (diabetic and control).

In another study, we investigated the possibility if iNOS is involved in the pathogenesis of kidney disease, and if therapeutic options may reduce its expression. We used the extract of *Urtica pilulifera* as a therapeutic option. A diabetic rat model was established. Study findings showed that there was a significant expression of iNOS in diabetic group compared with control group (P= 0.000). It was also interested to find that the extract of *U. pilulifera* significantly decreased the expression of iNOS in diabetic kidneys [3]. We conducted a study to investigate the expression of the inducible form of NO (iNOS) in the brain of a chronic mouse model of PD and to study the effect of endurance exercise training on its expression. The findings of our study showed that the level of iNOS was significantly increased in striatum (ST) of sedentary SPD mice compared to SC mice (P > 0.03). Exercise decreased the level of iNOS, but not significantly in EC group compared with SC group (p>0.8) [4].

We conducted another study to investigate the expression of inducible nitric oxide synthase (iNOS) in the skeletal muscles of PD and to examine the effect of treadmill exercise training on iNOS expression in these skeletal muscles. Study findings showed significant expression of iNOS in gastrocnemius muscle in SPD group compared to SC (p<0.05) (Erekat et al., 2013) [5].

We conducted a study to investigate the hypothesis that the healing properties of *Rubia tinctorum* L. against thermal injuries are significantly associated with the expression of iNOS and HSP70. The results of this study showed that treated rabbits with dried hexane extract have increased percentage of burn contraction in comparison with control. Furthermore, the data indicated that the expression of HSP70 increased in treated groups with the plant extract when compared with control groups, while the expression of iNOS was higher in control groups than treated ones. Taken together, the positive outcomes for healing from burns is due to the over expression of HSP70, low expression of iNOS [6]. The study of [7] aimed to investigate the expression of iNOS in cardiac muscle of rat with alloxan-induced diabetes. Study findings showed significantly increased expression of iNOS in the heart of diabetic rats (p<0.05).

Alkhatib et al. [8] conducted a study to investigate the impacts of diabetes on liver through exploring the diabetic effects on expression of HSP70 in liver tissue and to explore the effects of the extract of *U. pilulifera* on liver of diabetic groups treated with *U. pilulifera*, and to investigate its effects on the expression of HSP70 in liver tissue. Study findings showed three important aspects. Diabetes downregulated significantly the expression of HSP70 in liver (P= 0.000). Treatment with *U. pilulifera* significantly upregulated the expression of HSP70 in diabetic groups (p=0.000). Taken together, the present study showed that there is significant therapeutic potential of using *U. pilulifera* in upregulating the expression of HSP70 in liver of diabetic rats. It is of special interest to induce HSP response through *U. pilulifera* as it is unique, exciting, and inexpensive.

In their study, [9] conducted a study to study the effects of the extract of *U. pilulifera* on the expression of HSP70 in the kidneys of diabetic rats. Study findings showed that diabetes significantly downregulated the expression of HSP70 compared with control group in kidneys (P= 0.000). Treatment with *U. pilulifera* increased the expression of HSP70 significantly in kidney tissue (P= 0.000). It is possible to conclude that diabetic patients can benefit from using *U. pilulifera* to cope with oxidative stress attributed to

diabetes. Laiche et al. [10] conducted a study to explore the effect of exercise training on the expression of HSP70 in brains of mice with induced Parkinson disease. Study findings showed that the expression of HSP70 was significantly downregulated in the brain of mice with Parkinson disease ($p \leq 0.05$) compared with control groups. It was interesting to find that exercise training upregulated the expression of HSP70 in EC significantly ($p \leq 0.05$) compared with control group and insignificantly ($p > 0.05$) in EPD compared with PD.

Conclusions

Our Studies Clearly Showed That the Hypothesis That We Have Put "The Progression of a Disease Depends On Downregulation of Heat Shock Protein 70 (Hsp70) And Upregulation of Inducible Nitric Oxide Synthase (iNOS): A New Medical Hypothesis" Is Logical and Can Help in Finding Molecular Bases for Treating Diseases.

References

1. Ekmekcioglu S, Grimm EA, Roszik J (2017) Targeting iNOS to increase efficacy of immunotherapies. Human Vaccines & Immunotherapeutics 13: 1105-1108.
2. Al-khatib A (2013) Co-expression of iNOS and HSP70 in diabetes type 1 makes a rational hypothesis to explain the diabetic neuropathy. European scientific journal 9: 145-156.
3. AlKhatib AJ, Laiche F, Alkhatatbeh MA, Bello AM, Muhammad IA, et al. (2014) Leaf extract of *U. Pilulifera* downregulates the expression of iNOS in kidneys of diabetic rats. European Scientific Journal 10: 302-309.
4. Al-Jarrah M, Bataineh Z, Obaidat H, Walton L, AlKhatib A (2013) Endurance exercise training protects against the upregulation of nitric oxide in the striatum of MPTP/probencid mouse model of Parkinson's disease. Neuro Rehabilitation 32: 141-147.
5. Erekat N, AlKhatib A, Al-Jarrah M (2013) Endurance exercise training attenuates the up regulation of iNOS in the skeletal muscles of chronic/progressive mouse model of Parkinson's disease. J Neurol Res 3: 108-113.
6. Alsarhan A, Mansi K, Aburjai T, Al-Khatib A, Alzweiri M, et al. (2013) HSP70 and iNOS biomarkers in evaluating the healing properties of *Rubia tinctorum*. European Scientific Journa 9: 241-254.
7. Al-Jarrah M, Ahmad M, Maayah M, Al-Khatib A (2012) Effect of Exercise Training on the Expression of p53 and iNOS in the Cardiac Muscle of Type I Diabetic Rats. Journal of Endocrinology And Metabolism 2: 176-180.
8. AlKhatib AJ, Shah MS, Alkhatatbeh MA, AlKhatib IA, Maikano AB, et al. (2014) *Urtica pilulifera* ameliorates diabetic impacts through upregulation the expression of HSP70 in liver of diabetic rats. European Scientific Journal 10: 296-302.
9. Alkhatib AJ, Laiche F, Alkhatatbeh MA, Alrasheidi SA, Murtala, et al. (2014) *Urtica pilulifera* upregulates the expression of heat shock protein (hsp70) in kidneys of diabetic rats. European Scientific Journal 10: 276-282.
10. Laiche F, Noureddin D, Alkhatib A, Muhammad M (2014) Exercise Training Upregulates the Expression of HSP70 in Brain of Mice with Induced Parkinson Disease. Journal of Animal and Veterinary Advances 13: 302-305.