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review Article

Heat Shock Protein 27 (HSP27) Antibody and amphetamine and other substance abuse: A review study

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Abstract

Introduction: Heat Shock Protein (HSP) expression is observed in central nerve system at different stressful condition like hypothermia, hypoxia, trauma, status epilepticus, and drug abuse. Also, HSP is suggested as a molecular protection for cellular damaged proteins. The aim of this review was to evaluate and summarize the studies about the role of HSP in psychotic caused by substance abuse.

Materials and Methods: In this review article, all the articles published up to December 2014 in both Persian and English language about the relationship between heat shock protein and drug abuse had been evaluated. These studies were searched in database of SID, IranMedex, IranDoc, Margiran, Science Direct, Ovid, Google Scholar, PubMed, CINAHL and using key words of HSP27 AND drug abuse. The used keywords were selected based on MeSH Database. To collect data, Data Extraction Form was used that it was designed based on the objective of the study. The result of this search was to obtain 11 related articles that 5 articles were excluded due to lack of inclusion criteria and ultimately 6 articles entered to the study.

Results: The oldest performed study was related to 2001 and the most recent was in 2014. 3 studies (50%) were performed on rat and 3 (50%) on mice. 4 articles was about morphine abuse, 1 about amphetamine abuse, and 1 about phenobarbital.

Conclusion: All the researches showed that HSP27 increases after substance withdrawal, and it seems that it has damage protective effect.

Keywords: Heat Shock Protein, Substance abuse, Withdrawal

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Introduction

Substance-related disorders are associated with drugs abuse including alcohol. Amphetamines after hashish and marijuana are the most common illegal drugs in different countries (1). As a general class, amphetamines are named as sympathetic mimic, stimulants, and mental stimulants. Classic amphetamines have initial impact on the release of catecholamines, specifically dopamine from presynaptic terminals. This effect is stronger especially for dopaminergic neurons, which exists from tegmental area to the cerebral cortex and the limbic area. The pathway is called the reward pathway, and its activation is probably the major addictive mechanism of amphetamines (2).

The significant symptom of amphetamine-induced psychosis is the paranoia. The features of amphetamine-induced psychotic disorder, including the frequency of hallucinations,, appropriate affection, hyperactivity, strong sexuality, confusion, irrelevant words and little evidence of thought disorder (e.g. loosening of associations), distinguish paranoid schizophrenia from psychotic disorder induced by amphetamine (3).

One of the recently discovered autoantibodies proposed in the pathogenesis of psychiatric disorders particularly psychotic disorders is heat shock protein antibody (4). Two hypotheses have been raised about the role of this protein. The first hypothesis refers to its role in the pathology and immunology mechanism of disorders, while the second hypothesis supports its protective role against harmful factors during the neurological development and acute conditions of disease (5).

HSP expression is observed in the central nervous

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system in different stressful conditions, such as hypothermia, hypoxia, traumatic injury, and status epilepticus. Also, HSP is suggested as a molecular protection for cellular damaged proteins (6). HSP based on kDa molecular weight is divided the types of 27, 60, 70, 90, … (6-9). Gene expression of heat shock proteins in addition to heat is increased in response to various environmental stresses, such as lack of a certain nutrient shortage, oxidative stress, and UV radiation.

This process is mediated by the release of heat shock factor and their bindings to heat shock factors in the area surrounding the heat shock protein genes increase their expression. Heat shock proteins are a large family of cellular proteins that are present in most living organisms. There are three main categories of HSP including HSP90 (85-90 kDa), HSP70 (68-73 kDa), and HSP with low molecular weight (16 to 47 kDa). In normal cells, these proteins are involved in many cellular activities. HSP with low molecular weight are made only in stressful situations (10).

In some studies, it has been shown that HSP27 and other types of HSP with low molecular weight have a role in the intracellular transferring and prevent the release of cytochrome from mitochondrial during oxidative stress, suppress the activity of Caspase 3 and 9 and prevent cell damage (11-13). HSP27 has three major phosphorylations (Ser15, Ser78 and Ser82). Many studies suggested that phosphorylated HSP27 is cytoprotective against a lot of pathologies (14-16). According to the role of these proteins in psychiatric disorders, in this article, related studies to heat shock proteins in substance abuse are discussed and summarized.

Materials and Methods

In this review, all English and Persian articles published till December 2014 related to the relationship between heat shock protein and drug abuse were evaluated. These studies were searched in database of SID, IranMedex, IranDoc, Margiran, Science Direct, Ovid, Google Scholar, PubMed, and CINAHL using key words of HSP27 and drug abuse. The keywords were selected based on MeSH Database. To collect data, Data Extraction Form, which was designed based on the objectives of the study, was used. The result of this search was to obtain 10 related articles. 5 articles were excluded based on the inclusion criteria. Ultimately 5 articles were selected to enter the study.

Qualitative assessment of the articles:

First, 20 articles were obtained in the search of electronic journals and reference lists. Three articles were excluded due to repetition. Accordingly, 2 independent researchers reviewed the abstracts and related articles were identified. In the case of discrepancy between the views of two researchers, third advisory was asked for help. Finally, among 17 obtained abstracts, 10 relevant studies were identified, and their full texts were provided. In the evaluation of full texts, 5 irrelevant articles were excluded from the study (Figure 1). The remaining 5 studies underwent qualitative analysis. Qualitative analysis of the articles was performed using CONSORT checklist (Moreno-Ramírez). Due to the heterogeneity in results, it was not possible to perform a meta-analysis in this study.

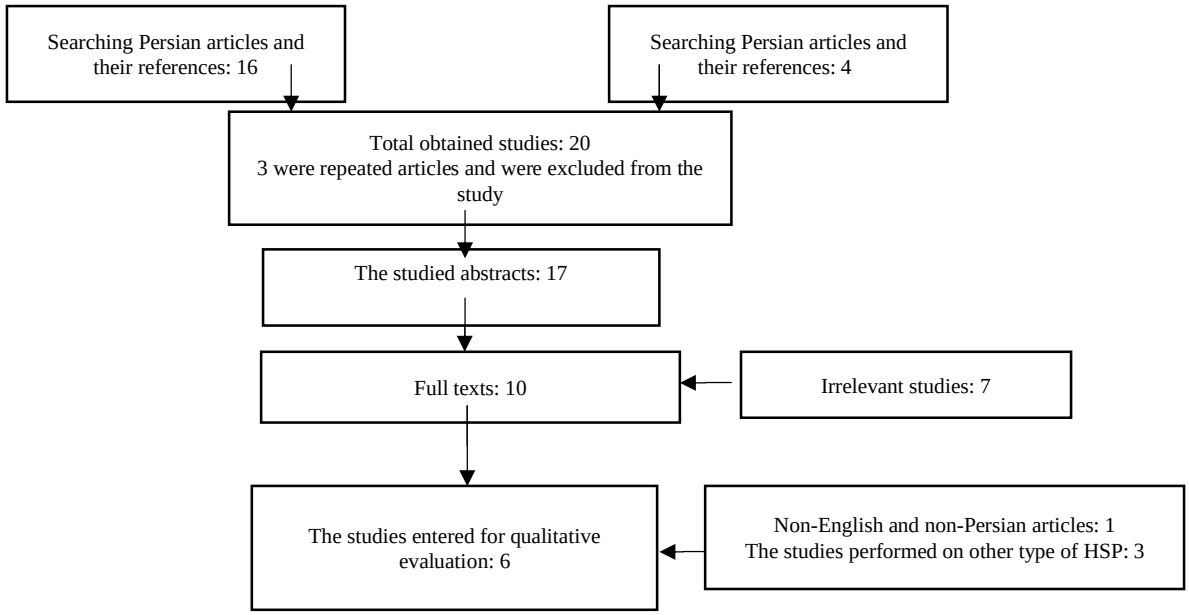

Diagram 1. The assessed studies and studies which entered to evaluation

Results

The oldest study was in 2001 and the most recent one was in 2014. Three studies (50%) were performed on rats and 3 (50%) on mice. The general information about the aforementioned studies is summarized in Table 1.

Table 1. General data of mentioned studies

Conclusion	Method	Study population	Year	Reference number
Increased expression of HSP27	Morphine withdrawal	Mice	2014	11
Increased expression of HSP27	Morphine withdrawal	Mice	2012	9
Increased expression of HSP27	Morphine withdrawal	Mice	2012	12
Increased expression of HSP27	Morphine withdrawal and naloxone administration	Rat	2011	13
Increased expression of HSP27	Withdrawal of 3 and 4 Methylenedioxym ethamphetamine	Rat	2011	14
Increased expression of HSP27	Acute withdrawal of phenobarbital	Rat	2001	15

In the study conducted by Bauer and Davis the level of m-RNAHSP was studied by injecting amphetamines to 15 rats. The level of HSP 70 increased 2 times after 16 hours of amphetamine administration and induced hyperthermia (10). The two studies conducted in Spain showed that HSP27 increases in patients who are at opioid withdrawal period (11,12), and the level of this protein is higher in the heart and the left ventricle (12). A study in Sweden showed that HSP27 and HSP70 levels increased in mice exposed to amphetamines (13).

Discussion

With regards to the increase in the neurobiological approach to psychiatric diseases, the studies have been performed on the relationship of HSP and major psychiatric disorders such as depression, bipolar disorder, and schizophrenia (6,9). Heat shock proteins are a large family of cellular proteins, which are present in most living organisms. Many studies have been carried out on the role of HSP in the etiology and pathogenesis of various diseases. Among these, we can mention its role in cardiovascular disease, metabolic disease and its relationship with other inflammatory proteins (18-20). Neurological diseases also are not an exception and studies have been conducted in this area as well (10,11).

It has been shown that HSP27 and other types of HSP with low molecular weight have a role in intracellular transferring, prevent the release of cytochrome from mitochondria during oxidative stress, suppress the activity of caspase 3 and 9, and prevent cell damage (15). HSP27 has three major phosphorylation parts. Many studies suggested that phosphorylated HSP27 has cytoprotective activity against a lot of pathologies (16). A study showed that HSP27 is made in the cortical area of brain in response to stress (e.g. seizures) (17).

In a recent study conducted in Korea, it is showed that HSP is associated with psychosis incidence and its treatment response in schizophrenic patients with schizophrenia. In this study, 288 schizophrenic patients were compared with 281 healthy individuals, and showed that HSP70 in patients with schizophrenia is associated with a worse prognosis (18). Another study in Germany showed that during neuroleptic treatment, autoantibodies level increases against heat shock protein, and the rate of increase in HSP60 can play an important role in response to treatment in patients with schizophrenia (19).

In some studies, it has been shown that HSP27 and other types of HSP with low molecular weight play a role in intracellular transferring and prevent the release of cytochrome from mitochondria during oxidative stress, suppress the activity of caspase 3 and 9 and prevent cell damage (21-23). HSP27 has three major phosphorylation parts. Many studies suggested that phosphorylated HSP27 has cytoprotective activity against a lot of pathologies (15). David Boyer and colleagues in their study showed that HSP 70 level increased 2 times after 16 hours of amphetamine administration and induced hyperthermia (10).

Bidmon study showed that HSP27 is made in the cortical region of the brain in response to stress (eg, seizures) (20). The study performed in Spain showed that HSP has established Astroglial Cytoskeletal stereocilia and plays an important role in response to oxidative stress (22). In some other articles, the role of this protein in reconstruction of brain tissue after ischemic injury in newborns has been evaluated (14). Some studies have shown that administration of phosphorylated recombinant HSP can be effective on preventing the complications in ischemic stroke (21).

According to the mentioned studies, the necessity of future studies about identification of the role of this protein and human studies on the relationship of

drug abuse and the HSP27expression. The main limitation of this study was the absence of human studies on the relationship of drug abuse and the HSP27expression.

Conclusion

According to the role of heat shock proteins in psychiatric disorders, the perfect role of these and type of low molecular weight (HSP27) that it seems it products in stressful conditions and it may be has a protective role is still unknown. Therefore, determining the precise function of this protein can be effective in the treatment of disorders caused by drug abuse and the prevention of its complications. Also, detailed human studies are needed.

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