Original Article

Broiler Heart Muscle Monoaminergic Receptors Alteration in Response to Chronic Heat Stress: Based on Transcription Analysis

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ABSTRACT

Chronic heat stress affects numerous physiological and behavioral mechanisms. Epigenetic changes following prolonged cyclic heat stress, creating new opportunities for molecular biology research. One of these changes involves monoamines, such as serotonin, epinephrine, norepinephrine, dopamine, and their transmission. Broiler chickens are highly susceptible to heat stress, and their hearts become insufficient during the growth phase, leading to hypertrophy of the left heart. RNA-seq data were obtained from NCBI with accession number SRP082125. The expression level of genes was determined with DESeq2 packages. Gene Ontology qualification, including biological processes, cellular components, and molecular role (MF), was performed from the Gene Ontology Resource. Cyclic heat stress in broilers significantly altered monoamine receptor expression. Twenty-nine genes of the monoamine pathway changed their expression in the left heart. Significant downregulation of expression was statistically associated with the *ADRB1*, *HTR2A*, and *PNMT* genes and upregulation of the *MAOA* gene ($P<0.01$). STRING database was used to construct the protein-protein interaction network; based on network analysis, the *HTR2C*, *HTR2A*, and *HTR5A* genes were identified as the major nodal genes in the network followed by *MAOA*, *DRD2*, *DRD5*, *HTR1B*, *DRD1*, *DRD3*, and *HTR2B* genes occupying the second important place in the network module. In conclusion, heat stress treatment prevented cardiac hypertrophy and altered the expression of monoamine genes. This would imply that monoamine transmission plays an important role in the development of cardiac hypertrophy, and that cyclic-chronic heat treatment modulates the cardiac monoaminergic system. These molecular biomarkers could be useful for screening, diagnosis, and treatment of cardiac hypertrophy.

Keywords: Broiler, Gene expression, Heart, Heat stress, Hypertrophy, Monoamine

1. Introduction

Stress is a disruptor of homeostasis, the common consequences of which are mental and physical illnesses. The hypothalamic-pituitary-adrenal (HPA) axis and adrenergic pathways are the main contributors to stress and their activation leads to an increase in corticosteroid levels, depletion of body reserves, a decrease in the immune system, and performance decline in stressful situations (1). Heat stress is associated with an increase in body temperature, an increase in blood corticosteroids and catecholamines, and a decrease in serotonin levels (2).

There is an interaction between the HPA and monoaminergic neurotransmitter systems in the regulation of stress-related behaviors (3).

The chemical products of the monoaminergic system are histamine, catecholamines (dopamine, norepinephrine, and epinephrine), and tryptamines (serotonin and melatonin).

Serotonin controls various physiological functions, such as the cardiovascular system, respiration, immune system, energy balance, and body temperature. Serotonin balance and brain serotonin levels compared with norepinephrine and dopamine have shown delayed recovery in rats with short and long heat exposure. This suggests that brain serotonin levels are more damaged during heat stress and it takes more time to recover (3).

These neurotransmitters, their receptors, and degradation pathways are represented in the cardiovascular system (4).

Several animal studies suggest a function of serotonin in heart disease and drug-induced valvular heart disease (5). In rats administered serotonin over a prolonged period, there has been increased cell proliferation and thickening of the heart valves, which is similar to changes observed in patients with carcinoid heart disease (6, 7). 5-HT role in cardiac hypertrophy was demonstrated using genetically modified mice. These studies showed that overexpression of 5-HT_{2A} receptors in the heart resulted in hypertrophic cardiomyopathy and was associated with mitochondrial dysfunction (8). Similarly, the predominant isoform expressed in the ventricle has recently been shown to be an important source of reactive oxygen species (ROS) in the heart (9, 10).

Furthermore, the ability of MAO-A to produce ROS increases with age, which is regularly associated with heart failure, and microarray gene expression profiling revealed upregulation of the *MAOA* gene in cardiac hypertrophy and failure (11, 12).

A similar situation exists in commercial meat poultry. Fast-growing broilers may have increased mortality due to heart failure resulting in maladaptive cardiac hypertrophy leading to overt contractility pathogenesis, thereby increasing mortality. Because of intensive genetic selection for early, rapid growth, modern broiler strains are affected by sudden death and a higher prevalence of heart diseases (13).

Therefore, changes in the monoaminergic system in the brain were detected in the rat during experimental conditioning by short and long heat stress. We investigated the possible changes in cardiac muscle monoamine receptors based on transcriptome analysis in adult broilers after long-term chronic heat stress conditioning in broilers.

2. Materials and Methods

2.1. Animal treatment

In this experiment, broilers were divided into two groups 21 days after hatching, one of which was raised under thermoneutral conditions, and the other group was treated at 35°C for 8 h per day until 42 days of age. Finally, six chicks were selected from each group and the left heart was removed and stored at -80°C for the next total mRNA extraction.

2.2. Data acquisition, quality control, and data cleaning

The publicly available left heart gene expression data set was downloaded from NCBI (http://www.ncbi.nlm.-nih.gov/sra/SRP082125) (14). Transcriptional profiling of left heart samples from broiler chickens treated with or without chronic heat

stress was performed on 6 samples for the treated and 6 samples for the control group.

Quality of readings. The quality control of sequencing reads was performed using FastQC software (0.11.8). Trimmomatics software (0.36) was used to remove low-quality reads and adaptor sequences. Reads with an average quality score of less than 20 were removed. The filtered reads were analyzed using FastQC.

2.3. Differential expression analysis

Filtered reads were mapped to the chicken reference genome (GCA_016699485.1) downloaded from the NCBI website using the Hisat2 program (2.1.0). Differentially expressed genes (DEGs) between groups (with or without chronic heat stress) were detected using the DESeq2 package (3.6).

2.4. Gene ontology analysis

The gene ontology (GO) resource (http://geneontology.org/) was used for GO enrichment analysis to identify some candidate genes involved in the cardiac monoaminergic system (Table 1).

Table 1. Gene ontology of genes related to monoaminergic of broiler treated with cyclic-chronic-heat stress condition

GO term	Fold enrichment	P value	FDR	Name of genes
serotonin receptor signaling pathway	> 100	1.47×10^{-28}	1.82×10^{-25}	HTR4, HTR7 HTR2A, HTR1F, HTR2C, HTR1E, HTR6, DRD4, HTR2B, HTR1B, HTR1A, HTR5A
cellular response to dopamine	> 100	3.25×10^{-35}	4.44×10^{-31}	DRD1, DRD2, DRD3, DRD4, DRD5, HTR4, HTR7, HTR2A, HTR1F, HTR2C, HTR1E, HTR6, HTR2B, HTR1B, HTR1A, HTR5A
regulation of serotonin secretion	> 100	1.48×10^{-05}	1.28×10^{-03}	HTR1B, HTR1A
regulation of blood pressure	37.10	1.56×10^{-08}	2.80×10^{-06}	ADRB1, DRD5, ADRA1D, ADRB2, DRD2, ADRA1A
regulation of systemic arterial blood pressure by norepinephrine-epinephrine	> 100	5.71×10^{-12}	1.62×10^{-09}	ADRB1, DRD5, ADRA1D, ADRB2, ADRA1A
positive regulation of blood circulation	81.45	9.32×10^{-06}	8.54×10^{-04}	ADRB1, ADRA1D, ADRA1A
regulation of heart rate	39.65	3.77×10^{-06}	3.96×10^{-04}	ADRB1, ADRA1D, DRD2, ADRA1A
vasodilation	89.21	7.27×10^{-06}	7.14×10^{-04}	ADRB1, ADRB2, DRD1
response to histamine	> 100	3.07×10^{-07}	4.19×10^{-04}	DRD3, DRD2, DRD4
negative regulation of calcium ion transmembrane transporter activity	> 100	4.79×10^{-06}	4.85×10^{-04}	DRD3, DRD2, DRD4
synaptic transmission, dopaminergic	> 100	8.32×10^{-11}	2.10×10^{-08}	DRD3, DRD2, DRD4, DRD1, DRD5
heat generation	> 100	8.82×10^{-05}	6.02×10^{-03}	ADRB1, ADRB2
vasoconstriction	> 100	5.72×10^{-10}	1.32×10^{-07}	HTR7, DRD5, HTR2B, HTR1B
phasic smooth muscle contraction	> 100	2.22×10^{-04}	1.30×10^{-02}	DRD2, HTR2B
smooth muscle contraction	69.38	4.63×10^{-07}	5.91×10^{-05}	HTR7, DRD2, HTR2B

2.5. Network analysis

After the identification of genes with different expressions, the string database was used to search for interacting genes, and Cytoscape software was used to visualize the network. In the network, the nodes represent the genes, and the edges represent the interactions between them. The three methods of degree centrality, betweenness centrality, and closeness centrality were used to calculate the topology scores of the nodes in the network PPI using the CytoNCA plugin.

3. Results

3.1. Identification of monoamine receptor gene expression

In the left heart of broilers treated with chronic cyclic heat stress, 16879 genes were expressed. According to the gene search ID and analysis of 29 genes, an association with the monoamine system was found (Table 2). Gene ontology also demonstrated the affiliation of these genes with monoaminergic pathways. AANAT (melatonin pathway), alpha-adrenergic receptors (ADRA1A, ADRA1D, ADRA2A, ADRA2B, ADRA2C), beta-adrenergic receptors (ADRB1, ADRB2), dopamine receptors (DRD1-5), serotonin receptors (HTR1A, HTR1B, HTR1E, HTR1F, HTR2A, HTR2B, HTR2C, HTR4, HTR5A, HTR6, HTR7, HTR7L, HTR1A, TPH1, TPH 2), catecholamine synthesis pathway (PNMT). Fold changes greater than 1.2 and less than -1.2 were considered increases and decreases in gene expression, respectively. With the exception of *ADRA1D*, *HTR1B*, and *HTR7*, gene expression was decreased. Significant downregulation involved *ADRB1*, *HTR2A*, *PNMT*, and *MAOA* genes ($P<0.05$). The data are shown in Table 3.

Table 2. The known hub genes related to monoaminergic system using network analysis

Gene symbol	Degree	Betweeness	Closeness
HTR2C	22	29.970354	0.8666667
HTR2A	20	19.531176	0.8125
HTR5A	19	39.649654	0.7878788
MAOA	18	21.890844	0.7647059
DRD2	18	14.550404	0.74285716
DRD5	18	17.070404	0.7647059
HTR1B	17	10.672866	0.74285716
DRD3	17	13.217721	0.74285716
DRD1	16	74.56556	0.7222222
HTR2B	16	32.036797	0.7222222
ADRA1B	15	16.767683	0.7027027
HTR1A	14	12.582173	0.68421054
ADRA1D	14	14.645996	0.68421054
ADRB1	14	19.584286	0.68421054
ADRA2C	14	4.7168756	0.6666667
DRD4	14	3.3742275	0.68421054
HTR1E	13	11.1500225	0.65
HTR6	12	6.8366523	0.63414633

Table 3. Monoaminergic genes expression in left heart of broiler under chronic heat stress condition

Feature ID	Fold Change	P-value	FDR
ADRA1A	1	1	1
ADRA1D	1.20197	0.233887	0.765532
ADRA2A	-2.16667	0.500726	0.991003
ADRA2B	-1.4087	0.134757	0.624864

ADRA2C	-2.66667	0.834906	1
ADRB1	-2.38682	1.13×10^{-03}	0.076125
ADRB2	1.142857	0.348328	0.884843
DRD1	-1.6129	0.180152	0.691437
DRD2	-3	1	1
DRD3	-1.25	1	1
DRD4	-1.83333	0.498708	0.989746
DRD5	-1	1	1
HTR1A	-1	1	1
HTR1B	1.020833	0.588431	1
HTR1E	1	1	1
HTR1F	-1	1	1
HTR2A	-2.0625	0.015004	0.545128
HTR2B	-1.575	0.611744	1
HTR2C	-2.5	0.708682	1
HTR4	-2.4	1	1
HTR5A	1	1	1
HTR6	-1.88889	0.439228	0.951297
HTR7	1.270492	0.115164	0.587409
HTR7L	-1	1	1
HTRA1	1.257214	0.14764	0.645158
HTRA2	-1.57327	0.014227	0.246542
HTRA3	-1.49143	0.182679	0.694732
MAOA	1.362393	0.010608	0.217556
PNMT	-8.66667	7.53×10^{-04}	0.060805

3.2. Gene network based on genes related to monoamine receptors:

In this context, the differentially expressed genes (DEGs) obtained from the above steps were used to construct the protein-protein interaction network (Figure 1). Subsequently, hub genes were identified based on the degree, betweenness, and closeness centrality (Table 2). *HTR2C, HTR2A,* and *HTR5A* are the most important hub genes and the hub of the network followed by *MAOA, DRD2, DRD5, HTR1B, DRD1, DRD3,* and *HTR2B* genes as the second important ranks in the network construct. Based on the network analysis, *HTR2C* was the main node in the center of the network, after that *HTR2A* gene had the most connections with other genes; consequently, these two genes have more functionality in the serotonergic pathway. In the dopaminergic pathway, DRD2 and DRD5 had the most connections with other nodes and edges of the network according to the network constructed, revealing their importance in the cardiac dopaminergic pathway. The beta-adrenergic and alpha-adrenergic receptors of ADRA1D, ADRA2C, and ADRB1 each have the same number of connections with edges and nodes of the network.

4. Discussion

In this data analysis, based on RNA Seq data from a broiler's left heart under chronic cyclic heat stress, monoaminergic systems, including serotonergic and catecholaminergic genes, were altered. These monoaminergic system genes are involved in the regulation of numerous body functions, such as emotional, cognitive, and cardiovascular activities. As shown in a scientific paper, heat stress significantly reduced body and standardized heart weight; however, cardiac hypertrophy was not observed in heat stress-treated chickens (14).

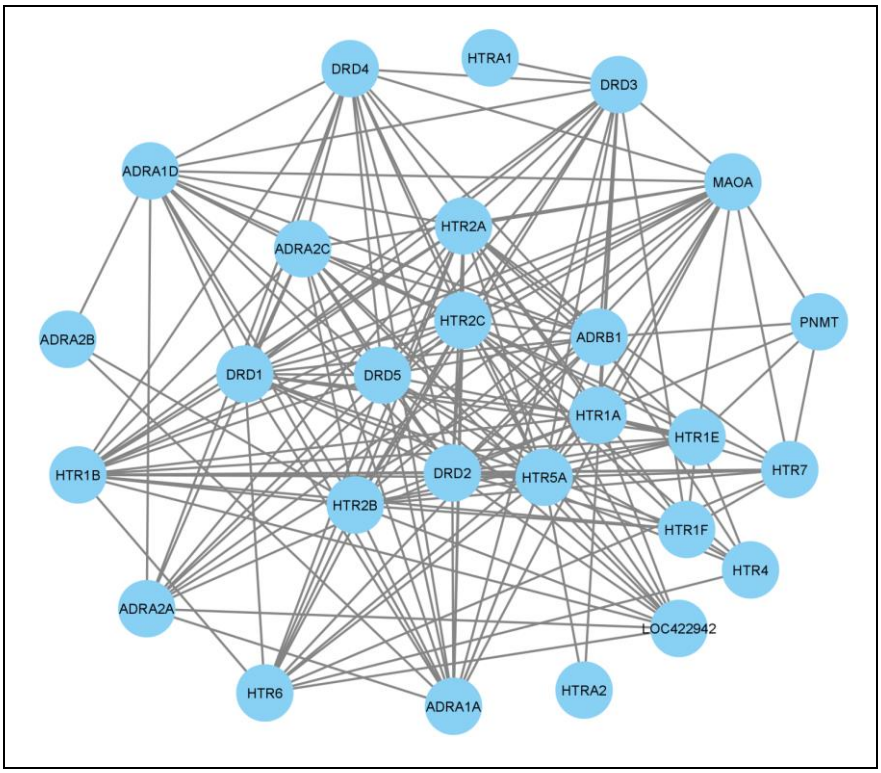

Figure 1. Constructed Network of key genes are involved in monoaminergic pathways of broiler heart

4.1. Serotonergic signaling pathway

14 genes related to serotonin receptors and tryptophan hydroxylase type I were differentially encoded in the control group and heat stress-treated chickens. Tryptophan hydroxylase I (TPH1) is the rate-limiting enzyme in the conversion of tryptophan to serotonin, with approximately 5% of tryptophan consumed in this manner and 95% degraded via the kynurenine pathway. The expression of the *HTR2A* gene was significantly downregulated. Hypertension and vasoconstriction in the heart are mediated by 5-HT_{2A}, and the blockade of 5-HT_{2A} controls hypertension and has cardioprotective effects (15). In heart failure and myocardial ischemia, endogenous release of 5-HT is stimulated, and blood level is increased in coronary artery disease (16). 5-HT exerts an inotropic effect on myocardial cells via 5-HT_{2A} (17). Consistent with this, a 5-HT_{2A} antagonist has been shown to be useful in the treatment of overloadinduced heart failure in mice (18). These results suggest the importance of serotonin receptors in heart failure and hypertrophy. Chronic cyclic heat stress may be able to prevent cardiac hypertrophy in broiler chickens by reducing the expression of serotonin receptor genes, particularly the *5-HTR_{2A}* gene.

4.2. Catecholaminergic signaling pathway

Catecholamine receptors have been found to be involved in the pathology of cardiac hypertrophy. *ADRB2* is involved in pathological hypertrophy and *ADRB1* in physiological hypertrophy (2). During exposure of broilers to heat stress, *ADRB2* gene expression decreased significantly, whereas *ADRB1* did not change significantly. This suggests that heat stress exposure prevents cardiac hypertrophy by altering beta-adrenergic receptor gene expression. Chicken heart alpha-adrenergic receptor genes showed no significant decrease under heat stress. It was reported that the bias of alpha-adrenergic receptors had no effect on cardiac hypertrophy in mice (19). The dopaminergic receptors DRD1-5 were expressed and not significantly downregulated in the heart of broiler chickens exposed to heat stress.

Dopamine receptors play an important role in the pathogenicity of heart failure; based on this, their deletion from cardiomyocytes reduced heart failure in mice, and accordingly, the manipulation of dopamine receptors had the potential to improve heart failure (20). Dopamine receptor overactivity and upregulation resulted in calcium trafficking in cardiomyocytes (21).

Norepinephrine is converted to epinephrine by phenylethanolamine N-methyltransferase (PNMT), a cytoplasmic enzyme. Overactivity of this enzyme has been observed during left ventricular hypertrophy (22). Most PNMT syntheses occur in the adrenal medulla, producing the major source of epinephrine in the blood (23). Although the heart has its own PNMT in some cardiomyocytes, the adrenal medulla is the major producer. Chronic heat stress significantly reduced PNMT gene expression in the left heart. Higher blood epinephrine levels correlate with the progression of heart failure (24). Thus, the induction of chronic heat stress in broiler chickens resulted in significant downregulation of PNMT gene expression and prevention of cardiac hypertrophy.

4.3. *MAOA* gene

Monoamine oxidases degrade biogenic amines. These amines include serotonin, catecholamines, and histamine. Ablation of this gene in mice resulted in an increase in brain serotonin and norepinephrine levels (25). MAO-A is found mainly in catecholaminergic neurons. In contrast, MAO-B is most abundant in serotonergic and histaminergic neurons. These monoamine oxidases are expressed in cardiomyocytes and are responsible for metabolizing exogenous amines, terminating the action of amine neurotransmitters, and regulating the contents of intracellular amine stores (26). In broiler hearts, *MAOA* gene expression was significantly increased under chronic heat stress. Increased MAO-A activity is associated with increased H_2O_2 production. MAO-induced H_2O_2 production at lower and higher concentrations resulted in hypertrophy and apoptosis of cardiac myocytes, respectively. Hyperactivity of 5HT2A and compensated cardiac hypertrophy have also been reported in MAO-A knockout mice (27). Although two mechanisms are involved in nonphysiological cardiac hypertrophy, MAO-A activity and 5HT2A, treatment with chronic heat stress significantly reduced *5HT2A* gene expression and increased MAO-A in broiler chickens, suggesting that serotonin plays a greater role in the induction of cardiac hypertrophy. Hydrogen peroxide is a potent trigger for the production of ROS, leading to mitochondrial dysfunction, decreased ATP production, and heart failure (28). Thus, there is a close relationship between H_2O_2 production and ROS in the heart.

In conclusion, decreased gene expression related to monoamines in left ventricular heart muscle resulted in the inhibition of cardiac hypertrophy in broiler chickens. Among them, the genes *MAOA, 5HT2A, PNMT,* and *ADRB1* were significantly altered. Accordingly, these genes had the greatest association with cardiac hypertrophy, and cyclic-chronic heat stress prevented heart failure in broiler chickens by alterations in the above genes.

Authors' Contribution

Studying, writing: Y.B
Software analyzing Z.R and A.B

Ethics

The study was approved by the Research Ethics Committee of the University of Jiroft, Jiroft, Iran.

Conflict of Interest

The author declared no conflict of interest.

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