A STUDY FOR THE ROLE OF OESTROGEN ON THE IMMOBILIZATION STRESS INDUCED CARDIOVASCULAR CHANGES

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٢٠٠٩

بسم الله الرحمن الرحيم

"وأنزل الله عليك الكتاب والحكمة

وعلمك مالم تكن تعلم

وكان فضل الله عليك عظيماً"

(آية ١١٣،سورة النساء)

In the Name of Allah, The All-Merciful,
The Ever-Merciful

"Allah has revealed to you the Book-the Quran-to guide you and acquaint your heart with wisdom, and he imparted to you the knowledge of what you never knew except from Him. And Allah's grace and blessings on you have, indeed, been abounding".

(SURAH 4: AN-NISA 113)

(AL-MONTAKHAB, 2006)

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Abstract

Coronary heart disease (CHD) develops in women on average 10 years later than in men. This lag has been attributed, to the protective effects of estrogens before menopause. Both natural and synthetic estrogens have antiinflammatory plus vasoprotective effects.

64 female albino rats were included in this study and classified into four main groups; each group included 16 rats.

Group1 (Control group), group 2 immobilization group (IMO), group 3 IMO + ovarectomy (OVE), group 4 (IMO+ OVE + estrogen supplementation 10 µg/100 Kg, once daily for 2 weeks).

Immobilization stress (IMO) group showed significant increase in systolic blood pressure (SBP) and diastolic blood pressure (DBP). Also there was significant increase in gene expression of c-FOS (functional marker of cellular activation) and heat shock protein (cardioprotective substance, HSP70) & significant decrease in contractility index in comparison to control group.

Ovarectomized (OVE) + IMO group showed significant increase in SBP, DBP, c-FOS, and significant decrease in atrial naturetic peptide (ANP) & HSP70 in comparison to IMO group.

Administration of estrogen to OVE rats caused a significant decrease in SBP, DBP, c-FOS and a significant increase in ANP & HSP70 after immobilization stress in comparison to IMO+ OVE group.

In conclusion, estrogen supplementation therapy attenuates the cardiac changes that occur in ovarectomized rats after immobilization stress, taking into consideration the side effects of estrogen.

Keywords

- Stress
- Estrogen
- Ovarectomy
- Cardiovascular
- Coronary heart disease
- c-FOS
- Atrial naturitic peptide
- Heat shock protein70
- Postmenopausal women

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List of Appreviations

ANP : Atrial naturetic peptides

AP-1 : Activating protein-1

AVP : Arginine-vasopressin

BNP : Brain naturetic peptide

CHD : Coronary heart disease

CHF : Congestive heart failure

CNP : C-type naturetic peptide

CRP : C-reactive protein

DPN : diaryl-propiol-nitrile

DBP : Diastolic blood pressure

DNTPs : Deoxynucleotide triphosphate

EB : Ethidium Bromide

EC : Endothetial cell

ER α : Estrogen Receptor alpha

ER ϐ : Estrogen Receptor beta

FGF2 : Fibroblast growth factor 2

GAS : General adaptation syndrome

GC : Glucocorticoids

GFR : Glomerular filtration rate

GIT : Gastrointestinal tract

GPR30 : G protein-coupled receptor

GSK3 : Glycogen synthase kinase-3

GTC : guanidine thiocyanate

HPA : Hypothalamic-pituitary-adrenal axis

HPRI : Human Placental Ribonuclease Inhibitor

Hsp70 : Heat shock protein 70

IMO : Immobilization stress group

LC/NE : Locus ceruleus and other noradrenergic cell groups of the adrenal medulla and pons

LH :Lutinizing hormone

LVEDP : Left ventricular end-diastolic pressure

MAPK : Mitogen-activated protein kinases

MAPK/ERK: Mitogen-activated protein kinase /Phosphoinositide 3-kinase pathway

MHC : myosin heavy chain

MMLV : Moloney murine leukemia virus

MMP-9 : Matrix metalloproteinase

MPP : Methyl-piperidino-pyrazole

MR : Mineralo-corticoid receptor

NEP : Neutral endopeptidase

NO : Nitric oxide

NPRA : Natriuretic peptide receptor

PCWP : Pulmonary capillary wedge pressure

PDGF : Platelets derived growth factor.

PELP1 : Prolin, glutamic acid and leucine rich protein

PET : Positron emission tomography

PKA : Protein kinase A

PKC : Protein kinase C

PPT : propyl pyrazole-triol

PVN : Paraventricular nuclei

SHBG : Sex hormone binding globulins

TAE : Tris-Acetate EDTA buffer

TRH : Thyrotropin releasing hormone

TSH : Thyroid stimulating hormone

VLDL : very low density lipoprotein

VSMCs: Vascular smooth muscle cells.

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Introduction and aim of the work

The incidence of cardiovascular diseases is low in pre-menopausal Women, whereas it is increased in post-menopausal women. Estrogen supplementation therapy prevents the increase of cardiovascular diseases in post- menopausal Women (Grodstein et al., 2001).

The Effects of estrogen on cardiovascular diseases were attributed principally to the modification of serum lipid concentration and coagulation pathways, while direct actions of estrogen on the cardiovascular system contributed substantially to the cardiovascular protective effects of estrogen because estrogen receptors (ER∝ and ERβ) are expressed in the blood vessels and in the heart (Mendelsoh and Karas, 2005).

Immobilization stress (IMO) in the rat provides an excellent animal model of emotional stress, which activates the hypothalamic-pituitary-adrenocortical system and the sympathoadrenal system (Kvetnansky et al., 1995).

c-Fos mRNA is a functional marker of cellular activation induced in cellular stress & estimated in the brain, adrenal gland & heart to know the protective mechanism of estrogen, while heat shock protein 70 (HSP 70) and atrial naturetic peptides (ANP) are cardio protective substances. (Ueyama et al., 2003, Ueyama et al., 1999).

c-Fos is belonging to the immediate early gene family of transcription factors and has a leucine-zipper in DNA binding domain, which is responsible for adhesion forces and dimerization. Transcription of c-Fos is upregulated in response to many extracellular signals as growth factors (Karin Milde-Langosch, 2005).

ANP is released by atrial myocytes, in response to high blood pressure. ANP acts to reduce the water, sodium and adipose loads on the circulatory system, thereby reducing blood pressure to normal levels (Makikallio et al., 2002).

HSPs maintain cellular homeostasis and survival in response to stressful cellular conditions. HSPs are actively secreted and have important extracellular functions. HSP70 release may be the result of nonspecific processes, such as cell lysis. Interestingly, some studies have provided evidence that specialized membrane microdomains, termed lipid rafts, may play a role in HSP70 exocytosis (Hunter-Lavin et al., 2004).

The aim of the present work is to study the effects of (IMO) on cardiac functions and its modulation by estrogen supplementation, to know the underline protective mechanism of estrogen, the expression of c-FOS mRNA (stress induce cellular activation) & some cardio-protective substances like (ANP & HSP mRNA) were measured in heart.

Estrogens and stress

In fact, a reduction of estrogen levels following menopause might increase the vulnerability of women to stress while estrogen supplementation attenuates the exaggerated response to stress or to increased sympathoadrenal activity (Komesaroff et al., 1999).

A unique form of acute cardiac attack called “takotsubo cardiomyopathy”, or “transient left ventricular apical ballooning” similarly occurs predominantly in postmenopausal women in association with emotional or physical stress (Ako et al., 2006; Wittstein et al., 2005; Akashi et al., 2003 & Kurisu et al., 2002).

Effects of estrogen on cardiovascular diseases were attributed principally to the modification of serum lipid concentration and coagulation pathways, while direct actions of estrogen on the cardiovascular system contributed substantially to the cardiovascular protective effects of estrogen because estrogen receptors (ERα and ERβ) are expressed in the blood vessels and in the heart (Mendelsohn et al., 2005 & Mendelsohn et al., 1999)

Both ERα and ERβ are also widely expressed in the central nervous system (Shughrue et al., 1997).