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Cardiac Response to Hepatic Ischemia-Reperfusion: Effect of Exercise and Oxytocin Compared to L-arginine

Thesis
Submitted for Partial Fulfillment of M.D Degree in Physiology

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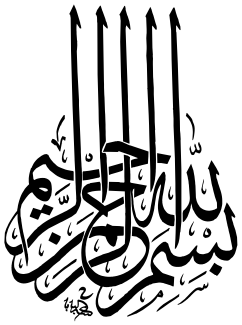
(2021)



" قالوا سبحانك لا علم لنا
إلا ما علمتنا
إنك أنت العليم الحكيم "

سورة البقرة (آية 32)

Acknowledgement

It seems very difficult to select the suitable words to express my deep thanks and gratitude to ALLAH.

I would like to thank Prof. Dr. **Mona Ahmed Ahmed**, Professor of Physiology, Faculty of Medicine, Ain Shams University, for suggesting and planning this work, her meticulous supervision, constructive systematic ideas beside her cooperation and endless efforts that greatly formulated this work and her scientific guidance throughout the entire work.

I would like to thank Prof. Dr. **Bataa Mohamed Aly EL-Kafoury**, Professor of Physiology, Faculty of Medicine, Ain Shams University, for her expert guidance, kind support and encouragement.

I would like to thank Dr. **Dalia Abdel-Salam Saad**, Associate Professor of Physiology, Faculty of Medicine, Ain Shams University, for her limitless help and keen supervision.

I would like to thank Dr. **Doaa Mohamed Abd el-Wahed,** Lecturer of Physiology, Faculty of Medicine, Ain Shams University, for her careful supervision and faithful assistance.

I would like to thank Dr. **Walaa Baher Mostafa,** Associate Professor of Histology and Cell Biology, Faculty of Medicine, Ain Shams University, for her contribution in the histopathological study.

I would like to thank Prof. Dr. **Laila Ahmed Rashed**, Professor of Medical Biochemistry and Molecular Biology, Faculty of Medicine, Cairo University, for her contribution in the biochemical studies.

Last but not least, I would like to thank all members of the Physiology Department for their cooperation and support.

ABSTRACT

Background: Hepatic ischemia reperfusion (IR) injury is considered a main cause of liver damage and dysfunction, and contributes to a high morbidity and mortality. The L-Arg/NO pathway seems to be relevant during the process of IR in multiple organs including the liver. Acute intense exercise was found to challenge the liver with increased ROS and inflammation onset, whereas regular training was found to induce hepatic antioxidant and anti-inflammatory improvements. Oxytocin, besides its classical functions, exhibits a potent antistress, anti-inflammatory and antioxidant effects.

Objective: This study was designed to determine the possible effect of hepatic IR injury on the function and structure of the liver and the heart, as a remote organ, as well as the response of the isolated hearts following exposure to in vitro cardiac IR. Also, to investigate the potential effect and mechanism(s) of exercise training and oxytocin, either each alone or together, in comparison to, the nitric oxide donor, L-arginine in modulation of liver IR-induced hepatic and cardiac disturbances.

Materials and Methods: Sixty two adult male Wistar albino rats were allocated into 6 groups: Group I: Sham-Operated Control, Group II: Hepatic IR in which rats were subjected to 30 minutes of partial (70%) hepatic ischemia followed by 2 hours of reperfusion, Group III: L-arginine-treated Hepatic IR in which rats received L-aginine (L-Arg) once daily by oral gavage for one week, and then subjected to hepatic IR procedure, Group IV: Exercise-Trained Hepatic IR in which rats were subjected to swim exercise 2 hours daily, 6 days/week for 4 weeks, and then subjected to hepatic IR procedure, Group V: Oxytocin-Treated Hepatic IR Group in which rats received oxytocin (Oxy) once daily by subcutaneous injection for one week, and then subjected to hepatic IR procedure, and Group VI: Exercise-Trained and Oxytocin-Treated Hepatic IR in which rats were exposed to swim exercise as in group IV and received Oxy as in group V and then subjected to hepatic IR procedure. All rats were subjected to determination of body weight (BW), absolute and relative liver and heart weights, serum levels of alanine transferase (ALT), aspartate transferase (AST), creatine kinase-MB (CK-MB) and cardiac troponin I (cTnI), plasma levels of malondialdehyde (MDA), total antioxidant capacity (TAC), nitrite and tumor necrosis factor-α (TNF-α) as well as In vitro study of isolated hearts perfused in a Langendorff preparation to record intrinsic activity of the heart under baseline condition and Responses of the heart during 30 minutes of reperfusion following 30 minutes of total global ischemia, together with histopathological examination of the liver and heart tissues.

Results: Hepatic IR group displayed deterioration of hepatic and cardiac functions and structures evidenced by significant increase in serum levels of liver function tests; ALT and AST, and myocardial injury parameters; CK-MB and cTnI together with worsening of liver and cardiac histopathological picture as well as deterioration of basal and postischemic recovery of systolic function and myocardial flow as compared to sham group..

L-Arg, Oxy, exercise and the combined treated groups ameliorated hepatic and cardiac functional and structural derangement induced by hepatic IR. which was evident by the significant decrease in serum levels of ALT, AST, CK-MB and cTnI together with the significant elevation in antioxidant capacity (TAC) and nitrite that was associated with significant decline in lipid peroxidation (MDA) and inflammation (TNF-α), besides regression of the hepatic and cardiac histopathological score.

In L-Arg treated group, the hepatoprotection was mainly due to increased NO production as the increase in plasma level of nitrite was significant compared to all treated groups and approached the control values.

L-Arg, Ex, Oxy and combined Ex + Oxy As compared to L-Arg pretreatment, the hepatoprotection offered by exercise training was mainly due to its antioxidant and anti-inflammatory effects as the increase in plasma level TAC was significant even reaching the control values and the plasma level of TNF-α was significantly decreased.

Also, the oxytocin treated group exerted more anti-inflammatory effects as compared to L-Arg treated group as plasma level of TNF-α was significantly decreased.

Its obvious that when exercise and Oxy were used together, the hepatic function parameters almost approached control values as serum ALT was only 1.3 times that of control level and serum AST was completely restored to normal. In addition, the combination of regular exercise and oxytocin dampened the inflammatory response and lipid peroxidation to be only 1.5 and 1.3 times that of control levels respectively, together with enhancing the radical scavenging and antioxidant activities that were normalized to reach control levels and increasing NO activity. On comparison with L-Arg, combination of both exercise and Oxy in this study displayed significant decrease in serum levels of ALT and AST together with significant decrease in plasma levels of MDA, nitrite and TNF-α, as well as, recession of histopathological injury, to a greater extent than in L-Arg. L-Arg, Ex, Oxy and combined Ex + Oxy were effective in abrogation of hepatic and cardiac functional and structural derangement induced by hepatic IR, owing to their antioxidant, anti-inflammatory and nitric oxide enhancing effects. In addition, the cardiac favorable effects of Ex, Oxy and combined Ex + Oxy were better

than that of L-Arg, with the combined treatment offering the superior beneficial effect that almost approached control values. Meanwhile, the effect of L-Arg in improvement of basal and postischemic myocardial flow, surpassed, treatment with oxytocin, and combination of both exercise and oxytocin.

Conclusion: Combination of both exercise and Oxy displayed more pronounced hepatoprotection on comparison with L-arginine on hepatic structural and functional changes induced by hepatic IR and such superiority of combined treatment over L-arginine could be attributed to their more prominent antioxidant and anti-inflammatory effects but not due to their nitric oxide-enhancing effect and the effect of L-Arg in improvement of basal and postischemic myocardial flow, could be explained by its superior role in NO production

Key Words: Liver, ischemia reperfusion injury, L-Arginine, Nitric oxide, exercise, oxytocin.

Contents

List of Abbreviations

Abbreviation	Full name
% change	Percent change
ALT	Alanine transferase
ANP	Atrial natriuretic peptide
AST	Aspartate transferase
BW	Body weight
CAT	Catalase
cGMP	Cyclic guanosine monophosphate
CK-MB	Creatine kinase-MB isoenzyme
CM	Cardiomyocyte
cNOS	Constitutive nitric oxide synthase
cTnI	Cardiac troponin I
Cum	Cumulative
ELISA	Enzyme-linked immunosorbent assay
eNOS	Endothelial nitric oxide synthase
ET	Endothelin
Ex + IR group	Exercise-trained hepatic ischemia-reperfusion group
Ex + Oxy + IR group	Exercise-trained and oxytocin-treated hepatic ischemia-reperfusion group