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Fenofibrate prevents isoproterenol-induced left ventricular hypertrophy and pump dysfunction in rats

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DECLARATION

I, Tlangelani Maswanganyi, hereby declare that this dissertation is my own work (except where acknowledgements indicate otherwise). It is being submitted for the degree of Master of Science in Medicine in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

……

Mr Tlangelani Maswanganyi

Signed at…….....this.....day of…… 2010

Dr Siyanda Makaula (Supervisor) ……...

Signed at……..this……. day of …… 2010

Dr Richard Brooksbank (Co-Supervisor) ……

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CONFERENCE ATTENDANCE AND PRESENTATIONS

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T Maswanganyi, R Brooksbank, P Mgandela, AJ Woodiwiss, GN Norton, S Makaula. Fenofibrate prevents isoproterenol-induced cardiac pump dysfunction: the role of mithochondrial gene regulation. Congress of the Physiology Society of Southern Africa (PSSA). University of Pretoria, South Africa (2008). *Oral presentation.* 16-19 September 2008.

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ABSTRACT

The role of metabolic remodelling in heart failure is not fully understood, significant evidence has accumulated to suggest that it may be central to the development of left ventricular (LV) remodelling and LV dysfunction. Heart failure is also characterized by sustained neurohumoral activation. We have previously demonstrated that chronic low dose administration of isoproterenol contributes to cardiac structural and functional changes, however, little is known about metabolic and mitochondrial changes that may accompany the development of isoproterenol-mediated heart failure. In the current study, we hypothesised that metabolic dysregulation and loss of mitochondrial integrity mediates left ventricular hypertrophy (LVH) and left ventricular (LV) systolic dysfunction in the isoproterenol model of heart failure. Furthermore, modulation of expression of key metabolic genes and mitochondrial transcription factors by fenofibrate, a peroxisome proliferator-activated receptor alpha (PPARα) agonist, will preserve left ventricular function.

To achieve this, male Sprague-Dawley rats weighing between 250-300g were injected with low dose isoproterenol (0.04 $mg.kg^{-1}.day^{-1}$) and/or administered with fenofibrate (100 $mg.kg^{-1}.day^{-1}$) for five weeks. Thereafter, metabolic substrates such as glucose, FFAs and TG concentrations were obtained. Left ventricular hypertrophy (LVH) and cardiac function were assessed using echocardiography. Expressions of metabolic and mitochondrial genes such as PPARα, AMP-activated protein kinase alpha 2 ($AMPK\alpha_2$), PPARγ coactivator-1 (PGC-1α), mitochondrial transcription factor (TFAM) and nuclear respiratory factor-1 (NRF-1) were determined using real-time polymerase chain reaction. Mitochondrial integrity was assessed using transmission electron microscopy.

Administration of isoproterenol significantly increased left ventricular mass (LVM) and decreased endocardial fractional shortening (FS_{end}); isoproterenol also induced myofibrillar

derangement, mitochondrial derangement and cristae disruption. Fenofibrate prevented isoproterenol-induced increase in LVM and improved FS_{end}. Fenofibrate co-administration prevented loss of mitochondrial integrity possibly via TFAM. Furthermore, fenofibrate may have induced metabolic remodelling via upregulation of AMPKα_2 and downregulation of cardiac PPARα and PGC-1α.

Therefore our data suggests that fenofibrate-mediated cardioprotection against isoproterenol-induced LVH and LV systolic dysfunction was accompanied by metabolic switching and preservation of mitochondrial integrity. While isoproterenol did not induce any changes in metabolic genes, fenofibrate-mediated cardioprotection could have been through changes in metabolic genes.

ABBREVIATIONS

ACC	Acetyl CoA carboxylase
ACS	Acyl-CoA synthetase
ADP	Adenosine diphosphate
AMP	Adenosine monophosphate
AMPKα_2	AMP-activated protein kinase alpha 2
ANOVA	Analysis of variance
ATP	Adenosine triphosphate
BM	Total body mass
CPT	Carnitine palmitoyl transferase
FA	Fatty acid
FABP	Fatty acid binding protein
FAO	Fatty acid oxidation
FARE	Fatty acid response element
FAT	Fatty acid translocase
FATP	Fatty acid transport protein
FFA	Free fatty acid
FS_{end}	Endocardial fractional shortening

FS_{mid}	Midwall fractional shortening
GAPDH	Glyceraldehyde 3-phosphate dehydrogenase
GLUT-4	Glucose transporter-4
HM/TL	Total heart mass-to-tibial length ratio
LCAD	Long-chain acyl-CoA dehydrogenase
LVED PWT	Left ventricular end-diastolic posterior wall thickness
LVEDD	Left ventricular end-diastolic diameter
LVES PWT	Left ventricular end-systolic posterior wall thickness
LVESD	Left ventricular end systolic diameter
LVH	Left ventricular hypertrophy
LVM	Left ventricular mass
LVM/TL	Left ventricular mass-to-tibial length ratio
MCAD	Medium chain acyl-coA dehydrogenase
NRF-1	Nuclear respiratory factor-1
NS	Not significant
PGC-1α	Peroxisome proliferator-activated receptor gamma coactivator-1 alpha

PPARα	Peroxisome proliferator-activated receptor alpha
ROS	Reactive oxygen species
RT-PCR	Real-time polymerase chain reaction
RVM	Right ventricular mass
RVM/TL	Right ventricular mass-to-tibial length ratio
RXRα	Retinoid X receptor-alpha
SD	Sprague-Dawley
SEM	Standard error of the mean
SNS	Sympathetic nervous system
TFAM	Mitochondrial transcription factor
TG	Triglyceride
TL	Tibial length
UCP	Uncoupling protein
VFM	Visceral fat mass
VLCAD	Very long-chain acyl-CoA dehydrogenase

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CHAPTER ONE: INTRODUCTION

CHAPTER TWO: MATERIALS AND METHODS

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