INSULIN-LIKE GROWTH FACTORS

IN THE ISCHAEMIC HEART

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Abstract

Cardiac muscle has very limited ability to regenerate following injury. Loss of muscle due to myocardial infarction (MI) is therefore compensated for by hypertrophy of the surviving cardiac muscle. Deposition of inflexible scar tissue in the infarct zone leads to subsequent dysfunction of the heart, often culminating in chronic morbidity and eventual death due to heart failure.

Insulin-like growth factor I (IGF-I) and insulin-like growth factor II (IGF-II) are members of a family of insulin-related peptides involved in tissue development, repair and replacement. Their involvement in these roles has been clearly demonstrated in skeletal muscle, but remains unclear in cardiac muscle. The aim of this thesis, therefore, was to undertake a comprehensive evaluation of the insulin-like growth factor axis following induced MI in sheep, in order to determine the relationship between time-based changes in the myocardium and insulin-like growth factor levels, and subsequently to determine the therapeutic effect of GH or IGF-I treatment on cardiac function following MI.

To achieve the aims of the thesis, a model of MI was developed from the existing cardiology technique of percutaneous transluminal coronary angioplasty. Using this model, MI was induced in adult ewes by selected coronary artery occlusion under fluoroscopic guidance. Subsequently, the model was further developed into one of stable heart failure, utilising serial microembolisations targeted by echocardiography.

Results showed that, in the cardiomyocytes bordering the infarct, IGF-I mRNA, protein and receptor binding increased, whereas IGF-II mRNA and protein levels did not vary, although IGF-II receptor binding increased.

Following these findings, IGF-I levels were manipulated by subcutaneous injections of either growth hormone or IGF-I, and by intra-pericardial IGF-I delivery via catheter.

Results showed that neither growth hormone nor subcutaneous IGF-I were able to effect an improvement in cardiac function, although there were indications that a longer duration of treatment with subcutaneous IGF-I might have done so. Intra-pericardial IGF-I, however, resulted in a significant and sustained improvement in cardiac function.

In conclusion, surviving cardiomyocytes at the infarct border show marked changes in IGF-I localisation, production and specific binding, indicating that IGF-I is directly involved in post-infarct events, possibly in the maintenance of cardiac function by the induction of hypertrophy. Delivery of IGF-I directly into the pericardium results in a significant improvement in left ventricular ejection fraction which is sustained after cessation of treatment. Such a result indicates that IGF-I may have a role as a therapy in the failing heart.

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ALS	acid-labile subunit
ATP	adenosine-5-triphosphate
BP	binding protein
BSA	bovine serum albumin
C	Celsius
cDNA	complementary deoxyribonucleic acid
Ci	Curie
cm	centimetre
CPM	counts per minute
C-terminal	carboxyl terminal
CV	coefficient of variation
Cx	circumflex (coronary artery)
Da	Dalton
DAB	diaminobenzidine
DEPC	diethyl pyrocarbonate
DNA	deoxyribonucleic acid
DSS	dissucinimidyl suberate
E.coli	Escherichia coli
ECG	electrocardiograph
EDTA	ethylene diaminetetra-acetic acid disodium salt
EF	ejection fraction
EDD	end diastolic diameter
ESD	end systolic diameter
g	gravity
g/l	grams per litre
GH	growth hormone
h	hour
HCl	hydrochloric acid
^{125}I	iodine-125
^{131}I	iodine-131
iv	intravenous
IGF	insulin-like growth factor
IGF-I	insulin-like growth factor I
IGF-II	insulin-like growth factor II
IGFBP	insulin-like growth factor binding protein
kDa	kilo Dalton
LAD	left anterior descending (coronary artery)
LV	left ventricle

LVEDD	left ventricular end diastolic diameter
LVESD	left ventricular end systolic diameter
M	molar, moles per litre
MI	myocardial infarction
m	metre
mM	millimolar, millimoles per litre
mm	millimetre
mg	milligram
mg/ml	milligrams per millilitre
min	minute
MGF	mechanogrowth factor
mRNA	messenger ribonucleic acid
MSA	multiplication stimulating activity
MW	molecular weight
nmol	nanomolar, nanomoles per litre
NSILA	non-suppressible insulin-like activity
N-terminal	amino terminal
P	probability
pH	hydrogen ion concentration
PAGE	polyacrylamide gel electrophoresis
PBS	phosphate buffered saline
PMSF	phenyl methyl sulphonyl fluoride
PTCA	percutaneous transluminal coronary angioplasty
r	recombinant
rh	recombinant human
ro	recombinant ovine
RIA	radioimmunoassay
RT	room temperature
RV	right ventricle
SD	standard deviation
SDS	sodium dodecyl sulphate
SED	standard error of the difference
SEM	standard error of the mean
SERCA	sarcoplasmic reticulum calcium ATP-ase
TCA	trichloroacetic acid
vol	volume
v/v	volume per volume
w/v	weight per volume

This Thesis Is Dedicated To

My Wife, Barbara,

Without Whose Love, Patience and Understanding,

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