Chapter 7

Discussion and future perspectives
Liver X receptors (LXRs) have been extensively studied in various organ systems for their function as transcriptional regulators of cholesterol homeostasis, glucose and lipid metabolism, and inflammatory and immune responses. The most well described effects of LXRs are on the reverse cholesterol transport system where LXR activation facilitates the removal of cholesterol from peripheral tissue, rendering them attractive targets in cardiovascular disease.

To date, little is known regarding the role of LXRs in the heart. Studies performed in LXRα knockout mice and pharmacological activation of LXRs with a non-selective agonist, T09, implicate LXRs in the protection against pathological cardiac hypertrophy (1,2). However, both of these approaches are confounded by systemic entities given residual effects from whole-body deletion of LXRα (3), as well as off-target LXR activity, which include lipogenic (4), anti-inflammatory (5), and blood pressure lowering (6) effects. This thesis thus sought to investigate the heart-specific effects of LXRα activation in cardiac pathophysiology. We hypothesized that cardiac LXRα would attenuate the development of cardiac hypertrophy and protect against cardiac dysfunction in an intrinsic, heart-specific manner. To this end, we used a transgenic approach to generate mice with cardiac-restricted overexpression of the murine NR1H3 gene encoding LXRα, described in Chapter 3.

**Cardiac LXRα transgenic mouse model**

The magnitude of left ventricular (LV) overexpression of LXRα protein achieved in our transgenic (LXRα-Tg) mice was nine-fold compared to transgene-negative littermates (Wt). This level of induction is indeed representative of a physiological range since pathological stimuli, such as chronic pressure overload (Chapter 4) and ischemia/reperfusion injury (7), trigger a similar increase in cardiac LXRα protein expression as displayed in LXRα-Tg mice. Further, the LXRα transgene resulted in functionally active LXR since known target genes were upregulated. Since we hypothesized that LXRα is anti-hypertrophic, we assessed evidence for a basal “atrophic” phenotype. However, cardiac LXRα overexpression only led to a slight reduction in LV mass of around 6-8%, but overall, gross cardiac morphology and function were unaffected in young and aging LXRα-Tg mice. Further extensive studies conducted in these mice disclosed a prominent metabolic phenotype of increased myocardial glucose uptake, as well as a trend toward increased fatty acid (FA) oxidation and myocardial leanness (Chapter 3). The latter is in contrast to synthetic LXR agonism, which caused increased myocardial lipid accumulation (8).

**Cardiac LXRα overexpression protects against pathological cardiac hypertrophy and dysfunction**

To investigate whether heart-specific LXRα overexpression is cardioprotective, LXRα-Tg mice were subjected to various hypertrophic perturbations. Herein, we show that, irrespective of the trigger or stimulus, constitutive LXRα activation consistently attenuated the development of pathological LV hypertrophy induced by transverse aortic constriction (TAC), angiotensin
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Chapter 3, as well as a metabolic challenge imposed by high fat diet (HFD)-induced obesity and insulin resistance (Chapter 5). From these observations we draw several conclusions. First, by circumventing confounding systemic factors of LXR activation, we establish that the beneficial effects conferred by LXRα are indeed heart-specific. Second, LXRα overexpression resulted in an attenuation of adverse myocardial remodeling processes that included cardiomyocyte hypertrophy and fibrosis, as well as prevention of cardiac dysfunction. Third, since diverse forms of stress, such as chronic increases in afterload, neurohormonal activation, and metabolic disturbances, induce hypertrophic growth via a multitude of signal transduction pathways and transcriptional activators, we infer that LXRα converges on a nexus of common, overlapping growth signals in the attenuation of hypertrophy, rather than antagonize distinct pathways specific for a given stimulus.

Mechanism of action

Our LXRα transgenic mouse model provided several novel insights into LXR functioning in the myocardium. In LXRα-Tg hearts, gene array profiling uncovered a regulatory role for LXRα in several metabolic pathways, including glucose and FA metabolism, and microPET imaging revealed a strong propensity for cardiac glucose uptake. In addition, natriuretic peptides, ANP and BNP, were strongly induced with cardiac LXRα overexpression, which, in concert with enhanced glucose reliance, recapitulate the fetal heart. We investigated this phenomenon further in the context of chronic pressure overload (Chapter 3) and obesity-induced type II diabetes (Chapter 5) where myocardial metabolism is known to be dysregulated.

Studies of cardiac metabolism implicate enhanced glucose reliance in the protection against pathological hypertrophy and heart failure (9-12). Our studies indicate that mice deficient for LXRα have impaired myocardial glucose uptake capacity in response to hypertrophic perturbation, whereas cardiac LXRα overexpression substantially increased glucose uptake levels that associated with improved functional outcome (Chapter 3), suggesting that cardiac LXRα orchestrates an adaptive metabolic response to hypertrophic stress. Further, we show that elevated glucose uptake levels are sustained by myocardial LXRα overexpression despite obesity-induced systemic insulin resistance and hypertriglyceridemia, stimuli that impede the capacity for glucose uptake (Chapter 5). Since both the diabetic heart and failing heart are prone to the development of cardiac insulin resistance (13,14), LXRα may therefore serve as an important tool in sensitizing the heart to glucose under these conditions. Inasmuch, the long-term consequences of LXRα-mediated glucose uptake and utilization require further evaluation, for example in the failing heart where myocardial metabolism is dysregulated as a result of impaired substrate usage and mitochondrial dysfunction. With heart failure, there is a chronic reduction in FA oxidation due to downregulation of PPARα, which leads to cardiac dysfunction via insufficient production of myocardial ATP. Mitochondrial function is unperturbed in hypertrophic LXRα-Tg hearts, and interestingly, FA oxidation rates are moderately increased (Chapter 3, Supplement). Whether this bears any significance on
improving mitochondrial energetics in heart failure warrants further assessment.

Further, in Chapters 3 and 5, we observed induction of natriuretic peptide expression by cardiac LXRα, which may be, in large part, at the basis of the anti-hypertrophic effects of LXRα. Regulation of ANP and BNP by LXRα is complex as we provide evidence for both an indirect effect via glucose-O-GlcNAc-dependent signaling (Chapter 3), as well as through direct interaction with a putative LXR response element, or LXRE, in the promotor region of ANP/BNP (Chapter 5).

To unravel the relationship between LXRα and natriuretic peptides, we performed further mechanistic studies. Firstly, nutrient signals from altered glucose homeostasis triggers gene transcription through glycosylation of transcription factors (15). In LXRα-Tg hearts, increases in glycolytic metabolism relative to glucose oxidation led to activation of the hexosamine biosynthesis pathway (HBP), an ancillary pathway of glycolysis, and downstream increases in protein O-GlcNAcylation. We further found GATA4 and Mef2c, transcriptional activators of natriuretic peptides, to be glycosylated, which establishes the link between glycolysis and modulation of natriuretic peptides, ANP and BNP. In broader schemes, these data highlight the importance of energy-independent signaling pathways of glycolysis in pathological cardiac hypertrophy, and emphasize the need for future studies that further elucidate O-GlcNAc targets effectual in cellular function and survival. Secondly, we implemented bioinformatical screening tools in Chapter 5 to locate conserved LXRE sequences in the ANP/BNP promoter region. In chromatin immunoprecipitation assays, we found LXRα to physically interact with this region, indicating that LXRα modulates natriuretic peptide expression in a direct manner, and show, for the first time, heart-specific gene targets for LXR.

**Genetic versus pharmacological LXR activation**

In Chapter 4, we tested a novel, high-affinity LXR agonist, AZ876 (AstraZeneca, MöIndal, Sweden), for its efficacy in pathological cardiac hypertrophy and remodeling. Using the established TAC model as described in Chapter 3, we demonstrate that preventative treatment with AZ876 protected against cardiac hypertrophy, and that adverse fibrotic remodeling and deterioration of heart function were more progressive in untreated versus AZ876-treated mice. The advantage of AZ876 over first-generation compounds, such as T09 and GW3965, is that it is more selective for LXRs with respect to other nuclear receptors (16), and chronic administration does not incur adverse lipogenic side effects or affect blood pressure, suggesting that the effects of AZ876 agonism on the heart are more specific. In further support of this notion, our in vitro studies indicate that LXR activation with AZ876 exerts cell-specific effects on cardiomyocytes and cardiac fibroblasts, reducing cellular hypertrophy and preventing collagen synthesis, respectively.

Taken together, applying both genetic and pharmacological approaches to evaluate the role of LXRα in the heart increases our understanding of its heart-specific effects, and provides further evidence to support a protective function for LXR in pathological cardiac
hypertrophy. However, our findings also disclose several discrepancies regarding these approaches in activating LXR in cardiac pathophysiology. One of the primary differences between LXRα overexpression and ligand activation involves the transcriptional profile of several key genes implicated in cardioprotection. Constitutive LXRα activation upregulated genes encoding the glucose transporters, Glut1 and Glut4, as well as the abovementioned natriuretic peptides, ANP and BNP, whereas this was not apparent with chronic LXR agonism. It is plausible that LXR agonism may exert transient effects on gene transcription since other studies have demonstrated that the effect of pharmacological LXR activation on, for example, Glut4, occurs within the first hours of treatment, but subsides with chronic stimulation (17). Also, differences in isoform activity may contribute to the observed discrepancies as LXRα is fully induced (and active) with cardiac-specific overexpression, whereas AZ876, a dual partial agonist, only partially activates LXRα.

**Importance of LXRα in the hypertrophic disease process**

As a potential therapeutic target, it is important to establish when, during the remodeling process, LXRα plays a role – in the initial stages of the disease, the compensated phase of hypertrophy, or in the decompensated or failure stage.

Our primary aim was to examine the effect of LXRα on pathological cardiac hypertrophy, therefore, in Chapters 3 and 4, we chose for an intervention that produced relatively compensated hypertrophy with structural remodeling, and conducted our murine TAC experiments over a period of five to six weeks; hearts generally develop failure with longer durations of eight weeks or more (18). Overt heart failure, on the other hand, is characterized by eccentric LV remodeling with dilatation of the LV, and severe dysfunction, and is further complicated by several pathological responses such as renal impairment, ascites, and pulmonary edema, which altogether confound the evaluation of hypertrophy in the heart.

We also examined the effect of LXRα activation at an early time point one week post TAC (Chapter 3, Supplement), which is characterized by acute processes such as inflammation and apoptosis. Development of cardiac hypertrophy at this time point was attenuated in LXRα-Tg hearts, including molecular determinants of hypertrophy, inflammation, and apoptosis. Whether LXRα is protective in the failing heart remains to be established, and pharmacological reversal studies need to be performed to further evaluate the therapeutic potential of LXRα. Nevertheless, as discussed in Chapter 2, the ideal window of opportunity for therapeutic intervention in heart failure pathogenesis is in the relatively early stages when cardiac remodeling is still largely reversible, and our preclinical data suggest that LXRα is a viable target during this phase.

**Future perspectives**

Translating these basic findings from cardiac-restricted LXRα overexpression studies to desired outcomes in clinical settings requires genetic manipulations such as gene therapy, which would be the most applicable technique for increasing LXRα expression in
patient hearts. However, the current status regarding gene therapy is that it is a high risk treatment option, and its safety and effectiveness remains unproven. Thus, bridging the gap between preclinical studies and a clinically viable therapeutic strategy most likely lies in the development of highly specific and selective LXR ligands that minimize lipogenic and neurological side effects, and are well tolerated in clinical trials.

Limiting the range of LXR signaling is achieved through selectivity regarding isoform- and tissue-specificity, and different co-repressor/co-activator combinations. Much of the current interest in developing suitable compounds is channeled towards designing LXRβ-specific ligands that target induction of the reverse cholesterol transport pathway in atherosclerotic disease, and circumvent the hepatic lipogenic signaling pathways mediated primarily by LXRα (19). However, the challenge with isoform-specific agonists is that there are very minor differences in the ligand binding domain of LXRα and LXRβ (20). Many of the second-generation LXR compounds are therefore partial agonists in that they increase the affinity of LXRs to both co-activators and co-repressors, whereas first-generation agonists fully release co-repressors from the LXR/RXR heterodimer complex, fully activating LXRα. Our studies with AZ876, a dual partial agonist, indicate that a ligand of this class was effective in attenuating cardiac hypertrophy and fibrosis (Chapter 4). Although LXRα and LXRβ appear to act in a functionally redundant manner in several cellular processes, there may, however, be isoform-specific differences in limiting a certain process. In the heart, there is mounting evidence to suggest that LXRα and LXRβ respond differently to various pathological stimuli, and that LXRα is the more responsive isoform for protection against myocardial infarction (7), pathological hypertrophy (1,2) (Chapter 4) as well as in streptozotocin-induced diabetes (21). Therefore, the ideal agonist in treating cardiac disease may favor stronger activation of LXRα over β.

A strategy to exclusively target LXR pathways in a given cell, or tissue, such as in the heart, is to modulate the LXR co-regulatory transcriptional complex, which impacts its DNA-binding and transcriptional activity. The recruitment of different co-regulatory proteins has been suggested to contribute to tissue-specific responses (22,23), and the final effect of a given agonist depends on the relative availability of certain co-activators and co-repressors in a given cell (24). The cardiac LXRα transgenic mouse model may represent a good starting point to evaluate the co-factor profile and determine which co-regulators are co-induced with cardiac LXRα overexpression. We have observed, for example, that the co-activator, Pgc1a, is substantially upregulated in LXRα-Tg hearts.

As discussed at the beginning of this thesis, we now understand that LXRα is a pleiotropic factor, exerting both systemic and myocardial-specific effects, and thus a plausible target in heart failure pathogenesis (reviewed Chapter 2). LXR activation may be beneficial in targeting a multitude of co-morbidities such as atherosclerosis and vascular disease, diabetes, and renal disease, as well as distinct myocardial pathologies related to myocardial
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Infarction, cardiac hypertrophy, and diabetic cardiomyopathy. So, although there are many opportunities to target LXR system-wide, when considering an LXR agonist, unfortunately “one size does not fit all.” Instead, what we may envision for the future is a repertoire of LXR agonists tailored to various diseased states, where, for example, a dual partial agonist may suffice in treating systemic co-morbidities and still have efficacy in the heart, whereas a tissue-selective LXR agonist with high affinities for cardiac LXRα may be more suitable for treating myocardial disease.
REFERENCES


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SUMMARY

Heart failure is one of the leading causes of mortality worldwide, and cardiac hypertrophy is an independent risk factor for heart failure development. Cardiac hypertrophy occurs due to stress or injury to the heart, such as hypertension, increased neurohumoral activation, and myocardial infarction. To compensate, the heart undergoes remodeling, a process that is initiated via molecular, cellular, and interstitial changes that structurally and functionally alter the myocardium. However, with unremitted stress, cardiac remodeling becomes maladaptive, perpetuating the progression toward cardiac dysfunction and heart failure.

A hallmark of the remodeling process is the alteration in myocardial metabolism as the heart reverts to increased glucose utilization that is characteristic of the fetal heart. Studies of cardiac metabolism implicate enhanced glucose reliance in the protection against pathological hypertrophy and heart failure. Currently, there are no metabolic modulators that are part of the guideline-based therapy for heart failure. Despite the success of current pharmacological strategies which aim to reduce hemodynamic afterload and growth through antagonism of the renin-angiotensin-aldosterone system and beta-blockade, heart failure remains nonetheless elusive. Interventions in metabolic remodeling thus represent a promising therapeutic adjunctive for targeting pathological hypertrophy and heart failure development.

Liver X receptors (LXRs) are nuclear receptors that have emerged as important therapeutic targets in cardiovascular disease given their atheroprotective and anti-inflammatory functions. LXRs also play a central role in lipid and glucose metabolism. Although it has been suggested that pharmacological LXR activation may protect the heart, lipogenic side effects of current LXR agonists preclude their clinical applicability, while the heart-specific effects of LXRs in cardiac pathophysiology and metabolism remain largely unknown. The aim of this thesis (chapter 1) was to investigate the cardiac-specific effects of LXRα activation in pathological hypertrophy, and further establish a cardioprotective role for LXRs in the pathogenesis of heart failure.

In chapter 2, we reviewed current evidence regarding the broad mode of action of LXRs and postulated that LXR activation may be both an important local and systemic target in heart failure development. Multiple co-morbidities impact the pathogenesis of this syndrome, and numerous studies demonstrate protective mechanisms for LXRs in several of these co-morbidities, including vascular and kidney disease, diabetes, and hypertension. In the heart, recent data implicate a beneficial role for LXR activation in myocardial infarction and diabetic cardiomyopathy, altogether, supporting the notion that LXRs are an integrative, pleiotrophic target with therapeutic potential for intervening in heart failure.
In chapter 3, we used a transgenic approach to selectively overexpress LXRα in murine hearts, and demonstrate that the cardioprotective effects of LXRα are indeed heart-specific in the attenuation of cardiac hypertrophy, myocardial fibrosis, and dysfunction. LXRα transgenic mice were protected from diverse hypertrophic perturbations, such as chronic pressure overload and angiotensin II stimulation. Gene profiling analyses uncovered novel roles for LXRα in several metabolic pathways, including glucose and fatty acid metabolism, and microPET imaging studies disclosed a strong propensity for cardiac glucose uptake. Moreover, in response to hypertrophic stress, LXRα overexpression markedly enhanced the capacity for glucose uptake, whereas this adaptation was impaired in LXRα-deficient mice. Further, cardiac LXRα promoted energy-independent utilization of glucose by activating the hexosamine biosynthesis pathway, resulting in downstream O-GlcNAc modification of transcription factors inducing natriuretic peptide expression, which we identified as a putative end effector of LXRα-mediated anti-hypertrophic effects in the heart.

Pharmacological studies were conducted in chapter 4 to further elucidate the role of LXR in the heart. A novel high-affinity LXR agonist, AZ876, was tested for its efficacy in pathological cardiac hypertrophy and remodeling. The advantage of AZ876 over first-generation compounds is that it is more selective for LXRs with respect to other nuclear receptors. In a murine model of pressure overload, preventative treatment with AZ876 protected against cardiac hypertrophy, and fibrotic remodeling and deterioration of heart function were less progressive in AZ876-treated versus untreated mice. Importantly, this occurred independently of blood pressure or adverse lipogenic side effects, suggesting that the effects of AZ876 agonism on the heart are more specific. These data are further supported by in vitro studies indicating cell-specific effects for AZ876 on cardiomyocytes and cardiac fibroblasts.

In chapter 5, we extended upon our observations in chapter 3 that LXRα mediates alterations in glucose metabolism in the adaptation to hypertrophic stress. Since myocardial energy metabolism is dysregulated in diabetes, we evaluated the consequences of high fat diet-induced obesity in LXRα transgenic mice. We found that cardiac LXRα nonetheless sustained increases in glucose uptake, despite systemic insulin resistance and hypertriglyceridemia. Since both the diabetic heart and failing heart are prone to the development of cardiac insulin resistance, we conclude that LXRα may serve as an important tool in sensitizing the heart to glucose under these conditions.

Finally, the aim of chapter 6 was to investigate metabolic markers in a clinical setting. Adiponectin is an adipokine with established insulin-sensitizing and anti-atherogenic properties. In a sub-analysis of the GIPS-III trial, we aimed to describe the relation between circulating adiponectin levels and left ventricular function and remodeling after myocardial infarction in patients treated with metformin or placebo. However, our results indicated that adiponectin did not associate with these parameters.
In summary, we show that, irrespective of the trigger or stimulus, constitutive LXRα activation consistently attenuated the development of pathological cardiac hypertrophy induced by pressure overload, angiotensin II stimulation, as well as high fat diet-induced obesity. Our LXRα transgenic mouse model provided several novel insights into LXR functioning in the myocardium. Overall, LXRα appears to be a key cardiac transcriptional regulator that mediates an adaptive metabolic response to pathological cardiac stress. Cardiac LXRα overexpression induced natriuretic peptide expression, which, in concert with enhanced glucose reliance, recapitulate the fetal heart. Since there is increased interest among pharmaceutical industries in developing metabolic modulators in general, as well as highly selective LXR agonists in particular, these findings have potential and substantial translational importance.
Hartfalen is wereldwijd één van de belangrijkste oorzaken van sterfte. Cardiale hypertrofie is een onafhankelijke risicofactor voor het ontwikkelen van hartfalen en daarom een belangrijk onderwerp van studie. Cardiale hypertrofie ontstaat na schade of langdurige drukbelasting, zoals hypertensie, toegenomen neurohormonale activatie of een myocardinfarct. Om hiervoor te compenseren ondergaat het hart “remodelering”, een proces dat wordt geïnitieerd via moleculaire, cellulaire en interstitiële veranderingen die het hart zowel structureel als functioneel veranderen. Echter, wanneer het hart onderhevig blijft aan hoge belasting, wordt een punt bereikt waarop het geremodeleerde hart niet meer kan voldoen aan de vraag, waardoor uiteindelijk cardiale dysfunctie en hartfalen zal optreden.

Ondanks het succes van de huidige farmacologische strategieën die gericht zijn op het reduceren van de afterload, door remming van het renine-angiotensine-aldosteron systeem en bèta-blokkade, blijft hartfalen een moeilijk te behandelen ziekte. Een belangrijk kenmerk van cardiale remodelering is verandering van het myocardiale metabolisme, dat terugkeert naar glucose gebruik wat ook in het foetale hart de dominante bron van energie is. Studies van het cardiale metabolisme hebben gesuggereerd dat een toename van glucose beschermend is tegen pathologische hypertrofie en hartfalen. Op dit moment maken modulators van het metabolisme echter (nog) geen deel uit van de, op richtlijnen gebaseerde, therapie voor hartfalen. Interventies in de metabole remodelering zijn dus een veelbelovende toevoeging voor de behandeling van pathologische hypertrofie en hartfalen.

Lever X receptoren (LXRs) zijn nucleaire receptoren die als veelbelovende therapeutische doelwitten gelden in cardiovasculaire ziekte gezien hun atheroprotectieve en anti-inflammatoire werking. LXRs spelen daarnaast ook een centrale rol in het lipiden en glucose metabolisme. Hoewel gesuggereerd is dat farmacologische activatie van LXR het hart beschermt, belemmeren de lipogene bijwerkingen van de huidige LXR agonisten klinische toepasbaarheid, terwijl de effecten van LXRs in cardiale pathofysiologie en metabolisme grotendeels onbekend blijven. Het doel van dit proefschrift (hoofdstuk 1) was om de hart-specifieke effecten van LXRs activatie in pathologische hypertrofie en hartfalen te onderzoeken en om de cardioprotectieve rol van LXRs in de pathogenese van hartfalen verder te bestuderen.

In hoofdstuk 2 hebben we de huidige studies met betrekking tot het brede werkingsmechanisme van LXRs geëvalueerd en hieruit maakten wij op dat activatie van LXRs zowel een belangrijk lokale als systemische factor bij de ontwikkeling van hartfalen kan zijn. Meerdere comorbiditeiten hebben invloed op de pathogenese van dit syndroom, en verschillende studies hebben de beschermende werking van LXR aangetoond in deze comorbiditeiten, met inbegrip van vasculaire ziekte, nierziekte, diabetes en hypertensie. Recente data laten zien dat LXR activatie in het hart een gunstige werking kan hebben, bijvoorbeeld bij een myocardinfarct en diabetische cardiomyopathie. Wanneer we alle
gegevens samennemen, ondersteunen deze de opvatting dat LXRs kunnen dienen als overkoepelende, pleiotrope factoren met voldoende therapeutisch potentieel voor behandeling voor hartfalen.

In hoofdstuk 3 hebben we een transgene benadering gebruikt leidend tot selectieve overexpressie van LXRα in muizenharten en hebben aangetoond dat de cardioprotectieve effecten van LXRα inderdaad hart-specifiek waren in het voorkomen van cardiale hypertrofie, myocardiale fibrose en cardiale dysfunctie. LXRα transgene muizen waren beschermd tegen hypertrofie in verschillende experimentele hartfalenmodellen van chronische drukbelasting en angiotensine II stimulatie. Genetische analyses toonden betrokkenheid van LXRα in verschillende metabole routes aan, inclusief glucose en vetzuur metabolisme, en daarnaast toonde microPET imaging een sterk verhoogde neiging tot glucose opname door het hart. Bovendien versterkte LXRα overexpressie het vermogen om glucose op te nemen als respons op hypertrofie en deze aanpassing was afwezig in LXRα-deficiënte muizen. Verder bevorderde cardiaal LXRα het energie-onafhankelijk gebruik van glucose door het activeren van de hexosamine biosynthese, resulterend in downstream O-GlcNAc modificatie van transcriptiefactoren en daardoor expressie van natriuretisch peptides, wat door ons geïdentificeerd werd als mogelijke mechanisme voor LXRα-gemedieerde anti-hypertrofe effecten in het hart.

Farmacologische studies werden uitgevoerd in hoofdstuk 4 om de rol van LXR in het hart nader te onderzoeken. Een nieuwe LXR agonist met hoge affiniteit, AZ876, werd getest naar effectiviteit in pathologische cardiale hypertrofie en remodelering. Het voordeel van AZ876 boven eerste generatie medicamenten, is dat het selectiever is voor LXR in vergelijking met andere nucleaire receptoren. In een muizenmodel van druk overbelasting beschermde preventieve behandeling met AZ876 tegen cardiale hypertrofie en vermindere de progressie van fibrose en verslechtering van hartfunctie in vergelijking met onbehandelde muizen. Dit effect was onafhankelijk van de bloeddruk of andere nadelige lipogene bijwerkingen, wat suggereert dat de effecten van AZ876 op het hart specifieker zijn. Deze data worden verder ondersteund door in vitro studies die wijzen op cel-specifieke effecten van AZ876 op cardiomycocyten en cardiale fibroblasten.

In hoofdstuk 5 hebben we onze observaties uit hoofdstuk 3 verder uitgewerkt, namelijk dat LXRα veranderingen in glucose metabolisme medieert als aanpassing op hypertrofische stress. Omdat het energiemetabolisme van het myocard verstoord is bij diabetes, hebben we de gevolgen van vetrijk dieet-geïnduceerde obesitas onderzocht in LXRα transgene muizen. We observeerden dat het cardiale LXRα een toename in glucose opname bleef laten zien, ondanks systemische insuline resistentie en hypertriglycerideremie. Aangezien zowel het diabeteisc h hart en falende hart gevoelig zijn voor de ontwikkeling van cardiale insulineresistentie, concludeerden we dat LXRα dient als een belangrijk instrument om het hart te sensitizeren voor glucose.
Tenslotte, was het doel in hoofdstuk 6 om metabole markers te onderzoeken in een klinische setting. Adiponectine is een adipokine met bekende insuline-sensitizerende en anti-atherogene eigenschappen. In een sub-analyse van de GIPS-III studie hebben we de relatie tussen circulerende adiponectine niveaus en linker ventrikel functie en remodelering onderzocht in patiënten na een myocardinfarct, die behandeld werden met placebo of metformine. Onze resultaten toonden echter dat adiponectine niet geassocieerd was met deze parameters.

Samengevat laten we zien dat, ongeacht de stimulus, LXRα activering consistent de ontwikkeling remt van pathologische cardiale hypertrofie, geïnduceerd door drukbelasting, angiotensine II stimulatie, of door obesitas geprovoceerd door een vetrijk dieet. Ons LXRα transgene muismodel heeft ons nieuwe inzichten verschaft wat betreft de functie van LXR in het myocard. Al met al lijkt LXRα een belangrijke cardiale transcriptionele regulator te zijn die de adaptieve metabole respons medieert als reactie op pathologische cardiale belasting. Cardiale overexpressie van LXRα leidde tot expressie van natriuretisch peptides, wat net als de verhoogde glucose afhankelijkheid, de situatie van het foetale hart simuleert. Aangezien de farmaceutische industrie belangstelling heeft voor het ontwikkelen van metabole modulators in het algemeen, evenals selectieve LXR-agonisten in het bijzonder, zijn onze bevindingen van potentieel en aanzienlijk translationeel belang.
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Chapter 7

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Megan
BIOGRAPHY

Megan Valerie Cannon was born in East London, South Africa. After matriculating from Clarendon Girls High School in 1995, she moved to North Carolina, USA, after being awarded an athletic scholarship from Campbell University. There she pursued a Bachelor of Science degree, alongside captaining the women’s tennis team, and graduated summa cum laude in 1999. She then moved to Austin, Texas, USA, and became an employee of North Austin Medical Center where she worked as an ARDMS registered cardiac sonographer performing mostly adult, but also neonatal echocardiography. In 2005, she entered graduate school at The University of Texas at Austin. In the Department of Exercise Physiology, she joined the Cardiac Metabolism research laboratory where she completed her Master of Science degree under the supervision and mentorship of Dr. Joseph Starnes. During her graduate studies, she held a teaching assistantship position at the College of Natural Sciences and taught anatomy and physiology. After graduating in 2008, she remained at UT Austin to conduct post-graduate research in the Muscle Physiology and Plasticity laboratory under the leadership of Dr. Roger Farrar. In 2010, she moved to Groningen, The Netherlands, to pursue a doctorate degree at the Department of Experimental Cardiology, University Medical Center Groningen. The outcome of her research is presented in this thesis.