Modulation of VLDL triglyceride metabolism

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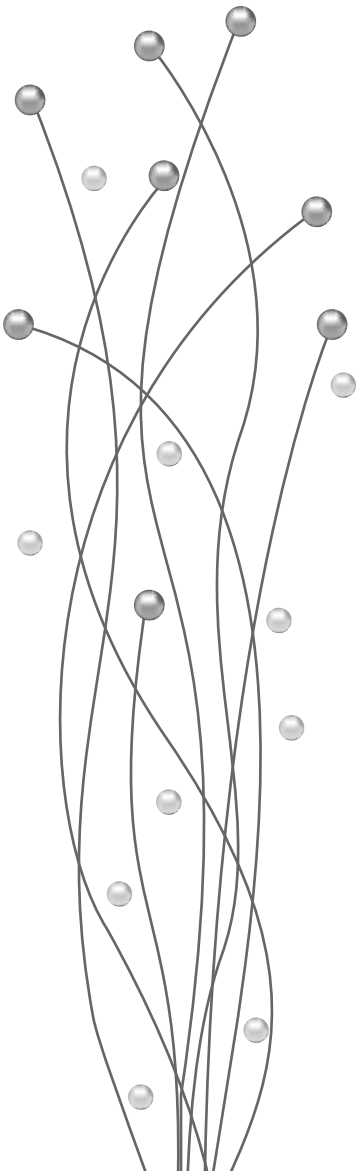
Chapter 8



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Summary

Nederlandse samenvatting
voor niet-ingewijden

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Summary

Obesity is characterized by excessive fat storage and is associated with various diseases like cardiovascular disease (CVD) and type 2 diabetes (DM2), thereby being a serious problem of public health. Excessive energy intake is an important cause of obesity since excess energy is primarily stored as fat. The stored fat is mobilized again during fasting in the form of fatty acids (FA). These FA are re-esterified in the liver in triglycerides (TG) that are secreted in VLDL particles to deliver FA to peripheral tissues where they can be used for energy.

One of the current views of the cause of diseases related to obesity is the (mis) handling of TG derived FA. Therefore it is important to understand pathways involved in the uptake, distribution, oxidation and storage of TG. In this thesis we have evaluated the effect of different interventions on VLDL-TG metabolism to gain a better understanding of its complex regulation. For these studies we used APOE*3-Leiden (E3L) and E3L.CETP transgenic mice that have a human-like lipoprotein metabolism and respond to lipid-modifying drugs in a ways similar to humans.

The first part of this thesis focuses on the effect of cholesteryl ester transfer protein (CETP) on VLDL-TG metabolism. CETP transfers cholesteryl esters and TG between lipoproteins and has been shown to have a major impact on cholesterol metabolism. Previous studies in E3L mice have shown that expression of CETP reduces HDL-C, increases LDL-C and thereby increases the risk to develop atherosclerosis. Whether CETP also has impact on TG metabolism was explored in **chapter 2**. Expression of CETP hardly affected VLDL-TG metabolism and did not influence high fat diet induced obesity in E3L mice. We concluded that CETP inhibitors are not likely to have adverse health effects related to TG metabolism.

The second part of this thesis addressed the effect of different pharmaceutical interventions on the regulation of VLDL-TG metabolism by nuclear receptors. Intermediates of lipid metabolism and hormones activate nuclear receptors after which they are transported to the nucleus where they regulate amongst other the expression of genes involved in energy homeostasis. These nuclear receptors include peroxisome proliferators activated receptors (PPARs) and the xenobiotic receptors pregnane X receptor (PXR) and constitutive androstane receptor (CAR).

In **chapter 3** we investigated the effect of the pharmacologic PPARα activator

fenofibrate on VLDL-TG metabolism. To this end, E3L.CETP mice were fed a western-type diet without or with fenofibrate. Treatment with fenofibrate lowered total plasma TG levels by increasing lipolysis of VLDL-TG. Unexpectedly, fenofibrate increased VLDL-TG production which is partly explained by increased FA turnover.

The effect of rifampicin on VLDL metabolism was studied in **chapter 4**. E3L.CETP mice were treated with the PXR agonist rifampicin, an antibiotic prescribed for the treatment of tuberculosis. Treatment with this drug is associated with hepatic steatosis and dyslipidemia. E3L.CETP mice were fed a western-type diet for 3 weeks followed by an additional 3 weeks diet without or with increasing doses of rifampicin. The highest dose of rifampicin used (0.10%) showed a decrease of both HDL and VLDL cholesterol levels whereas total TG levels were unaltered. This decrease in cholesterol was mainly explained by lowering of both HDL and VLDL particle production by the liver. However, the VLDL particles secreted were enriched in TG explaining why total TG levels were not affected by rifampicin.

In addition to drugs affecting nuclear receptors and lipid metabolism, chemical pollutants might also act as agonists for nuclear receptors. In **chapter 5** we describe the hypolipidemic effects of perfluoroakyl sulfonates (PFAS), a group of chemicals used for stain repellence and coatings. These compounds are higly resistant to degradation and bioaccumulate. PFAS activate PPARα as well as the xenobiotic receptors PXR and CAR, altogether reducing HDL and VLDL production by the liver as well as increasing VLDL-TG clearance by increasing lipolysis.

In **chapter 6** we examined the differences in hepatic gene expression in response to fasting or a high fat diet, both known to induce hepatic steatosis. However, only after high fat diet feeding this steatosis is associated with hepatic insulin resistance. To gain insight in the transcriptional processes leading to steatosis associated insulin resistance, C57Bl6/J mice were fed standard chow diet or a high fat diet for 2 weeks. After 2 weeks half of the mice fed chow were fasted for 16 hours whereas the other part of the chow fed mice and the high fat diet fed mice were fasted for 4 hours. Strikingly, fasting affected far more genes compared to control than feeding a high fat diet. Furthermore, hardly any overlap in gene expression profile was seen between fasting and a high

fat diet, suggesting completely different gene programmes are activated. High fat diet feeding was especially associated with activation of PPARα whereas fasting activated xenobiotic receptors PXR and CAR.

Chapter 7 discusses the observation that nuclear receptors have a major impact on lipoprotein metabolism and play a key role in the pathology associated with obesity. Nuclear receptors are used as targets for the development of drugs to treat the metabolic syndrome. However, although we only focussed on the effect of nuclear receptors on lipoprotein metabolism in this thesis, inflammation is also regulated by these nuclear receptors. Development of new drugs that target nuclear receptors focuses on organ-specificity as well as gene-specificity. However, a focus on dyslipidemia only might neglect the anti-inflammatory effects of novel potential drugs that could provide added benefit.

Nederlandse samenvatting voor niet-ingewijden

Ongezond overgewicht

Zwaarlijvigheid (**obesitas**) is het overmatig opslaan van vet in ons lichaam en leidt tot ziektes als hart- en vaatziekten en suikerziekte en is daarom een groot probleem in de gezondheidszorg. Of iemand obees is wordt bepaald aan de hand van je Body Mass Index (**BMI**): het lichaamsgewicht in kilogram, gedeeld door de lichaamslengte in meters in het kwadraat (kg/m^2). Een BMI tussen 18,5 en 25 wordt beschouwd als ideaal voor een gezond individu; een BMI van meer dan 25 wordt beschouwd als te zwaar (overgewicht); een BMI van meer dan 30 wordt beschouwd als obesitas. Overmatige inname van calorieën is één van de belangrijkste oorzaken van obesitas omdat de extra calorieën voornamelijk als vet worden opgeslagen. Wanneer we vasten wordt dit vet weer vrijgemaakt in de vorm van **vetzuren** zodat we het vet kunnen gebruiken als energie bron. De meeste van deze vetzuren gaan direct naar de lever waar ze worden omgezet in **triglyceriden** (TG). Deze TG bestaan uit een glycerol keten met drie vetzuren. TG worden vanuit de lever vervolgens weer vrijgelaten in de bloedbaan.

Transport van vet in ons lichaam

Omdat vet slecht oplost in water en bloed, moet vet 'oplosbaar' verpakt worden om getransporteerd te worden in ons lichaam. De verpakking van vet wordt ook wel een **lipoproteïne** genoemd. Afhankelijk van hun samenstelling hebben deze lipoproteïnen een ander dichtheid en worden ze als volgt ingedeeld: zeer lage dichtheid lipoproteïnen (**VLDL**) met voornamelijk TG, lage dichtheid lipoproteïnen (**LDL**) met TG en cholesterol en hoge dichtheid lipoproteïnen (**HDL**) met voornamelijk cholesterol. Het hebben van veel LDL is een risicofactor voor het ontstaan van aderverkalking terwijl HDL er juist voor beschermd. LDL is in de volksmond ook wel bekend als slecht cholesterol en HDL als goed cholesterol.

TG uit de lever komen in de bloedbaan terecht in VLDL om bij andere weefsels vetzuren af te leveren die als energie bron gebruikt kunnen worden. Omdat TG zeer groot is moeten deze eerst weer omgezet worden in losse vetzuren voordat ze door de weefsels opgenomen kunnen worden. Dit proces heet **lipolyse**. De reden dat vetzuren eerst via de lever in TG worden omgezet heeft te maken met het feit dat vetzuren zelf toxisch zijn. In weefsels worden ze daarom zo snel mogelijk óf verbrand óf weer omgezet in TG zodat ze geen schade kunnen aanrichten.

Verstoring TG transport in obesitas

Er wordt momenteel heel veel onderzoek gedaan naar de reden waarom mensen met obesitas een hoog risico lopen om hart- en vaatziekten en suikerziekte te ontwikkelen. Men denkt dat één van de oorzaken hiervoor is dat het lichaam verkeerd omgaat met TG en de vetzuren hiervan. Daarom is het belangrijk dat we meer inzicht krijgen in de stofwisseling processen betrokken bij de opname, het transport, de verbranding en de opslag van TG en vetzuren (**TG metabolisme**). In dit proefschrift onderzoeken we het effect van verschillende interventies op het metabolisme van VLDL-TG om zo beter inzicht te krijgen in de regulatie hiervan.

In het eerste deel van dit proefschrift hebben we gekeken naar het effect van cholesteryl ester transfer proteïne (**CETP**) op het VLDL-TG metabolisme. CETP is betrokken bij het verplaatsen van cholesteryl esters en TG tussen lipoproteïnen en we hebben eerder al laten zien dat CETP een grote invloed heeft op het cholesterol metabolisme. De werking van CETP leidt tot verlaagde niveaus van HDL cholesterol (goed cholesterol) en een toename van LDL cholesterol (slecht cholesterol) waardoor de kans op aderverkalking toeneemt. Of CETP ook effect heeft op TG is onderzocht in **hoofdstuk 2**. De werking van CETP heeft nauwelijks effect op het VLDL-TG metabolisme en heeft geen effect op de ontwikkeling van obesitas door het aangeboden dieet. Omdat CETP cholesterol verplaatst van HDL naar LDL en het goede cholesterol hierdoor afneemt, worden er medicijnen ontwikkeld om CETP te remmen en zo het goede cholesterol te verhogen. Het is belangrijk dat het remmen van CETP geen negatieve bijwerkingen heeft omdat CETP ook TG verplaatst tussen lipoproteïnen. We concluderen dan ook dat CETP remmers waarschijnlijk geen negatieve bijwerkingen zullen hebben met betrekking tot het TG metabolisme.

Regulatie van TG metabolisme

In het tweede deel van dit proefschrift hebben we gekeken naar de effecten van verschillende farmacologische interventies op de regulatie van het VLDL-TG metabolisme. **Nucleaire receptoren** spelen hierbij een grote rol. Dit zijn eiwitten in de cel die zijn betrokken bij de communicatie in de cel. Nucleaire receptoren herkennen specifieke moleculen in de cel, bijvoorbeeld vetzuren, en verplaatsen zich vervolgens naar de kern van de cel waar ze de **werking (expressie) van genen** beïnvloeden. Genen zijn onderdeel van ons DNA en bevatten de receptuur om 'machines' te maken. Deze machines zijn de werktuigen in onze cellen en hebben allemaal een eigen functie. Wanneer

de expressie van een gen toeneemt wordt er meer van die machine gemaakt. Op deze manier worden processen in onze cellen, en dus in ons lichaam, beïnvloed. Andere moleculen die herkend kunnen worden door nucleaire receptoren zijn hormonen en xenobiotica. Xenobiotica zijn moleculen die van nature niet in het lichaam voorkomen, bijvoorbeeld medicijnen die we slikken. Tot de nucleaire receptoren behoren de peroxisoom proliferator geactiveerde receptoren (**PPAR**), en de xenobioticum receptoren pregnaan X receptor (**PXR**) en constitutieve androstaan receptor (**CAR**).

In **hoofdstuk 3** hebben we het effect van de farmacologische PPARα activator fenofibraat op het VLDL-TG metabolisme onderzocht. Fenofibraat behoort tot de groep van de fibraten en hebben als belangrijkste functie het verlaging van TG in het bloed. Er werd altijd vanuit gegaan dat deze verlaging wordt veroorzaakt door minder productie van VLDL-TG én meer opname van VLDL-TG. Onze studie laat zien dat de verlaging van TG door fenofibraat geheel wordt verklaard door meer opname van VLDL-TG. Onverwacht veroorzaakt fenofibraat zelfs een verhoging van de productie van VLDL-TG door de lever. Deze toename wordt deels veroorzaakt door een toename in de omvorming en verplaatsing van vetzuren, oftewel meer **vetzuur omzet**. Verhoogde omzetting van vetzuren in het lichaam wordt als één van de oorzaken beschouwd voor het ontstaan van ziekten gerelateerd aan obesitas. Het is dus belangrijk dat we niet alleen weten wat medicijnen op totale niveau's doen van TG en cholesterol maar ook hoe medicijnen dit doen. Waarschijnlijk is de verhoogde omzetting van vetzuren met fenofibraat niet schadelijk omdat fenofibraat ook ontsteking remt. Ontsteking is ook belangrijk bij het ontstaan van hart- en vaatziekten en suikerziekte in mensen met obesitas.

Het effect van rifampicine op het VLDL metabolisme is onderzocht in **hoofdstuk 4**. Rifampicine is een antibioticum dat wordt voorgeschreven voor de behandeling van tuberculose. Maar rifampicine activeert ook PXR. Bij behandeling met dit medicijn zijn bijwerkingen als vervetting van de lever en verstoring van TG en cholesterol in het bloed bekend. In onze studie laten we zien dat rifampicine inderdaad PXR activeert en leidt tot een verlaging zowel HDL als VLDL cholesterol terwijl de TG niveau's onveranderd blijven. De afname van het cholesterol wordt veroorzaakt door minder productie van voornamelijk VLDL door de lever. Omdat de VLDL deeltjes uitgescheiden door de lever meer TG bevatten heeft rifampicine geen effect op het totale TG niveau.

Chemische verontreinigende stoffen hebben ook invloed op nucleaire receptoren. In **hoofdstuk 5** beschrijven we het effect van perfluoroakyl sulfonaten (**PFAS**) op het TG en cholesterol metabolisme. PFAS zijn chemische stoffen die worden gebruikt in anti-vlek middelen en in coatings. Nadeel van deze stoffen is dat ze biologisch slecht afbreekbaar zijn en daardoor ophopen in het milieu. We laten zien dat PFAS de nucleaire receptoren PPARα, PXR en CAR activeren, wat leidt tot remming van zowel de HDL als VLDL productie door de lever. Daarnaast stimuleren PFAS de lipolyse van VLDL-TG. Bij elkaar verklaart dit waarom cholesterol en TG sterk verlagen in onze studie.

In **hoofdstuk 6** hebben we gekeken naar de verschillen in lever gen expressie in reactie op langdurig vasten of een hoog vet dieet. Zowel langdurig vasten als een hoog vet dieet leiden tot vervetting van de lever maar alleen bij een hoog vet dieet is er ook sprake van dat de lever niet langer reageert op insuline. Dit wordt ook wel insuline resistentie genoemd en kan leiden tot suikerziekte. We hebben deze studie uitgevoerd om meer inzicht te krijgen in de regulatie van het vet metabolisme bij zowel lever vervetting als insuline resistentie. Opvallend is dat vasten de werking van veel meer genen beïnvloed vergeleken met controle dieren dan een hoog vet dieet. Daarnaast was er ook nauwelijks overlap in de genen die tot werking kwamen vergeleken tussen vasten en hoog vet dieet. Dit suggereert dat er compleet andere gen expressie programma's betrokken zijn bij het ontstaan van een vette lever tussen vasten en een hoog vet dieet. Hoog vet dieet geïnduceerde vette levers waren geassocieerd met activatie van PPARα terwijl na vasten vooral de xenobioticum receptoren PXR en CAR werden geactiveerd.

In dit proefschrift laten we zien dat nucleaire receptoren een grote invloed hebben op het VLDL-TG metabolisme en ook betrokken zijn bij het ontstaan van ziektes gerelateerd aan obesitas. Momenteel wordt er veel aandacht besteed aan het ontwikkelen van medicijnen die nucleaire receptoren beïnvloeden om zo ziekten in obese mensen te behandelen. Onze onderzoeken laten vooral zien wat het effect is van nucleaire receptoren op VLDL-TG maar ze hebben vaak ook invloed op ontsteking. Bij het ontstaan van ziektes bij obesitas zijn vaak vele verschillende processen betrokken waaronder het TG metabolisme en ontsteking. Door geïntegreerd onderzoek te doen naar deze verschillende processen kunnen we een beter beeld krijgen waarom mensen met obesitas ziek worden en goede medicijnen ontwikkelen.

List of publications

Bijland S, van den Berg SAA, Voshol PJ, van den Hoek AM, Princen HM, Havekes LM, Rensen PCN, Willems van Dijk K. CETP does not affect triglyceride production or clearance in APOE*3-Leiden mice.
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Curriculum Vitae

Silvia Bijland werd geboren op 13 juli 1980 te Zaanstad. Na het doorlopen van de Mavo en Havo behaalde ze haar VWO diploma in juni 2000 aan het Bertrand Russell College te Krommenie. In september dat jaar begon zij haar studie Biomedische Wetenschappen aan de Universiteit van Utrecht. Ze behaalde haar propedeutisch examen in 2001 en haar Bachelor diploma in 2003. Tijdens haar Master Developmental Biology and Biomedical Genetics heeft zij een drietal stages doorlopen. Tijdens haar hoofdvakstage heeft ze onderzoek verricht binnen de vakgroep Fysiologische Chemie van het Universitair Medisch Centrum Utrecht onder leiding van Drs. JA Riedl en Prof. Dr. JL Bos met als onderwerp 'Small GTPase Rap1'. Haar tweede onderzoeksstage heeft ze verricht onder leiding van Drs. MJ Adjobo-Hermans en Prof. Dr. D. Gadella Jr. bij de afdeling Molecular Cytology van het Swammerdam Institute for Lifescience te Amsterdam met als onderwerp 'Visualisation of dimerization C terminal domain PLCβ'. Daarnaast heeft ze nog een onderzoeksstage verricht bij de afdeling Endocrinologie van het Leids Universitair Medisch Centrum Leiden onder leiding van Drs. JFP Berbée en Dr. PCN Rensen met als onderwerp 'Role of apolipoprotein AIV in inflammation'. In 2006 behaalde zij haar Master diploma en aansluitend startte zij als promovenda met haar promotieonderzoek op de afdelingen Humane Genetica en Endocrinologie onder begeleiding van haar promotor Prof. Dr. Ir. LM Havekes en copromotores Dr. Ir. K. Willems van Dijk en Dr. PCN Rensen.