1 Introduction

1.1 Goals of the Thesis

Obesity in general as well as its associated diseases, like diabetes type 2, hypertension, cardiovascular diseases and others, have become a major problem in today's society. Examining therapies, exploring measures and possible causes led to perpetual further studies of the lipometabolism and its influencing factors.

Already in 1994 first studies had discovered small invaginations of the plasma membrane. These invaginations, known as caveolae, were extremely abundant in adipocytes. So this let one assume that they do have an influence on or role in the lipometabolism. [SLB+94]

Since then, a lot of publications dealing with exact that topic have been published. The aim of this thesis is to give a short overview of the state of the scientific knowledge concerning caveolae in the lipometabolism. The research is mainly based on public papers that were published between 1994 and 2010 via PubMed.

1.2 Abstract

Caveolae are small, non-clathrin-coated, invaginations of the plasma membrane. Their most characteristic components are caveolin dimers, cholesterol molecules and glycosphingolipids. [PS07]

Besides their function in signal transducing pathways and transcytosis [PS07], caveolae were found to be highly concentrated in the plasma membrane of adipocytes in 1994 [SLB+94]. As further research proved, caveolae can be related to several processes concerning the regulation of the glucose- and lipometabolism [PS07]:

The sodium-independent glucose transporter GLUT4 translocates from the intracellular compartment to the plasma mebrane due to an insulin stimulus. This happens parallel to the numerous translocation of caveolin proteins from the microsomes to the plasma membrane. The amount of caveolar structures within the plasma membrane increases as well and their conformation changes allow a higher number of GLUT4 receptors to associate with these caveolin-rich areas. [SLB+94]

Furthermore, caveolin proteins are phosphorylated due to an insulin stimulus. The dose-dependency of this phosphorylation shows great similarities with the dose-dependent phosphorylation of the insulin receptors, apparently related to the dose-dependent glucose uptake as well. [MBS95]

As cholesterol, GLUT4 and insulin receptors, all three significantly related to obesity and insulin-resistance, are located within caveolae, meaningful health impacts as a result of caveolar dysfunction can be assumed. Indeed, the cholesterol content of the plasma membrane decreases as a consequence of adipocyte hypertrophy and caveolin-$1^{-/-}$ mice show a significant decrease in caveolae and suffer from insulin resistance. New studies further suppose an inverse correlation between caveolin-1 levels and the body mass index. Moreover, caveolar dysfunction increases the PAI-1 levels, responsible for the raise of obesity and cardiovascular diseases. [VHYN04]

Insulin receptors are highly concentrated within the neck of caveolae [FPF+07], and their number dramatically decreases in caveolin-1-deficient mice. Additionally the coexpression of caveolin-1 and insulin receptors leads to a decreased mobility of the insulin receptors, assuming that caveolin-1 stabilizes the insulin receptors within the plasma membrane. The insulin receptors can be remobilized through gangliosides GM3 again, as they dissociate the IR-CAV1 complexes. And even intentional induced insulin resistances can be almost recovered through the supression of the GM3 biosynthesis. [KSS+07]

New drugs, already widely used in the United States, are the so-called statins which influence caveolae through their cholesterol level lowering function, including a decrease of cardiovascular diseases and mortality rates. Simvastin treatment, as well as cavolin-1-null mice, show a significant decrease of the circulating levels of the high molecular weight form of adiponectin, whereas the intracellular HMW adiponectin levels increase. This leads to the assumption that statins cause a secretion defect for adiponectin in adipocytes. Also the number of caveolae within the plasma membrane decreases as the majority appears as vesicular structures close to the plasma membrane, probably due to a disruption of the endogenous cholesterol synthesis. [KHM+09]

In most experiments concerning caveolae caveolin-$1^{-/-}$ mice are used. They are generated by heterozygous inter-breeding of mice with disrupted exons 1 and 2 of caveolin-1. This knockout has big influence on the adipose tissue as well as on the lung tissue, which is rich in caveolin-1 as well. Although the food uptake and the food absorption of wild-type mice and caveolin-1-deficient mice is the same, caveolin-$1^{-/-}$ mice are smaller and leaner and show a resistance to diet-induced obesity. Examining fat pads moreover reveals that they are significantly underdeveloped (reduced number of lipid droplets and reduced adipocyte diameter) and contain less caveolae. Interestingly the triglyceride levels of caveolin-$1^{-/-}$ mice are clearly raised whereas the free fatty acid levels remained the same. While wild-type mice quickly reach a steady-state rate of absorption and clearance, caveolin-$1^{-/-}$ mice continue to build up triglycerides for a longer time. These triglycerides are then stored within the brown adipose tissue, which does not contain a lot of caveolae. So the

resistance to diet-induced obesity may be due to the inability to convert triglycerides in lipoprotein form to triglycerides in lipid droplet storage form. [RCW+01]

All in all, caveolae have become target to even more studies and research work, as their discovered influence on and importance to the glucose- and lipometabolism becomes more and more explored.