CURRICULUM VITAE

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Adipokines: Link between Insulin Resistance and Obesity

Many cytokines and hormones are dysregulated in states of adiposity and insulin resistance and profoundly impair insulin sensitivity in rodent and humans. Evidence has been accumulating that adipocytes secrete several proteins including adiponectin, visfatin, IL-6, TNFα, MCP-1, PAI-1, and TIMP-1 which influence insulin sensitivity profoundly. Therefore, these so-called adipokines might provide a novel molecular link between increased adiposity and impaired insulin sensitivity. Several of these adipokines have now been shown regulate directly or indirectly a number of processes that contribute to the development of insulin resistance and endothelial dysfunction. Moreover, insulin-sensitizing thiazolidinediones, as well as insulin resistance-inducing hormones such as catecholamines, glucocorticoids, and GH but also adipokines by themselves appear to mediate part of their effects on glucose metabolism via regulation of adipokines. The 3T3-L1 adipocyte *in vitro* system enables investigations on the effect of various insulin resistance-inducing hormones on adipokine mRNA expression and protein secretion. Furthermore, studies using pharmacological inhibitors help to elucidate the intracellular signaling mechanisms used by hormones and adipokines.
To further investigate the molecular role of adipokines in obesity and insulin resistance the hormonal regulation of the adipokines visfatin, MCP-1, and PAI-1 *in vitro* is presented in this thesis. Furthermore, the correlation of TIMP-1 plasma levels and fat distribution, as well as increased adiposity in humans is determined in this thesis (Figure 1). In CHAPTER 2, it is

demonstrated that dexamethasone induces visfatin mRNA whereas GH, TNFα, and the β-adrenergic catecholamine isoproterenol significantly suppress synthesis of this adipocytokine *in vitro*. Furthermore, evidence was presented that intracellular cAMP accumulation is sufficient to downregulate visfatin mRNA. In CHAPTER 3 it is shown that IL-6 suppresses visfatin mRNA synthesis. Furthermore, this inhibitory effect is partially mediated via p44/42 MAP kinase but is not reversible by troglitazone pretreatment under the conditions studied.
The effect of isoproterenol on MCP-1 mRNA synthesis and secretion in 3T3-L1 adipocytes *in vitro* is examined in CHAPTER 4. It is shown that isoproterenol induces MCP-1 gene expression and protein secretion. Furthermore, it is shown that this stimulatory effect is mediated via β-adrenergic receptors and PKA. These results are in accordance with the classical view of isoproterenol activating G_S-protein-coupled β-adrenergic receptors leading to activation of adenylyl cyclase and PKA.
In CHAPTER 5, it is demonstrated that GH potently induces PAI-1 mRNA in fat cells. Furthermore, evidence is presented that proinflammatory interleukin (IL)-6 stimulates PAI-1 in rodent adipocytes which is in agreement with recently published results in human fat cells. Moreover, evidence is presented that basal and GH-induced PAI-1 synthesis are mediated via p44/42 MAP kinase.
Moreover, in CHAPTER 6, *in vivo* studies were performed to determine serum levels of the adipokine TIMP-1 in lean, subcutaneous and visceral obese patients. Here, evidence was provided that TIMP-1 is an independent predictor of adiposity in humans with highest levels seen in visceral obesity.
Taken together, the *in vitro* and *in vivo* studies of this dissertation further characterized physiology and regulation of various adipokines.

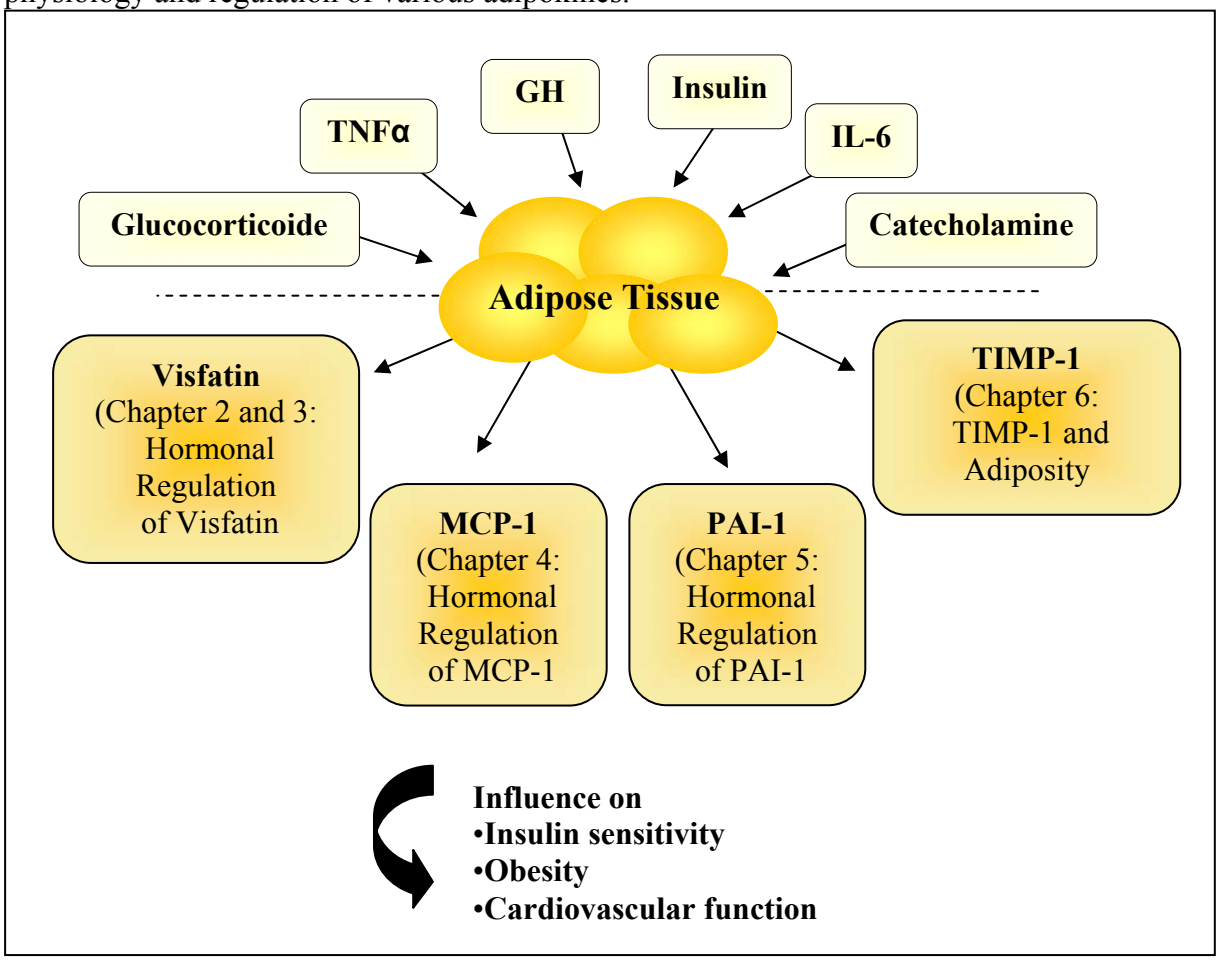

Figure 1: Adipose Tissue: Regulation of Adipokines