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End-organ damage in diabetes

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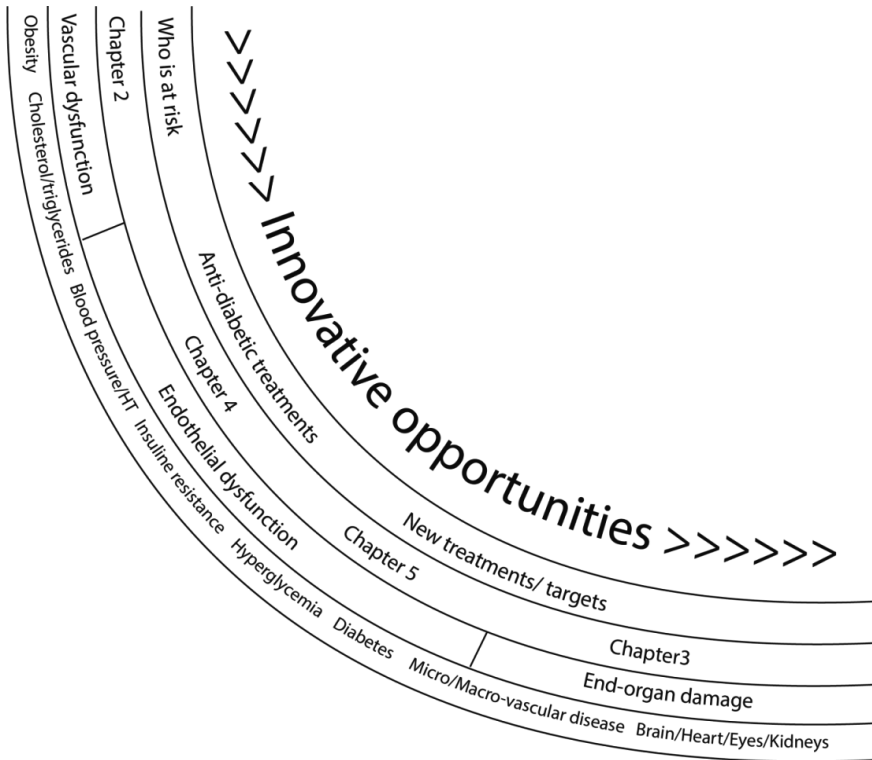
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Chapter 6

Summary and General Discussion



Summary and General Discussion

The world is currently witnessing an alarming increase in metabolic syndrome (MS) and diabetes, with an associated increase in morbidity, mortality and health care burden for the society. Type 2 diabetes mellitus (T2DM) accounts for approximately 90% of all diabetes cases and is associated with insulin resistance, which originates mainly from the increased prevalence of obesity resulting from a combination of lifestyle and genetic susceptibility[1]. Diabetes is associated with a spectrum of several disorders, including vasculopathy and end organ damage. To control and treat diabetes and its associated risks, proper tools and therapeutics are necessary. Preferably, such strategies should be based on the knowledge how to predict, prevent and properly treat the subjects or patients at risk.

In **chapter 2** of this thesis, we aimed to determine “who is at risk” by assessing the “predictability” of the end organ damage in the Zucker Diabetic Fat (ZDF) rat model of MS and T2DM development. Despite a similar blood glucose level, progression of renal damage in these diabetic rats varies among individuals. We showed that vascular properties of intra-renal vessels of ZDF uninephrectomized rats as assessed before development of overt diabetes predicts the future development of kidney injury in late diabetes. In this chapter, we demonstrated that both myogenic tone and endothelial function of still healthy individuals predict their progression towards kidney injury during diabetes development.

In **chapter 3** we examined the impact of diabetes on end organ damage in a less well-studied organ in ZDF diabetic rats: the brain. In particular, we found the diabetic state to induce features of neurodegenerative damage such as in Alzheimer’s (AD) disease. Our findings indicated that ZDF diabetic rats, similarly to AD, show disturbed protein homeostasis originating from an increase in protein aggregation formation along with the attenuation of protein clearance mechanisms, such as autophagy. Moreover, increased oxidative stress is present in the diabetic brain, which probably initiates a further development and progression of neurodegenerative damage[2]. Because of the involvement of oxidative stress in brain damage, H₂S, as a potent antioxidant agent[3], is suggested to play a prominent role in defense against protein aggregation. Cystathionine-β-synthase (CBS) represents one of the main enzymes responsible for H₂S production, which can inhibit the deleterious products formation such as advanced glycation end-products[4] [5]. First, we found a marked decreased expression of CBS in the brain of ZDF rats. Moreover,

exogenous H₂S not only protected brain slices of diabetic ZDF from oxidative stress damage and protein aggregation, but also those from normal rats when provoked with medium containing a high glucose concentration. These beneficial effects of H₂S can be brought about either by its anti-oxidant effect or by the inhibition of protein synthesis via the mTOR pathway [3][6]. Overall, our results suggest that the reduction in CBS expression contributes to the increased protein aggregation in ZDF animals. Consequently, maintaining or boosting brain H₂S production may represent a novel therapeutic approach to alleviate brain damage in diabetes.

Many therapeutics applied in T2DM are principally intended to optimize blood glucose level, either by increasing sensitivity of cells to glucose or by reducing glucose production. However, such therapies may also have additional impacts on the cardiovascular system even beyond hyperglycemic control. In **chapter 4**, we explored such ‘off-target’ properties of currently used drugs, i.e. metformin and vildagliptin. Particularly, we considered the control of high blood pressure to improve vascular function, representing an equally important measure in T2DM to reduce morbidity[7]. To this end, we assessed the pleiotropic effects of metformin and vildagliptin on vascular function in spontaneously hypertensive rats (SHR) with STZ-induced type 1 diabetes, a model in which the drugs do not influence glycemic control. Indeed, SHR rats showed both hypertension and endothelial dysfunction, i.e. two factors classically preceding the development of CVD[8]. We found that both hypertension and impaired endothelium-dependent relaxation (EDR) were counteracted by chronic metformin treatment, via an increase in aortic contractile prostaglandins (PGs) on the one hand but an even stronger increase in dilative NO and EDHF on the other hand. In particular, the metformin induced increase in EDHF production in (STZ)-SHR rats as compared to the rise in contractile PGs seems to signify that increased EDHF production was the most responsible for overall improvement of EDR. Similarly to metformin, vildagliptin also reduced blood pressure and restored endothelial function in SHR, mainly via the inhibition of COX-derived contractile PGs and increasing EDHF production. In contrast however, vildagliptin did not improve EDR in the diabetic SHR, which indicates that the pathophysiologic condition of hyperglycemia is also an important player in the modulation of the vildagliptin effect on aortic endothelial function. Interestingly, H₂S has recently been proposed as a potential EDHF. We showed that up-regulation of H₂S correlates with EDHF and with the decrease in systolic blood

pressure, which suggests that it may contribute to the antihypertensive effect of metformin and vildagliptin. Together, our results in **chapter 4** imply that pleiotropic effects of both metformin and vildagliptin improve vascular endothelial function in diabetes.

To really comprehend vascular dysfunction in diabetes we need to better understand its underlying mechanisms. Sphingosine-1-phosphate (S1P) and its receptors are involved in the series of reactions, which are significantly capable of modulating vascular function. However, the role of S1P in the physiological condition is not yet well understood. The function of S1P and its receptors in various vascular layers are responsible for its ultimate effect on vascular function [9]. Any dysregulation among these receptors may lead to cardiovascular dysfunction such as the impairment of vasomotor regulation and hypertension[9]. To address this, we investigated in **chapter 5** the function of S1P and its receptors in the non-diabetic condition by exploring the effect of chronic FTY720 treatment on endothelial function and myogenic tone. FTY720 is considered as an S1P receptor agonist, which is clinically applied for the treatment of multiple sclerosis (Fingolimod) [10] [11]. Our findings revealed that chronic treatment with FTY720 has a dual action on vascular function of mesenteric arteries. On the one hand FTY720 reduces the sensitivity of the mesenteric smooth muscle cells (SMC) to stretch-induced constriction, which in turn leads to a reduction of the vascular response to S1P. On the other hand, by increasing endothelial production of COX-derived contractile PGs, FTY720 compensates for contraction loss of the SMC to S1P and maintains the contractile properties of the vessel [12]. Finally, our findings show that the augmentation in vascular tone following to FTY720 treatment can be attributed to the increasing of the COX derived compounds which may get regulated by S1P2 receptors, and reduced S1P1 receptor expression.

Conclusion and future perspective:

In conclusion, T2DM is a progressive disease which finally leads to irreversible end organ damage. By identifying the functional properties of the kidney's microvasculature during the premature diabetic condition, this thesis for the first time highlights the physiologic variation in vascular function as an early predictor of renal damage and chronic kidney disease (CKD) in diabetes. Firstly therefore, our findings may be helpful to identify T2DM patients with a high risk of diabetic nephropathy. Secondly, we showed that metformin and vildagliptin, being classic anti-diabetic drugs, also exert promising pleiotropic effects that

could be of value to improve CVD outcomes in diabetes. Particularly, our findings may help us to better understand the vascular mechanisms by which metformin and vildagliptin exert their anti-hypertensive action. In this respect, our studies suggest H₂S to be a protective mediator in diabetes. Acting as a potential EDHF in vasomotor regulation [13,14], H₂S may help to improve endothelial dysfunction and render additional pharmacotherapeutic rationales to reduce vascular complications in diabetes. In addition, H₂S may act as an anti-oxidative agent which inhibits brain damage in diabetes. The cumulative beneficial effects of H₂S make it a promising candidate to be explored in therapeutic strategies.

Collectively, our findings provide innovative ways to improve organ preserving strategies in diabetes, theoretically by measuring of renal vascular function as a new approach to identify individuals at risk for nephropathy, by demonstrating the additional benefit of existing anti-diabetic drugs and by identifying novel drug targets including the H₂S system and the SIP(-receptor) pathways.

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