Novel aspects of the Renin-Angiotensin-Aldosterone System

Research impact

This thesis evaluated 1) several aspects that regulate the biosynthesis of aldosterone in primary aldosteronism 2) the interaction between the glycation pathway and renin-angiotensin-aldosterone system (RAAS). Inhibition of the RAAS in the context forms the cornerstone of the treatment of hypertension, diabetes and chronic kidney disease, and therefore a deeper insight and further optimisation of the RAAS is likely to have a large impact on clinical practice.

In the last decade, multiple discoveries have made primary aldosteronism (PA) a model for improving mechanistic knowledge in hypertension. Several mechanisms were identified to cause the inappropriate over-secretion of aldosterone in PA, such as elevated serum levels of parathyroid hormone, downregulation of TASK-2 K+ channel, gene mutations affecting ion channel [1]. In addition, PA patients show a higher cardiovascular disease (CVD) rate at the time of diagnosis than primary hypertensives [2,3]. Despite the identification of these mechanistic markers, understanding the molecular mechanisms involved in primary aldosteronism is important to improve diagnosis and therapeutic approaches of the disease.

The first part of this thesis provided compelling evidence that over secretion of aldosterone can be specifically blunted ex-vivo in aldosterone producing adenoma (APA) with KCNJ5 mutations by the use of macrolides, opening a new perspective for the diagnosis and treatment of PA patients. Current ongoing clinical studies aim to determine the diagnostic and therapeutic effect of macrolide treatment in patients with APA carrying KCNJ5 mutations, allowing non-invasive diagnosis and targeted treatment [4]. Currently APA is often treated with adrenal surgery, but not all individuals are eligible for this procedure, and therefore my findings in chapter chapter 4 are of potential interest for patients with APA.

In chapter 6 we focussed on the measurement of angiotensin II type-1 receptor autoantibodies (AT1AA).
The possibility to measure serum levels of AT1AA is a promising step to improve the diagnosis of primary aldosteronism. These AT1AA autoantibodies indicate loss of immunological tolerance towards tissues that express the angiotensin II type I receptor (AT1R) and are a target of arterial hypertension. This will be a major focus of future research. However, the presence of AT1AA not only in APA but also in some healthy donors, requires more studies to investigate the cut-off between normal subjects and APA patients and the specificity of these antibodies. Furthermore, as we identified a G protein–coupled estrogen receptor (GPER) as additional mediator of aldosterone secretion, GPER may also be a useful mechanism to be investigate in more detailed as a potential drug target.

In the second part of this thesis, the relation between advanced glycation endproducts (AGEs) and the activation of RAAS as a key driver of CVD and vascular complications are described.
Higher levels of specific AGEs are associated with a higher risk of CVD and inhibition of AGE formation and/or the blockade of the interaction between the RAAS and AGEs could be a viable option for therapy to prevent the progression of chronic kidney disease (CKD) and CVD in diabetic individuals.
Several compounds have been identified that lower AGE levels and/or inhibit AGE formation, including anti-hypertensive drugs such as angiotensin receptor blockers (ARBs) and angiotensin converting enzyme (ACE) inhibitors [5–8]. Although it has been demonstrated in a major clinical trial that the ARB irbesartan reduced progression of albuminuria, independently of blood pressure [9] and that this can have beneficial effects on cardiovascular outcome, we could not show any changes in plasma of dicarbonyl stress. However, it remains possible that the potential beneficial effects of ARBs are restricted to experimental models of diabetes. This finding is important for clinical practice as we show that at least the ARB irbesartan is unlikely to lower systemic glycation markers and therefore the glycation pathway likely remains untargeted in individuals with diabetes.

Furthermore, as we show in the first part of the thesis, higher levels of AT1AA are identify in APA, and persisted after cure of hyperaldosteronism suggesting a pathogenetic role of AT1AA in raising aldosterone biosynthesis in primary aldosteronism; it may be worth considering whether these antibodies that activate AT1-R are associated with higher methylglyoxal MGO levels and MGO-derived AGEs in individuals with APA. Experimental studies have shown that increased activation of AT1R by Ang II has been linked to increased formation of methylglyoxal [10]. However, our findings of no associations of plasma AT1AA with AGEs suggest that plasma levels of AT1AA may not adequately represent AGE accumulation in plasma, although we found an increase of AGEs after adrenalectomy. Larger studies with a long-term follow-up time are required to further clarify the importance of post-adrenalectomy levels on AGEs.

Evidence of the interconnection between the RAAS and the glycation pathway on cardiovascular disease remains incomplete, although our studies have added some evidence for a role of angiotensin II to decreased expression of Glo1 enzyme and subsequent increase formation of AGEs. Based on these findings future research should focus on many other biological aspects of angiotensin II in relation to dicarbonyl stress, to further elucidate how the RAAS and the AGE pathway are intertwined.
In conclusion, the glycation pathways and RAAS may be promising targets improve both prediction and treatment of CVD, and that additional research may lead to the identification of novel targets to reduce the global impact of CVD and diabetic complications.

References

1. Seccia TM, Caroccia B, Gomez-Sanchez EP, Gomez-Sanchez CE, Rossi GP. The Biology of Normal Zona Glomerulosa and Aldosterone-Producing Adenoma: Pathological Implications. *Endocrine Reviews* 2018;39(6):1029–1056.
2. Milliez P, Girerd X, Plouin PF, Blacher J, Safar ME, Mourad JJ. Evidence for an increased rate of cardiovascular events in patients with primary aldosteronism. *Journal of the American College of Cardiology* 2005;45(8):1243–1248.
3. Savard S, Amar L, Plouin PF, Steichen O. Cardiovascular complications associated with primary aldosteronism: A controlled cross-sectional study. *Hypertension* 2013;62(2):331–336.
4. Maiolino G, Ceolotto G, Battistel M, Barbiero G, Cesari M, Amar L, Caroccia B, Padrini R, Azizi M, Rossi GP. Macrolides for KCNJ5–mutated aldosterone-producing adenoma (MAPA): design of a study for personalized diagnosis of primary aldosteronism. *Blood Pressure* 2018;27(4):200–205.
5. Miyata T, Van Ypersele De Strihou C, Ueda Y, Ichimori K, Inagi R, Onogi H, Ishikawa N, Nangaku M, Kurokawa K. Angiotensin II receptor antagonists and angiotensin-converting enzyme inhibitors lower in vitro the formation of advanced glycation end products: Biochemical mechanisms. *Journal of the American Society of Nephrology* 2002;13(10):2478–2487.
6. Monacelli F, Poggi A, Storace D, Durante A, Traverso N, Viviani GL, Odetti P. Effects of valsartan therapy on protein glycoxidation. *Metabolism: Clinical and Experimental* 2006;55(12):1619–1624.
7. Forbes JM, Cooper ME, Thallas V, Burns WC, Thomas MC, Brammar GC, Lee F, Grant SL, Burrell LM, Burrell LA, Jerums G, Osicka TM. Reduction of the accumulation of advanced glycation end products by ACE inhibition in experimental diabetic nephropathy. *Diabetes* 2002;51(11):3274–82.
8. Forbes JM, Thomas MC, Thorpe SR, Alderson NL, Cooper ME. The effects of valsartan on the accumulation of circulating and renal advanced glycation end products in experimental diabetes. *Kidney International, Supplement* 2004;66(92):S105–S107.
9. Parving HH, Lehnert H, Bröchner-Mortensen J, Gomis R, Andersen S, Arner P, Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study Group. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *New England Journal of Medicine* 2001;345(12):870–8.
10. Miller AG, Tan G, Binger KJ, Pickering RJ, Thomas MC, Nagaraj RH, Cooper ME, Wilkinson-Berka JL. Candesartan attenuates diabetic retinal vascular pathology by restoring glyoxalase-I function. *Diabetes* 2010;59(12):3208–3215.