6. Summary

The incidence of the Metabolic Syndrome in the industrialized countries is increasing more and more due to malnutrition and physical inactivity. It comprises an accumulation of different and mutually intensifying diseases and risk factors, which mostly share the same causes. An important pathogenic factor is the insulin-resistance which is often a consequence of increased obesity.

The AT1-Antagonists are the latest group of antihypertensive drugs, whose efficiency and safety has been controlled in big clinical trials during the last few years. Another important result of these studies was a reduction of the incidence of new onset diabetes in AT1-Antagonist-treated patients, whose reason and mechanism are still unclear.

Adiponectin is an adipozytokine which has been discovered in the last few years. It does not only correlate strongly with insulin-sensitivity, it had also been demonstrated in different knock-out animal-models that it even induces an insulin-sensitization.

This work deals with the question whether there is an influence of AT1-Antagonists on the expression of adiponectin and whether the positive effect of these antihypertensive drugs on insulin-sensitivity is achieved by a modulation of this adipozytokine.

With the murine 3T3-L1 adipocyte model used to analyze the influence of the RAS on the expression of adiponectin *in-vitro* at first an AT2R-mediated induction of the adiponectin protein expression by Ang II could be found.

Further experiments showed that certain AT1-Antagonists, whose PPARγ-activating properties could be recently revealed by our group, caused an even stronger induction of the adiponectin protein expression being completely independent of Ang II or the AT1R.

Investigations with different PPARγ-activating and non-activating AT1-Antagonists and with the PPARγ-antagonist GW 9662 revealed, that also the found stimulation of the adiponectin protein expression is PPARγ-mediated.

Interestingly this stimulation of the adiponectin protein expression couldn´t be confirmed on the transcriptional level and therefore pointed towards a post-transkriptional mechanism of the adiponectin increase.

The analysation of the cellular adiponectin-depletion in the presence of the protein-synthesis inhibitor cycloheximide indicated that the cellular impoverishment of adiponectin could be inhibited by Irbesartan-treatment. This allowed the interpretation of an inhibitory action of the AT1-Antagonist regarding the adiponectin-depletion.

Inhibitors of the most important protein-degradation pathway in eucaryots, the Ubiquitin-Proteasome-System, caused like Irbesartan a stabilisation of the cellular adiponectin-levels and illuminated for the first time a possible degradation of this adipozytokine via this pathway. Also the Irbesartan-mediated stabilisation of the adiponectin protein expression turned the inhibition of this system into a probable cause. And yet the activity of the central proteasome particle couldn´t be diminished by Irbesartan, assuming an interference in a different area of the degradation cascade.

The cognitions of the modulation of adiponectin by PPARγ-activating AT1-Antagonists found *in-vitro* were further verified in a rat model of insulin-

resistance, the obese fa/ fa ZF-Rat. A 3-week Irbesartan-treatment was able to improve parameters of insulin-sensitivity significantly which was associated with a stabilisation of the adiponectin plasma-levels in contrast to a significant reduction in the control animals.

Furthermore *ex-vivo* studies could also demonstrate directly the PPARγ-mediated induction of the adiponectin-expression by Irbesartan in contrast to the non-PPARγ-activating AT1-Antagonists in the epididymal fat tissue of the rat.

Finally the fat depot-specific distribution of adiponectin was analyzed. The experiments were not able to detect a difference between the expression in a visceral in contrast to the one in subcutanious fat tissue. But interestingly a markedly reduced expression in pericardial fat tissue was measured. The thereupon investigated myocardium of the animals delivered a first proof of the presence of adiponectin in heart tissue, whose concentration corellates even more strongly with the one in the surrounding pericardial fat tissue. These results allowed the conclusion that adiponectin in the pericardial fat tissue somehow gets into the myocardium and there causes distinct effects as an adipocytokine. Now further studies could clarify the way of adiponectin into the myocardium and its function in that tissue.

The results presented within this framework provide important knowledge regarding the RAS- and PPARγ-mediated modulation of the adipocytokine adiponectin and therefore point to a possible mechanism of the insulin-sensitizing actions of the AT1-Antagonists, found in clinical studies. This work moreover supplies new approaches for the development of new AT1-Antagonists, being antihypertensive and insulin-sensitizing by simultaniously blocking the AT1R and activitating the PPARγ thus leading to a better therapeutic trategy for the treatment of the metabolic syndrome.