Old dogma, new aspects - Role of angiotensin converting enzymes in the cardiovascular continuum

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The renin angiotensin aldosterone system (RAAS) plays a pivotal role in the cardiovascular pathophysiology and represents a starting point of cardiovascular diseases. Textbooks agree that the angiotensin converting enzyme (ACE) is produced in human endothelia related tissues. The goal of my work is to investigate this fact and the endothelia related enzymes (ACE, ACE2) in contrast of their endogenous regulation and secretion processes in a clinical based study.

Lung tissue- and blood samples were collected from patients with lung surgery at the Department of Thoracic Surgery, University of Debrecen (n=71). We performed fluorescent based ACE, ACE2 activity measurements and ELISA experiments. In addition, we determined the ACE genotype and recorded the medical history. To the investigation of the ACE secretion mechanism, primary Human Aortic Endothelial Cells (HAOEC) was used under cell cultured circumstances. To measure the proper activity of tissue bound ACE2 we performed experiments with the special fluorescent substrate Abz-SPY (3-nitro).

We found a significantly elevated ACE activity in the circulation respectively genotype groups ID (9.645 ± 0.4223 U/ml, n=36, p=0.0043) and DD (11.20 ± 0.6203 U/ml, n=26, p=0.0005) when compared to II (6.966 ± 0.5166 U/ml, n=9) group. Surprisingly, we did not find any genotype difference among the ACE activities in the lung tissue (ID: 3.034 ± 0.1996 U/ml, n=36, p=0.6421; DD: 2.709 ± 0.2495 U/ml, n=26, p=0.7920) when compared to the II (2.833 ± 0.3179 U/ml, n=9) patient group. Furthermore, signs for endogenous ACE inhibition were found.

The direct administration of ACE specific substrate Abz-FRK (Dnp) to our HAOEC cell culture resulted 299.6 U/ml ACE activity which was inhibited over 90% via 200 nM Captopril. On the contrary, we cannot reveal any ACE2 specific activity in our cell culture system.

Experiments with fluorescent substrate Abz-SPY (3-nitro) did not reveal any ACE2 signal in circulation in contrary at tissue related milieu we were able to measure ACE2 activity with high specificity.

Our data suggests that the genotype dependent source of ACE significantly contributes to the circulating ACE, which is different from the lung. The endogenous inhibition of ACE conveys the idea that ACE activity is endogenously regulated in vivo. HAOEC cell culture provides an optimal model system for investigation of the mechanism of ACE secretion. Abz-SPY (3-nitro) is a specific fluorescent substrate for tissue related ACE2 activity measurement which can help us to understand how the ACE2 shed into the circulation. All in all, these results could help us in the understanding of how a cardiovascular disease starts and evolves.