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Dual Action in Hypertension and Thrombosis

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Activation of Renin-Angiotensin-Aldosterone Axis (RAAA) has been identified as a risk factor for the development of atherosclerotic heart disease. Conversely, among the many antihypertensive classes, those that interrupt RAAA, such as Angiotensin Converting Enzyme (ACE) inhibitors reduce coronary events and improve survival after a myocardial infarction or a cerebral vascular event. These data implicate activated RAAA in vascular injury and in fact, angiotensin II, the effector molecule of RAAA plays a pivotal role on endothelial function. It is one of the most potent vasoconstrictive agents, acts as a growth factor and induces the formation of inflammatory mediators and oxygen free radicals. Links between the RAAA and cardiovascular pathology are further supported by evidence from transgenic and knockout animal models.

Fibrinolysis is controlled by the plasminogen activator system. The proteolytic activity of this system is mediated by plasmin, which is generated from plasminogen by one of two plasminogen activators (t-PA). Plasminogen activator inhibitor-1 (PAI-1) inhibits this process. Individuals with reduced fibrinolytic activity are at increased risk for ischemic cardiovascular events. Within the vasculature, angiotensin II stimulates the release of PAI-1, thereby reducing fibrinolytic activity. In cultured endothelial and vascular smooth muscle cells angiotensin II stimulates PAI-I expression. In clinical studies, PAI-I concentrations are more elevated in hypertensive patients with normal-to-high plasma renin activity compared to those with low plasma renin activity. Thus, the plasminogen activator system is largely controlled by RAAA. Of note, ACE catalyzes not only angiotensin II formation, but also bradykinin degradation. Bradykinin is a potent stimulus of vascular t-PA in humans and in animal models. ACE inhibitors reduce angiotensin II formation and bradykinin degredation, but AT1 angiotensin II receptor antagonists increase circulating angiotensin II levels and do not alter bradykinin metabolism. Therefore it is possible that ACE inhibition and AT1 angiotensin receptor antagonism differ in their ability to affect circulating PAI-I concentrations. For example, ACE inhibition with trandolapril, but not AT1 receptor antagonism with losartan, lower PAI-I antigen concentration in post-menopausal women. The clinical implications of these observations will be discussed.

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Conformation and Bioactivity

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Our laboratory has initiated a research activity to explore the conformational properties of known AT_1 antagonists derivatives of losartan (COZAAR) already in the market. In collaboration with the University of Patras the conformational properties of novel synthetic AT_1 antagonists prepared by the research group of Prof. J. Matsoukas will be compared with the existing AT_1 drugs. The aim of this study is of many folds:

(a) Explore the stereoelectronic properties of the drugs in different solvent environments and micelles that mimick the membrane bilayers in order to comprehend in their bioactive conformation.

(b) Superimpose their bioactive conformations with AT_1 receptor. The docking will aid in the design of novel antihypertensive drugs.

(c) Study their interactions with membrane bilayers. AT_1 antagonists are well known to interact with the intracellular helices. Therefore, it would be of interest to examine the role of the lipid environment before they reach the receptor. The combination of their interactions with membrane bilayers and AT_1 receptor will lead to their understanding of mechanism of action in the molecular basis.