Interaction of the autonomic nervous and the renin–angiotensin system in heart and kidney

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Introduction

Congestive heart failure is characterized by overactivity of the sympathetic nervous system and of the renin–angiotensin system. When plasma noradrenaline is elevated, patient survival is extremely poor [1] due to the high incidence of progressive heart failure and sudden cardiac death. There is substantial evidence to suggest that angiotensin (Ang) II may in part be responsible for an increase in noradrenaline release in this clinical setting [2]. Thus, activation of facilitatory Ang II receptors, located presynaptically on sympathetic nerve endings, leads to enhanced release of noradrenaline per nerve impulse. Chronic renal failure is associated with increased sympathetic tone [3], and sudden cardiac death is the most common cause of death in end-stage renal failure. Angiotensin-converting enzyme (ACE) inhibitor therapy is standard in chronic heart and kidney failure. Today, Ang II (AT1) receptor blockers as a new class of drugs are available. The ELITE study showed that heart failure patients treated with an ACE inhibitor had a lower mortality than those treated with an ACE inhibitor [4]. Now we investigate the relative contribution of AT1 and AT2 receptors to Ang II modulation of cardiac and renal transmitter release.

Methods

After loading with [3H]noradrenaline (atria, kidney) or [3H]hemicholine (atria), the nerves were stimulated electrically at 5 Hz, according to methods described earlier [5,6]. The effects of Ang II, the AT1 receptor blocker, EXP3174, and the AT2 receptor blockers, PD123319 and CGP42112A, were tested at different concentrations.

Results

Electrical nerve stimulation elicited noradrenaline release. Ang II (0.01–1 µM) increased noradrenaline outflow by ~80% in kidney and in heart atrium (Figure 1). EXP3174 (0.01 µM) shifted the concentration response curve for Ang II to the right (data not shown), whereas a 10 times greater concentration of EXP3174 (0.1 µM) abolished the Ang II-induced noradrenaline outflow (Figure 1). Interestingly, the AT2 receptor blockers PD123319 (1 µM) (Figure 1) and CGP42112A (1 µM) (data not shown) reduced the Ang II-induced increase of noradrenaline by ~50% over the whole concentration range of Ang II in atria. A combination of EXP3174 (0.01 µmol/l) and PD123319 (1 µmol/l) did not inhibit noradrenaline release to a greater extent than EXP3174 alone. An inhibition with PD123319 was not observed in renal cortex (Figure 1). Furthermore, acetylcholine release was increased by Ang II (0.01–1 µM) in atria.

Discussion

Sympathetic nerve endings in human heart and kidney possess Ang II receptors of the AT1 subtype which, when activated by Ang II, mediate an increase of noradrenaline outflow. This facilitatory effect of Ang II is prevented by EXP3174, the in vitro active form of the AT1 receptor blocker losartan. Furthermore, EXP3174, but not the ACE inhibitor captopril, totally blocked Ang I-induced noradrenaline release in human atria [7] and kidney [8]. Therefore, it was suggested that even in the presence of ACE inhibition, substantial amounts of Ang II can be formed from Ang I locally in the heart by enzymes other than ACE to enhance noradrenaline release. In contrast, EXP3174 had abolished Ang I effects on noradrenaline release [5]; therefore, these experimental findings may help to explain the results observed in the ELITE study.

However, especially in the heart, the situation may be far more complex. We found that AT2 receptor blockers attenuated the facilitatory effect of Ang II on noradrenaline release. This may be a non-specific effect. Nevertheless, an effect involving the parasympathetic nervous system is possible. This idea is supported by the fact that a parasympathetic innervation is lacking in the kidney, where AT2 receptor blockade was without an effect. Acetylcholine is known to inhibit noradrenaline release in the heart of animal models [6], acting through muscarinic receptors on sympathetic nerves. We have shown that Ang II increases acetylcholine release. We speculate that activation of AT1 receptors enhances and activation of AT2 receptors inhibits cardiac acetylcholine release. Thus, AT2 receptor blockade would enhance release of acetylcholine, activating inhibitory muscarinic receptors on sympath-
et of AT1 and AT2 receptor antagonists on Ang II-mediated modulation of noradrenaline release in (A) human atria and (B) renal cortex. An asterisk indicates significant effect of Ang II as compared with control. (Student’s unpaired t-test; \( P < 0.05 \)). + indicates significant inhibition by antagonists (ANOVA, \( P < 0.05 \)).


References


Diuretic therapy and diuretic resistance in cardiac failure

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Thiazides and loop diuretics have been the mainstay of treatment for symptomatic cardiac failure for the last 30–40 years. Diuretic therapy in congestive heart failure (CHF) is effective in relieving symptoms and improving cardiovascular haemodynamics [1–7]. The aim of the present report is briefly to review diuretic treatment in CHF, and to discuss underlying mechanisms of diuretic resistance (reviewed in more detail in [8]).

Diuretic therapy

Diuretic therapy in acute cardiac failure with loop diuretics i.v. reduces wedge pressure and increases

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