Invited Comment

Advantages of Ang II receptor blockade over ACE inhibition with respect to suppression of sympathetic activity: heartening news for the kidney?

Lars Christian Rump
Medizinische Universitätsklinik Freiburg, Innere Medizin IV, Freiburg, Germany

Introduction

It is generally accepted that hypertension and proteinuria are the two most important progression factors in chronic renal failure [1]. Antihypertensive drugs slow progression, and this has been attributed mainly to their blood-pressure-lowering effect. It is generally agreed, however, that in various types of chronic renal failure [2–4] angiotensin-converting enzyme (ACE) inhibitors are superior to other drugs. To explain such renoprotective properties of ACE inhibitors, multiple haemodynamic and growth mechanisms have been proposed relating either to diminished production of Ang II or accumulation of nitric oxide (NO) [5,6].

Today Ang II receptor antagonists are available as an alternative to ACE inhibitors. They block the actions of Ang II by an interaction with the AT1 receptor. It has remained unresolved, however, whether Ang II receptor antagonists are equivalent or even superior to ACE inhibitors in the treatment of hypertension in chronic renal failure. In the 'Evaluation of losartan in the elderly' (ELITE) study the mortality of patients with heart failure treated with an Ang II receptor blocker was lower when compared to an ACE inhibitor [7]. The higher mortality of patients treated with an ACE inhibitor was mainly due to sudden cardiac death. There is now also experimental evidence to suggest more complete suppression of cardiac noradrenaline release by Ang II receptor blockers than by ACE inhibitors [8] and this may explain the beneficial effect on sudden cardiac death. Chronic renal failure is characterized by sympathetic overactivity [9] as well as congestive heart failure. This is of interest in two respects. First, sudden cardiac death is the most common cause of death in patients with end-stage renal failure, and this may be due largely to sympathetic overactivity. Second, sympathetic overactivity may be involved in, and contribute to, progression of renal failure. For instance, inhibition of sympathetic nervous activity by the imidazoline receptor agonist moxonidine interfered with progression of structural damage in experimental chronic renal failure [10]. The question arises whether, in analogy to the message from the ELITE study, Ang II receptor blockers are superior to ACE inhibitors in renal failure as well. Some points relating to these issues will be discussed here.

Sympathetic control of heart and kidney

Both kidney and heart are densely innervated by the sympathetic nervous system. The renal sympathetic nerves control renal blood flow, renin secretion, and sodium reabsorption [11]. The cardiac nerves regulate cardiac output by influencing heart rate and contractility. Noradrenaline acts at the postganglionic neuro-effector junctions through adrenoceptors that are divided in three classes: α1, α2 and β receptors. In each class at least three subtypes have been cloned [12]. The amount of noradrenaline present at the receptor sites is determined by the firing rate of the sympathetic nerves, the rate of reuptake into the neurone, and the operation of presynaptic receptors. Presynaptic receptors are structures within the membrane of sympathetic nerve endings (Figure 1), which when activated either enhance or inhibit the amount of noradrenaline released per nerve impulse into the synaptic cleft. Of special importance are presynaptic receptors, which are activated by endogenous ligands such as noradrenaline, dopamine, prostaglandins, bradykinin, and Ang II. The operation of inhibitory presynaptic α-adrenoceptors [13,14], dopamine [15,16] and prostaglandin [17,18] receptors as well as facilitatory β2 adrenoceptors [19,20] has been demonstrated in heart and kidney.

Effects of angiotensin II on catecholamine release in the atrium of the heart and the kidney

Ang II can be formed in the blood stream by ACE from Ang I or locally within various cardiovascular...
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**Fig. 1.** Schematic diagram of a sympathetic nerve ending. Action-potential-induced exocytotic release of noradrenaline (NA) is modulated by presynaptic Ang II (AT$_1$) and bradykinin (B$_2$) receptors respectively. Losartan (EXP 3174) prevents Ang II-mediated facilitation without interfering with bradykinin degradation by kininase (ACE). Captopril is not able to prevent Ang II formation, since non-ACE pathways convert Ang I to Ang II. Captopril protects bradykinin from degradation by kininase and enables bradykinin to enhance NA release.

**Hypertension, Glomerulosclerosis, Arrhythmia**

tissues such as blood vessels, heart, and kidney [21]. Ang II dose dependently enhances noradrenaline release in isolated rat and human renal cortical [22,23] and right atrial slices [24] by up to 80%. This effect is due to activation of Ang II receptors of the AT$_1$ subtype, since it is blocked by EXP 3174, the active metabolite of the selective Ang II receptor antagonist losartan (Figure 1). AT$_1$ receptor antagonists have no effect in human renal cortex [23]. For the modulation of noradrenaline release by Ang II within cardiovascular tissue, locally formed Ang II is probably more important than the peptide formed in the circulation. Ang I, the precursor of Ang II, increases noradrenaline release in human renal cortex and atrium almost as effectively as does Ang II. This facilitatory effect of Ang I is abolished by EXP 3174 [8,23] indicating that it is entirely dependent on the conversion to Ang II and subsequent activation of presynaptic facilitatory Ang II (AT$_1$) receptors (Figure 1). The ACE inhibitor captopril 0.5 μmol/l fails to prevent the adrenergic facilitation by Ang I in human atria. Ten times higher concentrations are less effective that EXP 3174 (0.01 μmol/l) to block the effect of Ang I [8]. Similar results are obtained in human renal cortex [23]. Thus, even in the presence of ACE inhibitors, Ang II may be formed locally from Ang I by non-ACE pathways [8,21] in the heart and kidney to enhance noradrenaline release (Figure 1).

**Effects of bradykinin on catecholamine release in the atrium of the heart and the kidney**

Bradykinin is a peptide that is formed locally by the enzyme kallikrein from the substrate kininogen and by aminopeptidases from the peptide kallidin [25,26]. Kininase I, which is identical with ACE, degrades bradykinin to inactive fragments. There are two types of bradykinin receptors, i.e. B$_1$ and B$_2$ receptors. Most of the biological actions of bradykinin are mediated by the B$_2$ subtype. Bradykinin has a positive inotrop and right atrial slices [24] by up to 80%. This effect is due to activation of Ang II receptors of the AT$_1$ subtype, since it is blocked by EXP 3174, the active metabolite of the selective Ang II receptor antagonist losartan (Figure 1). AT$_1$ receptor antagonists have no effect in human renal cortex [23]. For the modulation of noradrenaline release by Ang II within cardiovascular tissue, locally formed Ang II is probably more important than the peptide formed in the circulation. Ang I, the precursor of Ang II, increases noradrenaline release in human renal cortex and atrium almost as effectively as does Ang II. This facilitatory effect of Ang I is abolished by EXP 3174 [8,23] indicating that it is entirely dependent on the conversion to Ang II and subsequent activation of presynaptic facilitatory Ang II (AT$_1$) receptors (Figure 1). The ACE inhibitor captopril 0.5 μmol/l fails to prevent the adrenergic facilitation by Ang I in human atria. Ten times higher concentrations are less effective that EXP 3174 (0.01 μmol/l) to block the effect of Ang I [8]. Similar results are obtained in human renal cortex [23]. Thus, even in the presence of ACE inhibitors, Ang II may be formed locally from Ang I by non-ACE pathways [8,21] in the heart and kidney to enhance noradrenaline release (Figure 1).

**Clinical advantages of Ang II receptor antagonists?**

The sympathetic nervous and the renin–angiotensin system interact. Sympathetic overactivity leads to increased formation and release of renin through activation of β-adrenoceptors [29] by noradrenaline. On the other hand, Ang II thus formed will act back to activate presynaptic Ang II (AT$_1$) receptors and further enhance noradrenaline release. This sequence of events has been proposed in severe congestive heart failure [30]. This circulus vitiosus contributes to the high plasma noradrenaline concentrations in heart failure, which predict poor survival: noradrenaline is proarrhythmic, leads to β-adrenoceptor downregulation, and has growth-promoting effects via x and β adrenoceptors [31].

Our findings that the ACE inhibitor captopril
unmasks a noradrenaline-enhancing effect of bradykinin and does not fully block the effects of Ang I may have some clinical implications. In the ELITE study plasma levels of noradrenaline decreased in the losartan group, but increased in the captopril group. Peak concentrations of unmetabolized captopril at a dose of 3 × 50 mg per day amount to 1.3 μmol/l in whole blood [32]. In our experiments we tested 0.5–5 μmol/l of captopril, which covers peak and steady-state concentrations of captopril at the doses given in the ELITE study. Thus one can assume that ACE inhibitors, in concentrations that effectively lower blood pressure, fail to completely block local Ang II-mediated effects on noradrenaline release. Apparently, non-ACE-dependent pathways are able to catalyse conversion of Ang I into Ang II [21]. Moreover, the facilitatory effect of bradykinin may be especially relevant during cardiac ischaemia, i.e. a situation characterized by a fourfold increase of bradykinin release [33].

There is no such thing as ‘renal arrhythmia’. Nevertheless, several findings suggest that long lasting sympathetic overactivation is injurious to the kidney, at least when renal disease is present [34]. Noradrenaline release from renal sympathetic nerves is increased in genetic models of hypertension [19,35] and in the 5/6 nephrectomy model of experimental renal failure (unpublished observations). In 5/6 nephrectomized rats, cutting the afferent renal nerves prevents severe hypertension that is otherwise commonly seen [36]. Furthermore, renal noradrenaline release can be inhibited by the imidazoline receptor agonist moxonidine in the kidney [37], even at concentrations that fail to lower systemic blood pressure. This manoeuvre interferes with the development of glomerulosclerosis in the renal ablation model of chronic renal failure in the rat [38]. This observation suggests that inhibition of sympathetic nerve activity is beneficial, e.g. by inhibiting cell proliferation, which is stimulated by noradrenaline via β-adrenoceptors [39], but other mechanisms are by no means excluded.

There is no doubt that introduction of ACE inhibitor therapy has been a milestone in the treatment of heart failure and of renal failure. I put forward the hypothesis that some beneficial effects of ACE inhibitors are due mainly to haemodynamic actions. Effects of Ang II on the cellular level are not totally obliterated, since local tissue Ang II formation occurs even when ACE activity is blocked. ACE inhibitors increase the concentrations of bradykinin, which enhances noradrenaline release.

I have provided several arguments that sympathetic overactivity is injurious not only to the heart but also the kidney. Therefore, based on a priori considerations, one should not administer agents that aggravate sympathetic overactivity in chronic renal failure. Although AT1-specific angiotensin-receptor blocker blockers are superior to ACE inhibitors in clinical [7] and experimental [8] studies that assess noradrenaline-dependent end points, it is too early to translate these preliminary observations into the recommendation to prefer Ang II receptor blockers over ACE inhibitors. Nevertheless, these arguments are of sufficient interest and appear sound enough to be communicated at this early stage to the nephrological community.

References

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