Central Sympathetic Inhibition by Mineralocorticoid Receptor But Not Angiotensin II Type 1 Receptor Blockade Are Prescribed Doses Too Low?

Frans H.H. Leenen, Marcel Ruzicka, John S. Floras

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Chronic sympathetic hyperactivity, characteristic of the majority of patients with hypertension or heart failure, can contribute to cardiovascular morbidity and mortality via a number of actions. Pharmacological strategies to prevent these adverse effects have had variable success. β-Blockers clearly benefit patients with heart failure but have less definitive effects in patients with hypertension, whereas α1-blockers or centrally acting agents have shown mixed results, and all of these classes can cause bothersome adverse effects. Device-based approaches, such as baroreflex activation therapy and renal denervation, have been shown to lower sympathetic activity in patients with hypertension, but beneficial actions on cardiovascular outcomes have yet to be demonstrated.

So, where do the central nervous system (CNS) actions of angiotensin II (Ang II), aldosterone, and, hence, Ang II type 1 (AT1) receptor and mineralocorticoid receptor (MR) blockers fit in? Experimental studies have demonstrated that both circulating Ang II and aldosterone act within the CNS to cause sympatho-excitation and raise blood pressure. Ang II stimulates AT1 receptors in nuclei of the lamina terminalis and thereby activates mainly angiotensinergic pathways to the paraventricular nucleus (PVN) and rostral ventrolateral medulla. Circulating Ang II, in addition, activates an MR-endogenous ouabain pathway. This slowly acting, neuromodulatory pathway appears responsible for most of the persistent neuronal activation in, for example, the PVN, and the progressive hypertension induced by circulating Ang II. Studies using central infusions of an aldosterone synthase inhibitor suggest that the CNS MR activation by Ang II largely depends on locally produced aldosterone rather than circulation-derived aldosterone. However, the progressive hypertension caused by a chronic increase in circulating aldosterone can also be prevented by specific CNS blockade of either MR or AT1 receptors, suggesting that both circulating aldosterone and Ang II may activate the same central pathways. It is possible that circulating aldosterone, similar to deoxycorticosterone acetate, also acts in the lamina terminalis and via Ang II activates local MR-endogenous ouabain pathways and thereby causes persistent activation of angiotensinergic sympatho-excitatory pathways. Irrespective of the actual central pathways being activated, the most remarkable point of these studies is that the well-known renal and vascular effects of both aldosterone and Ang II are not sufficient to cause chronic hypertension if their central actions are simultaneously prevented. Evidence from human studies for a central action of circulating aldosterone arises from studies of patients with an aldosterone-producing adenoma, who were found to have elevated muscle sympathetic nerve activity (MSNA). Both MSNA and blood pressure normalized after unilateral adrenalectomy. Studies from several laboratories have demonstrated that MR-mediated activation of angiotensinergic sympatho-excitatory pathways plays a pivotal role in several experimental models of hypertension and heart failure. Direct central infusions of MR blockers or AT1 receptor blockers have been shown to prevent or reverse both the sympatho-excitation and the magnitude of hypertension or heart failure and their complications.

The important next question is whether systemic treatment with MR blockers or AT1 receptor blockers is also capable of lowering the sympathetic hyperactivity of hypertension or heart failure. With respect to hypertension, this question is addressed in the well-designed study by Raheja et al in the present issue of Hypertension. These authors enrolled 17 stage I subjects into a randomized crossover comparison of the effect on ambulatory blood pressure and MSNA of 12 weeks of therapy with chlorthalidone (25 mg/d) alone, chlorthalidone plus spironolactone (25 mg/d), and chlorthalidone plus irbesartan (150 mg/d).

In principle, systemic treatment with such drugs should achieve similar central effects, if important determinants of efficacy, such as the location of the target receptor (ie, within or outside the blood-brain barrier), the lipophilicity of the drug used, and the drug dose selected are all thoughtfully considered. For example, with respect to irbesartan, the AT1 receptor blocker selected by Raheja et al in their study of hypertensive patients, we have shown previously in Dahl S rats consuming a high-salt diet that the degree of central but not peripheral AT1 receptor blockade parallels the antihypertensive effects of its systemic administration. These findings indicate that inhibition of the brain renin-angiotensin system can contribute importantly to the therapeutic effectiveness.
of AT$_1$ receptor blockers, such as irbesartan, if they are administered in doses sufficient to cause central AT$_1$ receptor blockade.$^5$

Most studies in humans of effects of such agents on the sympathetic nervous system have evaluated the effects of conventional, “clinically recommended” doses. For example, Krum et al.$^6$ used losartan 50 mg/d, and Raheja et al.$^2$ in the present issue of *Hypertension* used irbesartan 150 mg/d. Neither study showed a change in resting sympathetic tone, whether assessed by MSNA or whole body norepinephrine spillover. Although both studies had the merit of administering doses applied generally in clinical practice, the conclusion, by Krum et al.$^6$ that “reversal of sympathetic activation in hypertension cannot be expected with renin-angiotensin antagonism” should be considered premature. In contrast, Raheja et al.$^2$ considered the possibility that, in their study, central AT$_1$ receptors may not have been inhibited, and their results might have differed had a higher dose of irbesartan been given.

This hypothesis could be tested in several ways. Imaging the presence of AT$_1$ receptor blockers in specific brain regions, such as the PVN, using positron emission tomography or demonstrating central AT$_1$ receptor blockade by functional studies may be difficult at present. Alternatively, the effects of much higher doses than commonly prescribed (eg, losartan $\geq$200 mg/d or irbesartan $\geq$600 mg/d) on sympathetic outflow could be determined. The Heart Failure End Point Evaluation of Angiotensin II Antagonist Losartan Study provides evidence of clinical benefit from such a therapeutic strategy in chronic heart failure in that, compared with losartan 50 mg/d, losartan 150 mg/d reduced the rate of death or heart failure admission.$^7$ In a small, proof-of-concept experiment involving patients with mild-to-moderate heart failure (ejection fraction 31%) randomized to losartan 50 mg/d ($n=6$) or 200 mg/d ($n=7$) for 3 months we found that MSNA increased significantly in those allocated 50 mg/d but decreased significantly in those treated with 200 mg/d (preliminary unpublished data). Larger studies are clearly needed to validate the hypothesis that attenuation of central Ang II–dependent sympathetic hyperactivity in hypertension or heart failure is indeed achievable in humans by systemic treatment with high doses of AT$_1$ receptor blockers.

The benefits for outcome in patients with heart failure by treatment with MR blockers are quite clear across the present issue of *Hypertension*, by Krum et al,$^6$ that “reversal of sympathetic activation in hypertension cannot be expected with renin-angiotensin antagonism” should be considered premature. In contrast, Raheja et al.$^2$ considered the possibility that, in their study, central AT$_1$ receptors may not have been inhibited, and their results might have differed had a higher dose of irbesartan been given.

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The benefits for outcome in patients with heart failure by treatment with MR blockers are quite clear across the spectrum of severity, and even in patients already on a β-blocker, angiotensin-converting enzyme inhibitor, or AT$_1$ receptor blocker and a diuretic.$^8$ Regarding possible mechanisms that may contribute to this cardiovascular protection provided by MR blockers, MR in the CNS appear to play a pivotal role as well. Rats with heart failure after myocardial infarction develop extensive fibrosis in the peri-infarct zone and the noninfarct parts of the left ventricle, as well as the right ventricle. This fibrosis can be largely prevented by chronic central treatment with microgram doses of the MR blocker spironolactone. Central MR blockade not only prevents the sympathetic hyperactivity but also the increases in plasma and cardiac aldosterone after MI (for review, see Reference 9), altogether suggesting that CNS MR activation governs the magnitude of peripheral MR activation. As with AT$_1$ receptor blockers, the relevant question becomes whether systemic treatment with MR blockers can induce sufficient central MR blockade to prevent or reverse sympathetic hyperactivity in heart failure or hypertension. The answer appears to be yes. In rats with postmyocardial infarction heart failure, systemic and central treatment with spironolactone, both at low rates of micrograms per day, prevented similarly an increase in renal sympathetic discharge.$^{10}$ No studies appear to have assessed the effects of MR blockade on MSNA or norepinephrine spillover in humans with heart failure. In subjects with hypertension, Menon et al.$^{11}$ showed that 3 months of treatment with chlorthalidone at 12.5 to 25.0 mg/d and spironolactone 25.0 to 75.0 mg/d had similar effect on 24-hour blood pressure, but only chlorthalidone increased MSNA. Wray and Supiano$^{12}$ reported that, in older hypertensives, treatment for 6 months with hydrochlorothiazide or spironolactone at average doses of 42 and 71 mg/d lowered blood pressure similarly, but only spironolactone lowered plasma norepinephrine and the appearance rate of norepinephrine in the extracellular space. In the present issue of *Hypertension*, Raheja et al.$^2$ replicate the increase in MSNA by chlorthalidone found in their previous study,$^{11}$ and, most interestingly, show that this increase is fully prevented by concomitant treatment with spironolactone at 25 mg/d. In all of these studies, serum K$^+$ was maintained by supplementation as needed.

Together, these studies emphasize that this MR blocker is distinctly different from chlorthalidone or hydrochlorothiazide. Inhibition of CNS MR appears the most likely explanation for the observed sympatho-inhibition. In contrast to the high dose of AT$_1$ receptor blockers apparently needed, low doses of the MR blocker appear sufficient for this action, suggesting that the relevant MR population is readily accessible to spironolactone or its active metabolites. Whether other MR blockers exert a similar sympatho-inhibitory action should be assessed. Unanswered is whether this spironolactone-induced reduction in MSNA in hypertensive humans extends to cardiac or renal sympathetic tone, whether it is maintained during physical and mental sympatho-excitatory activities, and whether treatment with spironolactone or other MR blockers has greater impact on cardiovascular events than standard diuretic or sympatholytic agents.

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None.

**References**


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