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CORRESPONDENCE

Response to Thornton

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We appreciate the insightful comments of Dr Thornton regarding our commentary.[1] As he suggested in his letter to the editor,[2] angiotensin II and its receptor blockers (ARBs) have diverse effects in clinical and basic research. More specifically, in the central nervous system, angiotensin II directly stimulates fluid-regulatory centers, thereby stimulating drinking behavior, and thus the balance of water in the body is controlled physiologically. In contrast, angiotensin II stimulates the adrenal glands to increase aldosterone, causes sodium retention, and increases body fluid levels. Although these factors, as Dr Thornton suggested, are very important issues for researchers, we do not believe that a large amount of water and the incidental increase in the urinary volume can ameliorate renal function. If this were the case, many patients suffering from renal insufficiencies would be inclined to drink excessive amounts of water. Moreover, there is no evidence that a large amount of water can cure chronic kidney disease. Indeed, in the article we commented upon previously, Watanabe *et al.*[3] did not provide the drinking and urinary volumes of the animals. However, in our personal experience, the use of ARBs does not increase the urinary volume in OLETF rats (type 2 diabetes model rats with accompanying hypertension). In our commentary,[1] we first focused on the effects of ARBs in reducing the proteinuria associated with the protective effect toward glomerular epithelial cells (podocytes). Watanabe *et al.* also showed that olmesartan, an ARB, has protective effects on renal function resulting from the suppression of fibrosis in tubulo-interstitial tissue.[3] The increase in the renal plasma flow caused by ARBs is presumably sensitive to renal pathophysiological improvements rather than to excess water from the stimulated drinking behavior. As these rats showed 'hyperfiltration' before the use of ARBs, we concluded that the hemodynamic changes induced by the ARBs influenced renal function in the metabolic syndrome model.

A recent publication[4] by Thornton indicated that the increased drinking of water in response to the use of an angiotensin-converting enzyme inhibitor (ACEI) was responsible for the decrease in weight of obese animals. Of course, ACEI and ARB do not have the same pharmacological properties in suppressing the renin–angiotensin system (RAS). The hypothesis that ARBs might stimulate a drinking response cannot be completely ruled out. However, it is highly controversial whether the congenital knockout mice and the acquired receptor inhibition occur via the same mechanism. Although both the AT_1R knockout mice and the animals treated with ARBs have increased plasma angiotensin II levels, only treatments with ARBs have the effect of reducing angiotensin II levels in the kidney. This has been proven in several animal models associated with hypertension[5] and diabetes mellitus.[6] Moreover, Davisson *et al.*[7] reported that losartan, an ARB, decreased the water intake times elicited by intracerebroventricular angiotensin II infusion in AT_{1A} knockout mice. If ARBs can cross the blood–brain barrier, they could reduce angiotensin II levels in the brain despite an increase in plasma angiotensin II levels. Therefore, the possible penetration of ARBs into the brain should be discussed in the context of the debate about the increased water intake elicited by angiotensin II.

Taken together, it is not yet clear that the increased drinking response is associated with the maintenance of renal hemodynamics in obese animals. Thus, the effects of ARBs on the fluid regulatory centers in the metabolic syndrome model should be investigated, and water consumption and urine excretion must be monitored strictly in all animal experiments involving the use of drugs that block the RAS, in order to clarify this issue in the future.

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