Could AT1 Receptor Activation Increase Antioxidant Defense to Prevent Salt-Induced Vascular Dysfunction of 2 Kidney–1 Clip Hypertensive Rats?

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To the Editor: We read with interest the article “AT1 Receptors Prevent Salt-Induced Vascular Dysfunction in Isolated Middle Cerebral Arteries of 2 Kidney-1 Clip Hypertensive Rats” by Beyer et al., which reported that sustained effects of elevated angiotensin II levels in 2 kidney–1 clip (2K1C) hypertension maintain endothelium-dependent vasodilation through AT1 receptor-mediated preservation of antioxidant defense mechanisms despite significant elevations in blood pressure and salt-induced suppression of plasma renin activity. Renovascular hypertension in rodents is a well-known model of experimental hypertension characterized by increased levels of angiotensin II and oxidative stress. Since the pioneering studies by Griendling et al. that showed that angiotensin II acting on AT1 receptors activates the NADPH oxidase enzyme complex, leading to superoxide formation in the vessels, angiotensin II has been linked to oxidative stress in the context of vascular dysfunction and hypertension.

It has become clear now that elevated angiotensin II in different animal models of hypertension increases oxidative stress, leading to alterations in the brain, resulting in increased sympathetic activity, and in the periphery, resulting in reduction in nitric oxide bioavailability. For example, in renovascular hypertension, the central nervous system plays a crucial role in the maintenance of elevated blood pressure. Indeed, Burmeister et al. reported that viral delivery of copper/zinc superoxide dismutase to the paraventricular nucleus of the hypothalamus not only prevented the elevation in superoxide but also abolished renovascular hypertension. In addition, Braga demonstrated that 2K1C rats fed with a high-salt diet presented a more severe hypertension when compared with renovascular hypertensive rats fed with a normal-salt diet, which was related to increased sympathetic activity, superoxide accumulation, and increased NADPH oxidase activity in the rostral ventrolateral medulla.

In addition to the central effects of angiotensin II, Jung et al. demonstrated that endothelium-dependent relaxation to acetylcholine was attenuated in rings from renovascular hypertensive mice but not from renovascular hypertensive gp91phox-/- mice. Furthermore, reactive oxygen species scavenger Tiron, PEG-superoxide dismutase, and the NADPH oxidase inhibitory peptide gp91ds-tat enhanced acetylcholine-induced relaxation in aortae of renovascular hypertensive mice. These findings represent a conflict with those presented by Beyer et al. Of note, inhibition of protein kinase C, Rac, and the epidermal growth factor receptor kinase, elements involved in the activation of the NADPH oxidase, restored normal endothelium-dependent relaxation in vessels from renovascular hypertensive mice, reinforcing the concept that angiotensin II elicits oxidative stress through NADPH oxidase activation, resulting in vascular dysfunction. This series of evidence may shed some light on the article by Beyer et al., which suggests that angiotensin II may be beneficial to vascular dysfunction observed in renovascular hypertension.

In the article presented by Beyer et al., authors propose that angiotensin II, acting via AT1 receptors, may prevent vascular dysfunction caused by a high-salt diet, mainly because of upregulation of copper/zinc superoxide dismutase. Based on what has been discussed so far, it is very difficult to draw conclusions on the vascular actions of the angiotensin II without looking at the oxidant enzymes and downstream reactive oxygen species production. One could suggest that the upregulation of copper/zinc superoxide dismutase is in response to elevated superoxide accumulation rather than a possible antioxidant effect of angiotensin II. Therefore, the balance between antioxidant and pro-oxidant enzymes would make more sense.

DISCLOSURE

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REFERENCES


