Re: Heusser et al: Elevation of Sympathetic Activity by Eprosartan in Young Male Subjects

To the Editor:

Heusser et al\(^1\) examined effects of the angiotensin I receptor blocker eprosartan on the sympathetic nervous system in humans. The authors wrote in the Limitations of the Study section that "... only young men with arterial BP <160/100 mm Hg were tested." In reality, the subject population was normotensive. Table 1 in their article, which lists subjects' characteristics, shows that systolic arterial pressure was 127.0 and diastolic arterial pressure 76.0 mm Hg. By indicating value of <160/100 mm Hg the authors implied that they tested subjects with mild hypertension. In fact, they looked at effects of an antihypertensive drug in a normotensive population.

The authors concluded that eprosartan “caused augmented central neural vasoconstrictor outflow paralleled by increased plasma levels of norepinephrine, which casts doubt on its ability to dampen norepinephrine release from peripheral sympathetic nerve endings in humans.” The authors did not, however, provide data for proving the absence of inhibitory presynaptic effects. In contrast, they actually showed that eprosartan reduces norepinephrine influences. In the experiments on mental stress, heart rate was significantly lowered, which occurred in addition to a putatively increased basal sympathetic outflow and the increased sympathetic activity due to the stress. Also, blood pressure values were reduced, but not significantly.

Eprosartan did not induce hypotension in the normotensive study population, given that sympathetic outflow was increased. The untreated level of muscle sympathetic nerve activity was very low, however, and the nerve firing rate on eprosartan, although increasing a little, remained at the bottom end of the normal range. Furthermore, the treatment period of 1 week was too short for excluding a residual compensatory sympathetic response. Also the hypothesis that the elevation of plasma angiotensin II caused the augmented central sympathetic outflow could hold only for normotensive individuals. In patients with chronic renal failure, enalapril and losartan reduced sympathetic hyperactivity (Klein et al\(^2\)). Furthermore, addition of valsartan to an ACE inhibitor improved cardiac sympathetic nerve activity (Kasama et al\(^3\)).

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Reference


In Reply:

We thank Doctor Rupp for his interest in our article and take the opportunity to answer his questions. In the normotensive population, 24-h ambulatory blood pressure values are lower than those obtained in the office. Therefore, the threshold for definition of hypertension is lower than for office readings: 125/80 mm Hg.\(^1\) According to this definition, 18 of the 27 subjects that completed the study have to be considered as being hypertensive. Thus, it is not justified to regard the study population as being normotensive. The rationale of excluding moderate and severe forms of hypertension from our study is given in the last paragraph of the introduction.

In our study, eprosartan lead to significant increases in both sympathetic vasoconstrictor outflow to skeletal muscle vasculature and plasma norepinephrine levels (Fig. 2B of the original article). Hence, there is no convincing reason to assume that eprosartan inhibits the release of norepinephrine from sympathetic terminals in the study population. Because the methodology of measuring plasma levels for quantification of norepinephrine release is feeble, we cast into doubt this feature of eprosartan rather than rejecting it completely. We cannot exclude that there is a certain dampening of norepinephrine release, as we stated in the Limitations section. Moreover, relevant references arguing in favor of\(^2–4\) and against this view\(^5\) had been included in the original article.

As expected, mental stress resulted in a significant elevation of heart rate in both conditions (eprosartan: +12 beats/min; placebo: +15 beats/min); however, the stress-induced increase was significantly smaller with eprosartan. Because angiotensin II increases with mental stress and it has cardio-accelerating effects in dogs that are independent of the adrenergic system,\(^6\) AT1 antagonism could reduce the increase in heart rate provoked by mental stress. Moreover, Barki-Harrington et al\(^7\) have shown that the AT1