Angiotensin-(1–7) and Bradykinin in Norepinephrine Release in the Central Nervous System of Hypertension

To the Editor:

We read with great interest the recent article by Dr Gironacci and colleagues1 dealing with the sympatholytic action of angiotensin (Ang)-(1–7) in the central nervous system of spontaneously hypertensive rats (SHR). The results of their study demonstrated that Ang-(1–7) decreased the K+–induced norepinephrine (NE) release in the hypothalamus of SHR by stimulating the angiotensin type-2 (AT2) receptors, which might be consistent with their previous report.2 In addition, they indicated that the inhibitory effect of Ang-(1–7) on NE release was blocked by the nitric oxide (NO) synthase inhibitor Nω-nitro-L-arginine methyl ester and bradykinin (BK) B2 receptor antagonist icatibant. The authors proposed that Ang-(1–7) reduced NE release from the hypothalamus of SHR via the AT2 receptors, acting through a BK/NO-mediated mechanism.

Several studies have reported the possible mechanisms of altered NE release in the central nervous system of hypertension.3–5 In a study we presented earlier, the change in NE release induced by BK was investigated in the hypothalamus of normotensive and hypertensive rats.6 In an in vitro study using rat brain slices, we showed that BK increased the stimulation-evoked NE release in a dose-dependent manner. It was also demonstrated that a dihydropyridine (DHP)-sensitive calcium (Ca) channel agonist Bay K 8644 significantly potentiated the facilitatory effect of BK on NE release. In contrast, nicardipine, a DHP-sensitive Ca channel blocker, reversed the increase in NE release induced by BK and Bay K 8644. The finding might indicate a possible interaction of BK with DHP-sensitive Ca channels in the central nervous system of hypertension. Recently, it has been shown that BK might increase the intracellular Ca concentration via intracellular Ca-release and extracellular Ca-influx through the transduction of G protein in PC 12 cells.8 It can be speculated that multiple signal transduction pathways may be associated with the effects of BK.9 Therefore, we would like to know whether BK itself might have a synergistic effect with Ang-(1–7) on NE release in the hypothalamus of SHR in the present study of Dr Gironacci and colleagues. Further studies should be performed to assess more thoroughly the relationships between Ang-(1–7) and BK and their role in the regulation of central sympathetic nerve activity in hypertension.

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Response:

I read with interest Tsuda’s letter to the editor about our work. Measurement of kinin peptides gives important information about the functioning of the kallikrein-kinin system. Campbell et al10 have demonstrated that bradykinin (BK) levels in the brain of spontaneously hypertensive rats are similar to those found in normotensive rats, being ~6.5 fmoL/g tissue in 10-week-old rats and 12.1 fmoL/g tissue in 20-week-old rats.11 Tsuda et al12 showed that high concentrations of BK (1 and 3.3 μmoL/L) induced a 20% to 30% increase in stimulus-evoked [3H]norepinephrine (NE) release from hypothalamic slices of normotensive rats, that is, BK seems to exert a facilitative effect on NE release at the central level only at pharmacological dosis. In our study, when we used icatibant to block the endogenous formation of BK, the inhibitory effect of Ang-(1–7) on NE release disappeared, suggesting BK involvement. In addition, the inhibitory effect of Ang-(1–7) was also blocked in the presence of an inhibitor of nitric dioxide synthesis, suggesting that endogenous BK is mediating nitric oxide release, and in this way Ang-(1–7) diminishes NE release.4 Therefore, since central endogenous levels of BK are very low,1 a synergistic effect between Ang-(1–7) and BK on NE release when they have an antagonistic effect on that mechanism.13,14 Furthermore, adding exogenous peptides such as BK has limitations: Not only do the concentrations added fail to mimic endogenous levels, but also these exogenous concentrations of BK may not mimic the site of release and action of endogenous kinins because these peptides act mainly as autocrine (at the site of release) and paracrine autacoids (near the site of release) and not as endocrine hormones.6

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