SYNERGISTIC EFFECTS OF BRADYKININ AND BAY K 8644 ON NOREPINEPHRINE RELEASE IN THE HYPOTHALAMIC SLICES OF NORMOTENSIVE AND SPONTANEOUSLY HYPERTENSIVE RATS

Kazushi Tsuda¹, Ichiro Nishio¹ and Yoshiaki Masuyama²

¹ Division of Cardiology, Department of Medicine, Wakayama Medical College, Wakayama, Japan

² Tokyo Rosai Hospital, Tokyo, Japan

OBJECTIVE: Bradykinin (BK) is a nonapeptide, which is formed by proteolytic cleavage of a larger precursor, kininogen, and appears to be involved in a variety of physiological responses such as inflammation, pain generation and cardiovascular regulations. Immunohistochemical studies have shown that BK is widely distributed in both the central and peripheral nervous systems, which raises the possibility that BK could have a crucial role in the regulation of sensory, motor and autonomic nerve functions. On the other hand, it has been proposed that Ca^{2+} is necessary for many neural functions such as neurotransmitter release from nerve endings. In the present study, we have examined the effects of BK alone and in combination with the Ca^{2+} channel agonist and antagonist on norepinephrine (NE) release in rat hypothalamic slices, and evaluated the regulatory mechanisms of BK on noradrenergic transmission in the central nervous system.

DESIGN AND METHODS: Effects of BK alone and in combination with the dihydropyridine (DHP)-sensitive Ca^{2+} channel agonist (Bay K 8644) and the antagonist (nicardipine) on the release of NE were studied in the hypothalamic slices of normotensive and spontaneously hypertensive rats (SHR) in vitro.

RESULTS: (1) BK increased the stimulation-evoked NE release from hypothalamic slices of Sprague-Dawley rats in a dose-dependent manner (1 Hz: S2/S1 ratio, control 0.868 ± 0.016 , $n=6$, BK 1×10^{-6} mol/L 1.039 ± 0.018 , $n=6$, $P < 0.05$, BK 3.3×10^{-6} mol/L 1.130 ± 0.064 , $n=6$, $P < 0.05$). (2) The DHP-sensitive Ca^{2+} channel agonist, Bay K 8644, significantly potentiated the facilitatory effect of BK on NE release. In contrast, the DHP-sensitive Ca^{2+} channel antagonist, nicardipine, reversed the increase in NE release evoked by BK and Bay K 8644. (3) In the hypothalamus of SHR, the facilitatory effect of Bay K 8644 on the stimulation-evoked NE release was more pronounced than in the hypothalamus of Wistar-Kyoto (WKY) rats. (4) Moreover, BK in combination with Bay K 8644 increased the release of NE to a greater extent in SHR than in WKY rats (S2/S1 ratio with BK 3.3×10^{-6} mol/L and Bay K 1×10^{-6} mol/L, SHR 1.597 ± 0.027 , $n=6$, WKY 1.249 ± 0.060 , $n=6$, $P < 0.05$).

CONCLUSION: These results show that BK might increase NE release partially mediated by the DHP-sensitive Ca^{2+} channels in rat hypothalamus. Furthermore, the greater facilitation of NE release by BK and Bay K 8644 in SHR suggests that the peptide might actively participate in the Ca^{2+} -mediated regulation of central sympathetic tone in hypertension.

ACKNOWLEDGEMENTS: This study was supported in part by the grant-in-aid for Scientific Research (02670405 and 05670631) from the Ministry of Education, Science and Culture of Japan, by the Japan Heart Foundation (1989), by the Uehara Memorial Foundation (1989), by the Yokoyama Clinical Pharmacology Foundation (1991), by the Japan Clinical Pharmacology Foundation (1992), and by the Naito Foundation (1993).