Loss of Tonic Neuronal Activity to Release L-DOPA in the Caudal Ventrolateral Medulla of Spontaneously Hypertensive Rats. Takeaki Miyamae, Jin-Liang Yue, Yoko Okumura, Yoshio Goshima, and Yoshimi Misu. Department of Pharmacology, Yokohama City University School of Medicine, Yokohama 236.

We have proposed that L-3,4-dihydroxyphenylalanine (L-DOPA) is a transmitter in the CNS (Misu et al.: ADV PHARMACOL 32: 427, 1995). L-DOPA is probably a transmitter of the primary baroreceptor afferents terminating in the nucleus tractus solitarii (NTS) of rats. L-DOPA seems to be also a transmitter in the caudal and rostral ventrolateral medulla (CVLM and RVLM). The CVLM receives baroreceptor afferent information through NTS and has depressor neurons directly projecting to RVLM. Endogenously released L-DOPA tonically functions to activate depressor sites in CVLM and the recognition site for L-DOPA within depressor sites of CVLM differs from that for L-glutamate, another transmitter candidate. The impaired tonic neuronal activity to release L-DOPA in NTS, the enhanced tonic neuronal activity to release L-DOPA including a decrease in decarboxylation without an increase in formation of L-DOPA and an increase in the sensitivity of the recognition site to exogenous L-DOPA in RVLM are seen in adult spontaneously hypertensive rats (SHR), and these alterations of tonic L-DOPA systems may be involved in maintenance of hypertension in SHR (Yue et al.: NEUROSCIENCE 67: 95, 1995). We attempted to clarify whether or not such parameters of the tonic L-DOPA system in CVLM are altered to maintain hypertension in adult SHR.

Male 15-16-week-old SHR and control Wistar Kyoto rats (WKY) (Charles River) were anesthetized with urethane, artificially ventilated and paralyzed with D-tubocurarine. By microdialysis in the unilateral CVLM, basal L-DOPA release was constantly detectable and was lower in SHR than that in WKY. This release was reduced by tetrodotoxin (TTX, 1 μM) perfusion in WKY to a basal level in SHR, whereas the TTX-sensitive component of basal L-DOPA release was completely lost in CVLM of SHR. This loss suggests that no conduction of some neurons to release L-DOPA projecting to CVLM occurs as a main factor in SHR. Furthermore, this loss is not secondarily due to decrease in formation or increase in decarboxylation of L-DOPA, since no difference of respective activity of tyrosine hydroxylase and DOPA decarboxylase was seen between the bilateral CVLM regions of SHR and WKY. The loss of neuronal activity to release L-DOPA is not seen in NTS or RVLM of SHR and WKY, and thus may be an important key factor for the maintenance of hypertension in SHR.

By microinjections into depressor sites of CVLM, L-DOPA (10-300 ng) elicited dose-dependent depressor and bradycardic responses and greater depressor responses were seen at high doses in SHR without the difference of bradycardia, compared to WKY. This is a paradox to keep hypertension in SHR, suggesting two explanations. One possibility is that a control level started with much higher blood pressure in SHR reached the maximum greater depressor response, compared to WKY. The other preferable probability is that the sensitivity of the postsynaptic recognition site in CVLM of SHR to L-DOPA increases as a compensatory "functional denervation effect" against the loss of tonic neuronal activity to release L-DOPA. At present, however, it remains to be clarified which explanation is better, since L-glutamate (3-300 ng) also elicited greater depressor responses at high doses in SHR without the difference of bradycardia, compared to WKY. In addition, the increase in the sensitivity to L-glutamate might be rather related to the loss of tonic neuronal activity to release L-DOPA in CVLM, since at least exogenously applied L-DOPA increases by itself the basal release of endogenous L-glutamate in some brain area such as rat striata (Goshima et al.: BRAIN RES 617: 167, 1993).

The tonic neuronal activity to release L-DOPA is lost in CVLM of adult SHR, compared to WKY. This loss may play a key role in the central mechanisms for the maintenance of hypertension in SHR. Our findings further support the hypothesis that L-DOPA is a transmitter in rat CVLM.