Relevance of tonically functioning presynaptic β-adrenoceptors in renal and mesenteric arteries to development of hypertension in spontaneously hypertensive rats. Yoshimi Misu, Misako Kuwahara and Takao Kubo. Department of Pharmacology, Yokohama City University School of Medicine, Yokohama 232.

Presynaptic β-adrenoceptors are thought to mediate a positive feedback mechanism for norepinephrine release. We first demonstrated that the sensitivity of presynaptic β-adrenoceptors to a β-agonist is greater or has a clear tendency to be greater in superfused renal and mesenteric arteries and spleen strips from 5-week-old spontaneously hypertensive rats (SHR), compared to age-matched Wistar Kyoto rats (WKY), whereas there is no difference of the parameter between 15-week-old SHR and WKY (Kubo et al., Jpn J. Pharmacol. 36, 419-421, 1984). Data from previous reports are inconsistent at the hypertensive stages. Furthermore, there is no report of comparative studies of effects of β-antagonists alone on the neurotransmission in vascular tissues from SHR and WKY. In general, there is controversy about blocking actions of β-antagonists alone on presynaptic β-adrenoceptors (Misu & Kubo, Med. Res. Rev. 6, 196-225, 1986). We found that in guinea-pig pulmonary arteries dl-carteolol produced a most potent antagonism among β-antagonists tested against isoproterenol-induced facilitation of norepinephrine release, and furthermore that cumulatively applied dl-carteolol 10^-8 M to 10^-6 M readily and dose-dependently inhibited norepinephrine release, whereas d-carteolol produced no inhibition even at the highest dose (Kuwahara et al., Jpn J. Pharmacol. 39, Suppl. 324P, 1985). Thus, in the present experiments, we attempted to compare the action of dl-carteolol alone on norepinephrine release in renal and mesenteric arteries from young and adult SHR and age-matched normotensive WKY, in combination with obtaining an information whether or not presynaptic β-adrenoceptors involved tonically function in the positive feedback mechanism.

The arterial preparations from 4-week-old and 14-week-old SHR and age-matched WKY were preloaded with ^3H-norepinephrine, rinsed, set up and then superfused with Krebs medium. Transmural field stimulations (5 Hz, 2 msec, 10 V, 200 pulses in renal arteries and 100 pulses in mesenteric arteries) were repeated 4 times (S1 to S4) at 15 min intervals. Carteolol 10^-8 M, 10^-7 M and 10^-6 M was applied cumulatively immediately after the S1, S2 and S3 period of the stimulation and the effect was evaluated by a % release ratio of Sx/S1, respectively.

The evoked ^3H release in renal and mesenteric arteries from young SHR was greater than that from age-matched WKY, whereas there was no difference of the parameter in both arteries from adult SHR and WKY. Difference of the resting ^3H efflux was not seen between SHR and WKY at either stage. In renal arteries, carteolol 10^-6 M inhibited ^3H release in young SHR and the inhibition differed from no effect in age-matched WKY, but the inhibition was not seen in adult SHR and WKY. In mesenteric arteries, carteolol 10^-7 M and 10^-6 M dose-dependently inhibited ^3H release in young SHR and WKY, the antagonist 10^-6 M inhibited the parameter in adult SHR and WKY and the inhibition in young SHR was greater than that in age-matched WKY, whereas the inhibition in adult SHR was smaller than that in age-matched WKY. The findings in young SHR and WKY mean that the facilitation of neurotransmission mediated by presynaptic β-adrenoceptors is genetically enhanced in prehypertensive SHR and is one of causal factors in the hyperactivity of sympathetic nerve terminals. The results in adult SHR and WKY are also consistent with our previous findings (Kubo et al., 1984). The smaller inhibition in mesenteric arteries from adult SHR, compared to age-matched WKY, agrees with the fact that chronic elevation of blood pressure in rats leads to lessened activities of postsynaptic β-adrenoceptors in hearts and vessels.

In conclusion, presynaptic β-adrenoceptors may function to facilitate tonically the release of norepinephrine in renal arteries from young SHR and in mesenteric arteries from young and adult SHR and WKY. The modifications of these adrenoceptors in prehypertensive SHR appears to have causal relevance to development of the hypertension.