18) Diminished β_1 -Adrenoceptor Mediated Relaxation in the Arteries of SHR
Yasuaki Dohi, Seigo Fujimoto, Kyuzo Aoki*, Tomohiro Matsuda. Department of Pharmacology and *2nd Department of Internal Medicine, Nagoya City University Medical School, Nagoya 467, Japan.

We have reported that vascular relaxing response to β -adrenoceptor agonists is diminished in SHR before the development of hypertension (1). Since β -adrenoceptors have been classified into β_1 and β_2 subtypes, the present experiments were designed to investigate which subtype of β -adrenoceptors was related with diminished relaxation in SHR.

(METHODS) Femoral (FEM) and mesenteric arteries (MES) from 4-week-old SHR and WKY were cut into helical strips and set up in Krebs Henseleit buffer (95% O_2 : 5% CO_2 , 37°C). Each preparation was treated with phenoxybenzamine (2 μ M for 1hr) to block α -adrenoceptors. First, the strips were contracted with 30mM KCl and cumulative dose-response lines to β -adrenoceptor agonists (isoproterenol (ISO), norepinephrine (NE: β_1), fenoterol (FEN: β_2)) were obtained in the absence and the presence of increasing concentrations of an antagonist (atenolol (β_1) and butoxamine (β_2)). Relative potency was calculated from (antilog (neg. log ED_{50} agonist - neg. log ED_{50} ISO) x 100). pA_2 values were determined from plot of $-\log$ (concentration ratio - 1) vs $\log$ (antagonist concentration) ("Schild plots"). Second, since vascular relaxation may be affected by its contractile level and contractile response of the SHR arteries to KCl was different from that of the WKY arteries, the strips were contracted with KCl at doses producing 85% of the maximal KCl contraction, and relaxing responses to ISO, NE and FEN were compared between SHR and WKY.

(RESULTS) The relative potencies of ISO:NE:FEN were 100:7:6 (FEM) and 100:0.5:80 (MES) in WKY. The Schild plots for atenolol and butoxamine were superimposed independent of the agonist used in FEM, but in MES the Schild plots were separated depending on which agonist was used. pA_2 values for atenolol were 7.12 (NE) and 7.23 (FEN) and for butoxamine 4.97 (NE) and 4.99 (FEN) in FEM. In MES those for atenolol were 6.38 (NE) and 5.63 (FEN) and for butoxamine 6.37 (NE) and 6.17 (FEN). These data on WKY were not significantly different from those on SHR. When the strips were contracted at 85% of the maximum, pD_2 value ($-\log ED_{50}$) for ISO in SHR FEM (7.606 ± 0.034) was significantly different from that in WKY FEM (7.942 ± 0.048). In MES, on the other hand, pD_2 values for FEN were similar between two groups, but pD_2 values for ISO and NE were significantly small in SHR (7.378 ± 0.075 :ISO, 6.214 ± 0.084 :NE) when compared with WKY (7.638 ± 0.041 :ISO, 6.660 ± 0.049 :NE).

(DISCUSSION) The relative potencies of the agonists indicate that the predominant β -adrenoceptor subtype is β_1 in FEM and β_2 in MES. pA_2 values for each antagonist support the same conclusion. Since the Schild plots were superimposed in FEM and separated in MES, it is concluded that FEM contains homogeneous β_1 -adrenoceptors and MES contains predominantly β_2 subtype with minor population of β_1 subtype. From the data of pA_2 values it is indicated that in MES FEN acts mainly β_2 - and NE acts mainly β_1 -adrenoceptors. SHR have the same β -adrenoceptor subpopulation, and therefore it is less possible that the change of β -adrenoceptor subpopulation is related with the development of hypertension.

The second series of the experiment indicate that the affinity of β_1 -adrenoceptor agonists is diminished in SHR (FEM and MES), but the affinity of β_2 -adrenoceptor agonists is not changed in SHR (MES). The abnormality in β -adrenoceptor is not secondary to hypertension, but closely related with the mechanism of the development of genetic hypertension.

(1) Fujimoto S, Dohi Y, Aoki K, Asano M, Matsuda T: Eur. J. Pharmacol.

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