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INCREASED SENSITIVITY OF ALPHA$_2$-ADRENOCEPTORS MEDIATING PRESSOR RESPONSE IN SPONTANEOUSLY HYPERTENSIVE RATS

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In recent years, the presence of postsynaptic α_2-adrenoceptors in vascular smooth muscle (1,2) as well as their functional significance in mediating the pressor effect of α_2-adrenoceptor agonists in pithed normotensive rats (3) have been demonstrated. On the other hand possible alterations in their function under pathophysiological conditions have not been reported yet. It is for example unknown, if postjunctional vascular α_2-adrenoceptors might play a role in the development of some forms of hypertension. Therefore, in order to detect possible differences in postjunctional vascular α_2-adrenoceptor sensitivity between spontaneously hypertensive (SHR) and Wistar Kyoto (WKY) rats, in the following study the pressor effect of the α_2-agonist xylazine (4) was compared in ganglion-blocked, vagotomized SHR and WKY.

Male WKY and SHR at the age of 10-12 weeks were anesthetized with α-chloralose/urethane and the trachea was cannulated. For registration of diastolic blood pressure a catheter was placed into the left carotid artery and connected to a pressure transducer. Drugs were administered intravenously by way of a cannula inserted into a jugular vein. After vagotomy, 11 mg/kg pentoliniumtartrate was administered intravenously. Animals were respirated artificially and body temperature was maintained at 35.5°C by means of an infrared lamp switched by a rectal thermometer. An equilibration period of 30 min was allowed before initiation of experiments. In the control groups the increase in diastolic blood pressure following single doses of xylazine applied in a volume of 0.5 ml/kg was determined. Subsequent doses were applied after recovery of preinjection values. The effect of the α_1-adrenoceptor antagonist prazosin (1 mg/kg), the α_2-adrenoceptor antagonist yohimbine (3 mg/kg), and their combination was determined in separate groups of animals. Antagonists were administered 20 min previous to xylazine. Given are means ± S.E. Differences of means were calculated using Student's t-test. Statistical significance was assumed, if $P < 0.05$.

As visualized by Tab. 1, basal diastolic blood pressure before administration of xylazine was slightly higher in SHR than in WKY. This was also the case in the presence of prazosin or yohimbine. Only after the combination of α_1- and α_2-adrenoceptor blockade diastolic blood pressure of SHR was reduced to the level of WKY, the blood pressure of which was unaltered by α-adrenoceptor blockade. A possible explanation of this finding may be that under the, albeit high, dose of pentolinium used here some residual sympathetic activity acting via α_1- and α_2-adrenergic receptors might account for the slight increase in diastolic blood pressure in SHR.

Table 1: Diastolic blood pressure (mmHg) of ganglion-blocked, vagotomized rats in the absence and presence of prazosin (1 mg/kg) and/or yohimbine (3 mg/kg).

control	prazosin	yohimbine	prazosin + yohimbine
		WKY	
55.5 ± 2.6	53.0 ± 2.3	57.1 ± 1.2	57.0 ± 1.6
		SHR	
64.1* ± 2.0	66.9** ± 3.1	67.5** ± 1.9	57.1 n.s. ± 2.6

*$P < 0.05$, **$P < 0.005$, n.s. $P > 0.05$ vs. WKY
(n=6 in each experiment)

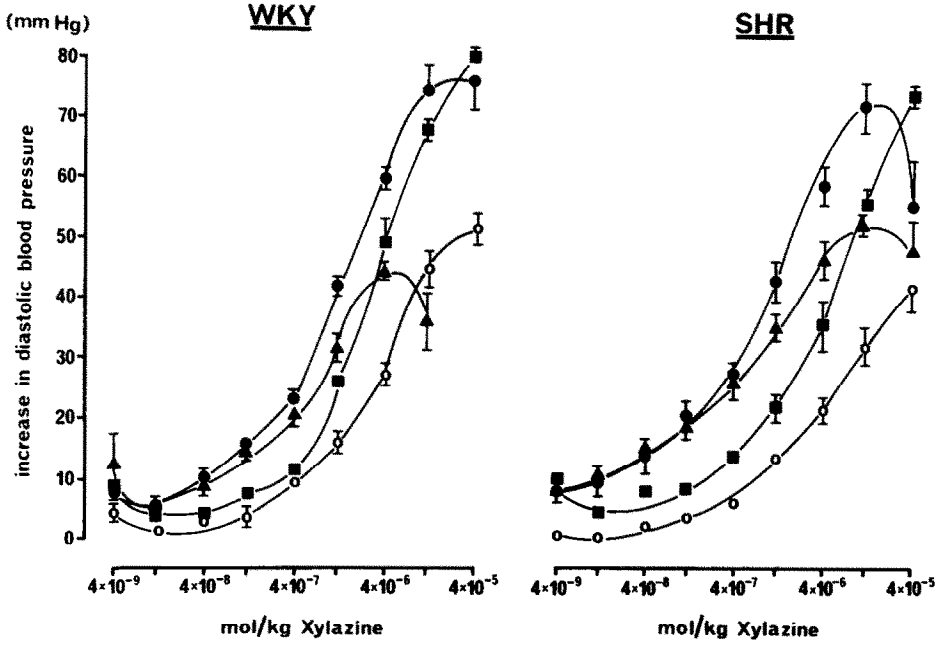

Fig. 1: Increase in diastolic blood pressure of ganglion-blocked, vagotomized WKY or SHR after xylazine alone (●) and after pretreatment with prazosin (▲), yohimbine (■), or prazosin + yohimbine (O) (n=6).

In WKY, the pressor effect of low doses of xylazine was practically unaffected by the α_1-adrenoceptor antagonist prazosin (Fig. 1). The maximal response of xylazine was always depressed in the presence of prazosin, since heart failure precluded further increases in blood pressure in both substrains.

When rats were pretreated with the α_2-adrenoceptor antagonist yohimbine (Fig. 1), the dose response curve of xylazine was shifted to the right in both WKY and SHR. As shown in Tab. 2, the dose which produced an increase in blood pressure of 25 mmHg was shifted to the right twice as much in SHR as in WKY. Also in the presence of α_1-adrenoceptor blockade by prazosin in SHR additional α_2-adrenoceptor blockade resulted in a significantly greater rightward shift of the dose response curve of xylazine than in WKY (Fig. 1, Tab. 2).

Table 2: -log of ED 25 mmHg of xylazine in ganglion-blocked, vagotomized rats in the absence or presence of prazosin (1 mg/kg) and/or yohimbine (3 mg/kg).

	WKY	SHR
control	6.98 ± 0.04	7.29 ± 0.16
prazosin	6.79 ± 0.10 n.s.	7.09 ± 0.13 n.s.
difference from control	0.19 ± 0.10	0.21 ± 0.13 n.s.
yohimbine	6.56 ± 0.03 **	6.38 ± 0.11 **
difference from control	0.42 ± 0.03	0.91 ± 0.11 ++
prazosin + yohimbine	6.11 ± 0.09 **	5.74 ± 0.14 **
difference from prazosin	0.68 ± 0.09	1.35 ± 0.14 ++

**$P < 0.005$, n.s. $P > 0.05$ vs. control, or in the case of prazosin + yohimbine vs. prazosin alone.
++$P < 0.005$, n.s. $P > 0.05$ vs. WKY
(n=6 in each experiment)

These results suggest that postjunctional α_2-adrenoceptors in the vasculature of SHR are more sensitive to stimulation by α_2-adrenoceptor agonists than those of their normotensive congeners WKY. No suggestion can be made from these experiments, if this α_2-adrenoceptor hypersensitivity in SHR might be a primary alteration or a consequence of hypertension. It is, however, interesting that α_2-adrenoceptor density is reported to be increased in SHR

renal plasma membranes (5) and brain (6). It is therefore possible that supersensitive populations of α_2-adrenoceptors might play a role in spontaneous hypertension of the rat interacting with the pathogenesis at their various locations.

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