than in SbR rats, possibly reflecting their lower adrenal catecholamine content (unpublished observation). However, under conditions of mild stress, plasma noradrenaline and adrenaline were found to be higher in SbH rats than in SbR rats suggesting that the sympathetic nervous system of SbH rats is hyperreactive to environmental stimuli. In this respect, Na^+ sensitive SbH rats do not differ from the Okamoto rats, where an increased activity of the nervous system has also been reported[15]. The present results concerning plasma catecholamines in Sabra rats are in agreement with other data obtained in SbH rats, such a reduction in cardiac noradrenaline content probably reflecting an increased turnover of the transmitter in nerve endings[16] and an increased tyrosine-hydroxylase activity in the medulla oblongata[17]. It was recently found that in all rats, except salt resistant rats, cell sodium content could be increased with excess sodium[18]. It appears therefore that hyperresponsiveness of the sympathetic nervous system accompanies the genetic sensitivity to Na^+.

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Tissue catecholamines following renal denervation in spontaneously hypertensive rats[1]

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Summary: The delay in blood pressure increase observed in spontaneously hypertensive rats following bilateral renal denervation appeared to be due to a temporary reduction of the renal catecholamines content.

We have previously reported that renal denervation delayed the increase in blood pressure by 2-3 weeks in spontaneously hypertensive rats (SHR) of the Okamoto strain[3], a finding which has been confirmed by others[4,5]. Although this result suggests that some action of the sympathetic system on renal functions was important in the development of hypertension, several questions remained unanswered: these concerned the completeness, the organ specificity, and the duration of the renal denervation brought about by our procedure. The present study was therefore undertaken to measure tissue catecholamines content in the kidney and other abdominal organs following the same maneuvre.

Methods: Male SHR's were used for these experiments. At the age of 5 weeks, the animals were divided into 2 groups. Group-1 (n = 24) was subject to bilateral renal denervation, and group-2 (n = 22) to a sham-denervation as previously described[3]. At 6, 8, 10, 14 and 17 weeks of age 4-5 rats in each group were anesthetized with pentobarbital, 40 mg/kg i.p. Arterial pressure was measured from a cannulated carotid artery. Then small portions of various abdominal organs were removed, rinsed in cold saline, blotted, weighed, placed into perchloric acid 0.4 N, and frozen at −30 °C until the catecholamines were measured. The organs assayed were the kidney, the small intestine, the adrenal and the spleen.

Tissue catecholamines (dopamine, and beta-hydroxylated catecholamines i.e. norepinephrine + epinephrine = NE + E) were measured according to the radio-enzymatic method described by Coyle and Henry[6]. NE accounts for the major portion of the beta-hydroxylated catecholamines in the kidney, the small intestine and the spleen; on the other hand, E is the major amine in the adrenal. The interassay coefficient of variation was 14% for dopamine, and 9.6% for NE (n = 20).

Results are given as mean ± SEM. Statistical comparison was made using either Student's t-test, or 1-way analysis of variance, followed by a Dunnett's test when a statistical significance for the mean effect was reached. Differences for p-value less than 0.05 were considered significant.

Results and discussion. As previously described[3], the mean blood pressure of SHR with surgical and chemical denervation of their 2 kidneys was significantly below that of sham-denervated animals at 6, 8, 10 and 14 weeks of age; however hypertension developed in both groups, and there was no significant difference between the 2 groups by 17 weeks of age (table). The table also summarizes the measurements of tissue catecholamines in the kidney, and in 2 abdominal organs. Only NE + E contents are shown since dopamine follows the same pattern as its major metabolites. The large variations in SEM shown on the table are probably related to a greater reactivity of tissue catecholamines of SHR to

Mean arterial blood pressure (MAP) and catecholamines (NE+E) expressed as ng/g wet wt of tissue, or µg/organ, following renal denervation or sham-denervation in spontaneously hypertensive rats

Age Weeks	n	MAP mmHg	Kidney ng/g	Small intestine ng/g	Adrenal µg/organ
Denervated kidneys					
6	5	125±10*	3.4±1.0*	39.0±17.8	6.99±0.89
8	5	144±9*	8.7±2.3*	76.2±20.7*	9.98±0.63
10	4	146±6*	25.5±7.2*	63.4±8.4*	11.50±3.72
14	5	159±4*	43.8±18.7*	48.3±12.2*	12.28±3.66
17	5	181±12	35.3±10.6	63.2±13.9*	8.21±1.60
Sham-denervated kidneys					
6	5	151±2	239.4±150.8	254.1±132.5	5.26±0.90
8	5	164±4	59.2±7.0	143.0±24.6	8.76±1.88
10	4	163±2	79.2±21.1	165.1±42.6	12.92±1.86*
14	4	178±5	94.9±18.3	133.6±31.7	15.25±2.56*
17	4	193±13	81.8±25.8	187.0±42.9	6.74±1.36

* Value significantly different from that measured in the sham-denervated control group (Student's t-test), and from adrenal catecholamines content at 6 weeks of age, when a statistical significance for the mean effect was reached (analysis of variance), i.e. in group-2 ($F = 5.65$), but not in group-1 ($F = 0.95$).

surgical stress than normal Wistar rats (unpublished personal data).

NE+E disappeared almost completely from the denervated kidney the week after surgery. These low levels of renal NE+E at 6 weeks, and to some extent at 8 weeks of age, demonstrate the efficiency of our procedure on the renal biosynthesis of catecholamines, and lend further support to a major role played by catecholamines in the development of hypertension. The duration of renal denervation was apparently short since the NE+E content began to rise again 3 weeks after the surgical procedure. There was an interesting parallel between the mean blood pressure and the renal NE+E contents in rats with denervated kidneys: the NE+E content returned towards values found in sham-denervated animals as hypertension developed. From our data, we have no information about the mechanism through which renal catecholamines depletion delays the development of hypertension in SHR.

The adrenal catecholamines content showed no statistically significant difference between denervated and sham-denervated groups, but an age related increase from 6 to 14 weeks, that was statistically significant at 10 and 14 weeks of age in group-2. We cannot draw any conclusion from these differences, but one may wonder whether an increase of the adrenal secretion rate of catecholamines could not play a synergic role in the development of high blood pressure in SHR's.

The renal denervation did not affect significantly the catecholamine levels in the spleen (results not shown) but did so in the small intestine. However the evolution of arterial pressure appeared to correlate best with the renal levels of catecholamines since there was a significant difference in both arterial pressure and kidneys catecholamines levels from 6 to 14 weeks. On the other hand, the difference in catecholamines content persisted in the small intestine even at 17 weeks, at which time hypertension was fully developed.

In conclusion, our data show that bilateral denervation of kidneys in SHR is associated with a striking reduction of the renal NE+E content. Although the NE+E concentration in the small intestine is also reduced, the delay in blood pressure increase observed in SHR following bilateral renal denervation is best explained by a temporary destruction of renal noradrenergic fibres.

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Interactions of Δ^1-tetrahydrocannabinol with cannabinol and cannabidiol following oral administration in man. Assay of cannabinol and cannabidiol by mass fragmentography[1]

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Summary. Oral administration to man of 20 mg Δ^1-tetrahydrocannabinol (THC) together with placebo or 40 mg cannabinol (CBN) or 40 mg cannabidiol (CBD) gave evidence of a possible limited interaction of THC with CBN but not with CBD as indicated by average plasma THC levels. Peak CBD and CBN concentrations were similar to that of THC, viz. about 5-8 ng/ml.

The major pharmacological activity of cannabis is due to Δ^1-tetrahydrocannabinol (THC) and its 7-hydroxylated metabolite[2]. 2 other major constituents, cannabidiol (CBD) and cannabinol (CBN) show no or little psychoactive effect, respectively. Thus, 20-400 mg CBN or 20-100 mg CBD given p.o. to man, or 5-30 mg CBD i.v. produced no characteristic effects of cannabis[3]. Perez-Reyes et al. similarly concluded that CBD i.v. had no effect and CBN i.v. was $^1/_{10}$ as potent as THC in man[4].

Studies in animals have indicated interactions between the major cannabinoids[5-7]. CBD inhibited the mixed function oxidase system in vitro[6,7], although in man Lemberger et al.[7] found no pharmacokinetic interaction between CBD and secobarbital. When CBD was smoked together with