Renal denervation delays blood pressure increase in the spontaneously hypertensive rat

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Summary. Bilateral surgical and chemical denervation of the kidneys in spontaneously hypertensive rats, performed 5 weeks after birth, delayed blood pressure increase by 2–3 weeks without affecting the rate of development or the final level of hypertension.

The mechanisms leading to high blood pressure in the spontaneously hypertensive rat (SHR) of the Okamoto strain[3] are not yet fully understood. There are, however, several indications that neurogenic factors are involved, at least during the early stages of hypertension[4–12], although contradictory evidence has been published[13–15]. On the other hand, a systems analysis of arterial pressure regulation has led to the conclusion that the kidneys are almost invariably involved in hypertension[16]. It has been shown repeatedly that renal nerves influence sodium and water excretion by the kidney in acute experiments[17–19], although their effect in the long-term regulation of salt and water balance has been considered negligible[20,21]. Thus, as pointed out by Coleman et al.[22], spontaneous hypertension might result from increased sympathetic influences on the kidney. It was therefore of interest to study the effect of renal denervation on the development of high blood pressure in SHR.

Methods. Male spontaneously hypertensive rats from the Okamoto strain, kept in our laboratory for more than 30 generations, were used for these experiments. At the age of approximately 5 weeks, they were divided into 3 groups and treated as follows. Group I (n = 11) was subjected to bilateral renal denervation from a midline abdominal incision under ether anesthesia; the denervation was

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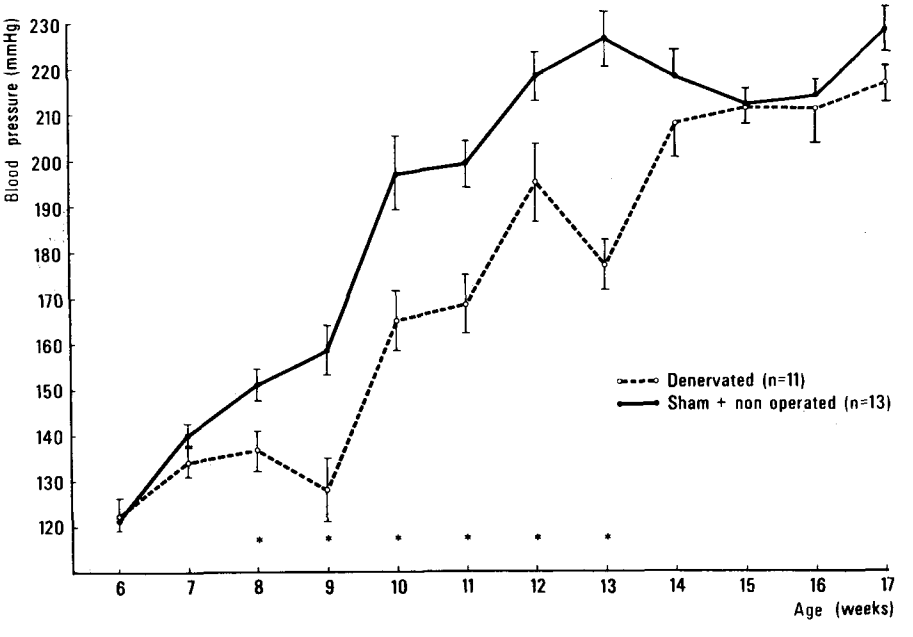

Development of hypertension in SH rats after renal denervation performed 5 weeks after birth compared with non denervated rats (sham denervated, n = 8, and non operated, n = 5, combined). An asterisk at the bottom of the figure indicates a significant difference between the 2 groups at the corresponding time.

performed by stripping both renal arteries and veins of their adventitia and coating them with a solution of 10% phenol in absolute alcohol for 5 min. Similar procedures have been shown to reduce kidney norepinephrine to undetectable levels as measured after 3–6 days[19] or 2 weeks[23]. Group II (n = 8) was subjected to a sham denervation, accomplished by exposing the renal vessels and applying an isotonic saline solution instead of phenol. Group III (n=5) was left untouched.

Arterial pressure and body weight were measured at weekly intervals starting 1 week after surgery, from 6 until 17 weeks of age. Blood pressure was measured by tail plethysmography in the awake, preheated rat[24]. At the end of the experiment, the rats were anesthetized with pentobarbital, 40 mg/kg, and the mean arterial pressure measured from a cannulated carotid artery. The animals were then sacrificed and the right kidneys excised and weighed. Results are given as means ± SE. Statistical comparisons were made using Student's t-test, and differences considered significant for a p-value less than 0.05.

Results and discussion. The figure illustrates the effect of bilateral renal denervation performed 5 weeks after birth on the development of high blood pressure in SH rats. Since there were no significant differences between sham-denervated and non-operated rats (groups II and III), these 2 groups have been combined and their arterial pressure compared with that of the denervated rats (group I). A significant difference existed between denervated and non-denervated rats from week 8 until week 13, the denervated rats having on the average a pressure 30 mm Hg below that of the non-denervated animals. From week 14 until the end of the experiment, the pressures were similar in the 2 groups. Direct measurement of mean arterial pressure at 17 weeks confirmed the absence of a significant difference in blood pressure between denervated and non denervated rats.

The figure also shows that between week 6 and week 9 there was no significant increase in blood pressure in the denervated rats, whereas a significant increase did occur in the non-denervated animals. On the other hand, a stable level of hypertension was achieved at week 12 in the non-denervated rats, but only at week 14 in the denervated group. Thus, hypertension was delayed by 2–3 weeks after renal denervation, but neither its rate of development nor its final level appeared modified by that procedure.

Body weight (b.w.) at the time of the denervation was 68.2 ± 2.1 g (group I); in group II and in group III at the same age, b.w. was 69.2 ± 2.8 and 67.5 ± 2.4 g respectively. Growth rate was significantly reduced in groups I and II compared to group III, especially during the first few weeks following surgery. At week 10, b.w. was 163.3 ± 8.0 g in group I, 174.4 ± 7.5 g in group II and 215.6 ± 5.5 g in group III, a value significantly greater than that of groups I and II. At the end of the experiment, b.w. was 294.2 ± 7.1 g in group III, a value still greater (although not significantly so) than that measured in group I (262.0 ± 11.7 g) or in group II (275.9 ± 6.0 g). As can be noted from these values, b.w. gain appeared also greater in group II than in group I, especially during the early period, although at no time were the differences significant. The weight of the right kidney at the time of sacrifice was not significantly affected by denervation (0.895 ± 0.041 g in group I vs 0.901 ± 0.030 g in group II).

These experiments indicate that bilateral renal denervation delays the development of high blood pressure in SH rats by 2–3 weeks. The experimental design does not permit us to answer several important questions concern ing the completeness and specificity of renal denervation, lack of systemic effects of phenol, and possible coincidence of reinnervation with the appearance of hypertension. Also, the study does not provide any explanation for the mechanisms which might link renal nerves to the appearance of hypertension in SH rats. Despite these obvious limitations, the present experiments may indicate an important relationship between sympathetic nervous system and renal function in SH rats pertaining to the hypertensive state.

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'Binding' of glycine and γ-aminobutyric acid to synaptosomal fractions of 6 regions of the feline brain; effects of strychnine[1]

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Summary. GABA (6×10^{-6} M) binding to synaptosome-enriched fractions of cat CNS exhibited a clear rostro-caudal gradient, whereas glycine (6×10^{-6} M) binding was greatest to particles of cerebellar cortex, and this was followed by medulla ≅ caudate nucleus ≧ cerebral cortex ≧ pons > corona radiata. Strychnine-SO_4 (10^{-3} or 10^{-4} M) inhibited the binding of GABA and glycine in all brain regions studied; at 10^{-5} M this drug inhibited the binding of both GABA and glycine only to particles of the cerebral cortex.

γ-Aminobutyric acid (GABA) and glycine may be inhibitory transmitters of the mammalian CNS[2–4]. Iontophoretic studies have revealed that the depressant action of GABA is more potent than that of glycine in higher structures of the CNS (e.g., cerebellar and cerebral cortices) than on lower centers, but that the action of glycine exhibits a reverse trend[3, 4, 5–8]. Therefore, central inhibitory mechanisms involving these amino acids might exhibit regional dependency. Recent studies which have shown that the 'binding' of GABA and glycine to various regions of the CNS appears to parallel their iontophoretic potencies, support this view[3, 9–13, 18]. In particular, it has been shown that a 'preferential binding' of GABA and glycine exists in synaptosomal fractions of rat cerebral cortex and spinal cord[10, 11, 18]. Other studies have provided further insight into the quantitative relationships which might exist between the depressant actions of these amino acids and the potencies of their mechanisms of receptor-interaction and 're-uptake'[14–18]. The present study was undertaken to compare the 'binding' of GABA