Genetically Hypertensive Rats: 
Relationship between the Development of Hypertension 
and the Changes in Norepinephrine Turnover 
of Peripheral and Central Adrenergic Neurons

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Summary. In genetically hypertensive rats, the norepinephrine turnover of peripheral and central adrenergic neurons was determined either by the decline in endogenous norepinephrine after inhibition of tyrosine hydroxylase or by the decay in the specific activity of norepinephrine after labelling the stores by intravenous or intraventricular injection of \(^{3}H\)-norepinephrine.

In the periphery (heart and submaxillary gland), the norepinephrine turnover of genetically hypertensive rats was reduced in proportion to the rise in systolic blood pressure. In the hypothalamus, medulla-pons and the residual parts of the brain, the turnover was unchanged both in the prehypertensive and the hypertensive state. The results indicate that the central adrenergic neurons, involved in the control of blood pressure, may act independently from the activity of peripheral baroreceptors. The elevated blood pressure resulting from an enhanced peripheral vascular reactivity to the physiological neurotransmitter norepinephrine may induce a compensatory inhibition of the activity of the peripheral adrenergic neurons. In the genetically hypertensive rats, neither the peripheral nor the central adrenergic nervous system seems to play a primary role in the development of hypertension.

Key Words: Spontaneous Hypertension — Norepinephrine Turnover — Heart — Salivary Gland — Brain Stem.

Introduction

Although a representative model for essential human hypertension is not yet available, the analysis of the factors determining the development of various forms of experimental hypertension may yield new insight in the pathogenesis of essential human hypertension and, additionally, lead to new therapeutic approaches.

In previous experiments it has been shown that the cardiac norepinephrine turnover of DOCA-salt hypertensive rats increases in proportion to the rise in blood pressure (de Champlain et al., 1967, 1969; Nakamura

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et al., 1971), whereas in the brain stem the norepinephrine turnover is delayed reciprocally to the acceleration in the periphery (Nakamura et al., 1971). The increased cardiac norepinephrine turnover seems to result from an increased activity of the sympathetic nervous system, since it was normalized by administration of ganglionic blocking agents (Nakamura et al., 1971). However, the delay in hypothalamus and medulla oblongata persisted, indicating that it is not secondary to the functional changes of the peripheral sympathetic nervous system. These data, together with those of Henning and Rubenson (1970), seem to indicate that the activity of adrenergic neurons in hypothalamus and medulla oblongata has a depressant effect on peripheral sympathetic nerve activity. In DOCA-salt hypertensive rats this depressant effect is decreased and thus leads to an increased activity of the peripheral sympathetic nervous system, which—at least partially—is responsible for the development of hypertension.

It was the purpose of the present experiments to study possible relationships between the activity of central adrenergic neurons and the activity of the peripheral sympathetic nervous system in another form of experimental hypertension, i.e., that occurring in genetically hypertensive rats.

Methods

Genetically Hypertensive Rats

Spontaneously hypertensive rats (hypertensive mutant of Wistar descent, Okamoto and Aoki, 1963) were bred at the animal farm in Füllinsdorf. For brother-sister inbreeding (20—22 generations) the animals were selected according to the height of their blood pressure. Male animals were used for the experiments when they had reached an age of 3—14 weeks. Age-matched normotensive male rats of a closed randomized colony of Wistar descent served as controls. The systolic blood pressure was measured in the unanesthetized rat by a tail-cuff method previously described in detail (Gerold and Tschirky, 1968).

Norepinephrine Turnover

The norepinephrine turnover in peripheral sympathetically innervated organs and various parts of the brain was determined according to steady-state kinetics (Brodie et al., 1966) either by measuring the decline in endogenous norepinephrine after inhibition of synthesis or by measuring the decay in the specific activity after injection of $^3$H-norepinephrine into the tail vein or the right lateral ventricle of the brain (Nakamura et al., 1971). For blocking the synthesis of norepinephrine (Spector et al., 1965) (±)-α-methyl-p-tyrosine methylester hydrochloride was given i.p. in doses of 300 mg/kg every 3 h. The animals were killed by decapitation 3, 6 and 9 h after the first dose. For measuring the decline in the specific activity of $^3$H-norepinephrine in the peripheral organs (Montanari et al., 1963), the animals were injected intravenously with 40 μCi of (±)-norepinephrine-$^3$H-hydrochloride (specific activity 7.47 Ci/mmole) and killed 10 min, 2, 6 and 18 h later. For the ventricular injection of $^3$H-norepinephrine, a permanent cannula was implanted.