

DECREASE IN NORADRENERGIC ACTIVITY IN HYPOTHALAMIC NUCLEI DURING THE DEVELOPMENT OF SPONTANEOUS HYPERTENSION

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SUMMARY

The results of two sets of experiments are reported. In the first set the *in vivo* accumulation of [^3H]noradrenaline from [^3H]tyrosine was measured in various brain regions of spontaneously hypertensive rats (SH-rats) and their normotensive controls of the Wistar-Kyoto strain (WK-rats) at the age of 3, 7 and 11 weeks. No differences were observed in [^3H]noradrenaline accumulation in any of these regions between WK- and SH-rats. In several brain regions of SH-rats, however, the tyrosine concentration, the amount of [^3H]tyrosine taken up and the specific activity of [^3H]tyrosine were found to be higher than in the corresponding regions of the brains of WK-rats.

In the second set of experiments we measured the noradrenaline concentration and the α -MPT-induced noradrenaline disappearance in several nuclei of the hypothalamus and the medulla oblongata of SH- and WK-rats at 3, 7 and 10 weeks after birth. A decreased α -MPT-induced noradrenaline disappearance was found in the paraventricular nucleus, the periventricular nucleus and the anterior hypothalamic nucleus of 3-week-old SH-rats compared to that of WK-rats of the same age. No significant differences were found in this parameter of 7-week-old SH- and WK-rats. A lowered noradrenaline disappearance was evident in the anterior hypothalamic nucleus and in the nucleus commissuralis of the medulla oblongata of 10-week-old SH-rats. At the age of 10 weeks the noradrenaline concentration in the anterior hypothalamic nucleus of SH-rats was significantly lower than in that of WK-rats.

These findings are indicative of a transient decrease in the activity of noradrenergic neurons in the anterior hypothalamus during the onset of the development of the hypertension. This is compatible with the transient increase in sympathetic activity

which, according to several authors, plays an important role in the onset of the hypertension in the SH-rats.

INTRODUCTION

Several lines of evidence indicate that medullary and hypothalamic catecholamine-containing neurons participate in the regulation of arterial blood pressure^{1,19}. Much of the neurochemical data supporting this hypothesis originates from studies comparing the spontaneously hypertensive rat (SH-rat), which was established as an inbred strain by Okamoto and associates (see ref. 17), with rats of the parent Wistar-Kyoto strain (WK-rat)^{3,12,22,24,26,31,32,34,35,37}. Part of the available data concerns the possible participation of adrenaline-containing neurons in this effect^{22,24,31,32,34,35}.

It seems highly likely that noradrenaline is involved as well^{3,14,22,31}. The finding by De Jong et al.³ and Versteeg et al.³¹ of higher levels of noradrenaline in the pons/medulla and in the discrete regions within these structures respectively, for SH-rats rather than for WK-rats at several ages, shows that differences exist but does not show in what direction catecholamine metabolism has altered in the SH-rat. Recently, Nagaoka and Lovenberg¹³ reported elevated tyrosine hydroxylase (TH) activity and dopamine- β -hydroxylase (DBH) activity in the hypothalamus of 5-week-old SH-rats and an enhanced DBH activity in the pons/medulla of 8-week-old SH-rats. These differences are suggestive of an enhanced synthesis (and release) of noradrenaline and/or dopamine in these structures of the SH-rat. Since these activities were measured in large brain parts the latter data are not necessarily relevant to the question whether catecholamine-containing neurons involved in the regulation of blood pressure within these structures in fact also synthesize and release these catecholamines at a higher rate.

We now report the results of two sets of experiments. In the first set we measured the *in vivo* accumulation of tritiated noradrenaline from [³H]tyrosine in parts of the brain of SH- and WK-rats (the parts were obtained using a dissection technique similar to that used by Nagaoka and Lovenberg¹³). Subsequently, we measured noradrenaline levels and α -MPT-induced noradrenaline disappearance in discrete brain regions within some of these structures.

METHODS

Animals. Male SH-rats (SHR-NIH-Cpb, F32) were used with WK-rats (Wistar-Kyoto-Cpb, F6) as controls. Rats were obtained from TNO (Zeist, The Netherlands). Animals aged 3, 7, 10 or 11 weeks were caged in groups of 6 and kept in the laboratory for one week. All rats were given rat chow and water *ad libitum*. Blood pressure measurements were carried out with a tail sphygmographic method¹¹.

In vivo accumulation of [³H]noradrenaline. The accumulation of [³H]noradrenaline in brain regions *in vivo* from intraperitoneal (i.p.) injected [³H]tyrosine was estimated as described by Neff et al.¹⁵ (see also ref. 30). Briefly, rats received 600 μ Ci [3,5-³H]tyrosine (The Radiochemical Centre, Amersham, 42 Ci/mmol) i.p. per 100 g

body weight; 10 min later the rats were decapitated. The brains were taken out rapidly and dissected according to Gispen et al.⁵. The brain parts (hypothalamus, mesencephalon, cortex and medulla oblongata) were homogenized in 4 ml 0.4 N HClO₄ containing 0.5 mg/ml Na₂S₂O₅. Tritiated tyrosine and noradrenaline were separated on Dowex 50W-X4 and Al₂O₃ columns³⁰. Samples of the fractions containing [³H]tyrosine and [³H]noradrenaline were counted in a liquid scintillation counter. Aliquots of the eluates were assayed for tyrosine³³ or noradrenaline¹⁰. The data were corrected for recovery which amounted to approximately 73% for tyrosine and 65% for noradrenaline. Data were expressed as mean \pm S.E.M. (n=6–7). The rate of synthesis of ³H-noradrenaline was calculated from the ratio of [³H]noradrenaline accumulated in 10 min, in pCi/g tissue and the specific activity of tyrosine (nCi/ μ g).

Noradrenaline levels and α -MPT-induced noradrenaline disappearance in discrete brain regions. In these experiments rats were decapitated for the measurement of endogenous noradrenaline levels and for the determination of the α -MPT-induced noradrenaline disappearance. The latter groups of rats were decapitated 2 h after they had received the inhibitor of the enzyme tyrosine hydroxylase (TH), DL- α -methyl-paratyrosine methylester hydrochloride (α -MPT, AB Biotec, Göteborg) (300 mg/kg i.p.). After decapitation brains were rapidly taken out and cut into 300 μ m serial sections in a cryostat at -10°C . Eight discrete brain regions were removed from the hypothalamus and the medulla oblongata according to Palkovits¹⁸ (for details see ref. 31); from the hypothalamus: the nucleus paraventricularis (NPV), the nucleus periventricularis (NPE), the nucleus hypothalamus anterior (NHA) and the nucleus interstitialis striae terminalis (NIST), from the medulla oblongata: the A₁-catecholaminergic cell groups (lateral reticular formation) and 3 parts of the nucleus tractus solitarii, viz. the nucleus solitarii proper (rostral to the obex) (NTS), the A₂-catecholaminergic cell groups (caudal to the obex) and the nucleus commissuralis (NCO). The noradrenaline concentration was assayed as previously described²⁹ and is expressed as pg noradrenaline/ μ g protein. The α -MPT-induced noradrenaline disappearance was expressed as the ratio of the noradrenaline concentration 2 h after α -MPT and the steady-state concentration $\times 100$.

All results are expressed as means, and are accompanied by their standard errors. The data were analyzed using Student's *t*-test; differences with a *P*-value of less than 0.05 were considered to be significant.

RESULTS

Animal data (Table I)

The data concerning blood pressure, heart rate and body weight are given in Table I.

In vivo accumulation of [³H]noradrenaline (Table II)

No significant differences were found in the rate of synthesis of [³H]noradrenaline in any of the brain parts of WK- and SH-rats 3, 7 and 11 weeks after birth. The tyrosine concentration of the medulla oblongata of 3-week-old SH-rats was significantly higher than that of WK-rats of this age. The same was the case for the

TABLE I

Body weight, blood pressure and heart rate of normotensive Wistar Kyoto controls (WK-rats) and spontaneously hypertensive rats (SH-rats) at various ages

Values are given as mean \pm S.E.M. (n = 6-7)

At age:	3 weeks		7 weeks		11 weeks	
	WK-rats	SH-rats	WK-rats	SH-rats	WK-rats	SH-rats
Body weight (g)	37 \pm 1	28 \pm 1*	161 \pm 3	154 \pm 6	274 \pm 3	276 \pm 3
Blood pressure (mm Hg)	95 \pm 0.7	93 \pm 1.9	125 \pm 0.8	159 \pm 2.5*	125 \pm 0.5	189 \pm 2.5*
Heart rate (beats/min)	399 \pm 20	391 \pm 20	365 \pm 7	410 \pm 7*	356 \pm 6	337 \pm 10

* $P < 0.001$ for difference between SH- and WK-rats.

cortex at 7 weeks and the mesencephalon at 11 weeks. At 3 weeks after birth the amount of [3 H]tyrosine accumulated and the spec. act. of tyrosine was significantly higher in all 4 brain parts of the SH-rats. Eleven weeks after birth the amount of [3 H]tyrosine accumulated in the medulla oblongata and the mesencephalon of SH-rats was higher than in that of WK-rats.

Noradrenaline content and α -MPT-induced noradrenaline disappearance (Table III).

Measurable amounts of noradrenaline could be detected in all nuclei. The concentration of noradrenaline in nuclei of 10-week-old SH-rats was comparable with those reported previously³¹. No significant changes in the noradrenaline content were found except in the NHA of 10-week-old SH-rats where a decrease of 60% was observed. The α -MPT-induced noradrenaline disappearance was decreased in the NPV, the NPE and in the NHA of SH-rats at the age of 3 weeks. A decrease in this parameter was also observed in the NHA and the NCO of 10-week-old SH-rats.

DISCUSSION

Using the ability of the rat brain to take up and store [3 H]noradrenaline, Coyle and Axelrod² have demonstrated that the development of catecholaminergic neurons in the brain starts around two weeks after gestation and is completed at about 4 weeks postnatally. In normal rats the time course of the development of the activity of the enzymes TH and DBH in the brain, and hence of the capacity to synthesize catecholamines, parallels that of noradrenaline uptake, thus reaching adult values at about 3 weeks after birth². In our experiments no differences were found in the accumulation of [3 H]noradrenaline from [3 H]tyrosine in hypothalamus, medulla oblongata or other parts of the brain of the SH-rat 3, 7 and 11 weeks after birth as compared to the accumulation by WK-rats of the same age, although at the age of 3 weeks, the difference in some brain parts almost reached statistical significance. As can be seen from table II, other parameters, viz. the tyrosine concentration, the [3 H]tyrosine concentration and the spec. act. of tyrosine, were significantly higher in some brain

TABLE II

In vivo accumulation of [^3H]noradrenaline from [^3H]tyrosine in brain parts of 3-, 7- and 11-week-old WK- and SH-rats

Rats received 600 μCi [3,5- ^3H]tyrosine i.p. per 100 g body weight and were decapitated 10 min later. The brains were rapidly taken out and dissected according to Gispen et al.⁵. The brain parts were homogenized in 4 ml 0.4 N HClO_4 containing 0.5 mg/ml $\text{Na}_2\text{S}_2\text{O}_5$. Following separation on Dowex 50W-X4 and Al_2O_3 columns (see refs. 15 and 30) the rate of [^3H]noradrenaline synthesis was calculated as the ratio of [^3H]noradrenaline (pCi/g tissue) and the specific activity of tyrosine (nCi/ μg). Values are given as mean \pm S.E.M. (n = 6–7).

Brain part		Tyrosine ($\mu\text{g/g}$)	[^3H]tyrosine (nCi/g)	Spec. act. tyrosine (nCi/ μg)	[^3H]noradrenaline tyrosine Spec. act.
<i>3 weeks</i>					
Medulla	WK	28.6 \pm 0.9	639 \pm 28	22.4 \pm 1.1	53.5 \pm 6.4
	SH	32.9 \pm 0.8*	923 \pm 50 [§]	28.7 \pm 1.9*	70.4 \pm 10.1
Hypothalamus	WK	18.1 \pm 1.0	443 \pm 28	24.9 \pm 2.0	248 \pm 23
	SH	18.1 \pm 1.4	589 \pm 40*	30.7 \pm 1.1*	324 \pm 37
Mesencephalon	WK	25.1 \pm 1.1	750 \pm 30	30.5 \pm 1.5	45.5 \pm 4.1
	SH	29.1 \pm 2.0	1031 \pm 70***	38.1 \pm 3.0*	58.0 \pm 4.8
Cortex	WK	13.2 \pm 0.8	721 \pm 35	55.6 \pm 3.8	3.4 \pm 0.8
	SH	14.7 \pm 0.4	1093 \pm 52 [§]	74.6 \pm 3.5***	4.4 \pm 0.7
<i>7 weeks</i>					
Medulla	WK	18.8 \pm 0.9	532 \pm 34	28.9 \pm 2.3	40.7 \pm 6.7
	SH	21.9 \pm 1.4	567 \pm 31	26.3 \pm 1.3	45.3 \pm 6.0
Hypothalamus	WK	34.2 \pm 2.8	382 \pm 34	11.9 \pm 1.8	226 \pm 56
	SH	37.4 \pm 3.1	387 \pm 41	10.7 \pm 1.4	252 \pm 52
Mesencephalon	WK	23.6 \pm 1.9	638 \pm 37	28.3 \pm 2.7	42.1 \pm 6.0
	SH	25.6 \pm 2.1	636 \pm 48	25.3 \pm 1.5	48.2 \pm 4.1
Cortex	WK	14.5 \pm 0.4	367 \pm 29	25.6 \pm 2.1	6.6 \pm 0.4
	SH	16.9 \pm 0.8*	401 \pm 22	24.0 \pm 1.5	6.9 \pm 0.5
<i>11 weeks</i>					
Medulla	WK	20.7 \pm 1.0	557 \pm 33	27.5 \pm 2.1	33.2 \pm 2.1
	SH	22.7 \pm 1.0	669 \pm 40*	29.8 \pm 1.8	33.7 \pm 2.0
Hypothalamus	WK	58.6 \pm 2.9	737 \pm 62	12.6 \pm 0.8	136 \pm 10
	SH	65.4 \pm 4.4	819 \pm 79	12.5 \pm 1.3	149 \pm 12
Mesencephalon	WK	20.9 \pm 1.4	556 \pm 42	27.2 \pm 2.1	31.0 \pm 3.7
	SH	25.0 \pm 1.2*	788 \pm 32 [§]	32.1 \pm 1.9	30.9 \pm 3.8
Cortex	WK	16.1 \pm 0.8	605 \pm 39	37.7 \pm 2.0	3.7 \pm 0.6
	SH	16.1 \pm 0.3	631 \pm 42	38.9 \pm 2.3	3.4 \pm 0.6

Differences between SH- and WK-rats: * P < 0.05; ** P < 0.01; *** P < 0.005; [§] P < 0.001.

regions of young SH-rats than of WK-rats of the same age. These differences might be the consequence of either an elevated uptake of tyrosine into the brain or of a lower utilization, e.g. due to a lower protein synthesis in the brain of the SH-rat.

Nagaoka and Lovenberg¹³ have reported that the activity of TH and of DBH in the medulla oblongata and hypothalamus of 3-week-old SH-rats was not different from that of 3-week-old WK-rats; at a later stage of spontaneous hypertension TH activity in the hypothalamus and DBH activity in both hypothalamus and medulla oblongata were higher than in WK controls¹³. Although the parameters measured by

TABLE III

Steady-state noradrenaline concentration and the noradrenaline concentration 2 h after α -MPT of discrete regions of the brains of WK- and SH-rats of 3, 7 and 10 weeks of age

For details see text. Abbreviations used: NIST, nucleus interstitialis striae terminalis; NPE, nucleus periventricularis; NPV, nucleus paraventricularis; NHA, nucleus hypothalamicus anterior; A₁, A₁-catecholaminergic cell group of the lateral reticular formation; NCO, nucleus commissuralis; A₂, A₂-catecholaminergic cell group; NTS, nucleus tractus solitarii. All values given as mean \pm S.E.M. (n = 6–7).

Brain region		Noradrenaline concentration					
		3 weeks		7 weeks		10 weeks	
		0 h conc. (pg/ μ g protein)	conc. 2 h after α -MPT (% of 0 h conc.)	0 h conc. (pg/ μ g protein)	conc. 2 h after α -MPT (% of 0 h conc.)	0 h conc. (pg/ μ g protein)	conc. 2 h after α - MPT (% of 0 h conc.)
NIST	WK	35.49 \pm 2.93	72 \pm 15	39.68 \pm 4.43	65 \pm 5	33.55 \pm 1.45	53 \pm 5
	SH	43.65 \pm 8.23	75 \pm 13	39.91 \pm 2.81	55 \pm 5	27.66 \pm 2.74	62 \pm 8
NPE	WK	46.23 \pm 4.62	50 \pm 5	46.75 \pm 5.61	64 \pm 5	43.66 \pm 4.08	67 \pm 5
	SH	43.92 \pm 3.16	73 \pm 4**	43.01 \pm 3.74	69 \pm 7	48.89 \pm 4.12	67 \pm 9
NPV	WK	32.56 \pm 10.93	37 \pm 6	32.86 \pm 2.96	49 \pm 3	30.68 \pm 5.73	63 \pm 7
	SH	46.55 \pm 1.50	55 \pm 6*	37.13 \pm 2.97	58 \pm 4	32.04 \pm 3.26	66 \pm 8
NHA	WK	45.58 \pm 5.92	30 \pm 3	46.29 \pm 2.29	64 \pm 5	42.92 \pm 3.52	44 \pm 3
	SH	48.31 \pm 4.10	45 \pm 3**	57.40 \pm 9.26	50 \pm 4	17.28 \pm 1.95*	64 \pm 2***
A ₁	WK	13.57 \pm 0.27	42 \pm 6	14.93 \pm 2.81	76 \pm 10	11.42 \pm 0.78	54 \pm 7
	SH	12.89 \pm 0.71	43 \pm 5	19.12 \pm 2.23	60 \pm 9	15.35 \pm 2.17	40 \pm 8
NCO	WK	14.52 \pm 3.77	50 \pm 12	17.23 \pm 5.11	66 \pm 16	17.46 \pm 1.93	45 \pm 5
	SH	6.06 \pm 0.72	40 \pm 6	26.16 \pm 3.90	53 \pm 8	16.03 \pm 3.76	80 \pm 11**
A ₂	WK	24.21 \pm 3.60	60 \pm 11	28.60 \pm 4.34	82 \pm 18	29.00 \pm 2.37	61 \pm 4
	SH	29.56 \pm 4.32	41 \pm 6	37.75 \pm 4.93	67 \pm 28	31.63 \pm 4.30	75 \pm 13
NTS	WK	12.85 \pm 2.04	51 \pm 7	10.02 \pm 0.99	45 \pm 8	13.81 \pm 0.98	38 \pm 4
	SH	14.02 \pm 2.39	54 \pm 8	9.30 \pm 1.54	25 \pm 5	9.39 \pm 1.83	59 \pm 14

For differences between SH- and WK-rats: * P < 0.05; ** P < 0.02; *** P < 0.01.

Nagaoka and Lovenberg and those measured in the present experiments are not directly comparable, the results are compatible with a slight overall elevation in catecholaminergic activity in the brain of SH-rats during the first weeks of life. It should be noted, however, that in both cases the differences are not restricted to brain regions known to be involved in blood pressure regulation^{1,19}, but occur in striatum¹³ and cortex (our results) as well. Also differences observed for a given brain region do not necessarily extend to particular areas within such a structure. This latter point is illustrated by the results of the experiments in which α -MPT-induced noradrenaline disappearance was measured in discrete nuclei. Whereas a tendency towards a higher rate of synthesis of [³H]noradrenaline in whole hypothalamus of 3-week-old SH-rats was found, it appears, as is shown in Table III, that the α -MPT-induced disappearance of noradrenaline was slower in 3 hypothalamic nuclei of 3-week-old SH-rats than of WK-rats, viz. the NPV, NPE and NHA. This indicates that the activity of some

particular catecholamine neurons projecting to the hypothalamus was lowered. From these data it might be concluded that a decreased activity of noradrenergic neurons terminating in the anterior hypothalamus is related to the onset and early development of genetic hypertension. This supposition is consistent with observations which point to the existence of a depressor influence of structures in the anterior hypothalamus. Hilton⁷ has demonstrated that electrical stimulation of the rostral hypothalamus of dogs resulted in a decreased blood pressure. Such a suggestion is also supported by the finding of Struyker Boudier and coworkers that micro-injections of noradrenaline and adrenaline in the anterior hypothalamus in normotensive rats caused a fall in blood pressure^{27,28}. As can be seen from Table III a decreased activity of noradrenergic neurons in the hypothalamus was mainly found in 3-week-old SH-rats. Interestingly, it has been shown^{6,14} that plasma DBH activity was enhanced in young SH-rats as compared to WK-rats, but reached normal values in adult SH-rats. Both these authors^{6,14} and others^{8,16,17,39} consider a transient elevation of sympathetic nerve activity as a causal factor in the hypertension of SH-rats. It could thus be that the decreased noradrenergic activity in the anterior hypothalamus is related to a diminished inhibition of systems participating in the control of sympathetic outflow during the onset of spontaneous hypertension. In this context it is interesting that treatment with L-DOPA reduces the blood pressure^{9,38} of adult SH-rats, presumably due to the lowered sympathetic nerve activity resulting from the increased catecholamine concentration in the central nervous system.

Apart from a lower noradrenaline concentration in the NHA of SH-rats at an age of 10 weeks, there were no differences in steady-state concentrations. It seems that differences in this parameter emerge at a later stage^{31,32}. It should be noted that Saavedra et al.²² reported a decreased noradrenaline concentration in various hypothalamic nuclei of both 4- and 14-week-old SH-rats as compared with WK-rats of the same age. The reason for these discrepancies with our present and previous^{31,32,34} findings is not known. In addition to decreased noradrenaline concentrations, Saavedra et al.²² also found decreased DBH activity in various hypothalamic nuclei of 4- and 14-week-old SH-rats. The observation of a decreased activity of the enzyme catalyzing the conversion of dopamine to noradrenaline in specific hypothalamic nuclei of young rats²² fits well the decreased noradrenaline turnover evidenced by our results. Since Saavedra et al.²² only studied 4- and 14-week-old SH- and WK-rats, data on the activity of DBH in discrete regions at other ages are lacking. It might well be, however, that following normalization at an age of 7–10 weeks, the activity of specific noradrenaline-containing neurons in the hypothalamus of SH-rats decreases again after 10 weeks of age. Evidence for a transient decrease in hypothalamic noradrenergic activity during the initial phase of the development of hypertension has also been presented for renovascular hypertension (ref. 20; and Wijnen et al., in preparation). On the basis of these findings it could be argued that the decreased noradrenergic activity in hypothalamic nuclei is the consequence rather than the cause of the hypertension. However, the blood pressure of SH-rats does not yet differ significantly from that of WK-rats at an age of 3 weeks. More data are needed to clarify this point.

In two previous papers^{34,35} we have focused our attention on the possible role of

adrenaline in the development of spontaneous hypertension. Elevated adrenaline levels were found in two hypothalamic nuclei, the NPV and NPE, when the blood pressure had almost reached a plateau³⁵. A similar elevation has been observed by Gianutsos and Moore⁴ who found an increased adrenaline content in whole hypothalami of 9- and 15-week-old SH-rats as compared with WK-rats of the same age. Whether this rise in adrenaline concentrations, which parallels the rise in blood pressure in the SH-rats^{4,35}, represents an enhanced or a decreased activity of adrenergic neurons remains unclear. It was hypothesized³⁵ that the elevation of adrenaline was the consequence rather than the cause of the rise in blood pressure. In this respect it should be noted that α -MPT-induced adrenaline disappearance was enhanced in the NPV during acute hypotension, induced by haemorrhage or treatment with guanethidine; this finding is a sign of hyperactivity of adrenaline systems as a consequence of a decrease in blood pressure³⁶.

Noradrenergic fibers terminating in the rostral hypothalamus originate, at least in part, in the A2 region of the medulla oblongata^{19,21,25}. This hypothalamic region thus receives direct input from the region of the nucleus tractus solitarii which contains the primary synapses of the baroreceptor fibers¹. In its turn the anterior hypothalamus, as part of a complex chain of pathways participating in the regulation of blood pressure, is connected directly²³ or indirectly with medullary areas responsible for the control of sympathetic activity. Therefore, it is concluded that in the SH-rat the lower activity in a noradrenergic hypothalamic inhibitory system might be related to enhanced sympathetic nerve activity. It is tempting to speculate that noradrenergic and adrenergic circuits to the hypothalamus are involved in different aspects of the regulation of blood pressure. Because of the occurrence of early changes in noradrenaline metabolism in discrete nuclei of the hypothalamus, it might be that the noradrenaline system to this brain region is involved in the onset of spontaneous hypertension, possibly in connection with enhanced sympathetic nerve activity, whereas alterations in the activity of the adrenaline-containing systems in the hypothalamus might be seen as a possibly compensatory change in activity trying to counteract the rise in blood pressure in the SH-rat.

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