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Substantia Nigra Lesions Attenuate the Development of Hypertension and Behavioural Hyperreactivity in Spontaneously Hypertensive Rats

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VAN DEN BUUSE, M., H. D. VELDHUIS, D. H. G. VERSTEEG AND W. DE JONG. *Substantia nigra lesions attenuate the development of hypertension and behavioural hyperreactivity in Spontaneously Hypertensive Rats.* PHARMACOL BIOCHEM BEHAV 25(2) 317–324, 1986.—The possible relation between changes in behaviour and the development of hypertension was investigated. Depletion of striatal dopamine by lesions in the substantia nigra of Spontaneously Hypertensive Rats (SHR) was associated with an inhibition of the development of hypertension. In the open field a decrease in rearing score was found with no effect on other parameters. Rearing activity was significantly correlated with blood pressure as well as with striatal dopamine content. Blood pressure was weakly, although significantly, correlated with striatal dopamine content. Neither blood pressure nor striatal dopamine content was significantly correlated with ambulation activity. In normotensive Wistar-Kyoto rats a decrease was also found in rearing activity after nigra lesions, although this effect was less pronounced. Antihypertensive treatment of SHR with captopril or hydralazine did neither affect striatal dopamine levels nor open-field behaviour. Induction of renal hypertension or DOCA-salt hypertension in Wistar rats did not influence brain dopamine or behaviour. The results support the suggestion that brain dopamine systems may play a role in the development of hypertension in SHR as well as in the changes in behaviour observed in these rats. Changes in behaviour do not appear to be mediated by changes in blood pressure per se.

Hypertension SHR Brain Dopamine Substantia nigra 6-Hydroxydopamine Hydralazine Captopril Open-field behaviour Exploration Locomotion

SPONTANEOUSLY Hypertensive Rats (SHR) are characterized by a genetically determined rise in blood pressure with age [29,43]. The pathogenic mechanism behind this hypertension remains unclear, although the central nervous system and especially brain catecholamines may play an important role in this respect [3, 4, 39].

A number of authors have described changes in behaviour of SHR when compared to the normotensive Wistar-Kyoto (WKY) controls [32]. These differences can primarily be attributed to hyperreactivity to environmental stimuli or stress. Thus, SHR have been described to react vigorously to sudden light, sound and tactile stimuli [32]. Cardiovascular and endocrine changes in response to environmental stimuli are also different in SHR when compared to WKY. For instance, when exposed to stress, SHR showed larger changes in blood pressure and heart rate [13,25] and plasma levels of catecholamines and corticosterone [10, 27, 31]. In an open field SHR exhibited higher locomotor activity and a higher rearing score [18,26].

Cardiovascular, endocrine and behavioural hyperreactivity has been suggested to contribute to the development of hypertension through adaptive changes caused by repeated increased pressor loads on the blood vessels already in response to mild environmental stimuli [6]. An inhibition of the rise in blood pressure in SHR has been described after isolation or after rearing of the animals in a quiet and dark environment, thus in the presence of a decreased level of external stimuli [12,20]. Furthermore, lesions of the central amygdala, an important input location for transmitting behavioural stimuli to other parts of the brain, has been shown to result in a less pronounced hypertension together with an inhibition of the exaggerated cardiovascular responses to stress [7,8]. However, the possible relation between changes in behaviour and the development of hypertension in the SHR has been questioned [26,32] and especially locomotor activity per se appeared to be determined by genetic factors independent of hypertension [14,42].

Recently, we have shown a decrease in open-field rearing behaviour of adult SHR after intracerebroventricular (ICV) injections with 6-hydroxydopamine (6-OHDA) at a prehypertensive age. No changes in ambulation were observed [36]. ICV 6-OHDA treatment resulted in a pronounced at-

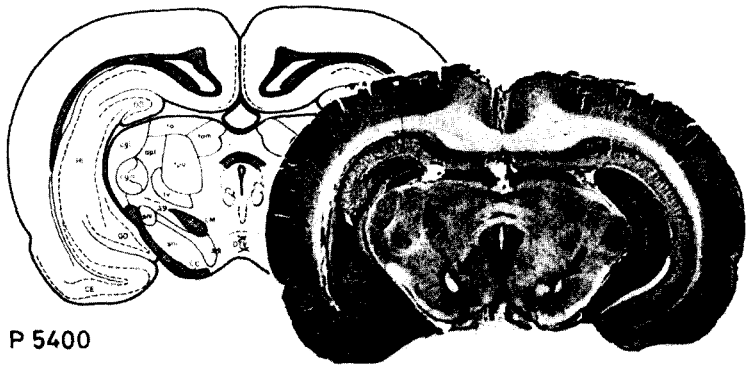

FIG. 1. Representative example of bilateral lesions in the substantia nigra (arrows) effective in SHR in attenuating the development of hypertension, depleting striatal dopamine levels and decreasing open-field rearing score. The indicated distance refers to the bregma as zero. For further details, see [35].

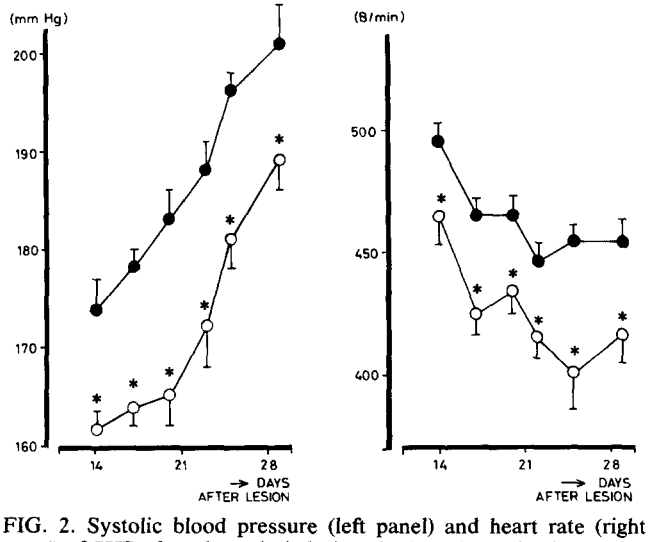

FIG. 2. Systolic blood pressure (left panel) and heart rate (right panel) of SHR after electrolytic lesions in the substantia nigra (open circles, n=26) or sham operation (closed circles, n=23). The number of days on the horizontal axis refers to the time after operation (day zero). *Indicates a significant difference between the groups ($p<0.05$). Bars indicate S.E.M.

tenuation of the development of hypertension [11, 34, 36]. This could implicate central catecholamine systems not only in the rise in blood pressure in SHR but also in at least part of the behavioural changes of these animals. However, after ICV 6-OHDA all three catecholamine systems in the brain are affected [19,34]. Brain noradrenaline is depleted most markedly after this treatment but the destruction of brain dopamine systems in SHR may be of particular importance in the effect of ICV 6-OHDA on the development of hypertension [34, 35, 37]. Moreover, extensive depletion of brain dopamine may induce sensory neglect [23,33]. Therefore, in the present experiments the effect of specific lesions in brain dopamine systems on changes in open-field behaviour and the development of hypertension was studied. The results strengthen the possibility of a direct relation between brain catecholamines (notably dopamine), behaviour and hypertension. Also, a mechanism may be indicated by which ICV 6-OHDA induces its effects on the development of hypertension in SHR.

METHOD

Animals

Male SHR/Cpb, WKY/Cpb [5] and Wistar/Cpb from TNO, Zeist, The Netherlands, were used. The animals were weaned at the age of four weeks and kept in our laboratory under a constant light-dark rhythm with standard pellet food and tap water available ad lib. The rats were housed 4–5 per cage.

Electrolytic Lesions

Bilateral electrolytic lesions in the area of the substantia nigra were carried out with a Grass lesion maker in anesthetized SHR and WKY 7–10 days after weaning. Anesthesia was induced with Hypnorm® (10 mg fluanison and 0.2 mg fentanyl per ml, Philips Duphar, Amsterdam, The Netherlands). Stereotactic coordinates with the toothbar set at +5 and the bregma as zero were posterior 1.6 mm, lateral 1.6 mm and ventral 8.4 mm. Lesions were made by passing a 20 sec 8 mA current through a stainless steel electrode of which 0.7 mm of the tip was uninsulated. Sham-treatment consisted of exposure of the skull and drilling holes at the appropriate locations. No electrodes were lowered in these groups. Histological control at the end of the experiment confirmed part of the substantia nigra pars compacta being destroyed by spherical lesions of approximately 1–1.5 mm in diameter. Localization, size and success-rate of the lesions was highly reproducible. Figure 1 shows a typical lesion after this treatment (see also [35]). No substantial damage of the ventral tegmental area occurred in this group.

In the second lesion experiment the above mentioned coordinates were varied to produce a range of dopamine depletions: posterior from 1.0 to 2.8, lateral from 0.5 to 2.2 and ventral from 7.6 to 9.2. The behavioural, cardiovascular and biochemical data from these groups were pooled for statistical correlational analysis.

Antihypertensive Treatment

From 7 weeks of age SHR received either 160 mg/l hydralazine or 500 mg/l captopril in their drinking water [30]. Controls had tap water.

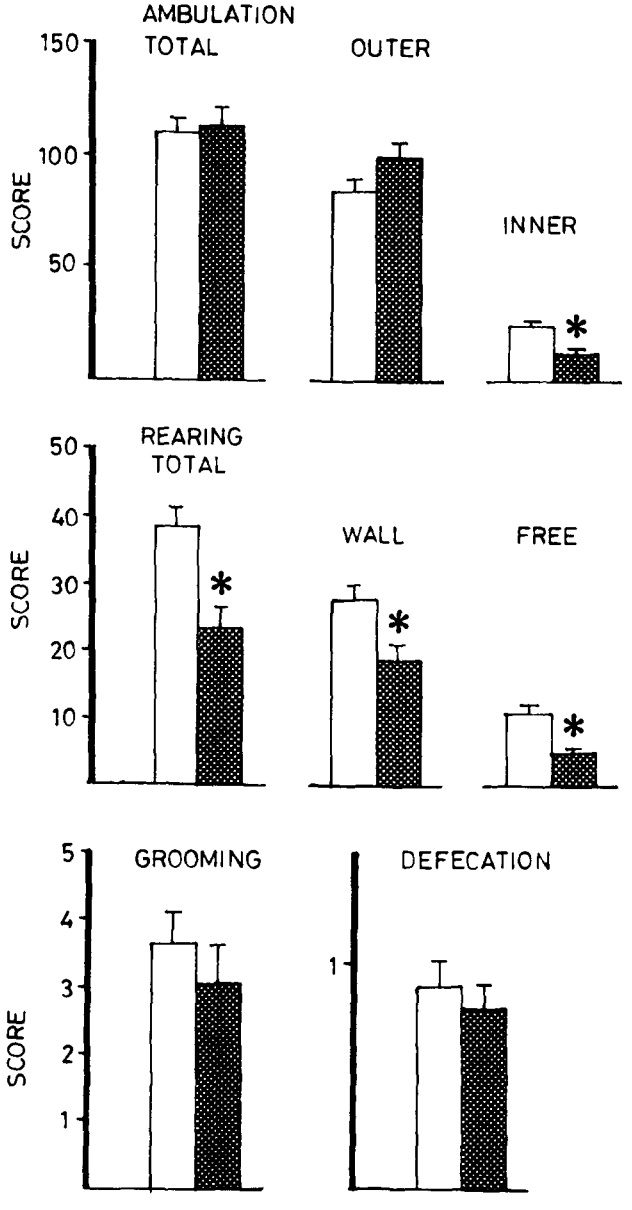

FIG. 3. Open-field behaviour of SHR with bilateral electrolytic lesions in the substantia nigra (stippled bars) or after sham operation (open bars). For the lesion group n=26, for the sham-operated group n=23. *Indicates a significant difference between the groups ($p<0.05$). Bars indicate S.E.M.

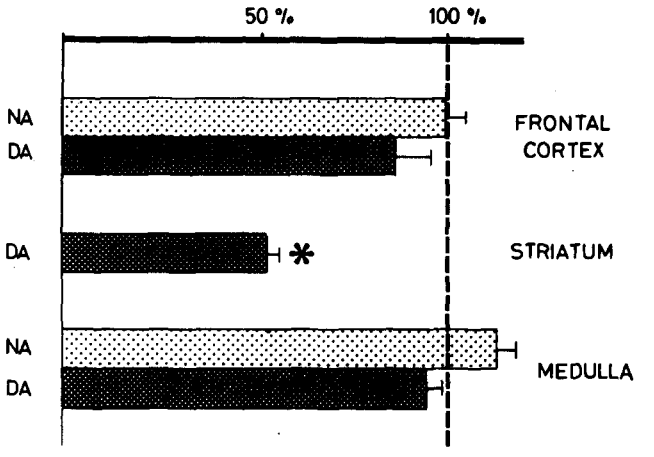

FIG. 4. Brain catecholamine concentrations of SHR with bilateral electrolytic lesions in the substantia nigra (n=26). Values are expressed as percentage of their respective controls (n=23). *Indicates statistical significance ($p<0.05$). Bars indicate S.E.M.

TABLE 1

MEAN VALUES (UPPER PANEL) AND CORRELATIONAL PARAMETERS (BOTTOM PANEL) ON THE DATA OF SYSTOLIC BLOOD PRESSURE, REARING AND AMBULATION IN THE OPEN-FIELD, AND STRIATAL DOPAMINE CONCENTRATION IN A GROUP OF SHR AFTER SHAM OPERATION (n = 23) OR ELECTROLYTIC LESIONS IN THE AREA OF THE SUBSTANTIA NIGRA (n = 78)

	Sham	Substantia Nigra Lesion
Blood pressure (mm Hg)	187 ± 3	166 ± 2*
Rearing (total score)	38 ± 3	21 ± 2*
Ambulation (total score)	110 ± 6	119 ± 6
Striatal dopamine Concentration (ng/mg)	12.02 ± 0.49	8.03 ± 0.34*
	r	p
Blood pressure with:		
Rearing total	0.244	0.007
Ambulation total	−0.032	0.375
Striatal dopamine with:		
Rearing total	0.331	0.001
Ambulation total	0.111	0.135
Blood pressure with striatal dopamine	0.175	0.039

*$p<0.05$ for difference between sham-operated and substantia nigra lesioned SHR.

Renal and DOCA-Salt Hypertension

At five weeks of age Wistar rats were operated under ether anesthesia. Renal hypertension was induced with a 0.20 mm solid silver clip around the left renal artery as reported earlier [21]. For DOCA-salt hypertension two 20 mg deoxycorticosterone pellets were implanted subcutaneously. These animals were given 0.9% saline as drinking water for the remainder of the experiment.

Blood Pressure and Heart Rate

Systolic blood pressure and heart rate were measured on conscious animals with a tail-cuff method as previously described [21]. For this, all rats were handled and trained for one week before actual values were obtained. For 2–4 weeks thereafter blood pressure and heart rate were measured at least three times a week. Rats from the experiment with renal and DOCA-salt hypertension were measured only once

TABLE 2

THE EFFECT OF LESIONS IN THE SUBSTANTIA NIGRA ON SYSTOLIC BLOOD PRESSURE, HEART RATE, OPEN-FIELD BEHAVIOUR AND BRAIN CATECHOLAMINES OF NORMOTENSIVE WKY

Treatment (n)	Sham Lesion (10)	Substantia Nigra Lesion (14)
Blood pressure (mm Hg)	157 ± 2	143 ± 2*
Heart rate (B/min)	428 ± 9	397 ± 8*
Open Field (score/5 min)		
Amb. outer	85 ± 5	75 ± 9
Amb. inner	11 ± 2	2 ± 1*
Amb. total	96 ± 5	77 ± 9
Rearing wall	8 ± 1	4 ± 1*
Rearing free	2 ± 1	0.2 ± 0.1*
Rearing total	10 ± 2	4 ± 1*
Grooming	5 ± 1	4 ± 1
Defecation	3 ± 1	3 ± 1
Noradrenaline (ng/mg)		
Frontal cortex	0.22 ± 0.01	0.16 ± 0.01*
Dopamine (ng/mg)		
Frontal cortex	0.32 ± 0.05	0.13 ± 0.04*
Striatum	10.90 ± 0.45	2.30 ± 0.30*

Data are mean ± S.E.M.
*$p<0.05$ for difference between WKY with lesions in the substantia nigra and sham-operated rats.

TABLE 3

THE EFFECT OF TREATMENT WITH HYDRALAZINE OR CAPTOPRIL ON SYSTOLIC BLOOD PRESSURE, HEART RATE, OPEN-FIELD BEHAVIOR AND STRIATAL DOPAMINE CONCENTRATION OF SHR

Treatment	control SHR	SHR + Hydralazine	SHR + Captopril
Blood pressure (mm Hg)	205 ± 3	148 ± 2*	148 ± 3*
Heart rate (B/min)	494 ± 13	488 ± 11	520 ± 5
Open Field (score/5 min)			
Amb. outer	77 ± 6	73 ± 5	84 ± 6
Amb. inner	25 ± 4	20 ± 2	28 ± 4
Amb. total	101 ± 7	92 ± 5	112 ± 9
Rearing wall	22 ± 2	24 ± 2	24 ± 2
Rearing free	6 ± 2	11 ± 3	8 ± 2
Rearing total	28 ± 3	35 ± 4	32 ± 4
Grooming	4 ± 1	4 ± 1	5 ± 1
Defecation	0.8 ± 0.4	1.3 ± 0.5	1.4 ± 0.6
Dopamine			
Striatum (ng/mg)	14.65 ± 0.77	13.25 ± 0.48	13.20 ± 0.87

For each group n = 10.
*$p<0.05$ for difference with control SHR.

under light ether anesthesia. When in other experiments only one value for blood pressure and heart rate is given, this value was obtained 4–5 days before the behavioural measurements and is representative for the whole particular experimental period.

Open-Field Experiments

Behavioural experiments were performed approximately three weeks after the operations, when differences in blood pressure were established.

The open field consisted of a walled circular arena (80 cm diameter, 31 cm height) of which the floor was divided into oblong blocks with an 8 cm radius circle in the centre. The rats were tested between 9.00 a.m. and 12.00 a.m. during five minutes after placement in the centre of the open field. During the observation period the room was illuminated only by a 60 W bulb approximately 50 cm from the floor of the open field. Ambulation score was determined as the number of floor units crossed in the outer ring (ambulation outer) or in the inner ring including the centre circle (ambulation inner). Rearing score was designated rearing wall when it occurred in the outer ring with the wall as support or clearly directed towards the wall, or rearing free. Furthermore, defecation (number of boluses) and the frequency and duration of grooming episods were scored [40].

Brain Catecholamines

After decapitation, brains were excised rapidly and dissected according to the method of Gispen *et al.* [9]. Brain parts were weighed, frozen on dry ice and kept at −80°C for catecholamine assay.

Brain noradrenaline and dopamine concentrations were measured in homogenates of frontal cortex, striatum, hypothalamus and/or medulla-pons either radio-enzymatically according to the method of Van der Gugten *et al.* [38] or with an HP-1081 HPLC system according to the method of Westenberg *et al.* [41]. Catecholamine concentrations are expressed as ng/mg tissue wet weight.

Statistical Analysis

For between-group comparison of cardiovascular, behavioural and biochemical data, analysis of variance and Duncan's multiple range test were used. Differences were considered statistically significant when $p<0.05$ [28]. All data are presented as mean±standard error of the mean (S.E.M.).

RESULTS

After bilateral electrolytic lesions in the substantia nigra the development of hypertension was delayed for approximately three weeks (Fig. 2). At all time-points substantia nigra lesioned SHR had a significantly lower systolic blood pressure when compared to sham-operated SHR. Also, heart rate was significantly lower in the lesioned rats at all time-points measured.

In Fig. 3 open-field behaviour of SHR with lesions in the substantia nigra is depicted. Locomotor activity was not different between the groups except for a lower score for ambulation inner in the lesioned animals. More pronounced effects were found on explorative behaviour. A significantly lower score for rearing total, as well as for rearing wall and rearing free separately, was observed in SHR with lesions in

TABLE 4

SYSTOLIC BLOOD PRESSURE, HEART RATE, OPEN-FIELD BEHAVIOUR AND STRIATAL DOPAMINE CONCENTRATION AFTER THE INDUCTION OF RENAL HYPERTENSION OR DOCA-SALT HYPERTENSION IN WISTAR RATS

Treatment (n)	Renal Hypertension (10)	Controls (5)	DOCA-Salt Hypertension (15)	Controls (5)
Blood pressure† (mm Hg)	210 ± 6*	138 ± 4	181 ± 1*	136 ± 3
Heart rate† (B/min)	478 ± 9	466 ± 24	453 ± 6	436 ± 11
Open Field (score/5 min)				
Amb. outer	121 ± 7	104 ± 9	105 ± 5	97 ± 12
Amb. inner	16 ± 3	20 ± 7	23 ± 4	14 ± 5
Amb. total	137 ± 10	124 ± 12	128 ± 6	110 ± 17
Rearing wall	15 ± 2	12 ± 3	12 ± 2	7 ± 1
Rearing free	4 ± 1	3 ± 2	3 ± 1	3 ± 1
Rearing total	19 ± 3	15 ± 4	15 ± 2	11 ± 3
Grooming	2 ± 1	3 ± 1	2 ± 1	5 ± 3
Defecation	4 ± 1	5 ± 1	6 ± 1	6 ± 2
Dopamine				
Striatum (ng/mg)	11.6 ± 0.5	10.5 ± 0.5	11.1 ± 0.2	10.2 ± 0.3

Data are mean ± S.E.M. three weeks after operations.
*$p<0.05$ for difference with respective sham treated controls.
†Blood pressure and heart rate were measured under light ether anesthesia.

the substantia nigra. Grooming and defecation scores revealed no differences between the groups.

The dopamine concentration in the striatum was significantly lower in substantia nigra lesioned SHR when compared to sham-operated controls (6.6±0.5 ng/mg vs. 12.4±0.5 ng/mg respectively). No differences were observed in catecholamine concentrations in frontal cortex and medulla-pons (Fig. 4).

In a large group of SHR stereotactic coordinates were varied to produce a range of biochemical, behavioural and blood pressure values. Mean values of the groups are shown in Table 1. Significant dopamine depletion was found after lesions involving the substantia nigra pars compacta. After lesions with more dorsal, ventral (pars reticulata), posterior or lateral coordinates, the depletion of dopamine in the striatum was small or absent. In these animals behavioural or blood pressure effects were also minimal. A detailed regional study is needed to further specify the critical site in the substantia nigra or the striatum.

Results of the correlational analysis of the individual data are shown also in Table 1. Only total scores for ambulation and rearing were used. Blood pressure was significantly correlated with rearing score but not with ambulation. Striatal dopamine concentration was significantly correlated with rearing score but not with ambulation. Blood pressure was weakly, but significantly, correlated with striatal dopamine concentrations.

The effect of lesions in the substantia nigra on blood pressure, heart rate, open-field behaviour and brain catecholamine levels of normotensive WKY is shown in Table 2. Although striatal dopamine was depleted to a greater extent in these animals (79% decrease in WKY, 47% decrease in SHR, Fig. 3), the effect on blood pressure was smaller in the normotensive rats. Substantia nigra lesions in WKY resulted in significantly lower scores for ambulation inner and all three rearing parameters when compared to sham-operated WKY. In contrast to SHR, however, lesioned WKY also showed lower concentrations of dopamine and noradrenaline in the frontal cortex.

The effect of treatment of SHR with hydralazine or captopril in their drinking water on blood pressure, heart rate, open field behaviour and striatal dopamine is shown in Table 3. Both treatments resulted in a markedly lower blood pressure but had no effect on either heart rate, dopamine concentration or open-field behaviour. Captopril-treated SHR showed an increase in water consumption. For instance, after two weeks of treatment captopril-treated SHR drank 42 ml per 24 hours per rat vs. 28 ml per 24 hours per rat for control SHR with no difference in body weight between the groups. Hydralazine-treated SHR drank an estimated amount of 29 ml per 24 hours per rat. Thus, the average dose ingested per rat at this time-point was approximately 21 mg captopril or 4.6 mg hydralazine per 24 hours.

Table 4 shows the effect of renal hypertension and DOCA-salt hypertension on open-field behaviour and striatal dopamine levels. Although both experimental groups showed higher systolic blood pressure values when compared to their respective control groups, no differences were found on open-field performance or striatal dopamine concentrations.

DISCUSSION

The present experiments were performed to investigate

the relation between changes in behaviour and the development of hypertension in SHR. Recently, we have shown that ICV 6-OHDA may inhibit the rise in blood pressure through depletion of brain dopamine rather than of noradrenaline [34, 35, 37]. Moreover, this treatment specifically affected explorative behaviour in the open field [36] with no effect on other parameters, e.g. locomotor activity. Before a direct relation between these two phenomena could be postulated, a more specific approach to deplete brain dopamine was required, however. Destruction of brain noradrenaline systems has been shown to affect various open-field parameters [1,24]. From previous studies it appeared that lesions in the substantia nigra of SHR may attenuate the development of hypertension [35] while causing specific depletion of dopamine in the striatum. Similar to ICV 6-OHDA treatment, in the present experiments lesions in the substantia nigra in young SHR not only inhibited the rise in blood pressure with age but also induced a pronounced decrease in rearing score in the open field. Both effects appeared quantiatively smaller than after ICV 6-OHDA. It should be noted, however, that dopamine depletion in the striatum was also less pronounced in substantia nigra lesioned rats. The substantia nigra pars compacta is an elongated structure containing the cell bodies of the A9 dopamine group [22,33]. Electrolytic lesions in this area may only damage part of this large cell-group and so induce only moderate destruction of the efferent system. ICV 6-OHDA will reach the whole brain and so cause depletion to a greater extent by destroying both terminals in the striatum (i.e., caudate nucleus) as well as cell bodies [19,33].

Surprisingly, WKY rats showed a larger degree of dopamine depletion after substantia nigra lesions than SHR, with also a lower dopamine concentration in the frontal cortex. Whether this means that the dopamine system in SHR is more capable of recovering after an initial damage, needs further investigation. Higher brain dopamine levels and increased dopamine receptor density in SHR when compared to WKY have been reported, though (for references see [39]). In contrast to the absence of an effect of ICV 6-OHDA an open-field behaviour of WKY [36], substantia nigra lesions caused lower rearing scores in this strain, as has also been shown for another normotensive strain [17]. The absolute decrease in rearing in WKY was smaller than that in SHR. The reason for the difference in effect of 6-OHDA treatment vs. substantia nigra lesions in SHR and WKY is unclear but could result from damage to other catecholamine systems after ICV 6-OHDA injections. An interaction between noradrenaline and dopamine systems with respect to their effects on open-field behaviour has been suggested earlier [15]. This interaction may be different in SHR when compared to normotensive rats.

In SHR, after lesions in the area of the substantia nigra the extent of striatal dopamine depletion was significantly correlated with the resulting effects on rearing activity and blood pressure but not with ambulation. Like striatal dopamine, blood pressure was correlated with rearing score (Table 1). The extent of dopamine depletion was thus more highly correlated with behavioural measures of reactivity than with blood pressure. Blood pressure was more highly correlated with behavioural measures than with dopamine depletion. These results could warrant the conclusion that brain dopamine system (i.e., the nigrostriatal pathway) influence the development of hypertension through behavioural mechanisms rather than a direct relation. It has been suggested also previously that rearing (but not locomotion) is a behaviour dependent on normal levels of striatal dopamine [17]. It should be noted, however, that although striatal dopamine levels can be considered as a marker of damage to the substantia nigra, dopamine depletion also in other terminal areas may be important for the effects on blood pressure. A more regional study of the effects of these lesions may give better information in this respect.

The ICV injection of dopamine has been shown to induce an acute decrease in blood pressure [2,16]. This effect appears to be in contrast to the antihypertensive effects of dopamine depletion in the present paper. However, it is likely that damage to the dopamine systems, either by ICV 6-OHDA or by substantia nigra lesions, does not directly affect blood pressure. Rather, the main effect of these treatments could be the result of changes in the behavioural response to environmental stimuli. The effects on behaviour which we have shown are unlikely to be caused by changes in blood pressure per se, since neither antihypertensive treatment nor induction of hypertension in normotensive rats induced in open-field behaviour. Interestingly, brain dopamine levels were also not changed after these treatments. Thus, the changes in behaviour may be causing the changes in blood pressure rather than the reverse. The mechanism for the interaction between changes in behaviour and the development of hypertension is at present unknown, but lower scores for exploratory rearing in the open field could be indicative of a decrease of the hyperreactivity ascribed to SHR [6,32]. Depletion of brain dopamine has been shown to induce a decrease in the relay of environmental stimuli (sensory neglect, see [23,33]). Thus, the exaggerated behavioural and cardiovascular responses of SHR may have been partly normalized by the lesions which in this way could induce a decrease in the level of pressor loads suggested to play a role in the development of spontaneous hypertension [6, 8, 13]. To support this hypothesis, the effect of various environmental stimuli on acute cardiovascular and endocrine responses in either ICV 6-OHDA-treated or substantia nigra lesioned SHR will have to be investigated. Also, the effect of various behavioural treatments on acute and chronic blood pressure could be investigated.

From the present results, however, we suggest a relation between brain dopamine, behaviour and the development of hypertension. Changes in blood pressure by themselves do not appear responsible for the changes in behaviour observed. It needs further investigation to establish in which manner the changes in behaviour may contribute to the development of hypertension in SHR [11, 34, 37].

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