INFLUENCE OF SINO-AORTIC BARORECEPTOR DENERVATION ON CATECHOLAMINES, CATECHOLAMINE-SYNTHESIZING ENZYMES AND CHOLINE ACETYLTRANSFERASE ACTIVITY IN THE BRAINSTEM NUCLEI OF THE RAT

Kazuo NAKAMURA and Keiji NAKAMURA
Department of Pharmacology, Nippon Roche Research Center, Kamakura 247, Japan
Accepted August 20, 1980

Abstract—At one week after sino-aortic baroreceptor denervation in the rat, aortic blood pressure and plasma contents of epinephrine and dopamine β-hydroxylase (DBH) activity were elevated during resting and conscious states. Stress-induced elevation of blood pressure and plasma epinephrine were markedly pronounced. These changes disappeared at four weeks after denervation. Sino-aortic deafferentation decreased choline acetyltransferase (ChAc) activity in the nucleus tractus solitarii (NTS) and locus coeruleus (LC) and increased DBH activity, norepinephrine levels, phenylethanolamine N-methyltransferase (PNMT) activity and epinephrine levels in the LC, accompanied with a reduction of DBH activity and norepinephrine contents in the nucleus hypothalamicus posterior. These alterations were confirmed one week after denervation but did not persist for a period of four weeks. At four weeks after denervation, ChAc activity was significantly decreased in the nucleus dorsalis nerve of the vagi but not in the nucleus ambiguous. During the transient hypertensive phase, sino-aortic deafferentation did not alter DBH and PNMT activities in the NTS, A2 cell and A1 cell areas, and both catecholamine levels in the NTS.

In conclusion, sino-aortic denervation transiently decreased ChAc activity in the NTS and LC, and enhanced synthesis and accumulation of norepinephrine and epinephrine in the LC accompanied with a decrease in norepinephrine contents and DBH activity in the nucleus hypothalamicus posterior, causally resulting in short-lasting labile hypertension and activation of the adrenal medulla.

There is no particular evidence to identify the role of sino-aortic baroreceptors in the development of hypertension. Recent studies provided evidence that the secondary neurons of the carotid sinus and aortic baroreceptor afferents are located in the nucleus tractus solitarii (NTS) (see Ref. in 1). Most probably all afferent baroreceptor fibers pass through the NTS, since the reflex effects are abolished after its bilateral destruction (see Ref. in 1). The bilateral electrolytic lesions in the NTS result in severe and acute hypertension in the rat (2, 3). Hypertension is also induced in the rat by sino-aortic baroreceptor denervation (4–6) and by bilateral surgical dissections placed on the lateral part of the NTS (7, 8). There are also data that brainstem catecholamines (CA) participate in the baroreceptor control of blood pressure and in the development of neurogenic hypertension (2, 9, 10).

CA containing cell bodies at A2 cell area
(11) send nerve terminals to the rostral portion of the rat NTS (11, 12). Denervation studies have shown that the primary afferent nerve fibers from the IXth and Xth cranial nerves terminate in the lateral portion of the rat NTS at the level of the obex and that some of the catecholaminergic neurons are located in the first presynaptic side of serial synapses (13), thereby suggesting the presynaptic modulation of CA in the second synaptic transmissions in serial synapses. However, recent studies revealed that the bilateral transections lateral to the NTS results in acute hypertension (7, 8) and the axonal degeneration in the rostral part of the NTS, but does not alter norepinephrine and epinephrine contents in the NTS and A2 cell areas (8).

The present studies were designed to examine the effect of sino-aortic baroreceptor denervation on CA synthesizing enzymes, dopamine β-hydroxylase (DBH) and phenylethanolamine N-methyltransferase (PNMT) activities, CA levels and choline acetyltransferase (ChAc) activity, a specific marker for cholinergic nerves in the brain (14, 15), in the NTS and related brainstem nuclei by combining a microdissection technique with sensitive radio-enzymatic assays.

MATERIALS AND METHODS

Male Wistar rats about 8–9 weeks old and weighing 250–270 g were used. Experiments were performed in one and four weeks after the transection of bilateral sino-aortic buffer nerves. For the denervation, both superior laryngeal nerves and both cervical sympathetic nerves were removed, and the carotid sinuses were isolated from connective tissues and denervated by painting with 10% phenol in ethylalcohol, with the rats under ether anesthesia (4, 5). For confirmation of the denervation, the loss of the bradycardiac response to norepinephrine-induced pressor reaction was examined. Aortic blood pressures were measured, without anesthesia or restraint, by a pressure transducer through a catheter implanted 3 days previously into the aorta near the orifice of the renal artery via the femoral artery (16).

In the second group of animals, the aortic blood samples (0.3 ml) for measuring CA levels were collected through a polyethylene cannula connected to the aortic catheter. The blood volume collected was replaced with saline. Values obtained under these conditions were considered as the resting basal values. One day after collecting the blood samples, aortic blood samples were obtained immediately after gently holding the trunk of animal for 30 seconds as a stress-load (16). Plasma norepinephrine and epinephrine levels were measured radioenzymatically (17). When dissecting the cerebral nuclei of the third group of animals, rat brain maps for DBH (18) and PNMT (19) were used. Each nucleus was punched out from the brainstem, as described previously (16, 20, 21). The individual nucleus was removed bilaterally with a tube knife (500 μm inner diameter) from a 300 μm cryostat section, using a microdissection technique (20). Tissues for DBH activity and CA assays were punched out and homogenized in two pooled pairs. DBH activities in the tissues homogenized into 75 μl of ice-cold 5 mM Tris buffer (pH 7.4) containing 0.2% Triton X-100 and plasma were determined radioenzymatically (16, 22). Tissues for PNMT activity were punched out and homogenized in one pair in 30 μl of ice-cold 5 mM Tris buffer (pH 8.6) containing 0.2% Triton X-100 and 0.2% bovine serum albumin. PNMT activities in the homogenates were measured radiometrically by the method of Moore and Phillipson (23). A pair of nuclei for ChAc activity was punched out and homogenized into 10 μl of 5 mM Tris buffer (pH 7.5) containing 0.1% Triton X-100. ChAc activities in the homogenates were measured
radiometrically, as described previously (24, 25). The protein in homogenates was assayed with bovine serum albumin as the standard (26). The rats were decapitated at 11:00 a.m.

RESULTS

Aortic Blood Pressure and Aortic Plasma Levels of CA and DBH Activity: Aortic blood pressures at resting state were slightly but significantly elevated one week after sino-aortic baroreceptor denervation and returned to the initial levels when measured four weeks after operation (Table 1). The heart rate did not change one week after denervation and was elevated four weeks later. In association with increased blood pressure, the aortic plasma levels of epinephrine and DBH activity were greatly elevated during resting states, one week after the denervation. Elevation of the plasma levels disappeared four weeks later. Plasma norepinephrine levels did not differ from sham-operated controls one and four weeks later (Fig. 1).

Influence of Stress on Aortic Blood Pressure, Heart Rate and Aortic Plasma Levels of CA and DBH Activity: Since epinephrine levels and DBH activity in the aortic plasma were markedly elevated one week after baroreceptor denervation, the effect of handling-stress was examined in conscious animals.

The stress induced by holding the trunk of the animal for a 30 second period immediately produced an elevation of mean aortic blood pressures and a concomitant decrease in heart rates. Evaluation of blood pressure returned to the initial levels when the animals were put back into the cage. The peak pressor response to the stress was significantly enhanced in denervated animals one week after operation (Table 1). The pronounced pressor response disappeared four weeks later. The holding stress markedly elevated the aortic plasma levels of epinephrine, norepinephrine and DBH activity. Sino-aortic denervation significantly increased the stress-induced elevation of plasma epinephrine levels one week and less extensively four weeks after operation (Fig. 1). Stress-induced accumulation of plasma norepinephrine or DBH activity did not differ in animal groups at four weeks after denervation and sham operation, respectively.

CA Synthesizing Enzyme Activity and CA Levels in the Brainstem and Spinal Nuclei: Denervation studies show that the primary afferent nerve fibers from the IXth and Xth cranial nerves terminate in the rostral (7) or lateral (13) part of the NTS innervated by fibers from CA containing cell bodies at A2 cell areas (11, 12).

We examined the possible cerebral effects

| Time after denervation | No. of animals | Mean aortic blood pressure (mmHg) | Heart rate (beats/min) |
|------------------------|----------------|-----------------------------------|-----------------------|
|                        |                | rest    | stress | rest    | stress |
| Sham control           | 7              | 112±2   | 136±8$ | 414±5   | 315±6$ |
| 1 week                 | 7              | 132±7** | 170±8***,† | 379±18 | 313±20† |
| Sham controls          | 6              | 115±2   | 148±8$ | 380±19  | 189±16$ |
| 4 weeks                | 6              | 121±2   | 143±48$ | 442±12* | 265±18**$ |

Data represent means±S.E.

*P<0.05 compared to corresponding sham controls, **P<0.02, ***P<0.01
†P<0.05 compared to corresponding resting controls, †P<0.01, §§P<0.001
Fig. 1. Plasma levels of epinephrine, norepinephrine and dopamine β-hydroxylase activity in sino-aortic baroreceptor denervated rats at resting and holding stressful states. Data are means ± S.E. from 5 animals at one and four weeks after denervation. DH activity units are defined as nmoles octopamine/h/ml plasma. Open, cross-hatched and dotted columns are sham-operated controls, those one and four weeks after denervation, respectively. a P<0.05 compared with corresponding resting values, b P<0.01, c P<0.001. *P<0.05 compared with corresponding sham-operated controls. **P<0.01, ***P<0.001.

Fig. 2. Dopamine β-hydroxylase activities in the brainstem and spinal cord of sino-aortic baroreceptor denervated rats. Enzyme activities defined as nmoles octopamine/h/mg protein are means ± S.E. from 12 samples (2 pooled pairs of nuclei/sample). Open and cross-hatched columns are sham-operated and denervated animals, respectively. a P<0.05 compared with corresponding controls. Abbreviations: IML spinal intermediolateral cell column at T2 level, NTS nucleus tractus solitarii, LC locus coeruleus, NHP nucleus hypothalamicus posterior, NPE nucleus periventricularis, NPA nucleus paraventricularis, NHA nucleus hypothalamicus anterior.
Fig. 3. Norepinephrine and epinephrine levels in the brainstem nuclei of denervated rats after sino-aortic deafferentation. Data are means±S.E. from 10 samples (2 pooled pairs of nuclei/sample). Open and cross-hatched columns are sham-operated and denervated animals, respectively. a P<0.05 compared with corresponding controls, b P<0.01. Abbreviations: see legend for Fig. 2.

Fig. 4. Phenylethanolamine N-methyltransferase activities in the brainstem and spinal cord of sino-aortic baroreceptor denervated rats. Enzyme activities defined as pmoles N-methylphenylethanolamine/h/mg protein are means±S.E. from 12 pooled pairs of nuclei. Open and cross-hatched columns are sham-operated controls and denervated animals, respectively. a P<0.05 compared with corresponding controls. Abbreviations, see legend for Fig. 2.

of sino-aortic baroreceptor denervation on CA synthesizing enzyme activity and CA content in the brainstem nuclei one and four weeks later. In rats with mild hypertension one week after denervation, there was a marked increase in DBH activity, nor-
epinephrine level, PNMT activity and epinephrine level in the locus coeruleus (LC), and a contrasting decrease in both DBH activity and norepinephrine contents in the nucleus hypothalamicus posterior (NHP) (Figs. 2–4). These alterations disappeared four weeks after denervation. There was no significant change in norepinephrine and epinephrine contents and DBH and PNMT activities in the NTS, and both enzyme activities in the A2, A1 cell areas, the spinal intermediolateral cell area at the spinal segment T2 level (IML), nucleus paraventricularis (NPA) and nucleus hypothalamicus anterior (NHA).

ChAc Activity in Brainstem Nuclei: To determine whether sino-aortic baroreceptor deafferentation affects cholinergic neurons in the NTS and its related nuclei, we examined ChAc activity as a selective marker enzyme of cerebral cholinergic neurons (14, 15) in these nuclei. Sino-aortic baroreceptor transection significantly decreased ChAc activity in the NTS and LC areas by 31% and 29%, respectively, one week after operation (Fig. 5). The reduction disappeared four weeks after operation, whereas the reduction became apparent four weeks later in the DNDV, an area which contains cholinergic cell bodies (27). Denervation did not change the enzyme activity in the A2 cell area, nucleus dorsalis nerve of the vagi (NDNV), nucleus ambiguus (AMB), A1 cell area and NHP, as determined one and four weeks later.

DISCUSSION

The present studies indicate that sino-aortic baroreceptor denervation produces a slight but significant elevation of aortic blood pressure, as measured one week after the operation. The hypertension disappeared four weeks later. The elevation of blood...
pressure consequent to baroreceptor deafferentation is not a stable and persistant type, as was also reported by others (5, 28, 29). However, the present results are not compatible with the previous reports describing consistent hypertension after sino-aortic denervation in rats (1, 4). The discrepancy may be explained by the use of anesthesia employed at the time of blood pressure measurement by these workers (1, 4). In denervated animals at resting and conscious states, plasma epinephrine levels were elevated, and both pressor response and selective accumulation of plasma epinephrine under stress were pronounced, the results suggesting the presence of activation of the adrenomedullary function. It has been demonstrated by other workers that adrenal epinephrine syntheses are increased in rabbits three weeks after sino-aortic denervation (29). Thus, elevation of plasma epinephrine level is an important factor in the determination of the hemodynamics (30) in denervated animals. Sino-aortic denervation studies in conscious dogs also indicated that denervation causing labile hypertension does not minimize variations in systemic arterial blood pressure (28). Dissection of rat splanchnic nerves leading to the adrenal medulla lowers adrenal venous output of epinephrine and norepinephrine (31) and arterial blood pressure (32), and electrical stimulation of a cut-end of the nerves frequency-dependently restores the corresponding parameters (31, 32). These previous findings indicate that plasma elevation of epinephrine contents, as observed in denervated animals, may be due to enhanced discharges of the sympathetic nervous system.

Regarding cerebral functional connection of denervated animals, there was a significant elevation of both CA and related synthesizing enzyme activities in the LC and a decrease in norepinephrine content and DBH activity in the NHP, one week after denervation. In denervated hypertensive animals, these results suggest activation of noradrenergic and adrenergic neurons in the LC and also a decrease in noradrenergic neuronal activity in the NHP. The LC may be involved in neuroendocrine changes associated with stress and anxiety (33). Electrical stimulation of the principal LC nucleus increases plasma ACTH levels in the cat (34) and plasma 3-methoxy-4-hydroxyphenylglycol in the rat (35), a major metabolite of norepinephrine, and causes hypertension in the rat (36) and cat (37). A spinal sympathetic pathway originating from the LC has also been demonstrated in the rat, on the basis of reduction in spinal DBH activity (38) and CA-containing nerve terminals (39) following LC lesion, and anatomically in the cat and monkey by the retrograde transport of horseradish peroxidase (40). Thus, activation of noradrenergic neurons in the LC may lead to activation of bulbospinal noradrenergic neurons which relay excitatory impulses to preganglionic vasoconstrictor neurons (41), and also may lead to activation of the adrenal medullary (31) and adrenocortical functions (34). Kariometric studies revealed that stress increases the nuclear diameter of the LC in the rabbit (42). Furthermore, midcollicular decerebration is reported to abolish the NTS-related hypertension after bilateral lesions of the NTS in the rat (3). Thus, the hypertension probably depends on the integrity of structures lying above the midcollicular level (3) and including the LC. Moreover, recent studies indicate that the hypertension seen in NTS-lesioned dogs results from a sustained increase in sympathetic tone (43). These results taken together show that selective elevation of norepinephrine and epinephrine levels and respective synthesizing enzyme activities in the LC may lead to transient, labile hypertension with concomitant accumulation of
plasma epinephrine.

Since the present results indicate that sino-aortic denervation does not change norepinephrine and epinephrine levels and the corresponding synthesizing enzyme activities in the NTS and A2 cell areas, we suggest that these catecholamines are not involved in baroreceptor afferent input to the NTS. The suggestion might be in agreement with the previous report that surgical deafferentation of the NTS of the rat by bilateral transection lateral to the nucleus and causing hypertension (7) degenerated the rostral part of the NTS and A2 areas with no alteration of norepinephrine and epinephrine contents in either area (8). Recent fluorescent and electron microscopical studies on the synaptic NTS organization at the level of the obex in the rat indicated that the majority of small neurons are non-catecholaminergic (13). The transection of IXth and Xth cranial nerves slightly decreases the number of axon varicosities (13) but does not alter catecholaminergic axon varicosities (Chiba, personal communication).

The present study revealed that ChAc activity in the NTS significantly decreased one week after denervation, while the decreased enzyme activity in the NDNV became significant four weeks later. No significant change was observed in the enzyme activity in the AMB. These results imply that decreased ChAc activity may be the result of degeneration of cholinergic neurons (14, 15), and that cholinergic neurons present in the NTS have closer connections with the NDNV than those with the AMB, in the rat. The present neurochemical data also indicate close interactions between NTS and LC. In both nuclei, there is decreased ChAc activity. The time difference in the decrease in ChAc activity in the NDNV, NTS and LC may be explained by the fact that the NDNV is known to contain cholinergic cell bodies, while the LC and probably the NTS have cholinergic nerve endings (27). Recovery of partially decreased ChAc activity in the NTS and LC 4 weeks after sino-aortic deafferentation may be the result of regenerative sprouting-like central noradrenergic nerve terminals, to maintain anatomical continuity with an innervated site. A retrograde tracer technique with horseradish peroxidase also confirms the existence of afferent projection from the NTS to the ventrolateral part of the LC in the cat (44). Accordingly, alterations in the LC seem to be due to the degeneration of cholinergic neurons in the NTS but not to elevation of blood pressure or adrenal function. The present study extends these observations by indicating that there is a close connection between presynaptic cholinergic nerve terminals and noradrenergic cell bodies in the LC.

As for a selective decrease in DBH activity and norepinephrine levels in the NHP, with no change in ChAc in the nuclei after denervation, recent histological studies using DBH antibody indicate that A2 cell groups project noradrenergic neurons to the hypothalamic nuclei, in the rat (45). Anterograde autoradiographic and retrograde horseradish methods also show that afferent fibers from the NTS project to the hypothalamus, in the rat (46). Thus, the decreased ChAc activity in the NTS as an indication of cholinergic degeneration (14, 15) may be causally related to decreased norepinephrine levels and DBH activity in the NHP. However, there has been no morphological evidence suggesting interaction of cholinergic neurons with noradrenergic neurons in the cerebral nuclei. Most probably a decrease in DBH activity and norepinephrine levels in the NHP counteracts the elevation of blood pressure after sino-aortic denervation, since electrical stimulation of the NHP causing the activation of the postjunctional α-adrenoceptors in the nuclei of the cat is known to
produce a pressor response (47). Moreover, the transient decrease in norepinephrine levels and DBH activity in the NHP is in agreement with the recent finding (48) that sino-aortic denervation in rats significantly decreases norepinephrine content in the NHP, one week but not four weeks later.

In conclusion, sino-aortic baroreceptor deafferentation transiently produces a decrease in ChAc activity in presynaptic cholinergic nerve terminals in the NTS and LC, elevates norepinephrine and epinephrine contents and corresponding synthesizing enzyme activities in the LC, causally resulting in short lasting hypertension and adrenal activation.

REFERENCES

1) Kirchheim, H.R.: Systemic arterial baroreceptor reflexes. Physiol. Rev. 56, 100–176 (1976)
2) Doba, N. and Reis, D.J.: The role of central and peripheral adrenergic mechanisms in neurogenic hypertension produced by brainstem lesions in rat (NTS-hypertension). Circulation Res. 34, 293–301 (1974)
3) Doba, N. and Reis, D.J.: Acute fulminating neurogenic hypertension produced by brainstem lesions in the rat. Circulation Res. 32, 584–593 (1973)
4) Krieger, E.M.: Neurogenic hypertension in the rat. Circulation Res. 15, 511–521 (1964)
5) Jones, J.V. and Hallbäck, M.: Cardiovascular reactivity and design in rats with experimental "neurogenic hypertension". Acta physiol. scand. 102, 41–49 (1978)
6) Thant, M., Yamori, Y. and Okamoto, K.: Baroreceptor function in spontaneously hypertensive rats. Japan. J. Physiol. 33, 501–507 (1969)
7) de Jong, W. and Palkovits, M.: Hypertension after localized transection of brainstem fibers. Life Sci. 18, 61–64 (1976)
8) Palkovits, M., de Jong, W., Zandberg, P., Versteeg, D.H.G., van der Gugten, J. and Leranth, C.: Central hypertension and nucleus tractus solitarius catecholamines after surgical lesions in the medulla oblongata of the rat. Brain Res. 127, 307–312 (1977)
9) Chalmers, J.P. and Wurtman, R.J.: Participation of central noradrenergic neurons in arterial baroreceptor reflexes in the rabbit. Circulation Res. 28, 480–491 (1971)
10) Nakamura, K., Ishii, H. and Nakamura, K.: Changes in catecholamine-containing neurons in the rat brainstem nuclei after sino-aortic denervation. Japan. J. Pharmacol. 29, Supp. 79P (1979)
11) Dahlinström, A. and Fuxe, K.: Evidence for the existence of monoamine-containing neurons in the central nervous system. I. Demonstration of monoamines in cell bodies of brainstem neurons. Acta physiol. scand. 62, Supp. 232, 1–55 (1964)
12) Palkovits, M. and Jacobowitz, D.M.: Topographic atlas of catecholamines and acetylcholinesterase-containing neurons in the rat brain, II Hindbrain (Mesencephalon, Rhombencephalon). J. comp. Neurol. 157, 29–42 (1974)
13) Chiba, T. and Kato, M.: Synaptic structures and quantification of catecholaminergic axons in the nucleus tractus solitarius of the rat: possible modulatory roles of catecholamines in baroreceptor reflexes. Brain Res. 151, 323–338 (1978)
14) Fonnum, F.: Topographical and subcellular localization of choline acetyltransferase in rat hippocampal region. J. Neurochem. 17, 1029–1037 (1970)
15) Yamamura, H., Kuhar, M.J., Greenberg, D. and Snyder, S.H.: Muscarinic cholinergic receptor binding: regional distribution in monkey brain. Brain Res. 66, 541–546 (1974)
16) Nakamura, K. and Nakamura, K.: Role of brainstem and spinal noradrenergic and adrenergic neurons in the development and maintenance of hypertension in spontaneously hypertensive rats. Arch. Pharmacol. 305, 127–133 (1978)
17) da Prada, M. and Zürcher, G.: Simultaneous radioenzymatic determination of plasma and tissue adrenaline, noradrenaline and dopamine within the femtomole range. Life Sci. 19, 1161–1173 (1976)
18) Swanson, L.W. and Hartman, B.K.: The central adrenergic system. An immunofluorescence study of the locations of cell bodies and their efferent connections in the rat utilizing dopamine β-hydroxylase as a marker. J. comp. Neurol. 163, 487–506 (1975)
19) Hökfelt, T., Fuxe, K., Goldstein, M. and Johanson, O.: Immunohistochemical evidence for the existence of adrenaline neurons in the rat brain. Brain Res. 65, 235–251 (1974)
20) Palkovits, M.: Isolated removal of hypothalamic or other brain nuclei of the rat. Brain Res. 59, 449–450 (1973)
21) Wijnen, J.J.L.M., Versteeg, D.H.G., Palkovits, M. and de Jong, W.: Increased adrenaline
content of individual nuclei of the hypothalamus and the medulla oblongata of genetically hypertensive rats. Brain Res. 135, 180–185 (1977)

22) Saavedra, J.M., Brownstein, M., Palkovits, M., Kizer, S. and Axelrod, J.: Tyrosine hydroxylase and dopamine β-hydroxylase: distribution in the individual rat hypothalamic nuclei. J. Neurochem. 23, 869–871 (1974)

23) Moore, K.E. and Phillipson, O.T.: Effects of dexamethasone on phenylethanolamine N-methyltransferase and adrenaline in the brains and superior cervical ganglia of adult and neonatal rats. J. Neurochem. 25, 289–294 (1975)

24) Fonnum, F.: A rapid radiochemical method for the determination of choline acetyltransferase. J. Neurochem. 24, 407–409 (1975)

25) Nakamura, K. and Nakamura, K.: Selective activation of sympathetic ganglia in young spontaneously hypertensive rats. Nature 266, 265–266 (1977)

26) Lowry, D.H., Rosebrough, N.J., Farr, A.L. and Randall, R.J.: Protein measurement with the folin phenol reagent. J. biol. Chem. 193, 265–275 (1951)

27) Cheney, D.L., LeFevre, H.F. and Recagni, G.: Choline acetyltransferase activity and mass fragmentographic measurement of acetylcholine in specific nuclei and tracts of rat brain. Neuropharmacology 14, 801–809 (1975)

28) Cowley, A.W., Liard, J.F. and Guyton, A.C.: Role of the baroreceptor reflex in daily control of arterial blood pressure and other variables in dogs. Circulation Res. 32, 564–576 (1973)

29) DeQuattro, V., Nagatsu, T., Maronde, R. and Alexander, N.: Catecholamine synthesis in rabbits with neurogenic hypertension. Circulation Res. 24, 545–555 (1969)

30) Caiñini, P., Permutt, S., Waddell, J.A. and Riley, R.L.: Effect of epinephrine on pressure, flow and volume relationships in the systemic circulation of dogs. Circulation Res. 34, 606–623 (1974)

31) Nakamura, K., Nakamura, K. and Suzuki, T.: Reciprocal changes in adreno-medullary and -cortical function in spontaneously hypertensive rats. Spontaneous Hypertension: Its Pathogenesis and Complications, p. 149–158, U.S. Dept. Health, Education and Welfare, Washington (1976)

32) Iriuchijima, J.: Sympathetic discharge rate in spontaneously hypertensive rats. Japan. Heart J. 14, 350–356 (1973)

33) Redmond, Jr. E.: Alterations in the function of the locus coerules: a possible model for studies of anxiety, Animal Models in Psychiatry and Neurology, Workshop Natl. Inst. Mental Health, Edited by Hanin, I. and Usdin, E., p. 293–305. Pergamon, Oxford (1977)

34) Ward, D.G., Grizzle, W.E. and Gann, D.S.: Inhibitory and facilitatory areas of the rostral pons mediating ACTH release in the cat. Endocrinology 99, 1220–1228 (1976)

35) Crawley, J.N., Hattox, S.E., Maas, J.W. and Roth, R.H.: 3-Methoxy-4-hydroxyphenethyl-ene glycol in plasma after stimulation of the nucleus coeruleus. Brain Res. 141, 380–384 (1978)

36) Ward, D.G. and Gunn, C.G.: Locus coeruleus complex: elicitation of a pressor response and a brain stem region necessary for its occurrence. Brain Res. 107, 401–406 (1976)

37) Przuntek, H. and Philippu, A.: Reduced pressor responses to stimulation of the locus coeruleus after lesion of the posterior hypothalamus. Arch. Pharmacol. 276, 118–122 (1973)

38) Ross, R.A. and Reis, D.J.: Effects of lesions of locus coerules on regional distribution of dopamine-β-hydroxylase activity in the rat brain. Brain Res. 73, 161–166 (1974)

39) Nygren, L.-G. and Olson, L.: A new major projection from locus coerules: the main source of noradrenergic nerve terminals in the ventral and dorsal columns of the spinal cord. Brain Res. 132, 85–93 (1977)

40) Hancock, M.B. and Fougerousse, C.L.: Spinal projections from the nucleus locus coerules and nucleus subcoeruleus in the cat as demonstrated by the retrograde transport of horseradish peroxidase. Brain Res. Bull. 1, 229–234 (1979)

41) Taylor, D.G. and Brody, M.J.: Spinal adrenergic mechanisms regulating sympathetic outflow to blood vessels. Circulation Res. 38, Supp. II, 10–20 (1976)

42) Bubenik, G. and Monnier, M.: Nuclear size variations in cells of the locus coerules during sleep, arousal and stress. Exp. Neurol. 36, 1–12 (1972)

43) Laubie, M. and Schmitt, H.: Destruction of the nucleus tractus solitarii in the dog: comparison with sino-aortic denervation. Am. J. Physiol. 236, H736–H743 (1979)

44) Sakai, K., Touret, M., Salvert, D., Legert, L. and Jouvet, M.: Afferent projections to the cat locus coerules as visualized by the horseradish peroxidase technique. Brain Res. 119, 21–41 (1977)

45) Ricardo, J.A. and Koh, E.T.: Anatomical evidence of direct projections from the nucleus of the solitary tract to the hypothalamus,
amygdala, and other-forebrain structures in the rat. Brain Res. 153, 1–26 (1978)

46) Silver, M.A., Jacobowitz, D., Crowley, W. and O’Donohue, T.: Retrograde transport of dopamine-β-hydroxylase antibody by CNS noradrenergic neurons: hypothalamic noradrenergic innervations. Anat. Rec. 190, 541 (1978)

47) Philippu, A., Roensberg, W. and Przuntek, H.: Effects of adrenergic drugs on pressor responses to hypothalamic stimulation. Arch. Pharmacol. 278, 373–386 (1973)

48) Brown, M., Chalmers, J.P., Petty, M.A. and Reid, J.L.: The involvement of catecholamines in the central connections of arterial baroreceptor reflexes in the rat. J. Physiol. 297, 42–43P (1979)