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Effect of posterior hypothalamic knife cuts on the baroreflex and hemorrhage-induced hormonal responses.

Shinya Makino* Kozo Hashimoto†

Zensuke Ota‡

*Okayama University,

†Okayama University,

‡Okayama University,

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Abstract

We made posterior hypothalamic knife cuts in rats to transect the fibers of the medial forebrain bundle (MFB) at the level of the mammillary body. The role of the MFB in the baroreflex and hemorrhage-induced hormonal responses was then examined in the unanesthetized, freely moving condition. The slopes for the relationship between changes in pulse interval and mean arterial pressure (MAP) in the posterior-cut group were significantly steeper than those in the sham-cut group both when there were phenylephrine-induced increases in MAP (1.13 +/- 0.07 vs 0.86 +/- 0.10 msec/mmHg) and nitroprusside-induced decreases in MAP (1.16 +/- 0.10 vs 0.77 +/- 0.05 msec/mmHg). This result indicates that posterior cuts elevated baroreflex sensitivity when MAP was increased or decreased. The resting MAP was not changed, but the resting heart rate (HR) was lowered by the posterior cuts. Furthermore, the posterior cuts augmented hypotensive hemorrhage-induced bradycardia. Hypotensive hemorrhage (16-17 ml/kg) caused elevation of the plasma catecholamine, ACTH and vasopressin (AVP) levels, but the posterior cuts attenuated these hormonal responses. These results indicate that the fibers in the MFB have a tonic inhibitory effect on the baroreflex in the resting condition, and play a stimulatory role in hemorrhage-induced catecholamine, ACTH and AVP responses.

KEYWORDS: medial forebrain bundle, baroreflex, catecholamine, vasopressin, adrenocorticotropic hormone

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Effect of Posterior Hypothalamic Knife Cuts on the Baroreflex and Hemorrhage-Induced Hormonal Responses

Shinya Makino*, Kozo Hashimoto and Zensuke Ota

Third Department of Internal Medicine, Okayama University Medical School, Okayama 700, Japan

We made posterior hypothalamic knife cuts in rats to transect the fibers of the medial forebrain bundle (MFB) at the level of the mammillary body. The role of the MFB in the baroreflex and hemorrhage-induced hormonal responses was then examined in the unanesthetized, freely moving condition. The slopes for the relationship between changes in pulse interval and mean arterial pressure (MAP) in the posterior-cut group were significantly steeper than those in the sham-cut group both when there were phenylephrine-induced increases in MAP (1.13 ± 0.07 vs 0.86 ± 0.10 msec/mmHg) and nitroprusside-induced decreases in MAP (1.16 ± 0.10 vs 0.77 ± 0.05 msec/mmHg). This result indicates that posterior cuts elevated baroreflex sensitivity when MAP was increased or decreased. The resting MAP was not changed, but the resting heart rate (HR) was lowered by the posterior cuts. Furthermore, the posterior cuts augmented hypotensive hemorrhage-induced bradycardia. Hypotensive hemorrhage (16-17 ml/kg) caused elevation of the plasma catecholamine, ACTH and vasopressin (AVP) levels, but the posterior cuts attenuated these hormonal responses. These results indicate that the fibers in the MFB have a tonic inhibitory effect on the baroreflex in the resting condition, and play a stimulatory role in hemorrhage-induced catecholamine, ACTH and AVP responses.

Key words : **medial forebrain bundle, baroreflex, catecholamine, vasopressin, adrenocorticotropic hormone**

The baroreflex is important in compensating for fluctuations in arterial pressure and venous return. Several investigators have examined the role of specific central regions in the baroreflex. Lesions of the nucleus tructus solitarius (NTS) or the ventrolateral medulla (VLM), the components of the primary baroreflex arc, have been reported to reduce baroreflex sensitivity (1-3). Suprabulbar control of the baroreflex has also been examined. However, the central modulation of the baroreflex is so complex that it has not been clarified. The medial forebrain bundle (MFB) is a major pathway connecting the brainstem and the forebrain (4, 5), which contains both ascending and descending projections. Many investigators have reported the role of ascending projections of the MFB in ACTH and vasopressin (AVP) secretion (6, 7). Descending projections seem to be involved in the regulation of sympathetic nervous activity and modulation of the baroreflex.

* To whom correspondence should be addressed.

However, the exact physiological role of the MFB has not yet been determined.

Fibers of the MFB are transected at the level of the mammillary body when posterior hypothalamic knife cuts are made (8). In this study, we examined baroreflex sensitivity after MFB transection to invenstigate the central modulation of the baroreflex. Furthermore, we examined plasma catecholamine, ACTH and AVP responses to hypotensive hemorrhage after transection of the MFB to investigate their role in hemorrhage-induced hormonal responses.

Materials and Methods

Surgical procedures. Male Wister rats (weighing 280–340 g) were used for *in vivo* experiments. The rats were anesthetized with intraperitoneal injection of sodium pentobarbital (Somnopentyl, Pitman-Moore Inc., NJ, USA, 42 mg/kg of body weight) and placed in a stereotaxic instrument. The incisor bar was lowered 3.3 mm from the interaural line. After incision of the scalp, a small hole was made in the skull between the lambda and bregma on the midline. A Halasz-type knife was inserted until its tip was located along the midline 4 mm posterior and 9.5 mm ventral to the bregma. Then it was rotated in a half turn rostrally. The knife was inserted, but not rotated, to produce a sham cut. Rats were caged individually, and received standard rat biscuits and water *ad libitum*. Five or six days later, we inserted a cannula into the femoral artery (PE50 polyethylene tubing; Intramedic, Clay Adams, USA) and the jugular vein (Silastic medical grade tubing; Dow Corning, USA) under pentobarbital anesthesia. The catheters were tunneled under the skin to exit at the nape of the neck.

Baroreflex sensitivity. On the day after cannulation, we examined baroreflex function in conscious, freely moving rats using phenylephrine and nitroprusside. PE50 polyethylene tubes were connected to the arterial and venous cannulas for monitoring arterial pressure and injecting vasoactive agents, respectively. The tube to the arterial cannula was filled with 0.9 % saline containing heparin, sodium salt, (500 U/ml). It was connected via a pressure monitoring kit (SCK-590, Spectramed Medical Products Pte Ltd., Tokyo Japan) to a Nihon Kohden recorder (connection board: RMP-6004, blood pressure amplifier: AP461G, heart rate counter: AT601G, recticorder: WT-625G, Tokyo, Japan) for continuous measurement of the pulsatile arterial pressure and heart rate (HR). The extension tube of the venous cannula was connected to a syringe containing either phenylephrine hydrochloride (PE) (Kowa Co., Japan) or sodium nitroprusside (NP) (Kishida Chemical Co., Japan). Graded doses of PE (3–20 μg/kg/min) or NP (3–12 μg/kg/min) were injected into the jugular vein over 1–2 min using a Harvard infusion pump (model 975, Harvard Apparatus Co., Inc., USA) until arterial pressure had reached a new steady-state level. Peak changes in HR corresponding to peak changes in mean arterial pressure (MAP) were then recorded. At least 30 min were allowed between each dose of PE or NP. The pulse interval (PI) was calculated by dividing 60,000 by the HR (msec/beats/min). The sensitivity of the baroreflex was determined in each rat by using least-squares regression to analyze the relationship between changes in PI (msec) and MAP (mmHg). The slope of the curve obtained was used as an index of baroreflex sensitivity. Individual measurements of reflex sensitivity were averaged and evaluated for statistical comparisons between the posterior-cut and sham-cut groups.

Hypotensive hemorrhage. On the day after the experiment on baroreflex sensitivity, blood was withdrawn extensive enough to cause hypotension in the conscious, freely moving condition. About 1 h prior to the experiment, a PE50 polyethylene tube was connected to the arterial cannula for collecting blood samples and monitoring arterial pressure. The cannula was flushed with heparin-containing saline and suspended outside the cage. Thirty min before induction of hemorrhage, 1 ml of blood was withdrawn from the cannula with a heparinized syringe for AVP assay, followed by replacement with 1 ml of saline. Then the cannula was connected to the pressure monitoring recorder, as described above. Blood was withdrawn (10 ml/kg over 3 min) to simulate hemorrhage, and the first 1.2 ml was collected to determine catecholamine (norepinephrine: NE, epinephrine: E) and ACTH levels. As we had confirmed preliminarily that withdrawal of 1 ml of blood 30 min prior did not affect plasma catecholamine and ACTH levels, the levels in this first 1.2 ml blood sample were regarded as baseline levels. Five min after the induction of hemorrhage, 2 ml of blood was withdrawn over 1.5 min for catecholamine, ACTH and AVP assays, and this was not followed by saline replacement. Thus, each rat was subjected to a "2 step" hemorrhage totalling 16–17 ml/kg of blood. Arterial pressure and HR were monitored until 15 min after the induction of hemorrhage, and then a further 2.5 ml of

blood was collected for catecholamine, ACTH and AVP assays.

Evaluation of the knife cut. Each rat was decapitated at the end of the experiment. The brains were rapidly removed and stored in 20% formalin. The brains were cut into 30 μm sections in the horizontal plane and stained with thionine. We examined whether the MFB was cut properly or not by light microscopy according to the atlas of Paxinos and Watson (9).

Hormone assays. Blood was collected into chilled plastic tubes and centrifuged (1,200 g) at 4°C. Plasma was then stored at −20°C pending assays. Plasma ACTH and AVP concentrations were measured with commercially-available radioimmunoassay kits (ACTH: DPC, Los Angels, USA; AVP: Mitsubishi-Yuka Co., Tokyo, Japan). Plasma catecholamine (NE, E) concentrations were determined by ion-pairing reverse phase high performance liquid chromatography with amperometric detection. The details of this catecholamine assay have been reported elsewhere (10).

Statistical analysis. Values are presented as mean ± SEM. The hemorrhage-induced MAP, HR, and hormonal responses were evaluated by analysis of variance, followed by Duncan's new multiple range test. Statistical analyses of the values for baroreflex sensitivity, resting MAP, resting HR and basal hormonal levels were conducted using Student's t-test.

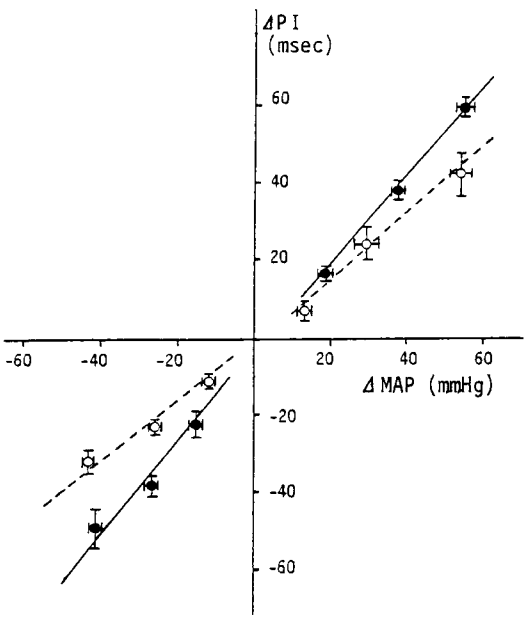

Fig. 1 Reflex changes in pulse interval (PI) in response to increases or decreases in mean arterial pressure (MAP) produced by intravenous injection of phenylephrine or nitroprusside, respectively. Significant differences in reflex control of PI were found by analyzing the slopes of individual regression lines (see Table 1). Values are mean ± SEM. Sham-cut group (n = 9), ○- - -○; posterior-cut group (n = 9), ●——●.

Results

Effect on baroreflex sensitivity. The slopes for the relationship between changes in PI and MAP in the posterior-cut group were significantly steeper than those in the sham-cut group both for PE-induced increases in MAP (1.13 ± 0.07 *vs.* 0.86 ± 0.10 msec/mmHg) and for NP-induce decreases in MAP (1.16 ± 0.10 *vs.* 0.77 ± 0.05 msec/mmHg) (Fig. 1, Table 1). The results indicate that baroreflex sensitivity was elevated by MFB transection when MAP was increased or decreased.

Effect on basal hormone levels and cardiovascular parameters. There was no difference in resting MAP between the sham-cut and

Table 1 Effect of posterior knife cuts on resting mean arterial pressure (MAP), heart rate (HR) and baroreflex responses to phenylephrine-induced MAP increase and nitroprusside-induced MAP decrease in conscious rats[a]

			Phenylephrine		Nitroprusside	
	MAP (mmHg)	HR (beats/min)	Slope (msec/mmHg)	Intercept (msec)	Slope (msec/mmHg)	Intercept (msec)
Sham-cut (n = 9)	104.0 ± 4.3	369 ± 8	0.86 ± 0.10	−2.36 ± 2.71	0.77 ± 0.05	−1.27 ± 0.99
Posterior-cut (n = 9)	106.6 ± 1.3	337 ± 7***	1.13 ± 0.07*	−3.76 ± 2.31	1.16 ± 0.10**	−3.61 ± 2.09

a : Values are means ± SEM. *, $p < 0.02$ *vs.* sham-cut group; **, $p < 0.01$ *vs.* sham-cut group; ***, $p < 0.001$ *vs.* sham-cut group.

posterior-cut groups, while resting HR in the posterior-cut group was significantly lower than that in the sham-cut group (Table 1). The basal levels of NE and E in the posterior-cut group were significantly lower than those in the sham-cut group (Table 2). Basal levels of ACTH and AVP in the posterior-cut group tended to be respectively lower and higher than those in the sham-cut group, although the differences were not statistically significant (Table 2). There was no significant difference in plasma osmolality between the two groups (data not presented).

Effect on hemorrhage-induced MAP and HR responses. Hemorrhage evoked reductions of MAP and HR in both the sham-cut and posterior-cut groups. HR in the posterior-cut group was significantly lower than that in the sham-cut group 7 min after the induction of hemorrhage (Fig. 2).

Effect on hemorrhage-induced hormonal responses. The plasma E level increased both 5 and 15 min after the hypotensive hemorrhage, while a significant elevation of the plasma NE level was seen only at 15 min. The posterior cuts attenuated the plasma E and NE responses to hemorrhage (Fig. 3).

Hypotensive hemorrhage elevated the plasma ACTH level, and the posterior cuts attenuated this hemorrhage-induced ACTH secretion (Fig. 4).

Hypotensive hemorrhage also elevated the plasma AVP level, and the posterior cuts attenuated this AVP secretion, too (Fig. 5).

Discussion

There are three major projections connecting the forebrain and the brainstem: the central tegmental tract (CTT), the dorsal tegmental bundle (DTB) and the dorsal periventricular system

Table 2 Effect of posterior knife cuts on basal hormonal levels in conscious rats[a]

	NE (pg/ml)	E (pg/ml)	ACTH (pg/ml)	AVP (pg/ml)
Sham-cut (n = 10)	153 ± 21	181 ± 24	23.6 ± 2.9	1.15 ± 0.27
Posterior -cut (n = 10)	116 ± 9**	125 ± 19*	18.6 ± 2.8	2.17 ± 0.39

a : Values are means ± SEM. NE, norepinephrine; E, epinephrine; AVP, vasopressin. *, $p < 0.02$ *vs.* sham-cut group; **, $p < 0.001$ *vs.* sham-cut group.

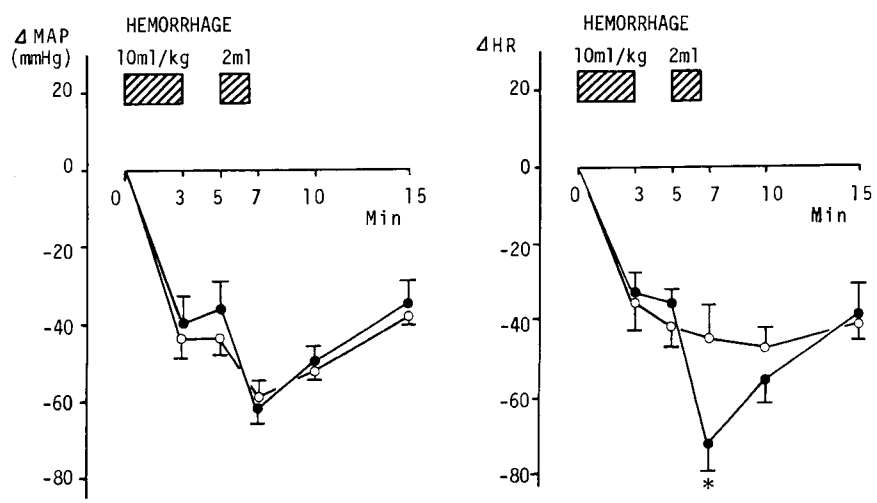

Fig. 2 Effect of posterior knife cuts on the hemorrhage-induced mean arterial pressure (MAP) and heart rate (HR) changes in conscious rats. Values are means ± SEM. *, $p < 0.01$ *vs.* sham-cut group. Sham-cut group (n = 9), ○——○; posterior-cut group (n = 9), ●——●.

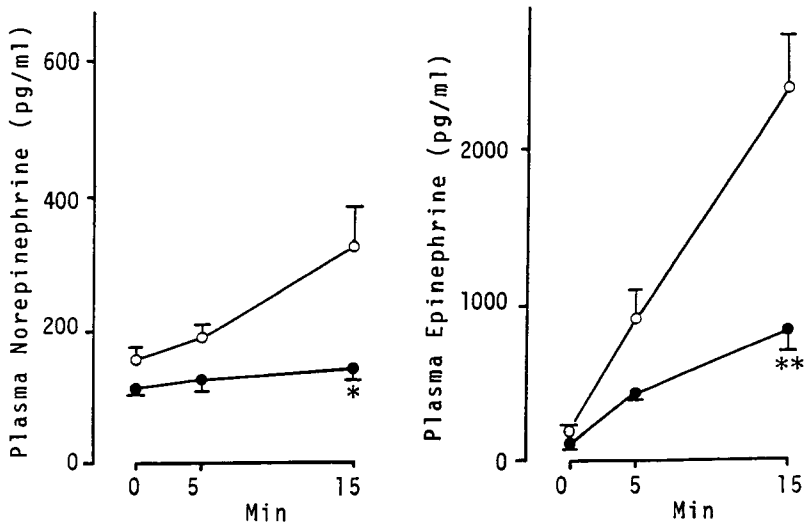

Fig. 3 Effect of posterior knife cuts on the hemorrhage-induced catecholamine secretion in conscious rats. Values are means ± SEM. *, $p < 0.05$ *vs.* sham-cut group ; **, $p < 0.01$ *vs.* sham-cut group. Sham-cut group (n = 10), ○——○; posterior-cut group (n = 10), ●——●.

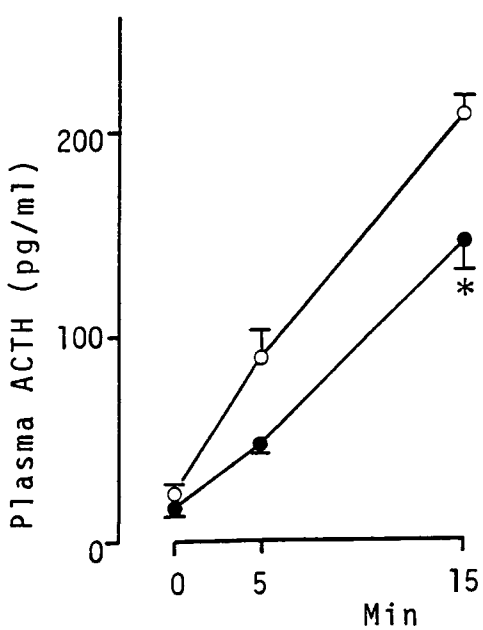

Fig. 4 Effect of posterior knife cuts on the hemorrhage-induced ACTH secretion in conscious rats. Values are means ± SEM. *, $p < 0.01$ *vs.* sham-cut group. Sham-cut group (n = 10), ○——○; posterior-cut group (n = 10), ●——●.

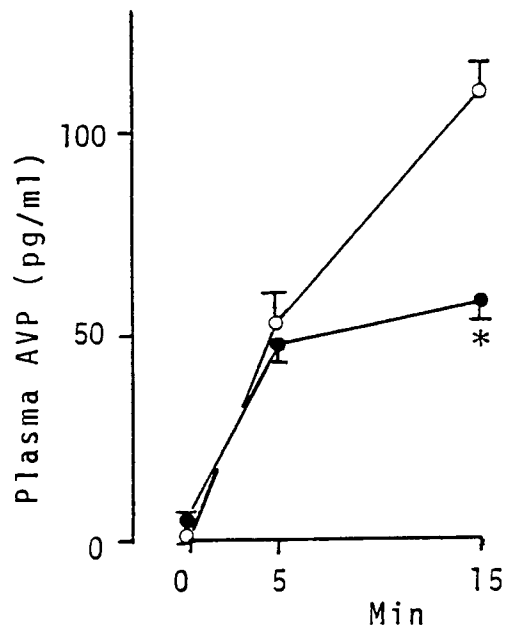

Fig. 5 Effect of posterior knife cuts on the hemorrhage-induced vasopressin (AVP) secretion in conscious rats. Values are means ± SEM. *, $p < 0.05$ *vs.* sham-cut group. Sham-cut group (n = 10), ○——○; posterior-cut group (n = 9), ●——●.

(DPS) (4, 5). The CTT and DTB respectively contain the ventral and dorsal noradrenergic bundle (VNAB and DNAB). The CTT assembles dorsal fibers through the tegmental catecholamine radiation (TR), and forms the MFB system at the meso-diencephalic junction. The DTB joins the MFB at the level of the mammillary body, where the bundle approaches the midline. Our posterior knife cuts involved both the MFB and the DTB. Fig. 6 shows a photomicrograph of a typical lesion. In some cases, cellular infiltration was seen in the posterior area of the thalamus, but not in the hypothalamus. Although a small number of fibers from the DPS joins the MFB via the TR, the DPS mainly runs distant from the MFB along the periventricular

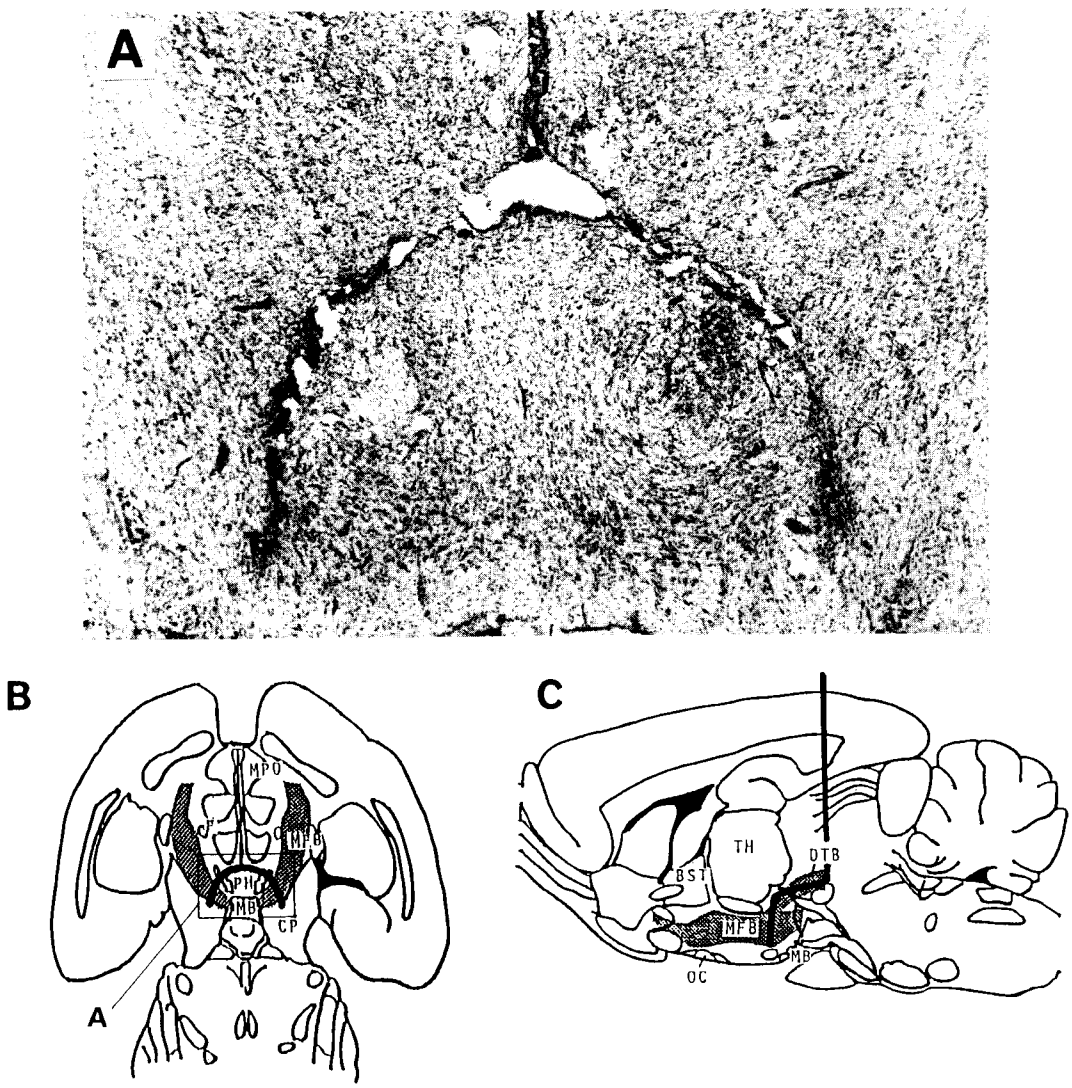

Fig. 6 Photomicrograph showing transection of the medial forebrain bundle in a horizontal section of rat brain (A). Schematic drawings of the horizontal (B) and sagittal (C) planes of a rat brain after posterior hypothalamic knife cuts. The figures are drawn according to Lindvall *et al.* (4), Nieuwenhuys *et al.* (5) and Paxinos and Watson (9). BST, bed nucleus stria terminalis; CP, cerebral peduncle; DTB, dorsal tegmental bundle; F, fornix; MB, mammillary body; MFB, medial forebrain bundle; OC, optic chiasm; PH, posterior hypothalamic area; TH, thalamus.

system and periaqueductal gray matter (4). Therefore, the DPS should be spared by the procedure we used. However, as we made each knife cut slightly more extensive than the MFB, the damage to other pathways cannot be completely excluded.

The structure and mechanism of the primary baroreflex arc have been well established. Lesions of the NTS (1) or the VLM (2, 3), the components of the primary baroreflex arc, are known to diminish baroreflex sensitivity. The suprabulbar mechanisms of the baroreflex have also been studied. Electrical stimulation of the hypothalamic defense area was shown to inhibit the baroreflex (11) and the activity of neurons in the NTS (12, 13). Electrical stimulation of the paraventricular nucleus (PVN) and the supraoptic nucleus (SON) also inhibited bradycardic responses elicited by carotid sinus nerve stimulation (14). On the other hand, lesions of the anterior hypothalamus, the depressor area, were found to reduce the baroreflex sensitivity (15). These experiments suggested that the higher centers might have a depressant effect on the baroreflex response, although it must be kept in mind that these experiment were performed under anesthesia or under unphysiological conditions. Conversely, it has been reported that decerebration at the collicular level does not alter baroreflex sensitivity (2, 16). Darlington *et al.* (17) also found that lesions of the PVN had little or no effect on the baroreflex in conscious rats. Thus, the physiological role of suprabulbar mechanism in the baroreflex remains controversial. We found that MFB transection elevated baroreflex sensitivity and lowered resting HR, whereas there was no effect on resting MAP in unanesthetized, freely moving rats. Several investigators (16, 18) have also reported that resting MAP was maintained in decerebrated rats. There may be functional separation in the brainstem neurons between determining baroreflex responsiveness and maintaining a normal blood pressure (18), and those neurons may have different thresholds to the influences of higher centers. On the other hand, resting HR level and HR responses accompanied by blood pressure changes are assumed to be determined by the balance between sympathetic and parasympathetic cardiac efferent nerve activity (19, 20). Hypothalamic stimulation is reported not only to increase cardiac sympathetic outflow but also to inhibit baroreflex-induced vagal activation (21). The reason why resting HR was lowered by MFB transection may be that a relative increase in parasympathetic outflow was caused by the elimination of the influence of the higher centers. The same increase in parasympathetic outflow may also be responsible for the augmented bradycardic responses to PE-induced hypertension in posterior cut rats. However, it is difficult to explain the augmentation of tachycardic responses to NP-induced hypotension by posterior cuts simply by this reason. Central modulation of baroreflex-mediated HR control is more complicated. Unlike previous reports (18, 22, 23), it is possible that higher centers might have a reciprocal effect to attenuate the cardiac sympathetic response and/or relatively increase parasymathetic outflow when MAP decreased. Anyway, the results suggest that the higher centers as a whole have a tonic inhibitory influence on the baroreflex control of HR responses both to PE-induced hypertension and to NP-induced hypotension in resting and physiological conditions, and that this effect is mediated at least partially through the MFB.

Recently, it has been reported that angiotensin II (22, 24), AVP (23, 25) and corticotropin-releasing factor (26) may play some roles in central modulation of the baroreflex. It is possible that the excitation of higher centers evoked by these neuropeptides may be transmitted via the MFB to the brainstem to inhibit the baroreflex. In fact, it has been demonstrated that stressful stimuli can induce hypertension with a reduction in baroreflex sensitivity in man (27). However, further study is necessary to clarify the role of the MFB under conditions of stress in which the higher centers are excited. The role of the DPS and possible interactions between the MFB and

the DPS also need to be clarified.

It is known that hypotensive hemorrhage evokes elevation of plasma catecholamine (especially E) levels (17), and a reduction in HR and renal nerve activity (RNA) (28, 29). Recently Victor *et al.* (30) observed that hypotensive hemorrhage evoked a reduction in RNA and an increase in adrenal nerve activity which resulted in catecholamine elevation. This may indicate that there are different reflex controls of regional sympathetic outflow which produce a complex and differentiated autonomic response to different organs in hypotensive hemorrhage. The fall of HR and RNA might be one of the protective reflex mechanisms which serve to keep effective regional blood flow (30). In this study, hypotensive hemorrhage evoked a decrease in HR and an elevation of plasma catecholamine (especially E) levels in sham-operated rats. Reduction in HR and elevation of plasma catecholamine by hypotensive hemorrhage was also seen in posterior-cut rats. However, the posterior cuts attenuated catecholamine secretion and augmented hemorrhage-induced bradycardia. Although we did not measure RNA, these results indicate that differential reflex control of regional sympathetic outflow may be primarily produced in lower centers in the brainstem, and that higher centers might have additional effects on such reflex control of regional sympathetic outflow. Furthermore, the catecholamine response was not completely suppressed in the posterior-cut rats. Two possible mechanisms could be responsible for this result. Firstly, lower centers in the brainstem may maintain hemorrhage-induced sympathetic outflow to some extent without the aid of higher centers. Secondly, if higher centers mainly integrate sympathetic activation, the DPS may play some role in the modulation of hemorrhage-induced sympathetic activation. Although many areas are known to be involved in suprabulbar cardiovascular regulation (31), we cannot conclude which is the anatomical location of higher centers from the results of this study. Further work is necessary to fully clarify suprabulbar mechanisms.

Hypothalamic corticotropin-releasing hormone (CRH) neurons are known to be controlled by catecholaminergic neurons. The origin of catecholaminergic neurons which innervate the PVN is the brainstem, and approximately 90 % of its fibers ascend in the VNAB (32). Many investigators have examined whether its effect is stimulatory or inhibitory (33), but the results remain controversial. We have previously found that catecholaminergic pathways may stimulate CRH-ACTH secretion via α-adrenergic mechanisms (34). Szafarczyk *et al.* (7) found that VNAB lesions reduced catecholamine concentrations in the hypothalamus and inhibited the ACTH response induced by ether stress. Murakami *et al.* (8) also demonstrated that the same posterior cuts as ours reduced the catecholamine concentration in the hypothalamus and attenuated ACTH responses induced by ether or immobilization stress. In this study, we found that posterior cuts attenuated hemorrhage-induced ACTH secretion, possibly indicating that catecholaminergic fibers ascending in the MFB have a stimulatory role in this respect. However, there are several problems with this conclusion. The first one is that this MFB transection was also assumed to involve the serotonergic fibers from the raphe nuclei. As the brain serotonergic system could affect CRH secretion (35), we cannot exclude the influence of this system on hemorrhage-induced ACTH secretion. The second problem is that ascending catecholaminergic fibers terminate not only in the parvocellular part in the PVN but also in the magnocellular part and the median eminence (36). It is still not clear whether hemorrhage-induced ACTH secretion is mediated by stimulation of CRH or AVP neurons in the PVN, or by release of CRH or AVP from the median eminence. The third problem is that a high level of circulating catecholamines may influence ACTH secretion at the pituitary level, and this issue also remains to be decided one way or another (33, 35). All these problems requires further investigation. At present, it is only

possible to say that ascending fibers in the MFB may stimulate hemorrhage-induced ACTH secretion.

Under resting conditions, baroreceptors are known to exert a tonic inhibitory influence on AVP secretion (37). Denervation of baroreceptor afferents and lesions of the NTS or VLM can markedly elevate the plasma AVP level (37–39). In the present study, the basal AVP level was slightly higher in the posterior-cut group than in the sham-cut group. Although this difference was not statistically significant, posterior cuts might attenuate a tonic inhibitory influence on basal AVP secretion. On the other hand, the noradrenergic fibers which innervate AVP-secreting cells in the PVN and the SON are reported to originate almost exclusively from the A1 cell group located in the caudal VLM (32). The functional role of ascending noradrenergic fibers in AVP secretion is still controversial. However, there is increasing evidence that they have a stimulatory effect (40–43). Lightman *et al.* (6) also found that lesions of the DNAB attenuated the release of AVP during mild hemorrhage. In this study, we found that posterior cuts attenuated hemorrhage-induced AVP secretion, suggesting that ascending fibers in the MFB have a stimulatory role and supporting previous reports.

In conclusion, the fibers in the MFB have a tonic inhibitory effect on the baroreflex at least under resting conditions, and play a stimulatory role in the hemorrhage-induced secretion of catecholamines, ACTH and AVP.

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