Pressor Responses to Hypothalamic Stimulation at Various Sinus Pressures in the Rabbit

M. Nagai and M. Iriki

Department of Physiology, Medical University of Yamanashi, Tamaho, Nakakoma, 409-38 Yamanashi, Japan

Abstract: The functional correlation between hypothalamic pressor inputs and baroreceptor inputs in controlling blood pressure was analysed employing a blind-sack preparation of the carotid sinus and electrical stimulation of a pressor area in the posterior hypothalamus. The peak blood pressure values induced by electrical stimulation of the hypothalamus with parameters causing maximal response were nearly independent of the resting blood pressure set by carotid sinus pressure. When the intensity of hypothalamic stimulation was decreased, the resulting pressure responses were positively correlated with the level of blood pressure set by blind-sack pressure. Renal sympathetic nerve activity (RSNA) at rest was well correlated with resting blood pressure. This correlation was, however, less evident during hypothalamic stimulation, indicating involvement of a nonvasoconstricting component in renal sympathetic innervation.

Key words: Hypothalamus, Carotid sinus, Renal sympathetic nerve activity, Blood pressure, Blind-sack pressure

INTRODUCTION

Various pressor and depressor sites have been identified using electrical stimulation of the hypothalamus, some of the sites were shown to be involved in specialized cardiovascular responses, for example, in sympathetic cholinergic vasodilation underlying the defence reaction. At the same time, the hypothalamus provides one of the integrative centres for blood pressure regulation, since both anterior and posterior hypothalamic areas receive barosensor input from arterial baroreceptors. Accordingly, lesions in the hypothalamic region impair the full range of baroreceptor reflex control of arterial pressure. Thus, the hypothalamus apparently serves two functions in blood pressure control: it provides intrinsic pressor and depressor effects associated with its diverse integrative functions, and it acts as a relay site in feedback control. However, it is not clearly understood how these two functions interact.

The present study was an analysis of the functional correlation between hypothalamic pressor input and carotid sinus baroreceptor input in blood pressure control. For this study, the effects of the combined manipulation of a blind-sack preparation of the carotid sinus and electrical stimulation of a pressor area in the posterior hypothalamus on arterial pressure responses and renal sympathetic nerve activity were analysed.
MATERIAL AND METHODS

The experiments were performed on Japanese white rabbits weighing 2.4–3.3 kg. The animals were initially anaesthetized with sodium pentobarbital, 30 mg/kg iv, and 14 mg/animal/h was continuously perfused as a supplemental dose through the femoral vein. A tracheal cannula was inserted, and artificial ventilation maintained with a Starling pump after the animal has been initially immobilized with succinylcholine, 40 mg/animal iv. The succinylcholine was continued at a dose of 18 mg/animal/h.

Arterial blood pressure was measured in the femoral artery, and mean arterial blood pressure (MAP) was calculated as

\[
MAP = \frac{BP + 1}{3}(BP - BP) \text{ diast. syst. diast.}
\]

Electrical activities of the renal nerve bundle were recorded with a bipolar Pt-electrode. Mass discharges were displayed on an oscilloscope (NIHON KODEN, VC-7) with a direct visual observation and simultaneously averaged over 1 sec intervals with an integrator (NIHON KODEN, RF-J-5). The averaged value of the renal nerve activity was evaluated by its height on the recording paper in mV. Rectal temperature was continuously measured with a thermistor probe. The animals were placed on a heating pad. The pad and room temperatures were adjusted to maintain body temperature between 37 and 39°C during the experiments.

A blind-sack preparation of one carotid sinus was prepared by ligating the internal and external carotid arteries on the left side, and a cannula connected to a reservoir filled with heparinized saline was inserted into the left common carotid artery. In some animals, small arteries in the vicinity of the carotid bifurcation were also ligated to make the blind-sack complete. The right-side carotid sinus was denervated, and the aortic nerves were bilaterally transected. Blind-sack pressure was controlled by means of a Hg-manometer connected to the reservoir. By adjusting blind-sack pressure, mean arterial pressure could be controlled at several different constant levels ranging from 121.7 to 34.6 mmHg.

The head of the animal was fixed in a stereotaxic device, and stainless steel concentric bipolar electrodes (Rhodos Medical Instruments, NEX-100) were inserted into the hypothalamus according to the stereotaxic coordinates given by Sawyer et al. (1954). To obtain the maximal pressor response, the electrode tip was micropositioned and the parameters of electrical stimulation were adjusted accordingly. In general, maximal responses were obtained by stimulation at 60–80 Hz with rectangular pulses, 0.5–0.6 msec in duration and 3.0–3.5 V in amplitude. To ascertain the site of stimulation, the brain was perfused with 10% formalin in situ after each experiment. Successive transverse sections were made with a freezing microtome and stained by the Klüver-Barrera method.

RESULTS

Electrical stimulation of the medial part of posterior hypothalamus was performed at various levels of blood pressure set by changing the sinus pressure in six rabbits. Sites and parameters of stimulation were adjusted so that maximal increases in blood pressure were evoked. Original recordings of blood pressure and renal sympathetic nerve activity (RSNA) are shown in Figure 1. Both blood pressure and RSNA were increased by electrical stimulation of a hypothalamic pressor area. While peak responses of blood pressure were not affected by pre-set levels of resting blood
Contribution of the Hypothalamic Rovulcula to the Carotic Sinus Pressor Responses

Fig. 1. Effects of hypothalamic stimulation on blood pressure (BP) and renal sympathetic nerve activity (RSNA) at various resting blood pressures controlled by changing the sinus pressure.

Left: BP (upper trace), RSNA (lower trace); Resting blood pressure was 50.0, 61.5, 73.1 and 88.5 mmHg from Left to right. Parameters of hypothalamic stimulation were 60 Hz, 0.5 msec, 3 V.

Right: Peak values of BP pressure and RSNA in relation to resting BP.

Table 1. Resting and peak values of blood pressure and RSNA at various sinus pressure levels. Means and standard errors are shown.

<table>
<thead>
<tr>
<th>Range of rest. BP</th>
<th>Sinus Pressure (mm Hg)</th>
<th>BP (mm Hg)</th>
<th>RSNA (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>rest.</td>
<td>max.</td>
</tr>
<tr>
<td>I. 40–49</td>
<td>125.7 ± 7.8</td>
<td>45.7 ± 0.8</td>
<td>146.8 ± 5.2</td>
</tr>
<tr>
<td>II. 50–59</td>
<td>117.5 ± 7.4</td>
<td>53.4 ± 1.0</td>
<td>146.1 ± 4.1</td>
</tr>
<tr>
<td>III. 60–69</td>
<td>102.5 ± 5.6</td>
<td>65.1 ± 0.4</td>
<td>149.9 ± 5.1</td>
</tr>
<tr>
<td>IV. 70–79</td>
<td>87.5 ± 4.1</td>
<td>75.0 ± 0.6</td>
<td>155.0 ± 3.3</td>
</tr>
<tr>
<td>V. 80–89</td>
<td>66.5 ± 4.5</td>
<td>85.1 ± 0.7</td>
<td>150.3 ± 5.5</td>
</tr>
<tr>
<td>VI. 90–99</td>
<td>45.0 ± 13.0</td>
<td>92.8 ± 0.9</td>
<td>152.2 ± 6.9</td>
</tr>
</tbody>
</table>

pressure, the peak of the RSNA response values varied and did not demonstrate a consistent relationship to resting blood pressure.

Table 1 summarizes the resting and peak response values for blood pressure and RSNA at various sinus pressure levels obtained from all rabbits examined. The resting blood pressure data were grouped into six, 10 mmHg ranges that were controlled by sinus pressure. Data from three trials obtained when the resting blood pressure was lower than 40 mmHg or higher than 100 mmHg were excluded for reasons of statistical analysis. A negative correlation between sinus pressure and resting blood pressure could be seen, however, the maximum blood pressure response values did not correlate with sinus pressure or with resting blood pressure. The average mean and the standard error of the peak blood pressure responses were 150.1 ± 1.7 mmHg; the peak pressure response values at different sinus and resting blood pressure levels did not differ statistically. Similarly, RSNA at rest revealed a
positive correlation with resting blood pressure, however, peak RSNA responses values did not differ statistically.

The differences between peak and resting blood pressures, i.e., the amplitude of the blood pressure increases, are demonstrated as a function of resting blood pressure in Figure 2A. The response amplitudes decreased as resting blood pressure increased. This corresponds to the stable peak response values shown in Figure 1 and Table 1. In contrast, the amplitudes of RSNA responses (dRSNA in the Figure) were distributed randomly and were independent of resting blood pressure (Fig. 2B), although resting blood pressure and resting RSNA at rest showed a positive correlation (Fig. 2C, Table 1). This was also observed when the absolute values of RSNA were evaluated. Resting RSNA varied from 0.03 to 0.45 mV in integrated values per minute, and peak RSNA values during hypothalamic stimulation were 0.99-3.18 mV. However, since the absolute resting RSNA values were too small to affect peak response values in many cases, a positive correlation between dRSNA at rest and blood pressure does not appear in the relationship between blood pressure and dRSNA in Figure 2C. On the otherhand, the ratio between the amplitude of blood pressure responses and of RSNA responses (dBP/dRSNA in Fig. 2D) decreased as resting blood pressure increased.

Fig. 2. Amplitudes of blood pressure responses (A) and RSNA (B), RSNA at rest (C) the ratio between amplitudes of blood pressure and RSNA (D) at various resting blood pressures.
In three rabbits the parameters of stimulation applied to the hypothalamic pressor area were reduced so as to cause submaximal increases in blood pressure. Figure 3 shows original recordings of blood pressure and RSNA. The fifth trace on the right demonstrates the maximal blood pressure response induced in the same animal by hypothalamic stimulation of 60 Hz, 0.5 msec and 3 V. Decreasing the intensity of stimulation to 40 Hz, 0.5 msec and 2 V resulted in the submaximal response shown in the four traces on the left. When submaximal stimulation was used, peak blood pressure response values increased with resting blood pressure, and the RSNA response showed the same tendency; this is summarized on the far right of Figure 3.

Histological examination revealed that the sites causing pressor responses were located in the medial part, within 1.5 mm of the midline, of the posterior hypothalamus; corresponding AP 0 to P2 according to the stereotaxic coordinates by Sawyer et al. (1954). The depth below the cortical surface was 12–14 mm. Except for one site in the nucleus paraventricularis, these active sites were located in the dorsal hypothalamic area.

DISCUSSION

The results of the present experiment can be summarized as follows: 1) Peak blood pressure values increases during maximal hypothalamic pressor stimulation were independent of the resting blood pressure set by sinus pressure (Table 1, Fig. 1); no algebraic summation between hypothalamic pressor input and baroreceptor input was found. 2) At submaximal hypothalamic pressor stimulation, inputs from the hypothalamus and the carotid sinus were additive (Fig. 3). With regard to RSNA the same relationships were observed. These results indicate an occlusion like phenomenon exists in the interaction between pressor neurone pools con-
trolled by baroreceptor afferents and the pressor neurones of hypothalamic origin. Accordingly, the lower level of autonomic efferents in the central nervous axis may be considered as a functional unit with a definite number of neurons, upon which descending constrictor inputs converge before they are conducted into preganglionic pathways. In such a neurone pool, presynaptic connections to neurones receiving constrictor input from the hypothalamus and input from neurones under baroreceptor control should overlap to a certain extent. If the activating input from each pool were sufficiently strong, this would account for the occlusion phenomenon.

In this experiment the sites causing blood pressure increases were located in the dorsomedial portion of the posterior hypothalamus. This area initiates the intrinsic pressor pathway of the hypothalamus. In case of electrical stimulation of the hypothalamic pressor area, it is difficult to identify the cause of pressor responses, because generally, increase heart muscle contractility, vasoconstriction and cardiac acceleration occur together as a complex responding to pressor stimuli. On the other hand, blood pressure changes due to baroreceptor stimulation are primarily caused by changes in vasoconstrictor tone; the change in cardiac output is small. Resting renal sympathetic nerve activity (RSNA) was well correlated with resting blood pressure in the present experiments (Fig. 2C); during maximal hypothalamic stimulation, however, there was no correlation between RSNA and blood pressure (Fig. 1, Fig. 2D). This indicates that sympathetic functions other than vasoconstriction participate in the blood pressure increase during hypothalamic stimulation.

In general, pressor responses accompanied by psychomotor behaviour, i.e., activation of the higher brain, seem to be independent of baroreceptor reflex. Riedel and Peter (1977) have shown the fibre group in the renal sympathetic efferents acts independent of the baroreceptor input that occurs during a blood pressure increase resulting from the central action of angiotensin II, although the same fibre group responds to baroreceptor input so long as an activation of the higher brain is not involved. The present results, however, have shown that summation of pressor inputs from the baroreceptors and the hypothalamus does occur to a certain extent.

Acknowledgement

We express thanks to Miss Junko Yamagata for her excellent secretarial assistance.

References


Contribution of the Hypothalamus and the Carotid Sinus in Pressor Responses

永井 正則，入来正利
山梨医科大学第一生理学教室

抄録：血圧調節に関して視床下部昇圧域からの入力と頸動脈洞圧受容器入力の相互関連を、腎交感神経遠心枝の活動を指標として検討した。実験にはペットバレピタール麻酔し、サクシニルコリンで不動化したウサギを用いた。一側の頸動脈分岐部の管壁標本を作成し、大動脈神経を両側で切断したうえで、頸動脈洞圧を任意に変化させ、体循環圧を様々なレベルに設定した。体循環圧の各レベルで視床下部内側の昇圧域の電気刺激を行ない、腎交感神経遠心枝の活動性的変化を観察した。以下の結果が得られた。①静止時の体循環圧と腎交感神経活動との関には正の相関が見られた。②視床下部昇圧域の電気刺激が一定強度以下の場合、刺激中の血圧値は静止時の体循環圧が高い程高かった。すなわち、尿受容器入力と視床下部入力の間に加算の関係が見られた。腎交感神経活動性についても同様であった。③視床下部刺激が最大反応を起こす強さの場合、刺激後の血圧値と腎交感神経活動性は、刺激前の体循環圧のレベルにかかわらず一定で、尿受容器入力と視床下部入力との加算効果は消失した。視床下部等の高位中枢の興奮によって起こる昇圧反応中は血圧反射は作用しないことが多いが、今回の実験結果は、一場強度以下の刺激では視床下部昇圧域からの入力と尿受容器入力が加算的に腎交感神経活動を変化させることが分かった。

キーワード：視床下部、頸動脈洞、腎交感神経活動、血圧、盲管法