There is considerable evidence that α-adrenergic mechanisms within medulla and hypothalamus play a role in cardiovascular regulation (1–4). Apart from the action on medullary mechanisms, clonidine has been reported to elicit hypotension by an action on hypothalamic α-adrenergic receptors and the possible mechanism of action of the drug applied into the hypothalamus has hitherto been discussed in relation to the descending pathways from the hypothalamus to the medullary cardiovascular control system (3, 5–8). Contrary to this, there has been no available report referring to an effect of clonidine on the ascending noradrenergic pathway from the locus coeruleus (LC) to the posterior hypothalamus (HPA), which is assumed to be involved in regulation of arterial blood pressure (9, 10). In addition, it is not clear whether clonidine acts either as an α-adrenergic agonist at the presynaptic receptor or as an α-adrenergic antagonist at the postsynaptic receptor (3, 11).

Guanfacine, N-amidino-2-(2,6-dichlorophenyl) acetamide HCl, which resembles clonidine in chemical structure, appears to produce its hypotensive effects as a result of presynaptic α-adrenoceptor stimulation at central sympathetic control systems, though the possible site of central action of the drug has not yet been defined (12, 13). Thus, it was of interest to investigate an effect of clonidine and guanfacine injected into HPA on the pressor response to electrical stimulation of the LC.

Cats of either sex weighing 2.2–3.5 kg were anesthetized with α-chloralose-urethane. After tracheotomy, the left carotid artery was catheterized for measurement of the blood pressure with a pressure transducer. A coaxial electrode was stereotaxically inserted into right or left LC (P2, L2, H-2) according to the atlas of Berman (14) for electrical stimulation with square wave pulses of 1 msec duration at 250 Hz, 3–5 V for 10 sec. Before the drug application, the LC was stimulated electrically three or four times every 10 min to elicit nearly a constant pressor response (a rise of the mean arterial blood pressure), and three pressor responses were averaged for the control. Then, a drug solution was injected into HPA (F 9.5, L 0.8, H -2.5) at a rate of 1 µl/30 sec with a microsyringe of 1 µl introduced through the guide cannula which was cemented to the skull, and the LC was stimulated to evoke a pressor response 10, 30, 60 and 90 min after injection. The drug effect was estimated by comparing the pressor responses before and after injection and statistical significance was calculated by using Student's t-test. Drugs used were noradrenaline (NA), phentolamine, clonidine and guanfacine.

In preliminary experiments, NA, phentolamine, clonidine and guanfacine each in a variety of doses were stereotaxically injected into HPA and their effects on the mean
arterial blood pressure were observed for 2 hours to determine the dose of each drug to be applied in stimulation experiments as follows: 32 nM for NA, 71 nM for phentolamine, 32 nM for clonidine and 100 nM for guanfacine.

Prior to every experiment, electrical stimulation of the LC of the cat was adjusted to evoke a rise of the mean arterial blood pressure by 40–50 mmHg, and then the control pressor responses were recorded three or four times. Lesion of HPA with 99.5% ethanol significantly diminished the pressor response to electrical stimulation of the ipsilateral LC. Microinjection of 0.9% NaCl solution into HPA did not produce any significant changes in the pressor responses to stimulation of the LC. After application of 32 nM of NA into the HPA, the pressor response to the LC stimulation was increased significantly from the control 42.8±2.9 mmHg to 55.4±2.4 mmHg (29.1%) at the maximum. Phenolamine in a dose of 71 nM reduced the pressor response to the LC stimulation from 40.6±2.3 to 36.8±1.5 mmHg (9.3%), but not significantly. Clonidine in a dose of 32 nM reduced the pressor response to the LC stimulation significantly from 45.0±1.2 to 32.9±1.5 mmHg (26.8%). Guanfacine in a dose of 100 nM also reduced the pressor response to the LC stimulation significantly from 44.4±1.7 to 38.0±2.1 mmHg (14.4%) (Table 1 and Fig. 1). Next an attempt was made to determine the effects of 99.5% ethanol and 32 nM of clonidine injected locally into HPA on the pressor response to electrical stimulation of the ipsilateral and the contralateral LC. A hundred µl of 99.5% ethanol reduced the pressor response to electrical stimulation of the ipsilateral LC much more significantly (from 46.4±1.6 to 30.6±2.0 mmHg in an average of 6 experiments) than that to stimulation of the contralateral LC (from 46.5±1.3 to 40.5±1.4 mmHg). Clonidine in a dose of 32 nM also reduced the pressor response to the ipsilateral LC stimulation more significantly (from 45.0±1.2 to 32.9±1.5 mmHg in an average of 7 experiments) than that to the contralateral LC stimulation (from 43.4±0.8 to 39.1±0.7 mmHg). A statistically significant difference existed between inhibition of the pressor response to the ipsilateral LC stimulation and that to the contralateral one by ethanol and clonidine applied into HPA, respectively.

Previously Philippu et al. showed that superfusion of the HPA with high concentrations of clonidine reduced the pressor response to electrical stimulation of the area, and concluded that inhibition of the pressor response with clonidine might be in part due to inhibition of NA release through some negative feedback mechanism in the hypothalamus (5). In the present experiments NA

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (nM)</th>
<th>Control (mmHg)</th>
<th>10 (mmHg)</th>
<th>30 (mmHg)</th>
<th>60 (mmHg)</th>
<th>90 (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.9% NaCl</td>
<td>42.9±1.2</td>
<td>40.0±1.6</td>
<td>43.5±1.4</td>
<td>44.7±0.8</td>
<td>44.4±0.9</td>
<td></td>
</tr>
<tr>
<td>Noradrenaline</td>
<td>32</td>
<td>42.8±2.9</td>
<td>47.3±2.4</td>
<td>51.7±2.4*</td>
<td>55.4±2.4**</td>
<td>53.7±2.1**</td>
</tr>
<tr>
<td>Phenolamine</td>
<td>71</td>
<td>40.6±2.3</td>
<td>37.5±2.6</td>
<td>37.8±1.8</td>
<td>36.8±1.5</td>
<td>37.6±1.2</td>
</tr>
<tr>
<td>Clonidine</td>
<td>32</td>
<td>45.0±1.2</td>
<td>38.6±1.7*</td>
<td>32.9±1.5**</td>
<td>38.6±2.0**</td>
<td>39.9±1.8*</td>
</tr>
<tr>
<td>Guanfacine</td>
<td>100</td>
<td>44.4±1.7</td>
<td>41.4±1.9</td>
<td>38.0±2.1*</td>
<td>41.4±2.3</td>
<td>41.5±2.7</td>
</tr>
</tbody>
</table>

Results are expressed as the mean of rise in arterial blood pressure±S.E.M. The number of experiments is shown in parenthesis. Statistical differences between the control pressor response and the pressor response after drug injection are represented by *P<0.05 and **P<0.01.
given into the HPA significantly increased the pressor response to electrical stimulation of LC, while clonidine, as well as guanfacine which is considered to be a presynaptic $\alpha$-adrenergic agonist (13), reduced it significantly. Therefore, it seems probable that clonidine and guanfacine act at least as an $\alpha$-adrenergic agonist at the presynaptic receptor to induce a diminished release of NA from the nerve endings of the ascending noradrenergic fibers from LC to HPA and to elicit inhibition of the pressor response to stimulation of the LC. On the other hand, the pressor response to the LC stimulation remained inhibited, not significantly, but slightly, after pretreatment with phentolamine. The failure of phentolamine to inhibit the pressor response significantly remains inexplicable until more detailed experiments can be carried out.

The pressor response to stimulation of the LC was much more significantly reduced by ethanol and clonidine injected into the ipsilateral HPA than by these drugs applied into the contralateral HPA. Therefore, it seems very probable that the ipsilateral control of noradrenergic neurons ascending from LC to HPA, which may be involved in the hypothalamic regulation of the arterial blood pressure, predominates over the contralateral control. This view is supported by the findings of Philippu et al. (15) that the release of NA in HPA was increased to a higher extent on stimulation of the ipsilateral LC than on stimulation of the contralateral LC.

REFERENCES
2) Palkovitz, M. and Zaborszy, L.: Progress in


