Modulation of the baroreceptor reflex by the dorsomedial hypothalamic nucleus and perifornical area

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McDowall, Lachlan M., Jouji Horiuchi, Suzanne Killinger, and Roger A. L. Dampney. Modulation of the baroreceptor reflex by the dorsomedial hypothalamic nucleus and perifornical area. Am J Physiol Regul Integr Comp Physiol 290: R1020–R1026, 2006. First published November 10, 2005; doi:10.1152/ajpregu.00541.2005.—Neurons within the dorsomedial hypothalamic nucleus (DMH) and perifornical area (PeF), which lie within the classic hypothalamic defense area, subserve the cardiovascular response to psychological stress. Previous studies have shown that electrical stimulation of the hypothalamic defense area causes inhibition of the cardiac and (in some cases) sympathetic components of the baroreceptor reflex. In contrast, naturally evoked psychological stress does not appear to be associated with such inhibition. In this study, we tested the effect of specific activation of neurons within the DMH and PeF on the baroreflex control of renal sympathetic nerve activity and heart rate in urethane-anesthetized rats. Microinjection of bicuculline (a GABA receptor antagonist) into the DMH caused dose-dependent increases in heart rate and renal sympathetic activity, shifted the baroreflex control of both variables to higher levels (i.e., increased the upper and lower plateaus of the baroreflex function curves, and increased the threshold, midpoint, and saturation levels of mean arterial pressure). The maximum gain of the sympathetic component of the baroreflex was also increased, while that of the cardiac component was not significantly changed. Increases in the midpoint were very similar in magnitude to the evoked increases in baseline mean arterial pressure. Microinjection of bicuculline into the PeF evoked very similar effects. The results indicate that disinhibition of neurons in the DMH/PeF region not only increases sympathetic vasomotor activity and heart rate but also resets the baroreceptor reflex such that it remains effective, without any decrease in sensitivity, over a higher operating range of arterial pressure.

baroreflex resetting; arterial pressure; renal sympathetic nerve activity; heart rate; stress

Acute psychological stress is known to evoke an integrated pattern of behavioral, neuroendocrine, and autonomic responses. For example, air-jet stress results in an increase in arterial blood pressure and heart rate (HR), together with anxiety-like behavior and increased secretion of ACTH (7, 20, 23, 26, 27). A substantial body of evidence indicates that the dorsomedial hypothalamic nucleus (DMH) plays a critical role in mediating these responses. In particular, inhibition of the DMH has been shown to greatly reduce the pressor response and tachycardia, as well as the increase in ACTH secretion and anxiety-like behavior, normally evoked by acute psychological stress (14, 17, 23, 26, 27) in conscious rats. Furthermore, acute psychological stress has also been shown to increase the level of c-fos expression in the DMH (1, 14, 28). The DMH, as well as the perifornical area (PeF), located more laterally, is part of the classical “hypothalamic defense area” (30), which was so named because stimulation of this region evokes a pattern of autonomic and behavioral changes that are typically observed when an animal is confronted with a threatening stimulus (for reviews see Refs. 5 and 9). The cardiovascular changes include increases in arterial pressure, HR, sympathetic nerve activity (RSNA), and skeletal muscle blood flow (3). As Hilton pointed out many years ago (8), the simultaneous increases in arterial blood pressure, HR, and sympathetic vasomotor activity imply modulation of the baroreceptor reflex control of HR and sympathetic vasomotor activity. Coote et al. (3) found that electrical stimulation of sites within the hypothalamic defense area in the anesthetized cat completely suppressed the reflex sympathoinhibition and bradycardia that are normally evoked by stimulation of baroreceptor afferent fibers. Consistent with these observations, it has also been shown that electrical stimulation of this region in the anesthetized cat inhibits neurons within the nucleus tractus solitarius (NTS) that normally receive an excitatory input from carotid sinus baroreceptors (15). This inhibition is mediated by GABA receptors (12). Similarly, Sévoz-Couche et al. (21) also reported that electrical stimulation of the DMH (which, as mentioned above, is within the hypothalamic defense area) in the anesthetized rat also greatly inhibits baroreflex bradycardia via GABAergic inhibition of NTS neurons. Such observations have led to the view that powerful inhibition of the baroreceptor reflex is an integral component of the cardiovascular changes evoked by activation of neurons within the hypothalamic defense area, including the DMH (9, 15, 21).

In contrast, however, studies in conscious rats and rabbits indicate that stress-evoked increases in arterial pressure and HR are accompanied by a resetting, rather than an inhibition, of the baroreceptor reflex (7, 20). In these studies, the baroreceptor reflex control of HR was reset to higher levels of arterial pressure with no reduction in the gain of the reflex. Similarly, Miki et al. (16) also found that the baroreflex control of HR and RSNA during exercise in the conscious rat was also reset to higher levels of arterial pressure without a reduction in gain.

Perhaps suppression of the baroreceptor reflex by electrical stimulation of the hypothalamic defense area (including the DMH), which is not observed during naturally evoked stress responses, is due to activation of fibers passing through the region, rather than activation of neurons within the region. It is well known that disinhibition of neurons within the DMH evokes cardiovascular changes typical of defensive behavior (including increases in arterial pressure, HR, RSNA, and skel-
etal muscle blood flow) (4, 5, 6, 11), but the effect of this stimulus on the operation of the baroreceptor reflex is not known. The purpose of this study, therefore, was to answer this question by determining the relation between induced changes in arterial pressure and reflex changes in RSNA and HR before and after disinhibition of neurons in the DMH and PeF over the full operating range of the baroreflex.

MATERIALS AND METHODS

General procedures. Male Sprague-Dawley rats (420 ± 16 g, 9–10 wk old) were supplied by the University of Sydney Laboratory of Animal Services. All experimental procedures were approved by the Animal Ethics Committee of the University of Sydney and were carried out in accordance with the guidelines for animal experimentation of the National Health and Medical Research Council of Australia. Anesthesia was initially induced by inhalation of isoflurane (2–3% in oxygen-enriched air). Body temperature was monitored with a rectal probe and maintained at 37–38°C with a heating pad. Catheters were placed in a femoral artery and vein. Isoflurane was withdrawn while being replaced by urethane (1.3 g/kg iv, with supplementary doses of 0.1 g/kg iv if required). The adequacy of anesthesia was verified by the absence of the corneal reflex and a withdrawal response to nociceptive stimulation of a hindpaw. A tracheotomy was performed, and the animals were artificially ventilated at a level that maintained end-tidal CO2 at 3.5–4.5%. Bilateral jugular vein cannulations facilitated the administration of vasoactive drugs. The head was placed in a stereotaxic frame with the tooth bar fixed 19 mm below the interaural line, and a small area on the surface of the cortex was exposed to allow for later insertion of micropipettes into the hypothalamus. The mean arterial pressure (MAP) and HR were derived from the pulsatile signal of arterial pressure using Chart software. MAP, HR, and RSNA were recorded continuously on a computer using Chart software.

Microinjections into the PeF, the tip of the micropipette was positioned stereotaxically (3.1 mm caudal to bregma, 0.5 mm lateral above the midline, and 8.6 ventral to the surface of the cortex). For microinjections into the DMH, the tip of the micropipette was positioned stereotaxically (3.1 mm caudal to bregma, 0.5 mm lateral above the midline, and 8.6 ventral to the surface of the cortex). For microinjections into the PeF, the corresponding coordinates were as follows: 3.1 mm caudal, 1.2 mm lateral, and 8.6 mm ventral.

Baroreflex function test. The baroreflex function curves were evaluated by measuring the reflex changes in HR and RSNA in response to decreasing and increasing MAP induced by intravenous infusion of a vasodepressor drugs sodium nitroprusside (SNP, 50 µg/ml; David Bull Laboratories) and phenylephrine hydrochloride (PE, 125 µg/ml; Smith and Nephew, respectively). SNP and PE were administered via the jugular vein in successive ramped infusions at an initial rate of 2.5 ml/h, increasing every 30 s by a further 2.5 ml/h, to a maximum rate of 25 ml/h. Infusions were ramped in this way to achieve an approximately linear change in MAP at a maximum rate of 1.5 mmHg/s. The maximum volume infused was ~1.2 ml. The infusion was stopped before the maximum rate was reached if further changes in pressure no longer elicited baroreflex changes in HR or RSNA or if MAP reached a minimum of 50 mmHg or a maximum of 200 mmHg.

Experimental procedures. In each experiment, three microinjections (4 and 40 pmol of bicuculline and aCSF vehicle solution) were made into the same site in the DMH and two (40 pmol of bicuculline and aCSF vehicle solution) into the same site in the PeF. All these injections were performed on the same side of the brain in each experiment (3 experiments on the right and 3 on the left). The order of the microinjections was randomized between experiments. After each injection, the pipette was washed out and replaced with a new pipette containing the vehicle or a lower dose of bicuculline, or, in cases where a higher dose of bicuculline was subsequently injected, the pipette was washed out and the injectate was replaced with a new solution containing the higher concentration of bicuculline.

The baroreflex function test (see above) was performed before any microinjections (preinjection control) and after microinjection of aCSF or bicuculline (4 or 40 pmol) into the DMH or PeF. When the control baroreflex tests were performed (i.e., before any injections), there was a ≥10-min waiting period after the test before aCSF or bicuculline was microinjected into the DMH or PeF. Subsequent microinjections were not performed until all cardiovascular variables had recovered to their baseline levels and were stable. This waiting period was ≥18 min after microinjection of aCSF and ≥25 and ≥35 min after microinjection of the low (4 pmol) and high (40 pmol) doses of bicuculline, respectively. After microinjections of bicuculline, there was a 2- to 8-min waiting period before the baroreflex function test was performed, at which time the MAP, HR, and RSNA had reached new increased levels.

At the end of the experiment, the rat was euthanized with an overdose of pentobarbital sodium, and the brain was removed and then fixed in 4% paraformaldehyde. Coronal sections (50 µm) were cut on a freezing microtome, and injection sites were determined using a fluorescence microscope.

Data analysis. To analyze the data for the baroreflex function tests, the signals representing MAP, HR, and RSNA were divided into consecutive blocks, such that for each block the average MAP was 5 mmHg greater or less than for the next consecutive block. The average HR and RSNA during the same block were determined, and these successive values were tabulated and graphed, with MAP as the abscissa and either RSNA or HR as the ordinate. Each data set was then analyzed using Prism software (version 4.0, Graphpad) to determine the logistic sigmoidal curve of best fit (13), which is described by the following equation

\[ y = A_3 / (1 + \exp[A_2(x - A_1)]) + A_4 \]

where \( y \) is HR or RSNA, \( x \) is MAP, \( A_1 \) is the y range (y at the top plateau – y at the bottom plateau), \( A_2 \) is the gain coefficient, \( A_3 \) is MAP at the midpoint (which is also the point of maximum gain), and \( A_4 \) is y at the bottom plateau. The computed baroreflex function curves were differentiated to determine the gain of the HR and RSNA components of the baroreflex across the full range of MAP. The range of y (HR or RSNA) was calculated as the difference between the values at the upper and lower plateaus of the curve. The threshold and saturation values for MAP were defined as the values of MAP that corresponded to the points where y was 5% (of the y range) below and above the upper and lower plateaus, respectively. The correlation coefficient \( (R^2) \) was also calculated as a measure of the goodness of fit of each sigmoidal curve to the raw data points.

To compare the values of the parameters of the equations of best fit after microinjections of aCSF or bicuculline into the DMH or PeF, ANOVA was followed by paired comparisons using the t-test, with application of the Helm step-down procedure for multiple comparisons where appropriate (22). \( P < 0.05 \) was regarded as statistically significant. Values are means ± SE.

RESULTS

Table 1 shows the baseline levels of MAP, HR, and RSNA measured just before microinjections of aCSF or bicuculline (4 or 40 pmol) into the DMH or PeF. In confirmation of previous results (11), microinjections of bicuculline into the DMH

\[ /\]
Table 1. Cardiovascular changes elicited by microinjection of bicuculline into DMH or PeF

<table>
<thead>
<tr>
<th></th>
<th>MAP, mmHg</th>
<th>HR, beats/min</th>
<th>RSNA, %baseline</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Δ</td>
<td>Baseline</td>
</tr>
<tr>
<td>aCSF Bicuculline</td>
<td>93 ± 2</td>
<td>1 ± 1</td>
<td>339 ± 12</td>
</tr>
<tr>
<td>4 pmol</td>
<td>93 ± 2</td>
<td>10 ± 1*</td>
<td>352 ± 16</td>
</tr>
<tr>
<td>40 pmol</td>
<td>93 ± 3</td>
<td>30 ± 2†</td>
<td>349 ± 12</td>
</tr>
<tr>
<td>PeF</td>
<td>94 ± 2</td>
<td>1 ± 1</td>
<td>339 ± 12</td>
</tr>
<tr>
<td>aCSF Bicuculline</td>
<td>97 ± 3</td>
<td>26 ± 3*</td>
<td>343 ± 11</td>
</tr>
<tr>
<td>40 pmol</td>
<td>97 ± 3</td>
<td>26 ± 3*</td>
<td>343 ± 11</td>
</tr>
</tbody>
</table>

Values are mean ± SE (n = 6). aCSF, artificial cerebrospinal fluid; DMH, dorsomedial hypothalamic nucleus; HR, heart rate; MAP, mean arterial pressure; PeF, perifornical area; RSNA, renal sympathetic nerve activity. *P < 0.05 vs. aCSF. †P < 0.05 vs. 4 pmol.

The shifts in the MAP-RSNA and MAP-HR curves evoked by microinjection of the lower (4 pmol) dose of bicuculline were in all cases significantly smaller than those evoked by microinjection of the higher (40 pmol) dose (Figs. 3 and 4). This is reflected by the fact that the increases in the midpoint, lower plateau, and upper plateau evoked by microinjection of 4 pmol of bicuculline were in all cases significantly smaller than those evoked by microinjection of 40 pmol of bicuculline into the DMH (Tables 2 and 3).

The R² values for the baroreflex function curves under the different experimental conditions were also calculated. For the control baroreflex tests, R² was 0.93 ± 0.05 to 0.99 ± 0.01; after microinjection of 4 or 40 pmol of bicuculline into the DMH or PeF, R² was 0.97 ± 0.01 to 0.99 ± 0.01.

DISCUSSION

The results of this study show that microinjection of bicuculline into the DMH or PeF caused a significant shift of the baroreflex control of RSNA and HR to higher levels (i.e., increased the upper and lower plateaus of these variables) and altered the operating range of MAP, such that the threshold, midpoint, and saturation levels were increased. In addition, the maximum gain of the RSNA component of the baroreflex was significantly increased, whereas the maximum gain of the HR component was not significantly changed. Furthermore, in the case of the DMH, the degree of shift of the baroreflex function curves was dose dependent. Thus, although disinhibition of neurons in these hypothalamic regions results in large increases in RSNA and HR, the baroreceptor reflex maintains its ability...
to reflexly alter these variables, but its operating range is increased to higher levels of MAP. This conclusion is in contrast to that of previous studies, which found that electrical stimulation of the hypothalamic defense area [which includes the DMH and PeF (30)] causes strong inhibition or even suppression of the baroreceptor reflex (3, 12, 15, 21). The possible reasons for the differences in our findings compared with those of these previous studies and the functional significance of our observations are discussed below after consideration of some methodological issues.

Methodological considerations. The stability of the preparation was demonstrated by baroreflex tests performed under three control conditions at different times during the experiment: before microinjections and after microinjections of the vehicle solution (aCSF) into each site. The baroreflex function curves were not significantly different from each other for all three control baroreflex tests. Low (4 pmol) and high (40 pmol) dozes of bicuculline were selected for microinjection because we previously showed (11) that these doses evoke graded responses of very different magnitude when injected into the DMH. The reliability of the baroreflex tests after microinjection of bicuculline into the DMH or PeF was indicated by very high $R^2$ values (0.97–0.99), thus demonstrating a close fit between the raw data points and the derived sigmoidal function curves.

It has been shown previously that the MAP-RSNA baroreflex function curve is very similar when tested in the same rats in the conscious state and under urethane anesthesia (24). Consistent with this finding, the midpoint of the MAP-RSNA
baroreflex function curves under resting control conditions in our study was very similar to that determined by Miki et al. (16) in the conscious rat. Furthermore, the magnitudes of the maximum and minimum reflex changes in RSNA relative to the RSNA value at the midpoint in our study were also very similar to those in the conscious rat (16). The range of the evoked baroreflex changes in HR in our study, however, as in previous studies in anesthetized rats (24, 29), was less than that observed in the conscious rat (16, 24, 29). Nevertheless, our results do not indicate that disinhibition of DMH or PeF neurons reduces the sensitivity of the cardiac component of the baroreceptor reflex.

Comparison with previous studies. In contrast to the effects of disinhibition of neurons in the hypothalamic defense area as shown in the present study, in previous studies electrical stimulation of sites within this area has been shown to cause

Table 2. Parameters describing baroreflex control of RSNA after microinjection of aCSF or bicuculline into DMH or PeF

<table>
<thead>
<tr>
<th></th>
<th>Threshold Level, mmHg</th>
<th>Midpoint, mmHg</th>
<th>Saturation Level, mmHg</th>
<th>Lower Plateau, %baseline</th>
<th>Upper Plateau, %baseline</th>
<th>Max Gain, %baseline/mmHg</th>
</tr>
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<tbody>
<tr>
<td><strong>DMH</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>aCSF</td>
<td>75 ± 3</td>
<td>104 ± 2</td>
<td>134 ± 6</td>
<td>3 ± 4</td>
<td>138 ± 6</td>
<td>−3.74 ± 0.60</td>
</tr>
<tr>
<td>Bicuculline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 pmol</td>
<td>75 ± 5</td>
<td>109 ± 2*</td>
<td>143 ± 7*</td>
<td>15 ± 5*</td>
<td>189 ± 13*</td>
<td>−4.24 ± 0.86</td>
</tr>
<tr>
<td>40 pmol</td>
<td>98 ± 2*†</td>
<td>127 ± 2*†</td>
<td>155 ± 4*</td>
<td>27 ± 4*†</td>
<td>274 ± 31*†</td>
<td>−6.70 ± 1.16*†</td>
</tr>
<tr>
<td><strong>PeF</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>aCSF</td>
<td>69 ± 7</td>
<td>104 ± 2</td>
<td>140 ± 7</td>
<td>3 ± 3</td>
<td>144 ± 3</td>
<td>−3.33 ± 0.46</td>
</tr>
<tr>
<td>Bicuculline</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>40 pmol</td>
<td>100 ± 3*</td>
<td>131 ± 4*</td>
<td>162 ± 6*</td>
<td>25 ± 3*</td>
<td>257 ± 26*</td>
<td>−5.66 ± 0.77*</td>
</tr>
</tbody>
</table>

Values are means ± SE (n = 6). Maximum (Max) gain is gain of sigmoidal curve of best fit at MAP corresponding to midpoint value. *P < 0.05 vs. aCSF. †P < 0.05 vs. 4 pmol.
strong inhibition or even suppression of the cardiac component of the baroreceptor reflex (3, 12, 15, 21). Coote et al. (3) found that the vasomotor component of the reflex is also suppressed by electrical stimulation of the hypothalamic defense area, although others reported that it is not affected (21).

In these previous studies, baroreflex function was determined by measurement of the reflex effects of a single large stepwise change in carotid sinus pressure or electrical stimulation of the aortic depressor nerve or carotid sinus nerve (3, 12, 15, 21). These methods, in contrast to the procedure used in the present study, do not allow an assessment of baroreflex function over the full operating range of the reflex. It is possible, therefore, that an observed reduction in the magnitude of an evoked reflex response to a standardized stimulus in these studies could reflect a shift in the operating range of the baroreflex (as we observed), rather than inhibition.

An alternative possible explanation for our failure to observe inhibition of the baroreflex is that the hypothalamic regions in which bicuculline was injected did not correspond to the regions in which electrical stimulation in previous studies in the cat or rat evoked such inhibition (3, 12, 15, 21). This seems very unlikely, however, because the hypothalamic defense area, as mapped in the cat and rat using electrical stimulation, includes the PeF and at least a large part of the DMH (3, 30). In addition, our results do not provide any evidence to suggest that neurons in the DMH and PeF have different effects on the baroreflex, because microinjections of bicuculline centered on each of these nuclei had very similar modulatory effects on the reflex.

It could also be suggested that in our study the increased activity of the neurons in the DMH or PeF was not sufficient to produce inhibition of the baroreflex. This also seems unlikely, because the larger dose (40 pmol) of bicuculline produced large increases in MAP, HR, and RSNA (Table 1) that are similar to or greater than those evoked by psychological stress in the conscious rat (7, 26, 27).

In contrast to electrical stimulation, bicuculline does not affect fibers of passage. It is therefore possible that the previously observed effects of electrical stimulation in inhibiting the baroreflex (3, 12, 15, 21) is a consequence of excitation of fibers passing through the DMH and PeF, rather than excitation of neurons within these regions. If that is the case, then such fibers may arise from neurons in other nuclei that do, when activated, cause suppression of the baroreflex.

Modulation of the baroreflex during naturally evoked stress responses. Although the modulatory effects on the baroreflex evoked by disinhibition of the DMH or PeF are quite different from those evoked by electrical stimulation of these regions, they are very similar to those that are associated with naturally evoked psychological stress. In particular, with regard to the cardiac component of the baroreflex, studies in conscious rats and rabbits demonstrated that, in response to air-jet stress, the MAP-HR function curve is shifted upward and to the right, without significant change in maximum gain (7, 20), as observed in the present study.

There do not appear to be any studies in which the MAP-RSNA function curves have been determined during psychological stress in conscious rats. During exercise in conscious rats, however, the MAP-RSNA function curve is shifted upward and to the right, with a significant increase in the maximum gain (16), in very similar fashion to the shift evoked by disinhibition of the DMH/PeF in the present study. Furthermore, the MAP-HR function curve was also shifted upward and to the right, but without any significant change in maximum gain (16). Very similar changes in baroreflex control of HR and blood pressure during dynamic exercise in humans have also been described by Potts et al. (19). Thus, in summary, the modulation of the baroreflex evoked by disinhibition of the DMH/PeF is very similar to that observed in acute psychological stress and exercise.

Also, increases in the midpoints of the baroreflex control of RSNA and HR evoked by disinhibition of the DMH or PeF were very similar to increases in baseline MAP evoked by the same stimulations. For example, microinjection of 40 pmol of bicuculline into the DMH and PeF increased MAP by 30 and 26 mmHg, the midpoints for the MAP-RSNA curves by 23 and 27 mmHg, and the midpoints for the MAP-HR curves by 28 and 26 mmHg, respectively. Similarly, psychological stress in conscious rats or rabbits also evokes increases in the midpoint of the baroreflex function curve of very similar magnitude to the evoked increase in MAP (7, 20). Although an increase in arterial pressure alone causes acute resetting of the baroreceptors themselves, within 5–15 min the magnitude of this is only 25–40% of the increase in pressure (2). Thus this would not account for the virtually complete resetting of the baroreflex to the higher levels of arterial pressure in response to disinhibition of neurons in the DMH/PeF that we observed, implying that this is due, at least in part, to a central mechanism.

The mechanisms responsible for such central resetting were not examined in this study. Electrical stimulation of the hypothalamic defense area inhibits, via GABA receptors, the activity of neurons in the NTS that receive an excitatory input from arterial baroreceptors (12, 15, 25). In these studies, the electrical stimulation caused complete or nearly complete abolition
of the responses of NTS neurons to baroreceptor stimulation, leading to the conclusion that the input from the hypothalamic defense area suppresses the baroreceptor reflex (15). Under conditions where the inhibitory input from the hypothalamus is less intense, however, the effect would be to raise the threshold and saturation levels of barosensitive neurons in the NTS to baroreceptor inputs, shifting the relation between arterial pressure and reflex changes in HR and RSNA to higher levels of pressure. Thus our observation that disinhibition of neurons in the DMH and PeF results in a graded shift in the baroreflex function curve to the right is consistent with previous findings that barosensitive NTS neurons receive GABAergic inhibitory inputs from the hypothalamus (12, 15, 25). We propose, however, that the normal function of these inputs is to reset the operating range of the baroreceptor reflex to higher levels of pressure, as observed in naturally evoked stress (7, 20), rather than to suppress the reflex.

**Perspectives**

It is well established that the DMH plays a pivotal role in integrating the autonomic, neuroendocrine, and behavioral response to acute stress (5). The results of this study, together with previous studies (5), indicate that neurons in the DMH/PeF region not only increase sympathetic vasomotor activity and HR as part of a stress-evoked response, but they also reset the baroreceptor reflex such that it remains effective, without any decrease in sensitivity, over a higher operating range of arterial pressure, which is appropriate to meet the challenge of different stressors. Whether the increases in sympathetic activity and HR and the modulation of the baroreflex are regulated by a common or separate population of neurons in the DMH/PeF region, however, is not known. Future studies are needed to answer this question.

**GRANTS**

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