Morrison, Shaun F., Alan F. Sved, and Alicia M. Passerin. GABA-mediated inhibition of raphe pallidus neurons regulates sympathetic outflow to brown adipose tissue. Am. J. Physiol. 276 (Regulatory Integrative Comp. Physiol. 45): R290–R297, 1999.—Sympathetic nerve activity to brown adipose tissue (BAT) regulates adipocyte metabolism of its stored lipid fuel and thus the thermogenesis in BAT. To determine if the discharge of neurons in the rostral raphe pallidus (RPa) can influence BAT thermogenesis, changes in sympathetic nerve activity to BAT were recorded after microinjection (60 nl) of the GABA<sub>A</sub> receptor antagonist bicuculline (500 µM) into the RPa in chloralose-urethan-anesthetized, ventilated rats. Bicuculline caused a large, rapid rise in the sympathetic nerve activity to BAT (which had also increased during acute hypothermia) from very low, normothermic control levels to maximum values (mean: 1.949 ± 604% control; n = 13) after 4–6 min. The sympathetic nerve discharge to BAT had a mean burst frequency (3.5 ± 0.3 Hz) that was significantly less than the heart rate (7.3 ± 0.2 beats/min), and it was not inhibited during baroreceptor reflex activation. Bicuculline-stimulated increases in the sympathetic nerve activity to BAT and cold-evoked increases in neuronal fos expression were localized to the RPa at the level of the caudal half of the facial nucleus. This dramatic increase in sympathetic nerve activity to BAT after disinhibition of neurons in rostral RPa is consistent with a major role for RPa neurons, perhaps as sympathetic premotoneurons for BAT, in medullary control of BAT thermogenesis.

METHODS
Sprague-Dawley rats (300–450 g; 11 male, 2 female) were anesthetized intravenously with urethan (0.8 g/kg) and chloralose (80 mg/kg) after induction with 3% isoflurane in 100% O<sub>2</sub> and cannulation of both femoral arteries, a femoral vein, and the trachea. Animals were positioned prone in a stereotaxic frame (incisor bar: –11.0 mm) with a spinal clamp on the tenth thoracic vertebra. Animals were paralyzed with d-tubocurarine (0.3 mg initial dose; 0.1 mg/h supplements) and artificially ventilated with 100% O<sub>2</sub> (50 cycles/min; tidal vol 3 ml). Small adjustments in minute ventilation were made as necessary to maintain end-tidal CO<sub>2</sub> between 4 and 5%. Throughout most of the experiment, colonic temperature was maintained at 37.5°C with a heat lamp and a heating plate beneath the animal. To provide a natural stimulus for the activation of the sympathetic nerve discharge to BAT, body temperature was lowered once in each animal by turning off the heat sources and, in some cases, placing dry ice in contact with the metal heating plate beneath the animal. This caused temperature to fall from 37.5°C to 34–35°C within 10 min, at which time the heat sources were turned on and body temperature returned to 37.5°C.

Postganglionic sympathetic nerve activity to BAT was recorded from the central cut end of a small nerve bundle dissected from the ventral surface of the right interscapular BAT after dividing the fat pad along the midline and reflecting it laterally. In some experiments, postganglionic sympathetic nerve activity was also recorded from the splanchic nerve after dissection distal to the suprarenal ganglion in the costovertebral angle. Nerve activity was recorded with bipolar hook electrodes in a monopolar configuration, filtered (1–300 Hz) and amplified (50,000) with a Cyberamp 380 (Axon Instruments), and digitized and recorded (Neurodata)
control recording period (30 min after hypothermia), a return to normal body temperature and a second control recording period (30 min after induction of acute hypothermia), microinjections of vehicle (saline) and of bicuculline into RPa, and electrical stimulation of RPa. No differences were observed between the parameters recorded during the first and second control periods. In some experiments, bolus injections of phenylephrine (10 µg/kg) were given to elevate arterial pressure and observe the effects of baroreceptor reflex activation on the BAT and splanchnic sympathetic nerve activities.

A stimulating electrode or a microinjection pipette (tip outside diameter 20 µm) was positioned stereotaxically in the RPa or neighboring regions after a partial occipital craniotomy and reflection of the atlanto-occipital membrane. Relative to the calamus scriptorius, the coordinates for the RPa were anterioposterior 3.0 mm, mediolateral 0.0 mm, and dorsoventral −2.6 mm. At the end of each experiment, a pipette containing a 1% solution of fast green dye was stereotaxically positioned at the site of microinjection and dye was electrophoretically deposited (15 µA anodal direct current for 8 min). After perfusion and histological processing, the locations of the microinjection sites in the RPa or neighboring areas were plotted on camera lucida drawings of sections through the rostral medulla (24). In some experiments, electrical stimulation was performed at the site of sympathetic preganglionic neurons in the second thoracic (T2) segment ipsilateral to the BAT sympathetic nerve recording. Stimulation, applied through a monopolar tungsten microelectrode (30 µm exposed tip), consisted of twin pulses, 1-ms duration, 6-ms interpulse interval, 20–100 µA, delivered at 0.4 Hz.

After digitization at 1 kHz, signals were analyzed with software written in the ASYST programing environment. The amplitude of the sympathetic nerve activity to BAT and the mean frequency of the bursts in nerve activity were derived from autospectral analysis. For each experimental condition, an average autospectrum of the sympathetic nerve activity to BAT was obtained by dividing a 20.5-s data record into nine 4.1-s segments with a 50% overlap. The value of the autospectrum at each frequency was computed as the mean value of the powers at that frequency in the individual autospectra of these nine segments. The amplitude of the sympathetic nerve activity to BAT was assessed as the mean value of the total power in the 1- to 10-Hz band of the averaged autospectrum. The mean burst frequency was obtained as the mean burst frequency within the 2-Hz interval containing the greatest power. Statistical significance was assessed with the Student’s paired t-test (P < 0.05).

The evoked expression of the immediate-early gene fos was used to localize neurons in the medial brain stem that were responsive to decreased body temperature. Rats (n = 4) were removed from their home cages and placed in individual hanging wire mesh cages in an environmental chamber maintained at 4°C. After 4 h, rats were removed from the cold and immediately anesthetized with an overdose of pentobarbital sodium (80 mg/kg ip). Within 5 min of the pentobarbital sodium injection, rats were perfused with a fixative of 4% paraformaldehyde and 2% acrolein (29). Control rats (n = 4) were treated in the same way except that the environmental chamber was set to 22°C. Brains were removed and sectioned at 30 µm using a freezing-stage microtome. Sections were stored at −70°C in a cryoprotectant solution and subsequently a one-in-six series of sections from each animal was stained immunocytochemically for Fos (16) using a polyclonal antibody raised against the NH2-terminal region of Fos (Oncogene Sciences; Manhasset, NY; lot no. 40890207). We examined Fos staining in the midline brain stem by light microscopy and did comparisons among rats and among rostrocaudal levels of the brain stem using a 0–4 rating scale in which 0 represented no Fos-positive cells, 1 represented few Fos-stained cells, 2 represented 1–10% of the cells in an area stained for Fos, 3 represented 10–50% of the cells in an area stained for Fos, and 4 represented >50% of the cells in an area stained for Fos.

RESULTS

The resting mean arterial pressure in the 13 rats studied was 110 ± 6 mmHg and the heart rate was 387 ± 13 beats/min. At normal body temperature, there was little spontaneous discharge on the sympathetic nerves to BAT (Fig. 1A). As body temperature was lowered, large bursts of spontaneous activity, suggesting the synchronous discharge of axons within the sympathetic nerve bundle, appeared on the sympathetic nerve to BAT (Fig. 1B). As illustrated in Fig. 1B, sympathetic nerve activity to BAT was increased to a maximum of 1.010% of the normothermic control value (Fig. 1A) when body temperature was lowered to 34.7°C. In 9 of 12 animals in which an acute hypothermic response was tested, lowering body temperature from 37.5°C to 34.5 ± 0.1°C produced a significant increase (413 ± 132% of control, P < 0.01) in sympathetic nerve activity to BAT. In the other three animals, the sympathetic nerve activity to BAT did not change from control levels despite reductions in body temperature to 34.0°C. As indicated by the averaged autospectrum (Fig. 1B), the hypothermia-induced increase of the sympathetic nerve activity to BAT was attributable to the emergence of bursts in nerve activity that occurred at a mean burst frequency of 2.2 Hz. The heart rate at this time was 5.1 Hz. On average, acute hypothermia also produced a slight rise in mean arterial pressure (7 ± 1.6 mmHg, P < 0.01) and heart rate (17 ± 4 beats/min, P < 0.01).

Similar to the elevation in sympathetic nerve activity to BAT that occurred in response to the natural stimulus of acute hypothermia, microinjection of the GABA<sub>A</sub> receptor antagonist bicuculline (60 nl; 500 µM) into the rostral RPa produced a prompt and dramatic increase in the sympathetic nerve discharge to BAT (Fig. 1C). There was no change in sympathetic nerve discharge to BAT after microinjection of the saline vehicle into RPa. In contrast to the response to acute hypothermia, all of the 13 animals that received bicuculline microinjections into RPa responded with an increase in the sympathetic nerve activity to BAT, characterized by a more frequent occurrence of bursts in nerve activity and an augmented amplitude of individual bursts. In the example in Fig. 1D, administration of bicuculline into RPa evoked a maximal increase in sympathetic nerve activity to BAT of 3,810% of control at 4 min after the microinjection. The mean increase in all animals was 1,949 ± 604% of control (P < 0.01). As illustrated in Fig. 1E, in this experiment, bicuculline microinjection into RPa elicited an increase in mean arterial pressure of 13 mmHg and a tachycardia of 30 beats/min. On
average, the bicuculline microinjection produced a significant increase in mean arterial pressure of 9 ± 1.6 mmHg (P < 0.01) and an increase in heart rate of 39 ± 8 beats/min (P < 0.01).

As determined from the autospectrum (Fig. 1D), the mean burst frequency of the sympathetic nerve activity to BAT was 2.8 Hz, while the heart rate was 5.8 Hz. For all animals, the average mean burst frequency (3.5 ± 0.33 Hz) in BAT sympathetic nerve activity during the maximal response to bicuculline microinjection was significantly (P < 0.001) less than the heart rate (7.3 ± 0.16 Hz) at this time. This result suggests that the medullary neuronal networks generating the bursts in sympathetic nerve activity to BAT are not influenced by pulse-synchronous baroreceptor afferent input. This was directly tested by observing the effect on the sympathetic nerve activity to BAT during the baroreceptor reflex stimulation produced by increasing arterial pressure with bolus injections of phenylephrine. For comparison, the baroreceptor reflex responses of the splanchnic sympathetic nerve, which is primarily vaso-motor in function, were simultaneously recorded. As illustrated in the example in Fig. 2, increases in arterial pressure sufficient to produce a prompt and nearly complete inhibition of splanchnic nerve activity were without effect on the amplitude of the sympathetic nerve activity to BAT. This was the case whether the baroreceptor reflex was stimulated while the sympathetic nerve activity to BAT was elevated during the response to microinjection of bicuculline into the RPa or during the response to hypothermia. During nine phenylephrine injections in three experiments, the amplitude of the sympathetic nerve activity to BAT during the peak increase in arterial pressure was 96 ± 7% of that at the baseline arterial pressure, while the amplitude of the splanchnic sympathetic nerve activity was reduced to 18 ± 9% of the level at the baseline arterial pressure.

Electrical stimulation (twin pulses; 6-ms interval; 1-ms duration; 0.25 Hz; 100 µA) in RPa evoked an excitatory potential in the sympathetic nerve activity to BAT (Fig. 3, trace 1). The amplitude of the potential increased as RPa stimulus intensity was raised from threshold stimulus currents of 8 ± 1.3 to 150 µA. The mean onset latency of the excitatory potential evoked from the RPa was 137 ± 4 ms, and the mean latency to the peak was 169 ± 4 ms. In five experiments, the latency of activation of the sympathetic nerve to BAT in response to twin pulses applied to the region of the ipsilateral intermediolateral nucleus in T2 was determined. The mean onset latency of the excitatory potential evoked from T2 was 64 ± 2.0 ms and the mean

Fig. 1. Effect of hypothermia and bicuculline microinjection into raphe pallidus (RPa) on sympathetic nerve activity to brown adipose tissue (BAT SNA), autospectrum of BAT SNA (BAT SNA PWR), arterial pressure (AP), and heart rate (HR). All panels are from same experiment. A: AP, BAT SNA, and BAT SNA PWR during control conditions (colonic temperature: 37.5°C). B: same traces as in A, during acute hypothermia (34.7°C). C: AP, BAT SNA, and HR responses to microinjection (arrow; 60 nl) of bicuculline (500 µM) into RPa. D: same traces as in A, during maximum effect of bicuculline microinjection into RPa. Note large difference in scale of BAT SNA PWR among traces in A, B, and D. Horizontal scale bar represents 2 s for AP and BAT SNA traces in A, B, and D, and 22 s for AP, BAT SNA, and HR traces in C. Vertical scale bar represents 80 µV for BAT SNA traces in A, B, and D; 60 µV for BAT SNA trace in C; and 400, 2,300 and 16,500 relative power units for BAT SNA PWR traces in A, B, and D, respectively.
latency to the peak was 106 ± 3.5 ms (Fig. 3, trace 2). In these animals, the mean differences between the onsets and peaks of the potentials evoked from the RPa and those from the $T_2$ stimuli were 69 ± 5.9 ms and 58 ± 7.7 ms, respectively. The mean distance between the RPa and the $T_2$ stimulation sites was 43 ± 2 mm.

In Fig. 4, the locations of the fast green dye deposits marking the locations of the centers of the bicuculline microinjections into the RPa in the 13 animals described in this study are plotted on a medullary cross section (24) corresponding to the median rostrocaudal location of the dye deposits. These sites were clustered in the rostral RPa at levels extending from the rostroventrolateral medulla (RVLM) to the middle of the facial motor nucleus. Figure 5 indicates the maximum changes in the sympathetic nerve activity to BAT produced by bicuculline microinjections (40 nl; 500 µM) into sites surrounding this RPa site. These response-mapping experiments, conducted in four animals, indicate that 1) bicuculline-evoked increases in sympathetic nerve activity to BAT are restricted to sites in RPa and 2) the responses on the sympathetic nerves to BAT are greatly reduced when bicuculline is applied to RPa sites either 1 mm caudal or 1 mm rostral to the RPa site, 3.0 mm rostral to the calamus scriptorius. These results indicate that a population of neurons playing a major role in controlling the sympathoexcitatory drive to BAT is concentrated in the RPa, 3.0 mm rostral to the calamus scriptorius, with elements of this population diminishing in number over 1 mm rostral and caudal to this site.

To provide further information on the localization of midline brain stem neurons potentially involved in regulation of the sympathetic nerve activity to BAT, the evoked expression of fos was determined immunocytochemically after acute exposure to a reduced environmental temperature (4°C). As indicated in Fig. 6, bottom, few Fos-stained neurons were present in the midline brain stem, or elsewhere, of control rats. In contrast, in each animal exposed to cold, there was a robust expression of fos in the ventral midline of the caudal pons/rostral medulla (Fig. 6B, top). The Fos-positive cells were present in a highly localized region, corresponding to the RPa and centered at the rostrocaudal level of the caudal facial motor nucleus. In each of the four cold-exposed rats, Fos staining in this region was rated 3–4, with this large proportion of Fos-
positive cells in RPa extending for <1 mm either rostrally or caudally (Fig. 6, A and C, top). This was in sharp contrast to the Fos staining in the RPa of control rats, which was scored 0 or 1 throughout its rostrocaudal extent.

DISCUSSION

These data indicate that GABA-mediated inhibition of neurons in the rostral medullary RPa plays a critical role in regulating the sympathetic outflow to BAT. Removal of this inhibition allows expression of a large and potentially maximal sympathetic outflow to BAT. With regard to temperature regulation, these results are consistent with a model in which the low level of spontaneous sympathetic nerve activity to BAT present at normal body temperatures results from a GABA-mediated inhibitory input to RPa neurons, possibly those projecting to the spinal intermediolateral nucleus (1, 18), which are elements of or outputs for the neural network responsible for generating the discharge in the

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Fig. 5. Dependence of amplitude of response of sympathetic nerve activity to BAT on site of microinjection of bicuculline. Symbols indicate percent increases relative to control amplitudes of sympathetic nerve activity to BAT as follows: ◆, <50%; □, 0–50%; △, 50–100%; ▲, 100–250%; ●, >500%. Drawings of coronal sections through rat brain stem at 4 (A), 3 (B), and 2 (C) mm rostral to calamus scriptorius were adapted from stereotaxic atlas of rat brain by Paxinos and Watson (24), bregma –10.30, –11.30, and –12.30, respectively. Amb, ambiguous nucleus; ROb, raphe obscurus nucleus; 6, abducens nucleus.

Fig. 6. Immunocytochemical staining for Fos in neurons of midline brain stem after 4-h exposure to environmental temperature of 4°C (Cold) or 22°C (Control). With reference to stereotaxic atlas of rat brain by Paxinos and Watson (24): A, B, and C correspond to approximately bregma –10.30, –11.30, and –12.30, respectively. Note large increase in fos expression in RPa at level of bregma –10.30 in animal exposed to acute hypothermia. Calibration bar represents 100 μm.
sympathetic nerves to BAT. The increase in sympathetic nerve activity to BAT in response to a fall in body temperature would be accomplished by a reduction in this GABAergic inhibition, disinhibiting RPa neurons and allowing increased excitatory drive to sympathetic preganglionic neurons controlling BAT thermogenesis.

The increase in sympathetic activity to BAT evoked by microinjection of bicuculline into the RPa was significantly greater than that occurring during the reflex response to the acute hypothermic challenge. Two possible explanations likely contribute to this observation. First, additional GABAergic inputs to RPa neurons (i.e., other than those whose reduced release may account for the reflex thermogenic response to a fall in body temperature) would appear to be capable of and important in regulating BAT thermogenic activity. The sources of such GABAergic inputs and whether they are controlled by hypothalamic neurons distinct from those involved in thermoregulation remain to be determined. Second, central thermoregulation is likely to be dampened by anesthesia, possibly resulting in an incomplete inhibition of the GABAergic inputs to RPa neurons during hypothermia. Chloralose has been suggested to increase the threshold and decrease the response dynamics of thermoregulation (13). This may also account for the absence of a response to hypothermia in a few of the animals that subsequently responded with increases in sympathetic nerve activity to BAT after bicuculline microinjection into RPa.

Microinjection of bicuculline into rostral RPa produced a large increase in sympathetic nerve activity to BAT, usually beginning within a few seconds and lasting for ~30 min. As shown in Fig. 1, B and D, the character of the individual bursts induced by bicuculline administration is similar to that of the bursts evoked by the physiological stimulus of lowering body temperature. This suggests that the bursts in sympathetic nerve discharge to BAT induced by disinhibition of RPa neurons are generated by the same or similar neural mechanisms as those generated under physiological conditions and that the disinhibition of RPa neurons may be a critical step in the activation of a variety of physiological responses involving an increase in BAT thermogenesis (e.g., fever, thermogenic response to hypothermia, and regulation of metabolic fuel storage by hormones such as leptin and insulin).

Prepontine transection (4, 5, 25, 26) or administration of procaine to sites in the lower midbrain (27) produces a thermogenic response characterized by an increase in brown adipose and body core temperature, presumably through an increase in sympathetic nerve activity to BAT. The conclusion reached in each of these studies is that the prepontine transections interrupted the descending inhibition of a BAT thermogenic mechanism in the lower brain stem. The results of the present study, showing that removal of GABAergic inhibition from RPa neurons elicits a large increase in sympathetic nerve activity to BAT, suggests that the hypothesized brain stem thermogenic mechanism resides, at least in part, in neurons within RPa. Furthermore, the results obtained both from 1) mapping the responses of the sympathetic nerve discharge to BAT after bicuculline microinjections into brain stem regions surrounding the RPa (Fig. 5) and 2) determining the midline brain stem sites exhibiting an increased fos expression after exposure to a cold environment (Fig. 6) suggest that the RPa neurons participating in this brain stem thermogenic circuit have a restricted rostrocaudal distribution, concentrated at the level of the caudal half of the facial nucleus. Our results with fos expression are similar to those obtained with a slightly different thermal stress protocol (6), although the rostrocaudal extent could not be determined from this previous work. A corollary to the thermogenic effects of the prepontine transections is that the neural networks necessary to generate the sympathetic nerve discharge to BAT are contained within the medulla. The location of the neurons providing the GABAergic inhibition to the RPa neurons regulating the sympathetic outflow to BAT remains to be determined.

The RPa, including the rostral regions receiving bicuculline microinjections, contains neurons with sparsely projecting axons that terminate within the intermediolateral nucleus (1, 18, 22, 28) and that could function as sympathetic premotoneurons for BAT. Indeed, a population of raphe-spinal neurons has been described (22) that are silent at normal body temperature and that project to the thoracic intermediolateral nucleus with an axonal conduction velocity of ~0.7 m/s. The results obtained by dividing the difference between the onsets (or peaks) of the potentials evoked in the sympathetic nerve to BAT from stimulation in the RPa and the intermediolateral region of the T2 spinal segment by the distance from the RPa to the T2 suggest that if these potentials were mediated over a direct raphe-spinal pathway, the conduction velocity of the pathway would be ~0.62–0.75 m/s, in close agreement with that of the raphe-spinal neurons identified previously (21). The results of the present study do not, however, distinguish between this possibility and one in which raphe neurons mediate an increase in sympathetic nerve activity to BAT via indirect pathways involving another sympathoexcitatory cell group with spinal projections to the sympathetic preganglionic neurons regulating BAT.

The absence of a correlation between the mean burst frequency in the sympathetic nerve activity to BAT and the heart rate and the lack of effect of baroreceptor reflex stimulation on the sympathetic nerve activity to BAT indicate that the medullary neural network generating the synchronous discharge of sympathetic fibers to BAT is not influenced by pulse-synchronous baroreceptor afferent input. This is in sharp contrast to the sympathetic outflow to cardiovascular targets, which is strongly modulated over the course of the cardiac cycle and which is markedly inhibited by elevations in arterial pressure (12, 14, 23), due principally to baroreceptor modulation of the discharge probability of cardiovascular sympathetic premotoneurons in the RVLM (2, 8, 17, 19, 23). On this basis, the present results suggest that BAT thermogenesis is regulated by a population of sympathetic premotoneurons, perhaps located in the...
RPa, that is distinct from those in the RVLM regulating vasoconstriction and cardiac function. It remains to be determined whether rostral RPa neurons also influence autonomic efferents to other target tissues (6) involved in thermo- or metabolic regulation and whether RPa neurons can influence, through intramedullary or spinal connections, the vasomotor and cardiac adjustments accompanying thermoregulatory and metabolic responses.

Perspectives

The results of the present study suggest a model for the brain stem component of thermoregulatory pathways in which the metabolic activity of BAT is determined by the level of GABA-mediated inhibition of a restricted population of RPa neurons, possibly those projecting to sympathetic preganglionic neurons in the spinal intermediolateral nucleus specifically regulating BAT metabolism. The low level of spontaneous sympathetic nerve activity to BAT present at normal body temperatures would result from a maintained activation of a GABAergic input to RPa premotor outputs for the neural network responsible for generating the discharge in the sympathetic nerves to BAT. The increase in sympathetic nerve activity to BAT in response to a fall in body temperature would be accomplished by a reduction in this GABAergic inhibition, disinhibiting RPa neurons and allowing increased excitatory drive to sympathetic preganglionic neurons controlling BAT thermogenesis.

If RPa contains the premotoneurons for sympathetic regulation of BAT, it would be comparable to the RVLM, which includes the bulbospinal neurons providing the excitatory drive to sympathetic preganglionic neurons regulating cardiovascular function. The discharge of both are limited by GABAergic inhibition, although apparently to differing degrees. Through a reduction in inhibitory input from the caudal ventrolateral medulla, sympathetic premotoneurons in RVLM increase their discharge to compensate for a fall in arterial pressure. Similarly, RPa neuronal activity would be increased to compensate for a decrease in body or environmental temperature, possibly responding to activation of thermoregulatory reflexes originating in the hypothalamus.

Evidence has been presented for control of distinct cardiovascular functions by unique subpopulations of sympathetic premotoneurons in the RVLM (3, 20). The possibility that separate populations of premotoneurons in the RPa and the RVLM regulate the sympathetic outflows to BAT and to vasoconstrictor and cardiac targets, respectively, suggests an expansion of this model to one in which sympathetic regulation of metabolic and cardiovascular functions occurs through neural networks that are more anatomically separated and that generate outputs with different rhythmic properties.

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