Central Orexin-A Augments Sympathoadrenal Outflow in Conscious Rabbits

Kiyoshi Matsumura, Takuya Tsuchihashi, Isao Abe

Abstract—We determined the cardiovascular and neurohormonal responses to intracerebroventricular administration of orexin-A in conscious rabbits. Intracerebroventricular injection of orexin-A elicited dose-related increases in mean arterial pressure and renal sympathetic nerve activity. Peak values of mean arterial pressure and renal sympathetic nerve activity induced by intracerebroventricular injection of 100 pmol of orexin-A (14.0±0.7 mm Hg and 55.4±14.9%, respectively) were obtained at 60 and 90 minutes after injection, respectively. Plasma epinephrine and glucose concentrations were significantly increased at 60 and 90 minutes after intracerebroventricular injection of orexin-A (control versus 90 minutes; for epinephrine, 38.0±12.8 versus 167.5±42.5 pg/mL, P<0.01; for glucose, 6.66±0.18 versus 7.75±0.14 mmol/L, P<0.01). Plasma norepinephrine and insulin concentrations increased at 60 and 90 minutes but did not attain significant values. Intracerebroventricular injection of orexin-A also caused significant increases in plasma vasopressin concentrations. However, pretreatment with an intravenous injection of pentolinium (5 mg/kg), a ganglion-blocking agent, abolished these cardiovascular and neurohormonal responses. On the other hand, intravenous injection of the same dose of orexin-A (100 pmol) used in the intracerebroventricular experiment failed to cause any cardiovascular and renal sympathetic nerve responses. These results suggest that intracerebroventricular orexin-A acts in the central nervous system and activates sympathoadrenal outflow, resulting in increases in arterial pressure and plasma glucose levels in conscious rabbits. (Hypertension. 2001;37:1382-1387.)

Key Words: catecholamines ■ central nervous system ■ glucose ■ peptides ■ renal nerves

Appetite and feeding behavior are regulated by many neurotransmitters, such as neuropeptide Y, corticotrophin-releasing factor, α-melanocyte–stimulating hormone, and melanin-concentrating hormone.1,2 The orexins are a recently identified class of neuropeptides that stimulate food intake.3,4 Orexin-A and orexin-B are 33– and 28–amino acid peptides, respectively, sharing a 46% identity.3,4 Immunohistochemical studies have shown that orexin-immunoreactive nerve fibers are present not only in the hypothalamus but also in the medulla.5–7 Intracerebroventricular injections of orexins have been seen to induce c-fos expression in the paraventricular thalamic nucleus, locus ceruleus, arcuate nucleus, central gray substance, raphe nuclei, nucleus of the solitary tract, dorsal motor nucleus of the vagus, suprachiasmatic nucleus, and suprarenal nucleus,8 suggesting the contribution of the peptides to autonomic and neuroendocrine control in the central nervous system.

Recently, Shirasaka et al.8 showed that intracerebroventricular injections of orexin-A and orexin-B cause increases in arterial pressure, renal sympathetic nerve activity (RSNA), and plasma catecholamine concentrations in conscious rats. Their results and immunohistochemical studies suggest that central orexins participate not only in the regulation of food intake but also in cardiovascular and sympathetic regulations. We anticipated that activation of sympathoadrenal outflow induced by intracerebroventricular injection of orexins might elicit an increase in plasma glucose levels. Moreover, we considered that central orexins might stimulate the secretion of vasopressin, because one of the putative brain regions in which orexins act to stimulate food intake is the hypothalamus.1 We hypothesized that intracerebroventricular injection of orexins stimulates the secretion of vasopressin and activates sympathoadrenal outflow, resulting in increases in arterial pressure and plasma glucose levels in conscious animals. Because compared with orexin-B, orexin-A is more potent in increasing arterial pressure and RSNA,8,9 we focused on the central effects of orexin-A in the present study. In addition, baroreceptor reflex and the sympathetic nervous system are greatly influenced by the anesthesia used in the experiments10,11; therefore, the present study was designed particularly to investigate the central effect of orexin-A on blood pressure, the sympathetic nervous system, and blood variables, including plasma catecholamines, vasopressin, insulin, and glucose levels, in conscious rabbits by directly recording the RSNA.

Methods

Preparation of Animals
The experiments were conducted on 26 male Japanese White rabbits weighing 2.5 to 2.7 kg. All experiments were carried out according

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to the institutional guidelines for animal experimentation at Kyushu University. Rabbits were anesthetized with pentobarbital sodium (30 mg/kg IV). Three days before experimentation, bipolar electrodes were implanted on the left renal sympathetic nerve, and a stainless-steel cannula was placed in the right lateral cerebral ventricle. RSNA was recorded as described previously. Briefly, under aseptic conditions, the left kidney was exposed retroperitoneally, and a branch of the renal nerve was separated from the renal plexus and the surrounding connective tissues with the use of a dissecting microscope. RSNA was recorded by a pair of electrodes made from polytetrafluoroethylene (Teflon)-insulated 7-stranded steel wire (Medwire). The area of the nerve and wire interface was embedded in silicone cement (Elastosil RT 604A and B cement, Wacker Chemicals).

A 23-gauge stainless-steel cannula was implanted into the right lateral cerebral ventricle, 4 mm lateral to the bregma and 6 mm below the cerebral surface. The position of the cannula in the lateral cerebral ventricle was confirmed by the staining of all 4 ventricles after injection of 0.1 mL dye at the end of the experiments. The cannula was fixed to the skull with 3 jeweler’s screws and dental cement. A 27-gauge obturator was used to seal the cannula. After surgery, disodium sulbenicillin (200 mg IV) was given to the rabbits to prevent postoperative infections.

At least 3 days after the surgical procedures, the following experiments were carried out on conscious rabbits placed in a box. On the day of the experiment, polyethylene catheters (PE-50) were inserted into the central ear artery and marginal ear vein under 1% lidocaine local anesthesia. The arterial catheter was connected to a pressure transducer (model P50, Gould Inc) to measure arterial pressure. Heart rate (HR) was monitored by use of a heart rate transducer (model 1332, NEC San-ei).

RSNA was amplified (model DPA-100E, Dia Medical System) and filtered (100 to 3000 Hz), and the waveforms were integrated after a full-wave rectification by using an integrator amplifier (model 1332, NEC San-ei) with the sample-hold function reset to baseline by an internal timer set at 5 seconds. The residual integrated RSNA that existed after intravenous administration of hexamethonium bromide (30 mg/kg IV) was taken as the noise level associated with nerve recording. This value was subtracted from absolute values of integrated RSNA before further data analysis was performed.

To minimize the influence of circadian changes in blood pressure and endocrine factors, the experiments were started at 9:00 AM and finished before 2:00 PM. All drugs for intracerebroventricular injection were dissolved in artificial cerebrospinal fluid (aCSF; in mmol/L: NaCl 133.3, KCl 3.4, CaCl₂ 1.3, MgCl₂ 1.2, NaH₂PO₄ 0.6, NaHCO₃ 32.0, and glucose 3.4).

Relationship Between Dose of Intracerebroventricular Orexin-A and Cardiovascular Responses
To determine the dose of orexin-A (Peptide Institute) needed to increase arterial pressure, aCSF (80 μL) and 10 and 100 pmol of orexin-A were injected intracerebroventricularly in the order of ascending concentrations (n = 5 for each). These doses of orexin-A were dissolved in 80 μL of aCSF. The administration of each dose of orexin-A was separated by 90 minutes. Arterial pressure, HR, and RSNA were monitored continuously.

Effect of Intracerebroventricular Orexin-A on Cardiovascular and Neurohormonal Responses
Two different groups of rabbits were used to determine the effect of intracerebroventricular orexin-A on cardiovascular and neurohormonal responses. After a control period, a blood sample (3.0 mL) was drawn from the arterial catheter to measure plasma catecholamines (epinephrine and norepinephrine), plasma vasopressin, plasma glucose, plasma insulin, plasma osmolality, and hematocrit in both groups. One group of rabbits (n = 6) was injected with orexin-A (100 pmol) in a volume of 80 μL, and another group (n = 5) was injected with aCSF (80 μL) via the intracerebroventricular cannula. Additional blood samples were drawn at 60 and 90 minutes after intracerebroventricular injection of orexin-A or aCSF. The blood samples were replaced by the same volume of 0.9% saline. Arterial pressure, HR, and RSNA were monitored continuously.

Effect of Pentolinium on Cardiovascular Responses Induced by Intracerebroventricular Injection of Orexin-A
To evaluate the contribution of the sympathetic nervous system to cardiovascular responses induced by intracerebroventricular orexin-A, pentolinium (5 mg/kg in 0.3 mL IV, Sigma Chemical Co), a ganglion-blocking agent, was injected in a different group of rabbits (n = 5). Five minutes later, a blood sample (3.0 mL) was drawn from the arterial catheter to measure plasma catecholamines (epinephrine and norepinephrine), plasma vasopressin, plasma glucose, plasma insulin, plasma osmolality, and hematocrit. Ten minutes after the intravenous injection of pentolinium, orexin-A (100 pmol) was injected intracerebroventricularly. An additional blood sample was drawn 60 minutes after intracerebroventricular injection of orexin-A. Additional pentolinium (2.5 mg/kg in 0.15 mL) was then injected intravenously to suppress sympathetic nerve activity at least 90 minutes after the intracerebroventricular injection of orexin-A. The last blood sample was drawn 90 minutes after the intracerebroventricular injection of orexin-A. The blood samples were replaced by the same volume of 0.9% saline. Arterial pressure, HR, and RSNA were monitored continuously.

Effect of Intravenous Injection of Orexin-A on Cardiovascular and Sympathetic Responses
To evaluate the leakage of intracerebroventricular injected orexin-A into the systemic circulation, the same dose of orexin-A (100 pmol) used in the intracerebroventricular injection experiment was injected intravenously (n = 5). Arterial pressure, HR, and RSNA were monitored continuously.

Blood Collection and Analysis
Blood samples for measurement of plasma catecholamines, vasopressin, and insulin were centrifuged at 4°C. Plasma for catecholamines was stored at −80°C, and other plasma was stored at −20°C until assay. The plasma catecholamine concentrations were measured by high-performance liquid chromatography, and plasma vasopressin and insulin levels were measured by radioimmunoassay. The assay sensitivities for vasopressin, catecholamines (epinephrine and norepinephrine), and insulin were 0.45 pg/mL, 10 pg/mL, and 1 μU/mL, respectively. Plasma glucose levels were measured by use of a Glucose Analyzer 2 (Beckman Instruments). Plasma osmolality was measured with a freezing-point osmometer (Osmotron-20, Orion Riken).

Statistical Analysis
All values are expressed as mean±SE. To determine the effects of intracerebroventricular and intravenous injections of orexin-A on cardiovascular and RSNA responses or blood variables, 1-way ANOVA with repeated measurements was performed, followed by the Duncan’s multiple range test to determine which means differed from the control means. In addition, 2-way ANOVA with repeated measurements was applied to compare the cardiovascular and neurohormonal responses to intracerebroventricular orexin-A with the responses to the intracerebroventricular administration of aCSF. A value of P<0.05 was considered significant.

Results
Relationship Between Dose of Intracerebroventricular Orexin-A and Cardiovascular Responses
Baseline values for mean arterial pressure (MAP) and HR before the intracerebroventricular injection of orexin-A were 94.0±2.5 mm Hg and 212.0±14.5 bpm, respectively. Intravenous injection of 0.05 was considered significant.
cerebroventricular injection of orexin-A elicited dose-related increases in MAP and RSNA (Figure 1). The results shown in Figure 1 illustrate the peak responses for MAP, HR, and RSNA obtained during a 90-minute recording period. Because 100 pmol of orexin-A caused significant increases in MAP and RSNA, we used this dose of orexin-A in the following experiments.

Effect of Intracerebroventricular Orexin-A on Cardiovascular and Neurohormonal Responses

Figure 2 shows the typical responses of MAP, HR, and RSNA that were elicited by intracerebroventricular injection of orexin-A (100 pmol). Intracerebroventricular injection of 100 pmol of orexin-A provoked significant increases in MAP and RSNA, and the peak values of these variables were obtained after 40 and 25 minutes, respectively (Figure 3).

After the peak values were obtained, MAP and RSNA decreased and returned to their baseline levels within 90 to 120 minutes. The interactions between the effect of the treatments (orexin-A or aCSF administration) and time course of MAP and RSNA in 2-way ANOVA with repeated measurements were \( P<0.0001 \) and \( P<0.0001 \), respectively. HR did not show any significant changes; however, the interactions between the effect of the treatments (orexin-A or aCSF administration) and time course of HR in 2-way ANOVA with repeated measurements was \( P=0.0001 \).

Table 1 shows the effects of intracerebroventricular injection of orexin-A or aCSF on plasma catecholamine and vasopressin concentrations and other variables. Intracerebroventricular injection of orexin-A caused significant increases in plasma epinephrine and glucose concentrations at 60 and
90 minutes. Plasma vasopressin concentration also significantly increased at 90 minutes after intracerebroventricular injection of orexin-A. Plasma norepinephrine and insulin concentrations increased at 60 and 90 minutes but did not attain the significant values. Plasma osmolality and hematocrit did not show any changes. In contrast, intracerebroventricular injection of aCSF failed to cause any significant changes in blood variables. The interactions between the effect of the treatments (orexin-A or aCSF administration) and the time course of epinephrine, norepinephrine, vasopressin, or glucose concentrations were statistically significant by 2-way ANOVA with repeated measurements ($P<0.05$ for each). Rabbits sat quietly in the box, and behavioral effects of intracerebroventricular orexin-A were not observed throughout the experimental period.

**Effect of Pentolinium on Cardiovascular Responses Induced by Intracerebroventricular Injection of Orexin-A**

After pentolinium administration, MAP fell from $90.8 \pm 2.5$ to $52.8 \pm 3.3$ mm Hg, and HR increased from $225.0 \pm 11.5$ to $276.0 \pm 34.0$ bpm. However, intracerebroventricular injection of orexin-A failed to cause any further responses in MAP or HR, and RSNA was almost completely suppressed until 90 minutes after injection of orexin-A. Table 2 shows the effects of pentolinium on blood variables induced by intracerebroventricular injection of orexin-A. Plasma epinephrine, norepinephrine, insulin, and glucose levels did not show any significant changes. Intravenous injection of pentolinium increased plasma vasopressin concentrations; however, intracerebroventricular injection of orexin-A failed to cause further changes in plasma vasopressin concentrations.

**Effect of Intravenous Injection of Orexin-A on Cardiovascular and Sympathetic Responses**

The same dose of orexin-A (100 pmol) used in the intracerebroventricular experiment was injected intravenously. After intravenous injection of orexin-A, arterial pressure, HR, and RSNA remained within 5% of their control values.

**TABLE 1. Effects of Intracerebroventricular Injection of 100 pmol Orexin-A or aCSF on Blood Variables**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Time</th>
<th>n</th>
<th>0 min</th>
<th>60 min</th>
<th>90 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine, pg/mL</td>
<td>aCSF</td>
<td>5</td>
<td>53.6±8.0</td>
<td>36.0±10.3</td>
<td>42.8±11.0</td>
</tr>
<tr>
<td></td>
<td>Orexin-A</td>
<td>6</td>
<td>38.0±12.8</td>
<td>108.7±27.3</td>
<td>167.5±42.5†</td>
</tr>
<tr>
<td>Norepinephrine, pg/mL</td>
<td>aCSF</td>
<td>5</td>
<td>238.2±27.2</td>
<td>179.8±30.0</td>
<td>189.4±19.4</td>
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<tr>
<td></td>
<td>Orexin-A</td>
<td>6</td>
<td>260.3±34.4</td>
<td>381.2±64.0</td>
<td>356.7±52.0</td>
</tr>
<tr>
<td>Vasopressin, pg/mL</td>
<td>aCSF</td>
<td>5</td>
<td>3.2±0.9</td>
<td>3.4±0.8</td>
<td>3.3±0.5</td>
</tr>
<tr>
<td></td>
<td>Orexin-A</td>
<td>6</td>
<td>2.5±0.6</td>
<td>4.4±1.1</td>
<td>5.5±1.1*</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>aCSF</td>
<td>5</td>
<td>0.364±0.003</td>
<td>0.363±0.003</td>
<td>0.362±0.003</td>
</tr>
<tr>
<td></td>
<td>Orexin-A</td>
<td>6</td>
<td>0.373±0.011</td>
<td>0.373±0.011</td>
<td>0.372±0.011</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>aCSF</td>
<td>5</td>
<td>6.48±0.13</td>
<td>6.53±0.17</td>
<td>6.67±0.14</td>
</tr>
<tr>
<td></td>
<td>Orexin-A</td>
<td>6</td>
<td>6.66±0.18</td>
<td>7.39±0.22</td>
<td>7.75±0.14†</td>
</tr>
<tr>
<td>Insulin, µU/mL</td>
<td>aCSF</td>
<td>5</td>
<td>13.4±3.1</td>
<td>11.6±1.3</td>
<td>12.2±1.3</td>
</tr>
<tr>
<td></td>
<td>Orexin-A</td>
<td>6</td>
<td>12.0±3.8</td>
<td>19.8±6.3</td>
<td>22.5±7.7</td>
</tr>
<tr>
<td>Osmolality, mOsm/L</td>
<td>aCSF</td>
<td>5</td>
<td>293.6±4.0</td>
<td>297.8±2.4</td>
<td>298.2±4.6</td>
</tr>
<tr>
<td></td>
<td>Orexin-A</td>
<td>6</td>
<td>309.5±3.0</td>
<td>309.0±3.8</td>
<td>304.2±2.6</td>
</tr>
</tbody>
</table>

Values are mean±SE. n indicates number of rabbits. *$P<0.05$ and †$P<0.01$ compared with control (0 min) by Duncan’s multiple range test.

**TABLE 2. Effects of Pentolinium on Responses of Blood Variables Induced by Intracerebroventricular Injection of Orexin-A**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine, pg/mL</td>
<td>12.0±2.0</td>
</tr>
<tr>
<td>Norepinephrine, pg/mL</td>
<td>96.8±51.2</td>
</tr>
<tr>
<td>Vasopressin, pg/mL</td>
<td>36.0±4.2</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>0.337±0.010</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>6.84±0.08</td>
</tr>
<tr>
<td>Insulin, µU/mL</td>
<td>14.0±1.9</td>
</tr>
<tr>
<td>Osmolality, mOsm/L</td>
<td>314.4±5.1</td>
</tr>
</tbody>
</table>

Values are mean±SE.
Discussion

The present study demonstrated that intracerebroventricular injection of orexin-A caused significant increases in arterial pressure, RSNA, and plasma epinephrine concentrations. Intravenous injection of pentolinium, a ganglion-blocking agent, abolished the responses of arterial pressure and of plasma epinephrine concentrations. These results suggest that the pressor response induced by the intracerebroventricular injection of orexin-A can be attributed primarily to enhanced sympathetic outflow, although plasma norepinephrine concentrations did not change significantly. Furthermore, intravenous injection of the same dose of orexin-A used in the intracerebroventricular injection experiment failed to cause any cardiovascular and sympathetic responses, suggesting that the responses induced by the intracerebroventricular injection of orexin-A were not caused by a leakage of orexin-A into the systemic circulation. To the best of our knowledge, this is the first study to demonstrate simultaneously the responses of RSNA, plasma catecholamines, vasopressin, insulin, and glucose levels to the central administration of orexin-A in conscious animals.

Intracerebroventricular injection of orexin-A (100 pmol) elicited only a small increase in HR in the present study. In contrast, Shirasaka et al demonstrated that intracerebroventricular injection of orexin-A (3 nmol) caused a significant increase in HR in conscious rats. This different response of HR might be attributed to both the difference in species used in the experiments and applied doses of orexin-A.

Central orexins stimulate food intake; however, the effects of orexin-A on blood glucose and insulin levels remain to be investigated. Haynes et al reported that intracerebroventricular infusion of orexin-A (18 nmol/d) for 8 days did not change blood glucose and plasma insulin levels in rats. In contrast, Nowak et al showed that a subcutaneous bolus injection of orexin-A (1 or 2 nmol) increased both blood glucose and insulin levels and that orexin-A stimulated insulin secretion in an in vitro perfusion system of a rat pancreatic preparation. In the present study, intracerebroventricular injection of orexin-A caused significant and long-lasting increases in plasma epinephrine and glucose concentrations. In contrast, plasma insulin levels increased but did not reach significant levels. The effects of orexin-A on blood glucose levels may vary depending on whether its administration is acute or chronic. The present study has an advantage in that the experiments were conducted on conscious animals and that serial changes of plasma catecholamine concentrations were determined. Parallel changes of plasma glucose levels and plasma epinephrine concentrations suggest a close relationship between these 2 variables. Hyperglycemia has been shown to be evoked by an increase in plasma epinephrine concentration; thus, this response of the plasma glucose level was likely attributable to the increased plasma epinephrine concentration. Subsequently, this increase in the plasma glucose level might induce a slight increase in the plasma insulin level in the present study.

Intracerebroventricular injection of orexin-A also elicited an increase in plasma vasopressin concentration. In the present study, because neither plasma osmolality nor hematocrit changed after intracerebroventricular injection of orexin-A and because increased plasma levels of epinephrine would be expected to cause an increase in venous return, the changes in the central venous pressure were not considered to stimulate the release of vasopressin. Orexin-containing fibers are present both in the paraventricular thalamic nucleus and in the supraoptic nucleus. In addition, intracerebroventricular injections of orexins have been shown to induce c-fos expression in both nuclei. Therefore, these anatomic and functional studies suggest that intracerebroventricular injection of orexin-A in the present study might directly stimulate the paraventricular nucleus or supraoptic nucleus of the hypothalamus, resulting in the release of vasopressin into the systemic circulation.

The present study did not clarify the exact site at which orexin-A acts in the central nervous system or the mechanisms of pressor response and activation of sympathetic nervous system induced by intracerebroventricular orexin-A. Recently, Chen et al demonstrated that intracisternal injection of orexin-A caused an increase in arterial pressure and that microinjection of orexin-A into the rostral ventrolateral medulla elicited a long-lasting increase in arterial pressure in anesthetized rats. Their findings suggest that intracerebroventricular orexin-A may directly stimulate the rostral ventrolateral medulla to activate the sympathetic nervous system and to increase arterial pressure. On the other hand, high orexin contents are reportedly present in the lateral hypothalamus, ventromedial hypothalamic nucleus, and paraventricular thalamic nucleus, and primary sites of the brain at which orexins act to stimulate food intake have been considered to be in the hypothalamus. Immunohistochemical study showed that orexin-A immunoreactive neurons in the tuberal hypothalamic nucleus project to the medulla. Therefore, intracerebroventricular orexin-A might primarily act at the hypothalamic nuclei and, subsequently, stimulate the cardiovascular center of the medulla, such as the ventrolateral medulla or the nucleus of the solitary tract. The fact that intracerebroventricular orexin-A stimulated vasopressin secretion in the present study may support this hypothesis. A study focusing on the microinjection of orexin-A into the hypothalamic nucleus in cardiovascular and sympathetic regulations.

Neurotransmitters, such as neuropeptide Y, agouti-related protein, cocaine- and amphetamine-regulated transcript, α-melanocyte–stimulating hormone, and orexins, have been shown to be involved in feeding in the central nervous system and to interact with leptin. These neurotransmitters seem to function together in cardiovascular and sympathetic regulations as well as in the regulations of food intake and energy expenditure. Central leptin activates the sympathetic nervous system and increases arterial pressure; conversely, central neuropeptide Y has been shown to suppress the sympathetic nervous system and decrease arterial pressure. Our recent findings also demonstrated that leptin inhibited the central cardiovascular action of neuropeptide Y in conscious rabbits. Orexin-A may also interact with these peptides to participate in cardiovascular and sympathetic regulation, although direct evidence remains to be demonstrated.

In conclusion, orexin-A exerted a central pressor action mediated primarily by enhanced sympathoadrenal outflow,
and these effects were accompanied by increases in plasma vasopressin and glucose levels. Orexin-A may participate in central cardiovascular and sympathetic regulation as well as in the regulation of appetite and food intake, although physiological implications have not yet been determined. Further studies are necessary to determine the exact site of the brain at which orexin-A acts to augment the sympathoadrenal outflow.

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References
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