Calcitonin gene-related peptide and substance P contribute to reduced
blood pressure in sympathectomized rats

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1Department of Medicine, Texas A&M University System Health Science Center College of Medicine and Scott & White Health System, Temple, Texas; 2Department of Surgery, University of Texas Medical Branch, Galveston, Texas; and 3Department of Pharmacology and Toxicology, Michigan State University, East Lansing, Michigan

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Supowit, S. C., R. T. Ethridge, H. Zhao, K. A. Katki, and D. J. DiPette. Calcitonin gene-related peptide and substance P contribute to reduced blood pressure in sympathectomized rats. Am J Physiol Heart Circ Physiol 289: H1169–H1175, 2005. First published May 6, 2005; doi:10.1152/ajpheart.00973.2004.—CGRP and substance P (SP) are produced in dorsal root ganglia (DRG) sensory neurons and modulate vascular tone. Sympathetic and sensory nerves compete for NGF, a potent stimulator of CGRP and SP, and it has been suggested that sympathetic hyperinnervation in spontaneously hypertensive rats may reduce the availability of NGF to sensory nerves, thus reducing CGRP and SP. The purpose of this study was to determine whether destruction of peripheral sympathetic nerves in normal rats would increase the availability of NGF for sensory neurons and enhance expression of CGRP and SP. Sympathectomy was produced in rats by guanethidine sulfate administration. Control rats received saline. Sympathectomized rats displayed reductions in blood pressure (BP) and atria norepinephrine levels, whereas NGF levels in the DRG, spleen, and ventricles were increased. Sympathectomy also enhanced CGRP and SP mRNA and peptide content in DRG. Administration of CGRP and SP receptor antagonists increased the BP in sympathetically innervated rats but not in the controls. Thus sympathectomy enhances sensory neuron CGRP and SP expression that contributes to the BP reduction.

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Calcitonin gene-related peptide (CGRP) and substance P (SP) are potent vasodilator neuropeptides that have been implicated in the regulation of regional organ blood flows and blood pressure (BP), both under normal physiological conditions and in hypertension (6, 7, 9, 10, 15, 16, 36, 43, 54). Immunoreactive CGRP (iCGRP), SP (iSP), and their receptors are widely distributed in the nervous and cardiovascular systems (6, 7, 9, 10, 15, 16, 23, 54). A prominent site of CGRP and SP production is the dorsal root ganglia (DRG) that contain the cell bodies of sensory nerves that terminate peripherally in blood vessels and in other tissues innervated by the sensory nervous system and that terminate centrally in the dorsal horn of the spinal cord. A dense perivascular CGRP and SP neural network is seen around the blood vessels in all vascular beds. In these vessels, CGRP and SP containing nerves are found at the junction of the adventitia and the media passing into the muscle layer (6, 9, 10, 15, 16, 23, 54). Indeed, these peptides are often colocalized in the same peripheral nerve terminals. CGRP and SP are released tonically and circulate normally in humans and animals (6, 9, 15, 25, 26, 54). Plasma CGRP is largely derived from perivascular nerve terminals and is thought to represent a spillover phenomenon related to the release of these peptides to promote vasodilation or other functions. Plasma SP also comes from these perivascular nerve terminals as well as the intestine. Receptors for CGRP have been identified in the endothelial layer, media, and intima of resistance vessels, whereas SP receptors (neurokinin-1 (NK1) receptor) are expressed by endothelial cells (6, 9, 10, 15, 16, 23, 25, 54).

The sympathetic nervous system is intricately involved in BP regulation and also modulates CGRP and SP expression in DRG neurons. Norepinephrine (NE) interacts with α2-adrenoceptors on primary afferent nerve terminals, thus inhibiting the production and release of CGRP and SP (18, 25, 30). There is a second mechanism by which the sympathetic nervous system may regulate neuropeptide expression in DRG neurons. Several lines of evidence indicate that in peripheral target tissues, sensory and sympathetic nerve terminals compete for NGF, a potent stimulator of CGRP and SP expression and release (18, 52). For example, 6-hydroxydopamine treatment, which destroys nerves and thereby prevents the uptake of NGF by sympathetic neurons, markedly increases the NGF content of DRG over control levels (34, 55). In addition, long-term sympathectomy of the rat results in significant increases in iCGRP and iSP in multiple tissues (1, 2, 8, 37). Finally, Bolden et al. (4) reported that surgical bilateral removal of the superior cervical ganglion significantly increased CGRP mRNA content in DRG.

If sympathectomy can elevate CGRP (and SP) synthesis in DRG neurons, perhaps as a result of increased availability of NGF, it is then possible that an increase in sympathetic nerves, relative to sensory nerves, could decrease the amount of NGF available for the sensory nerves that, in turn, could lead to a reduction in CGRP and SP synthesis. There is considerable data that sympathetic innervation and catecholamine content of vascular tissue is significantly greater in the spontaneously hypertensive rat (SHR) (24, 56). Our laboratory and other investigators (31, 47, 49) have previously reported that in the SHR there is an age-related decrease in the expression of CGRP that may contribute to the elevated BP observed in this setting. SP expression is also markedly reduced in this strain of genetically hypertensive rat (33). In addition, neonatal sympathectomy of the SHR significantly attenuates the development of hypertension. Whether CGRP (or SP) plays a role in this BP reduction is not known. In the present study, to clarify the interactions between the sympathetic and sensory nervous systems and NGF, chronic guanethidine sulfate administration...
was used to destroy peripheral sympathetic nerves in normal rats. We then measured BP, tissue catecholamine levels, NGF content in both DRG and peripheral target tissues, and the abundance of CGRP and SP mRNA and peptides in DRG neurons. In addition, CGRP and SP receptor antagonists were administered to determine whether these sensory neuropeptides were playing a role in the regulation of basal BP after sympathectomy.

MATERIALS AND METHODS

Animals. The animal protocols used for this study were approved by the University Animal Care and Use Committee of Texas A&M University System Health Science Center and Scott & White Health System and were in accordance with the National Institutes of Health Guidelines for the Care and Use of Laboratory Animals. Male Sprague-Dawley (Harlan Sprague Dawley, Houston, TX) rats (n = 8), initially weighing 150 g, were given guanethidine sulfate (50 mg/kg ip) 5 days/wk for 5 wk (38, 39). Control rats (n = 8) received injections of saline for the same time period. Once a week, animals were weighed and the systolic BPs were determined by the tail-cuff method (Gould, Cleveland, OH).

At the end of the treatment period each rat was anesthetized with halothane. Catheters were surgically placed in the left carotid artery, for continuous mean arterial pressure (MAP) and heart rate recording, and in the right jugular vein, for drug administration. The catheter used for MAP recording was coupled to a pressure transducer and recorder (Gould). Hemodynamic studies were then performed 3 h after surgery with the animals in a fully awake and unrestrained state. Our laboratory (29, 50) has previously validated the use of the CGRP and NK1 receptor antagonists by showing that CGRP8–37 (50 and 200 μg) and spantide II (350 and 150 μg) and were completely block the hypertensive effects of exogenously administered CGRP and SP, respectively. These same doses were used in the current study. Briefly, the antagonists were dissolved in neutral saline and injected slowly by hand for over ~15 s. In addition, in using DOC-salt hypertensive rats, subtotal nephrectomy (SN)-salt hypertensive rats, and their corresponding normotensive controls, we have shown that the BP response to CGRP receptor antagonist administration is similar 24 h after surgery compared with the 3 h used in this study (unpublished observations).

At the end of each experiment, the rats were deeply anesthetized with ketamine-xylazine via the cannulated jugular vein and then euthanized by decapitation. The atria, ventricles, spleen, and DRG were removed, weighed, frozen in liquid nitrogen, and stored at −80°C. For each animal, the DRG on one side of the spinal cord (cervical, thoracic, and lumbar) were separated from those on the other side of the cord such that half of the DRG were used for CGRP and SP mRNA analysis and the other half for CGRP and SP peptide quantification. Using this method, we were unable to determine whether there was any difference in the upregulation of these neuropeptides among the three anatomical regions.

Hybridization probes, RNA isolation and analysis, and radioimmunoassay. The α-CGRP hybridization probe was a 1.4-kb Sau 3A rat genomic restriction fragment containing CGRP exons 5 and 6 (41). The SP hybridization probe was a 0.56 kb BamHI CDNA restriction fragment of the rat SP (preprotachykinin-A) gene (18). The 18S rRNA hybridization probe was a 1.15-kb BamHI-EcoRI restriction fragment of the mouse 18S rRNA gene (5). The DNA inserts were labeled with [α-32P]-dCTP using a random hexanucleotide DNA labeling kit (Amersham, Arlington Heights, IL). Total cellular RNA was isolated from the DRG tissue by the guanidine-isothiocyanate method (42). The RNA samples were fractionated initially with the α-CGRP DNA probe. After hybridization, the membranes were washed and placed on a phosphor screen. The exposed screen was then placed in a Phosphor-Imager (Amersham, Piscataway, NJ) that generates an image of the hybridized RNA and quantifies the radioactivity in each hybridization signal. This process was repeated for the SP DNA probe and finally for the 18S rRNA hybridization probe that is used as an internal control to normalize the CGRP and SP mRNA hybridization signals.

To quantify iCGRP and iSP in the DRG tissue, commercially available rabbit anti-rat CGRP and rabbit anti-rat SP radioimmunoassay (RIA) kits (Phoenix Pharmaceuticals, Belmont, CA) were employed. The anti-CGRP antibody has 100% cross-reactivity with rat α-CGRP and 79% with rat β-CGRP. There is no detectable cross-reactivity with rat amylin, calcitonin, somatostatin, or SP. The anti-SP antibody has 100% cross-reactivity with SP and none with somatostatin, neurokinin-B, or neurokinin-A. All assays were performed as recommended by the supplier. The total protein content in each sample was determined by the Bradford method (Bio-Rad, Gaithersburg, MD).

Catecholamine analysis. NE and epinephrine (Epi) levels were measured in heart atria using a previously published method (8). Briefly, atria were homogenized in 0.2% perchloric acid-10% EDTA and stored at −70°C until the time of the assay. Tissue NE and Epi contents were determined by a high-pressure liquid chromatography-electrochemical detection procedure.

NGF analysis. NGF concentrations in the heart ventricles, spleen, and DRG were determined using the NGF Emax Immunoassay System (Promega, Madison, WI) under conditions recommended by the supplier.

Statistical analysis. Statistical significance was determined by the Student’s t-test or, where appropriate, by ANOVA, followed by the Tukey-Kramer multiple comparisons test. The acceptable level of significance was set at a value of P < 0.05. Data in the figures are presented as means ± SE.

RESULTS

Guanethidine treatment. Sympathectomy was produced in Sprague-Dawley rats by the chronic administration of guanethidine sulfate. As reported by other investigators (38, 39), the guanethidine-treated rats did not gain weight as rapidly as their saline-treated counterparts. This difference was significant by day 7 and was maintained throughout the treatment period (day 35 body weight, sympathomtomized rats, 271 ± 7 vs. control rats 304 ± 12 g; P < 0.05). Other than this attenuation of weight gain, the guanethidine-treated rats appeared healthy and alert with no obvious deleterious effects of the drug.

BP determinations. Because a reduction in systemic BP is often observed in sympathectomized rats (38, 39), tail-cuff systolic BP measurements were made on a weekly basis. As shown in Fig. 1A, by day 7 there was a significant decrease in systolic BP in the guanethidine-treated animals, and this decrease was maintained for the duration of the protocol. To determine whether the marked reduction in systolic BP observed in the guanethidine-treated rats was reflected in the MAP, at the end of the treatment period (day 35), rats had arterial (for continuous MAP recording) and intravenous (for drug administration) catheters surgically placed and were studied in a fully awake and unrestrained state. As expected, the MAP was significantly lower in the guanethidine-treated rats compared with control animals (guanethidine treated, 108 ± 3 vs. control 126 ± 5 mmHg; Fig. 1B). After this procedure, each animal was treated with intravenous infusions of saline, a CGRP receptor antagonist (CGRP8–37), and a SP receptor (NK1) antagonist (spantide II) to assess the possible contribution of CGRP and/or SP to the decreased BP observed in the sympathectomized rats. Administration of saline did not sig-
significantly change MAP in either group (sympathectomized rats 2.8 ± 0.5 vs. control 2.0 ± 0.9 mmHg). Likewise, as shown in Fig. 2A, bolus intravenous administration of two different doses of CGRP8–37 did not produce a significant alteration in MAP in the control group. In contrast, the infusion of CGRP8–37 to the guanethidine-treated rats rapidly (the MAP increase began ~15 to 20 s after antagonist administration) increased the MAP at both the lower (5.3 ± 0.9 mmHg) and higher (11.3 ± 2.5 mmHg) doses. The duration of the pressor activity of CGRP8–37 was relatively short (~90 s for the lower dose and 120 s for the higher dose). This transient effect of CGRP8–37 has been observed by other investigators (6, 22), who have used this antagonist in vivo, and most likely reflects the rapid proteolysis of this peptide in the circulation. Like-wise, administration of a bolus dose of spantide II significantly increased the MAP (7.8 ± 0.7 mmHg) in the sympathectomized rats compared with the control animals (Fig. 2B). The MAP began to rise 30 s after administration and was elevated for ~180 s similar to CGRP8–37. Spantide II is a peptide that is also rapidly degraded in the circulation (33). No significant changes in heart rate were observed with either antagonist.

Catecholamine levels in heart atria. Heart atria tissue was processed from both groups of rats to evaluate catecholamine levels. As expected, the guanethidine-treated animals displayed a marked reduction in both NE and Epi content compared with the control group (Table 1).

NGF content of DRG, heart ventricles, and spleen. NGF levels in DRG, heart ventricles, and spleen were examined by ELISA. Figure 3 shows that all three tissues from the guanethidine-treated rats displayed a significant increase (ventricles, 1.4-fold; spleen, 1.3-fold; and DRG, 1.5-fold) in NGF content compared with the same tissues from the control animals.

Fig. 1. Systolic blood pressure and mean arterial pressure (MAP) were decreased in the guanethidine-treated animals. A: tail-cuff method was used to measure systolic blood pressure in control (●; n = 8) and sympathectomized (SX) (▲; n = 8) rats during guanethidine treatment beginning at day 0. B: after guanethidine treatment (day 35), rats were instrumented for continuous MAP recording and were studied in a conscious and unrestrained state. Values are reported as means ± SE. *P < 0.05, **P < 0.01.

Fig. 2. CGRP8–37 and spantide II increase MAP in the guanethidine-treated animals. Rats were instrumented for continuous MAP recording and intravenous administration of saline, CGRP8–37, and spantide II. Studies were performed with rats fully awake and unrestrained. A: bolus doses of saline (50 µg, open bar) and CGRP8–37 (200 µg, solid bar) were given intravenously. B: bolus doses of saline and spantide II (350 µg) were given intravenously. MAP values are reported as means ± SE. *P > 0.05, SX vs. control animals.

Table 1. Effect of chemical sympathectomy on catecholamine levels in heart atria

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<th>NE (pmol/mg wet wt)</th>
<th>Epi (pmol/mg wet wt)</th>
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<tr>
<td>Control</td>
<td>6.10 ± 0.37</td>
<td>0.58 ± 0.01</td>
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<tr>
<td>SX</td>
<td>0.52 ± 0.01</td>
<td>0.02 ± 0.01*</td>
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Values are means ± SE (in pmol/mg wet wt); n, number of rats. SX, sympathectomized animals. *P < 0.05.
DRG from the sympathectomized rats were significantly elevated (1.7- and 1.9-fold, respectively) compared with the control rats.

DISCUSSION

The main findings of the present study are 1) sympathectomy produces an increase in NGF content in two target organs (spleen and heart ventricles) innervated by the sensory and sympathetic nervous systems; 2) CGRP and SP mRNA and peptide synthesis is enhanced in the sympathectomized animals; and 3) acute administration of either CGRP or SP receptor antagonists significantly increases the MAP in the guanethidine-treated rats but not the control animals, indicating that these sensory neuropeptides are contributing to the decreased BP that is observed in the sympathectomized rats.

Chemical sympathectomy with guanethidine selectively destroys the postganglionic noradrenergic neurons, whereas dopaminergic fibers and nonneural catecholamine-secreting cells are spared (17, 27, 38, 39). This destruction of peripheral sympathetic nerves occurs through an immune system-mediated response. Other investigators (1, 2, 17, 27) using a similar treatment protocol have reported a loss of ~95% of the nerve cells of the superior ganglia and dramatically lower levels of NE in all tissues except the adrenal gland and paraganglia. In the present study, we observed a >10-fold decrease in NE and Epi levels in the heart atria from the guanethidine-treated animals compared with the control group. This result is in line with heart catecholamine levels in sympathectomized and control rats reported by other investigators (17, 27, 38, 39) and, along with the BP reduction displayed by guanethidine-treated rats used for this study, is consistent with having achieved an almost total chemical sympathectomy.

Sympathetic and sensory nerves appear to compete for NGF produced by peripheral target tissues. Therefore, it was not surprising that there was a modest, but significant, increase in NGF content in DRG from the guanethidine-treated rats compared with controls. We also observed a similar increase in NGF levels in heart ventricles and spleen, both of which are target tissues for sympathetic and sensory nerves. Although we do not know whether NGF content is increased in other target tissues, this result is in agreement with a previous study (28) that showed that chemical denervation of adult rats with 6-hydroxydopamine significantly increased the concentration of this neurotrophin in the heart. In contrast, 6-hydroxydopamine treatment of neonatal rats did not change NGF mRNA levels in heart ventricles (13). The most plausible explanation for these observations is that in sympathectomized rats, NGF accumulates in target tissues because there is decreased uptake and sequestration of this protein by sympathetic nerves. This elevation of NGF content, in the absence of an upregulation in synthesis, is apparently sufficient to allow for both an increase in NGF uptake by sensory nerves and an accumulation of this neurotrophin in the target tissues.

Fig. 3. NGF levels were increased in the guanethidine-treated rats. After 5 wk of guanethidine treatment, heart ventricles (A), spleens (B), and dorsal root ganglia (DRG, C) were removed from control and SX rats and assayed for NGF content. NGF values are expressed as means ± SE. *P < 0.05.

Fig. 4. Guanethidine treatment results in increased CGRP mRNA and peptide expression in DRG neurons. A: Northern blot analysis of DRG total RNA samples from control and SX animals. The nylon membrane was initially hybridized with the 32P-labeled CGRP probe (top). It was then stripped and hybridized with the 32P-labeled 18S rRNA probe (bottom). B: densitometric measurement of CGRP mRNA normalized to 18S rRNA. C: DRG from control and SX rats were analyzed for immunoreactive CGRP (iCGRP) levels by RIA. Values are expressed as means ± SE. *P < 0.05, SX vs. control.
CGRP and SP mRNA and peptide content are also significantly increased in DRG from the sympathectomized rats compared with control animals. Although we did not measure CGRP and SP peptide content in peripheral tissues, these results are consistent with reports from other investigators that show an increase in the levels of these neuropeptides in a number of peripheral tissues after guanethidine or 6-hydroxydopamine treatment of rats. Moreover, this increase appears to be due to both a stimulation of sensory nerve sprouting and enhanced CGRP and SP production (1, 2, 8, 37). It is likely that the enhanced neuronal expression of CGRP and SP that we observed was due, at least in part, to the increased availability of NGF for the sensory nerves. The 5′ regulatory regions of both the α-CGRP/calcitonin and SP (preprotrachykinin-A) genes contain multiple sites for response cAMP regulatory element binding proteins (octamer binding protein, basic helix-loop-helix proteins) that are all regulated by NGF (18, 19, 26), and several lines of evidence indicate that NGF stimulates long-term CGRP and SP expression in mature sensory neurons both in vitro and in vivo (35, 44, 46, 49).

The marked reduction in tissue catecholamine levels produced by destruction of peripheral sympathetic nerves may also contribute to the enhanced production of CGRP and SP in the guanethidine-treated rats. NE interacts with α2-adrenergic receptors on primary sensory nerve terminals in both the spinal cord and the periphery, thus inhibiting the release of CGRP and SP (30, 46). Using primary cultures of adult DRG neurons, we (46) demonstrated that α2-adrenergic agonists significantly decrease long-term CGRP mRNA accumulation and iCGRP release and that the inhibitory effects of these agents are mediated by attenuation of the stimulatory actions of NGF. This is important because sensory (and sympathetic) neurons receive a continuous supply of NGF from their peripheral target tissues, and it appears that this neurotrophin plays a critical role in determining the set point for basal CGRP and SP expression and release (35).

Taken together, these data suggest that the increase in NGF availability and decrease in NE are the stimuli that are responsible, at least in part, for the presumed increase in CGRP and SP release in the sympathectomized animals. Other local and circulating factors that can regulate both short-term release and long-term production and release of CGRP and SP include other neurotrophins (6, 35, 49), glucocorticoids (44), bradykinin and prostaglandins (6, 54), mediators of inflammation (6, 54), endothelin (6, 54), and the renin-angiotensin system (6, 40). It is possible that some of these factors could be altered by the guanethidine treatment and contribute to the observed results. There is also the potential that the alterations in sensory nerve function described in this study may relate to the guanethidine itself. There may be a chronic inflammatory response to the drug, and/or destruction of the sympathetic fibers could produce an inflammatory response, thus causing tonic CGRP and SP release. To the best of our knowledge, there are no reports in the literature that describe such a phenomenon, but it cannot be completely dismissed either. There are, however, two reports suggesting that this is not the case. First, Nielsen (39) administered guanethidine (40 mg/kg) daily for 3 mo, followed by a discontinuation for 1 day or 3 mo. MAP was lowered by 33 and 54 mmHg at the discontinuation times of 1 day and 3 mo, respectively. These data demonstrate that the hypotensive response produced by sympathectomy does not require the continued presence of guanethidine but does not rule out a chronic inflammatory response initiated by the drug. Moreover, in the previously mentioned study by Bolden et al. (4), sympathectomy was done surgically by bilateral removal of the superior cervical ganglia. Significant increases in GAP-43 mRNA, a specific marker for axonal outgrowth, were observed in cervical and thoracic DRG up to the longest time point studied (45 days after surgery) compared with the sham-operated controls. Likewise, there was a marked increase in iCGRP in sensory nerve fibers in the eye from 2 wk to the 45-day time point. CGRP mRNA content was also significantly elevated in cervical and thoracic DRG. Thus major alterations in the long-term expression of sensory nerve peptides were induced by sympathectomy produced by surgical rather than chemical methodologies.

The BP reduction observed during the course of the guanethidine treatment is consistent with the results obtained by other investigators (38, 39) using similar doses of this drug and treatment times. In addition, administration of CGRP or SP receptor antagonists at doses that completely blocked the depressor effects of their exogenous agonist counterparts significantly increased the MAP in the sympathectomized rats but were without effect in the normotensive controls. Thus it appears that these neuropeptides play a role in the BP reduction that accompanies sympathectomy. This interpretation must be
qualified by the fact that the antagonist administration was done acutely, so one must be cautious when extrapolating this result to the long-term setting. It should be noted that complete deletion of the α-CGRP gene as seen in two different strains of CGRP knockout mice produces a significant increase in basal mean BP (21, 40). This phenotypic change likely involves multiple mechanisms, including the direct loss of a potent vasodilator (21) and/or the activation of the sympathetic nervous system (38) and the renin-angiotensin system (40). In the mouse, it is not uncommon that the deletion of a particular gene produces a different phenotype compared with pharmacological inhibition of its activity or blockade of its receptor (12).

Our antagonist studies are, however, consistent with a growing body of evidence that endogenous CGRP and/or SP can play a significant role in the regulation of systemic vascular tone under certain conditions that produce a major challenge to blood pressure homeostasis. In previous studies (3, 11, 14, 20, 32, 33, 45, 50, 51, 53) the participation of these sensory neuropeptides in the regulation of systemic BP has been observed primarily in rodent models of experimental hypertension. In these studies our laboratory and others have reported that CGRP and/or SP play a compensatory vasodilator role in pulmonary hypertension (3, 11, 32, 53); DOC salt (30, 50); SN salt (51); two-kidney, one-clip (14); and L-NAME-induced pulmonary hypertension (3, 11, 32, 33, 45, 50, 51, 53) the participation of these sensory neuropeptides, including CGRP and SP, from their peripheral innervation of the rat uterus during maturation. In vivo gene transfer of prepro-calcitonin gene-related peptide to the lung attenuates chronic hypoxia-induced pulmonary hypertension in the mouse. Influence of gene transfer in vivo. Regul Pept 108: 129–133, 2002.


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