Monoamine- and Histamine-Synthesizing Enzymes and Neurotransmitters Within Neurons of Adult Human Cardiac Ganglia

Sanjay Singh, MS; Patricia I. Johnson, PhD; Adil Javed, BS; Thackery S. Gray, PhD; Vassyl A. Lonchyna, MD; Robert D. Wurster, PhD

Background—Cardiac ganglia were originally thought to contain only cholinergic neurons relaying parasympathetic information from preganglionic brain stem neurons to the heart. Accumulating evidence, however, suggests that cardiac ganglia contain a heterogeneous population of neurons that synthesize or respond to several different neurotransmitters and neuropeptides. Reports regarding monoamine and histamine synthesis and neurotransmission within cardiac ganglia, however, present conflicting information or are limited in number. Furthermore, very few studies have examined the neurochemistry of adult human cardiac ganglia. The purpose of this study was, therefore, to determine whether monoamine- and histamine-synthesizing enzymes and neurotransmitters exist within neurons of adult human cardiac ganglia.

Methods and Results—Human heart tissue containing cardiac ganglia was obtained during autopsies of patients without cardiovascular pathology. Avidin-biotin complex immunohistochemistry was used to demonstrate tyrosine hydroxylase, L-dopa decarboxylase, dopamine β-hydroxylase, phenylethanolamine-N-methyltransferase, tryptophan hydroxylase, and histidine decarboxylase immunoreactivity within neurons of cardiac ganglia. Dopamine, norepinephrine, serotonin, and histamine immunoreactivity was also found in ganglionic neurons. Omission or preadsorption of primary antibodies from the antisera and subsequent incubation with cardiac ganglia abolished specific staining in all cases examined.

Conclusions—Our results suggest that neurons within cardiac ganglia contain enzymes involved in the synthesis of monoamines and histamine and that they contain dopamine, norepinephrine, serotonin, and histamine immunoreactivity. Our findings suggest a putative role for monoamine and histamine neurotransmission within adult human cardiac ganglia. Additional, functional evidence will be necessary to evaluate what the physiological role of monoamines and histamine may be in neural control of the adult human heart. (Circulation. 1999;99:411-419.)

Key Words: cardiac ganglia ■ catecholamines ■ serotonin ■ histamine ■ immunohistochemistry

Classically, cardiac ganglia were considered collections of cholinergic neurons that “simply” relayed parasympathetic information from preganglionic brain stem neurons to the heart. Recent evidence, however, suggests that cardiac ganglia contain a heterogeneous population of neurons capable of synthesizing or responding to several different neurotransmitters and neuropeptides. Enzymes involved in the synthesis of nitric oxide,1,2 dopamine,3,4 and norepinephrine3–5 exist within nonhuman mammalian cardiac ganglia. Vasoactive intestinal peptide,1,2,6 somastatatin,1,2 and neuropeptide Y1–4,7 immunoactivity also exists within cardiac ganglia. Receptor characterization studies suggest not only cholinergic but also β-adrenergic,1–3,8,9 serotonergic,10 and purinergic11,12 receptors on ganglionic neurons. Furthermore, electro-physiological studies show that neurons within cardiac ganglia respond to application of cholinergic6 as well as adrenergic,1,9,13–15 histaminergic,16 purinergic,1,11,12 and peptidergic1,13,15,17 agonists and antagonists. In contrast to the simple relay model, the diverse neurochemistry of cardiac ganglia suggests potentially complex neuronal processing within cardiac ganglia.

The presence of monoamine and histamine neurotransmission within cardiac ganglia is currently debated, and studies examining these systems present conflicting information or are limited in number. For example, early studies using histofluorescence techniques do not report catecholamines within neurons of rat or guinea pig cardiac ganglia.18 Recently, however, key marker enzymes in catecholaminergic neurons, including tyrosine hydroxylase and dopamine...
**Neurotransmitters in Human Cardiac Ganglia**

**Methods**

**Human Heart Tissue Procurement and Preparation**

Human heart tissue without apparent gross or histological cardiovascular pathology was obtained from autopsies at Loyola University Medical Center (Table 1). Transmural heart tissue from regions in which cardiac ganglia are concentrated, the para sinoatrial and para-atrioventricular nodal regions (Figure 1), was excised and fixed with 10% formalin in 0.01 mol/L PBS (Biochemical Sciences, Inc) for 24 to 48 hours. The tissue was cryoprotected in 20% sucrose buffered with 0.01 mol/L PBS for 24 hours. Twenty-micron thick frozen sections were placed on cryoprotected in 20% sucrose buffered with 0.01 mol/L PBS for 24 to 48 hours. The tissue was washed, in this and in remaining washes, with 0.01 mol/L PBS containing Triton X (0.25%). Fisher Scientific) for 1 hour. Primary and secondary antibodies were diluted in 0.01 mol/L PBS with 0.25% Triton X and 2% normal donkey or goat serum. The tissue was washed, in this and in remaining washes, with 0.01 mol/L PBS containing Triton X (0.25%). Fisher Scientific) for 1 hour. The tissue was washed, in this and in remaining washes, with 0.01 mol/L PBS containing Triton X (0.25%). Fisher Scientific) for 1 hour. For example, heart transplantation effectively isolates the heart from extrinsic sympathetic and parasympathetic innervation and cardiac ganglia provide the only direct innervation of donor tissue for many months after transplantation. Moreover, heart transplantation effectively isolates the heart from extrinsic sympathetic and parasympathetic innervation and cardiac ganglia provide the only direct innervation of donor tissue for many months after transplantation. Characterization of cardiac ganglia neurochemistry may suggest pharmacological approaches to better manage the recently transplanted heart. An understanding of neurotransmitter systems in cardiac ganglia may also provide insight into physiology of the healthy heart and into neural control of the diseased human heart. The purpose of this study was, therefore, to determine whether monoamine- and histamine-synthesizing enzymes and neurotransmitters exist within neurons of adult human cardiac ganglia.

**Immunohistochemistry Protocol**

Ubiquitous endogenous peroxidases were quenched with 1% H₂O₂ (Sigma) in 0.01 mol/L PBS without Triton X for 1 hour. The tissue was incubated in this, and in remaining washes, with 0.01 mol/L PBS containing Triton X (0.25%, Fisher Scientific) for 1 hour. Primary and secondary antibodies were diluted in 0.01 mol/L PBS with 0.25% Triton X and 2% normal donkey or goat serum. The tissue was washed, in this and in remaining washes, with 0.01 mol/L PBS containing Triton X (0.25%). Fisher Scientific) for 1 hour. Immunohistochemical Controls

Omission of primary antibodies from the incubation solution and immunostaining with the resultant antisera served as a negative control. Serotonin in platelets or sympathetic nerve fibers around blood vessels in the heart provided positive internal controls, and the rat brain stem and human adrenal medulla provided positive external control tissue. Rat and human tissue procurement was in accordance with the Loyola University Medical Center Institutional Animal Care and Use Committee and the Institutional Review Board for the Protection of Human Subjects guidelines, respectively. Preadsorption controls were performed by incubation of primary antibodies with the respective antigen (10⁻⁸ to 10⁻⁷ mol/L) for 24 hours, centrifugation, and immunostaining with the resultant supernatant. L-Dopa decarboxylase, tryptophan hydroxylase, and histidine decarboxylase are not available commercially in purified form; therefore, preadsorption controls with these enzymes could not be performed.

**Quantification and Photomicroscopy**

Monoamine levels change in postmortem tissue, and because postmortem-to-fixation times varied among cases examined, neurotransmitter immunoreactivity was evaluated qualitatively. Protein stability is much greater in postmortem tissue, and thus, neurons immunoreactive for monoamine- and histamine-synthesizing enzymes were evaluated quantitatively. Positively stained neurons were quantified from 5 to 8 cases until the sample size exceeded 300 total neurons. If 2 antibodies were used to detect the same enzyme, then quantification was restricted to the

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**TABLE 1. Clinical and Autopsy Data for Cases Used in This Study**

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Heart Weight, g</th>
<th>LV Thickness, cm</th>
<th>RV Thickness, cm</th>
<th>Delay to Fixation, h*</th>
<th>Autopsy Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>F</td>
<td>320</td>
<td>1.4</td>
<td>0.4</td>
<td>18</td>
<td>Malignant lymphoma</td>
</tr>
<tr>
<td>19</td>
<td>M</td>
<td>300</td>
<td>1.4</td>
<td>0.5</td>
<td>5</td>
<td>Cystic fibrosis and acute pneumonia</td>
</tr>
<tr>
<td>29</td>
<td>F</td>
<td>400</td>
<td>1.6</td>
<td>0.4</td>
<td>12</td>
<td>Acute myelogenous leukemia</td>
</tr>
<tr>
<td>54</td>
<td>M</td>
<td>410</td>
<td>1.6</td>
<td>0.4</td>
<td>19</td>
<td>Non-small cell lung carcinoma</td>
</tr>
<tr>
<td>58</td>
<td>F</td>
<td>380</td>
<td>1.4</td>
<td>0.4</td>
<td>5</td>
<td>Emphysema and severe pneumonia</td>
</tr>
<tr>
<td>63</td>
<td>F</td>
<td>360</td>
<td>1.5</td>
<td>0.6</td>
<td>15</td>
<td>Idiopathic pulmonary fibrosis</td>
</tr>
<tr>
<td>63</td>
<td>F</td>
<td>440</td>
<td>1.7</td>
<td>0.5</td>
<td>20</td>
<td>Emphysema and acute pneumonia</td>
</tr>
<tr>
<td>65</td>
<td>M</td>
<td>400</td>
<td>1.5</td>
<td>0.4</td>
<td>24</td>
<td>Hepatic infarct after cholecystectomy</td>
</tr>
</tbody>
</table>

LV and RV indicate left and right ventricular, respectively. *Time interval between death and tissue fixation.

β-hydroxylase, were found in rat and guinea pig cardiac ganglia. To the best of our knowledge, no studies examining the presence of phenylethanolamine-N-methyltransferase (PNMT, which synthesizes epinephrine), tryptophan hydroxylase (which synthesizes serotonin), and histidine decarboxylase (which synthesizes histamine) within cardiac ganglia exist in the literature. Furthermore, very few studies have examined the neurochemistry of adult human cardiac ganglia.

Immunohistochemical reagents. The tissue containing cardiac ganglia and form a reservoir for the mounting medium (Biomedical Specialties) was used to surround and 0.5% chromium sulfate (Sigma). A 5-mm-thick line of DePex slides coated with 0.005% poly-L-lysine (Sigma Chemical Co) for 24 hours. Twenty-micron thick frozen sections were placed on cryoprotected in 20% sucrose buffered with 0.01 mol/L PBS for 24 to 48 hours. The tissue was excised and fixed with 10% formalin in 0.01 mol/L PBS containing Triton X (0.25%). Fisher Scientific) for 1 hour. Polyclonal and monoclonal antibodies against monoamine- and histamine-synthesizing enzymes and neurotransmitters were used in this study (see Table 2). Primary and secondary antibodies were diluted in 0.01 mol/L PBS with 0.25% Triton X and 2% normal donkey or goat serum. The tissue was incubated with primary antibodies for 24 hours at room temperature and washed. Biotinylated donkey anti-rabbit or mouse anti-rabbit secondary antibodies (Jackson Immunoresearch Laboratories, Inc) were applied for 1 hour, and the tissue was washed. Streptavidin conjugated with horseradish peroxidase (Kirkegaard & Perry Laboratories, Inc) was applied for 1 hour, and the tissue was washed again. To visualize the biotin-streptavidin–horseradish peroxidase complex, the tissue was incubated in a 0.3% H₂O₂, 0.035% diaminobenzidine (Sigma), 2.5% nickel solution for 10 to 20 minutes. The immunostained tissue was dehydrated in ethanol and xylene and coverslipped with DePex mounting medium.

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antibody that produced better staining. Digital photomicrographs were generated with a Carl Zeiss Ultraphot II microscope (Brinkmann Instruments) and a 4- by 5-in PhaseOne Studiokit digital cameraback (PhaseOne). Photomicrograph composites were constructed in Adobe Photoshop 4.01 (Adobe Systems, Inc) and printed on a Fujix Pictrography 3000 digital image printer (Fuji Photo Film USA, Inc). Digital image manipulations were restricted to conventional photographic techniques, including tonal, color, and sharpness adjustments.

Results
Antibody Characterization and Experimental Controls
Antibody specificity and cross-reactivity were characterized by respective vendors with immunoblot analysis and preadsorption controls (Table 2). All antibodies used in this study have been used previously and published references demonstrating their immunohistochemical applications exist in the literature (Table 2). Omission of primary antibodies from the antisera and subsequent incubation with human heart tissue abolished specific staining within cardiac ganglia (Figure 2). Diminution and elimination of staining with increasingly higher dilutions of antibodies, until specific staining was abolished, served as an additional negative control to confirm antibody specificity. Primary antibodies were preincubated with their respective antigens and centrifuged; staining with the resulting supernatant eliminated specific staining in all cases examined (Figure 2). The human adrenal medulla, human heart, and rat brain stem, known to contain the antigens studied, verified antibody binding in positive control tissue (Figure 2).

Catecholamine-Synthesizing Enzymes
Tyrosine hydroxylase, L-dopa decarboxylase, dopamine β-hydroxylase, and PNMT immunoreactivity was found in neurons within cardiac ganglia. Staining for catecholamine-synthesizing enzymes was localized to the neuronal soma and to dendritic and axonal processes. Staining with the Pel-Freeze antibody resulted in tyrosine hydroxylase immunoreactivity in 77% of neurons within cardiac ganglia (Figure 3). In certain histological sections, tyrosine hydroxylase–immunolabeled nerve fibers and terminal varicosities were found in close apposition to neurons within cardiac ganglia (Figure 3, inset). Strong labeling for L-dopa decarboxylase was also found in neurons within cardiac ganglia. Among ganglionic neurons, 80% were L-dopa decarboxylase–immunoreactive (Figure 3). Anti-
bodies from Protos against dopamine β-hydroxylase labeled ~70% of neurons within cardiac ganglia. PNMT antibodies from 2 vendors also specifically labeled neurons within cardiac ganglia (Figure 2). Quantitative staining patterns were similar to those observed for the other catecholamine-synthesizing enzymes. PNMT immunoreactivity using antibodies from Protos was found in 72% of neurons within cardiac ganglia.

**Indoleamine-, Histamine-, and Acetylcholine-Synthesizing Enzymes**

Tryptophan hydroxylase and histidine decarboxylase immunoreactivity was also found in neurons within cardiac ganglia. As with staining for the catecholamine-synthesizing enzymes, immunolabeling was localized to the neuronal soma and to dendritic and axonal processes. Tryptophan hydroxylase immunoreactivity, detected with Protos antibodies, was found in 72% of neurons within cardiac ganglia (Figure 3). Approximately 40% of neurons were labeled with antibodies directed toward histidine decarboxylase (Figure 3). Choline acetyltransferase has classically been associated with neurons in cardiac ganglia; monoclonal antibodies against choline acetyltransferase immunolabeled 80% of neurons within cardiac ganglia (see Figure 1).

**Monoamine and Histamine Neurotransmitters**

Immunoreactivity for the catecholamines dopamine and norepinephrine was found in neurons within cardiac ganglia. Immunostaining for dopamine and norepinephrine was qualitatively similar to that of their synthetic enzymes. Antibodies specific to epinephrine are not commercially available and, therefore, epinephrine immunoreactivity could not be directly demonstrated. Immunoreactivity for the indoleamine serotonin and for the imidazole histamine was also present within neurons of adult human cardiac ganglia. A conservative estimate suggests that half the neurons within cardiac ganglia are immunoreactive for serotonin or histamine. Examples of immunostaining for dopamine, norepinephrine, serotonin, and histamine are provided (Figure 4).

**Discussion**

Our results suggest that enzymes involved with the synthesis of dopamine, norepinephrine, epinephrine, serotonin, and histamine exist within neurons of adult human cardiac ganglia. Immunoreactivity toward tyrosine hydroxylase, L-dopa decarboxylase, dopamine β-hydroxylase, PNMT, tryptophan hydroxylase, and histidine decarboxylase was found in neurons of adult human cardiac ganglia. Immunoreactivity toward dopamine, norepinephrine, serotonin, and histamine was also found in ganglionic neurons. Localization of key marker enzymes, such as tyrosine hydroxylase or histidine decarboxylase, and their related neurotransmitters in ganglionic neurons suggests a putative role for monoamine and histamine neurotransmission within adult human cardiac ganglia. Additional, functional evidence will be necessary to evaluate what the physiological role of monoamines and histamine may be in neural control of the adult human heart.

**Immunohistochemical and Histochemical Studies**

Previously published animal model studies suggest that neurons within cardiac ganglia express monoaminergic and histaminergic traits. For example, dopamine β-hydroxylase but not tyrosine hydroxylase immunoreactivity is found within rat cardiac ganglia near the sinoatrial node, whereas dopamine β-hydroxylase and tyrosine hydroxylase immunoreactivity are found in ganglia near the atrioventricular node of guinea pigs. Tyrosine hydroxylase–immunoreactive nerve fibers projecting through cardiac ganglia and varicosities adjacent to neurons also occur. This anatomic juxtaposition of catecholaminergic nerve fibers, which may be of intrinsic or extrinsic cardiac origin, against principal ganglionic neurons suggests a functional relationship. Immunoreactivity for tyrosine hydroxylase and dopamine β-hydroxylase also exists in rat and mouse cardiac ganglia. Tyrosine hydroxylase in adult guinea pig ganglia, and dopamine β-hydroxylase in newborn guinea pig ganglia. In humans, tyrosine hydroxylase immunoreactivity is found in prenatal and neonatal cardiac ganglia, although none has been reported in adolescent or adult human cardiac ganglia. Neuropeptide Y– and serotonin-immunoreactive neurons also occur in cultured fetal human cardiac ganglia.

Seventy percent to 80% of guinea pig cardiac ganglia reportedly express catecholaminergic characteristics, including mechanisms to take up L-dopa and synthesize dopamine uptake and norepinephrine. Cardiac ganglia also contain...
monoamine oxidase activity and adrenergic varicosities around ganglionic neurons that persist despite 6-hydroxydopamine chemical sympathectomies. These observations suggest that many neurons within cardiac ganglia express catecholaminergic characteristics and that some project to other intrinsic neurons. Neurons within mammalian cardiac ganglia also contain neuropeptide Y and neuropeptide Y precursor immunoreactivity, which is usually associated with catecholaminergic neurons. Even after surgical sympathectomy, 50% of the atrial neuropeptide Y content remains within the heart, suggesting that cardiac ganglia may be an intrinsic source of neuropeptide Y. Our unpublished observations suggest that neurons within adult human cardiac ganglia contain neuropeptide Y immunoreactivity.

Inconsistencies in the literature are probably due to several factors, including sensitivity of the technique and antibodies used, state and source of the tissue examined, and the developmental stage or species examined. Catecholamine histofluorescence is relatively insensitive for catecholamine detection compared with immunohistochemistry; catecholamines in ganglionic neurons may exist below the threshold for detection by histofluorescence techniques. Similarly, immunohistofluorescence is among the least sensitive of immunohistochemistry protocols but was used in most studies citing negative monoaminergic findings within cardiac ganglia. Conversely, the avidin-biotin complex, nickel diaminobenzidine protocol used in this study incorporates sequential amplification steps that render it an extremely sensitive immunohistochemical protocol. Our ability to detect hitherto undocumented catecholaminergic markers in human cardiac ganglia may be related to sensitivity of the technique used in this study. Furthermore, monoamine levels decline in postmortem tissue, even after fixation, and delays in tissue processing may hinder the detection of monoamines. Regional differences also exist in the expression of catecholaminergic markers in the rat heart, and thus, examination of different atrial regions by different authors may also explain some inconsistencies in the literature.

**Enzymatic and Pharmacological Studies**

Several functional studies of enzymes and neurotransmitters in the heart suggest a nonsympathetic, atrial source of catecholamines. For example, tyrosine hydroxylase and dopamine β-hydroxylase activity is greatest near the sinoatrial node, right atrial appendage, left atrium, and interatrial septum and lowest in the ventricles and interventricular septum. Interestingly, this distribution corresponds closely to the distribution of cardiac ganglia in the human heart. PNMT activity is 10-fold higher in rat atria than...
Figure 3. Digital photomicrographs showing neurons within cardiac ganglia immunoreactive for monoamine- and histamine-synthesizing enzymes. Top, Multipolar neurons immunostained for tyrosine hydroxylase, the rate-limiting enzyme in catecholamine synthesis. Note processes emanating from neuronal soma (arrow; bar = 30 μm). Inset, Varicose tyrosine hydroxylase–immunoreactive nerve fibers (left arrow) encircling a non–tyrosine hydroxylase–immunoreactive neuron (+) adjacent to a tyrosine hydroxylase–stained neuron (right arrow; bar = 70 μm). Neurons within cardiac ganglia were immunoreactive for L-dopa decarboxylase and dopamine β-hydroxylase (arrows). Along with PNMT, these enzymes render neurons within cardiac ganglia capable of synthesizing catecholamines. Neurons in cardiac ganglia were also immunoreactive for tryptophan hydroxylase, which synthesis serotonin, and histidine decarboxylase, which synthesizes histamine. Bars = 50 μm.
ventricles and is higher in atrial tissue than any other tissue examined except the adrenal medulla. Even after chemical sympathectomy, the epinephrine content of the atria decreases by only 50%, suggesting an intracardiac source of epinephrine. Despite bilateral adrenal demedul-lation of rats, 33% of the circulating epinephrine normally found in the heart remains. In humans, the heart releases epinephrine in vivo and expresses relatively high levels of atrial PNMT activity. In addition, significant levels of circulating epinephrine persist in patients even after bilateral adrenalectomies. Because of the technical constraints of these functional studies, the cellular source of the enzymatic activity has yet to be unambiguously identified. However, our findings suggest that the extra-adrenal, intracardiac source of epinephrine may be neurons within cardiac ganglia.

Virtually all neurons in rat and guinea pig cardiac ganglia express β-adrenergic receptors, principally of the β2-receptor subtype. If epinephrine is released from neurons within cardiac ganglia, then that epinephrine may influence other ganglionic neurons in a paracrine or endocrine manner. Physiological studies show that adrenergic activation of neurons within cardiac ganglia modulates calcium currents in rats and augments heart rate and ventricular contractility in dogs. In acutely autotransplanted canine hearts, β-adrenergic activation of cardiac ganglia also increases the heart rate and ventricular contractility. In addition to adrenergic receptors, 5HT2 and 5HT1 receptors exist in rat cardiac ganglia. Our unpublished observations suggest that 5HT2 receptors are expressed on neurons within human cardiac ganglia. Furthermore, activation of H1 and H2 receptors in canine cardiac ganglia and H1 receptor activation in isolated guinea pig hearts augments heart rate and ventricular contractility. Our findings also suggest that some neurons within human cardiac ganglia may synthesize and perhaps corelease neurotransmitters. Examples of central and peripheral neurons that corelease acetylcholine and GABA or contain serotonin and tyrosine hydroxylase or PNMT immuno-reactivity exist in the literature.

**Clinical Implications and Conclusions**

Cardiomyopathies are associated with increased levels of circulating catecholamines and increased sympathetic tone. Catecholamines and neuropeptide Y measurements in the coronary sinus of patients with idiopathic dilated cardiomyopathies at rest and after dobutamine infusion show that catecholamine levels increase but that neuropeptide Y levels remain the same. This differential release of catecholamines and neuropeptide Y into the coronary sinus suggests different, possibly overlapping, sources of catecholamines and the neuropeptide Y in the human heart.
Sympathetic activation is associated with neuropeptide Y release; thus, these observations, along with our findings, suggest that cardiac ganglia may also contribute to increases in the levels of catecholamine levels in hearts of patients with cardiomyopathies. Furthermore, tyrosine hydroxylase and dopamine β-hydroxylase activities are accentuated in the failing hamster heart,45 although the locus of the accentuated activity is unclear. Some of the increased enzymatic activity may be due to increased sympathetic activation, but the possibility that cardiac ganglia contribute to the measured increases in enzyme activities during heart failure should also be considered.

The dogma in cardiac neurophysiology has long been that the sole messenger between vagal preganglionic neurons, postganglionic neurons, and cardiac myocytes is acetylcholine. A growing body of anatomical and functional evidence, however, necessitates a reevaluation of this theme. Diverse phenotypes and receptors expressed by neurons within cardiac ganglia also suggests that the effects of prescription drugs and drugs of abuse on ganglionic neurons be reevaluated. If, indeed, neurons within cardiac ganglia use monoamine and histamine neurotransmission, then drugs that influence these neurotransmitters centrally46 (ie, fluoxetine or cocaine) may also be reevaluated. As diverse phenotypes and receptors expressed by neurons within cardiac ganglia also suggests that the effects of prescription drugs and drugs of abuse on ganglionic neurons be reevaluated. If, indeed, neurons within cardiac ganglia use monoamine and histamine neurotransmission, then drugs that influence these neurotransmitters centrally46 (ie, fluoxetine or cocaine) may also be reevaluated. Further studies of the relationship of chromaffin cells and adrenergic nerve fibers to the cardiac ganglia of several species. J Pharmacol Exp Ther. 1967;158:227–240.

Acknowledgments

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