Autonomic Ganglia: Target and Novel Therapeutic Tool

Steven Vernino, M.D.¹, Paola Sandroni, M.D.², Wolfgang Singer, M.D.², and Phillip A. Low, M.D.²,*

¹Department of Neurology, UT Southwestern Medical Center, Dallas, TX
²Department of Neurology, Mayo Clinic, Rochester, MN

Abstract

Nicotinic acetylcholine receptors (AChR) are ligand-gated cation channels that are present throughout the nervous system. The muscle AChR mediates transmission at the neuromuscular junction; antibodies against the muscle AChR are the cause of myasthenia gravis. The ganglionic (α3-type) neuronal AChR mediates fast synaptic transmission in sympathetic, parasympathetic, and enteric autonomic ganglia. Impaired cholinergic ganglionic synaptic transmission is one important cause of autonomic failure. Pharmacological enhancement of ganglionic synaptic transmission may be a novel way to improve autonomic function.

Ganglionic AChR antibodies are found in patients with autoimmune autonomic ganglionopathy (AAG). Patients with AAG typically present with rapid onset of severe autonomic failure. Major clinical features include orthostatic hypotension, gastrointestinal dysmotility, anhidrosis, bladder dysfunction, and sicca symptoms. Impaired pupillary light reflex is often seen. Like myasthenia, AAG is an antibody-mediated neurological disorder. The disease can be reproduced in experimental animals by active immunization or passive antibody transfer. Patient may improve with plasma exchange treatment or other immunomodulatory treatment. Antibodies from patients with AAG inhibit ganglionic AChR currents.

Other phenotypes of AAG are now recognized based on the results of antibody testing. These other presentations are generally associated with lower levels of ganglionic AChR antibodies. A chronic progressive form of AAG may resemble pure autonomic failure. Milder forms of dysautonomia, such as postural tachycardia syndrome, are associated with ganglionic AChR in 10–15% of cases. Since ganglionic synaptic transmission is a common pathway for all autonomic traffic, enhancement of autonomic function through inhibition of acetylcholinesterase is a potential specific therapeutic strategy for autonomic disorders. Increasing the strength of ganglionic transmission can ameliorate neurogenic orthostatic hypotension without aggravating supine hypertension. Recent evidence also suggests a potential role for acetylcholinesterase inhibitors in the treatment of postural tachycardia syndrome.

Keywords

autonomic neuropathy; thymoma; gastrointestinal dysmotility; orthostatic hypotension

Introduction

The autonomic nervous system has a unique neuroanatomical structure. Unlike the somatic motor and sensory systems, the autonomic system is composed of groups of neurons (ganglia)
with extensive synaptic connections outside the central nervous system. Like the somatic motor nerves, peripheral autonomic nerves originate with cholinergic motor neurons in the brainstem and spinal cord that project to the periphery. These preganglionic nerves synapse with neurons in autonomic ganglia. The peripheral autonomic neurons, especially in the case of the intrinsic enteric autonomic nervous system, also synapse extensively with each other. Fast synaptic transmission within autonomic ganglia is mediated by acetylcholine acting on nicotinic acetylcholine receptors (AChR).

In peripheral autonomic ganglia, neuronal AChRs (ganglionic AChR) are expressed by neurons in sympathetic, parasympathetic, and enteric ganglia. The ganglionic AChR is structurally similar to the well-characterized muscle AChR at the neuromuscular junction and contains the neuronal α3 AChR subunit most commonly associated with the β4 subunit. Transgenic mice that are homozygous for null mutations in the α3 gene lack ganglionic AChR and die prematurely due to severe autonomic failure.1 As synaptic transmission in peripheral autonomic ganglia is central to autonomic function, defective ganglionic transmission will lead to diffuse autonomic failure. Conversely, potentiation of ganglionic transmission may be an elegant way to improve autonomic function in a variety of autonomic disorders.

**Autoimmune autonomic ganglionopathy**

Impaired synaptic transmission in autonomic ganglia appears to be the cause of at least one form of autonomic failure. Patients with autoimmune autonomic ganglionopathy (AAG) often have antibodies against the ganglionic AChR. By analogy with MG, autoantibodies specific for neuronal ganglionic AChR could disrupt cholinergic synaptic transmission in autonomic ganglia and lead to autonomic failure.

AAG has also been known as acute pandysautonomia, autoimmune autonomic neuropathy, idiopathic autonomic neuropathy, or subacute autonomic neuropathy. Ganglionopathy is the preferred term because experimental data indicate that the primary pathophysiology of this disorder affects autonomic ganglia rather than damage to autonomic nerve fibers. This first clear descriptions of this disorder were from Young et al. in 1969,2, 3 and the features of the classical subacute form of the disease in a review of 27 Mayo Clinic cases.4 Other clinical phenotypes of AAG have been more recently recognized (as discussed below).

The usual patients are previously healthy, young or middle-aged individuals. There is a female predominance of about 2 to 1.4–6 In its usual course, AAG presents as severe panautonomic failure that reaches peak severity within a few days or weeks.3, 4, 6 The course may be monophasic with slow spontaneous recovery. Although the initial reports stressed the near complete recovery of autonomic function, only one patient in three has a marked improvement.4 The majority of patients have incomplete recovery with persistent autonomic deficits.

The typical patient with AAG has diffuse autonomic failure affecting all limbs of the autonomic nervous system. Sympathetic failure is manifested as orthostatic hypotension (OH) and widespread anhidrosis. Parasympathetic failure presents as dry mouth, dry eyes, sexual dysfunction, urinary retention, impaired pupillary light response, and fixed heart rate. Problems with the enteric autonomic nervous system lead to gastrointestinal dysmotility with any combination of anorexia, early satiety, postprandial abdominal pain, vomiting, diarrhea, constipation, or intestinal pseudoobstruction. The most common presenting symptoms are orthostatic hypotension or gastrointestinal dysmotility, each of these occurring in 70 – 80% of patients.

In many cases, an antecedent viral syndrome (such as upper respiratory symptoms or gastroenteritis) is reported, but no specific infectious agent has been consistently identified. AAG may also be associated with recent immunization or minor surgical procedures. An
identical subacute presentation of autonomic failure with prominent gastrointestinal
dysmotility can occur in a paraneoplastic context with small-cell lung cancer or thymoma. A
small number of cases of AAG coexisting with myasthenia gravis have been reported, usually
in the context of thymoma. All of these clinical features suggest an immune-mediated basis
for this disease.

Patients have normal strength and reflexes. About 25% of patients describe minor sensory
symptoms, such as tingling, but objective sensory loss is not present. Motor and sensory nerve
conduction studies are normal. Laboratory autonomic testing typically reveals evidence of
diffuse autonomic failure, including OH, cardiovagal and baroreflex failure and widespread
anhidrosis. The plasma norepinephrine levels are typically reduced and do not increase
appropriately during standing.

Ganglionic AChR antibodies

Antibodies that specifically bind to the ganglionic AChR are detectable in about 50% of
patients with subacute AAG. Ganglionic AChR autoantibodies are not found in healthy control
subjects or in patients with myasthenia gravis. Seropositivity is highly associated with the
diagnosis of idiopathic or paraneoplastic autonomic failure and can distinguish these disorders
from other forms of autonomic dysfunction.

Ganglionic AChR antibodies are detected with a radioimmunoprecipitation assay which uses
solubilized membranes from a human neuroblastoma cell line (IMR-32) complexed with a high
affinity ligand for ganglionic AChR, 125I-labeled epibatidine. This assay is similar to the
method used to detect muscle AChR antibodies in patients with myasthenia gravis. The ability
of serum to precipitate the radiolabeled AChR provides a quantitative measure of specific
antibody binding. Patients with AAG often have high antibody levels (> 0.5 nmol/L). Lower
antibody levels (0.05 – 0.20 nmol/L) may be found in patients with limited forms of
dysautonomia, including those with isolated gastrointestinal dysmotility, diabetic autonomic
neuropathy, or postural tachycardia syndrome. Ganglionic AChR antibodies are also found (at
lower levels) in a small minority of patients with other paraneoplastic neurological disorders
related to thymoma and small-cell lung cancer (including Lambert-Eaton syndrome and
myasthenia gravis).

Serum levels of ganglionic AChR binding antibody are significantly correlated with severity
of autonomic dysfunction. Patients with high antibody levels have the most severe and
widespread autonomic failure. On follow-up testing, the ganglionic AChR antibody level
correlates with changes in clinical and laboratory indices of autonomic dysfunction. Improvement in autonomic function is associated with a decline in antibody levels. These
findings suggest that ganglionic AChR antibodies are direct pathophysiologic effectors of
autonomic dysfunction.

As yet, the pathogenesis of subacute pandysautonomia in patients that do not harbor ganglionic
AChR antibodies is unknown. The patients are presumed to have an autoimmune disorder
based on the clinical similarities to seropositive patients. These patients might harbor
ganglionic AChR antibodies that do not circulate in the blood because they are entirely
sequestered in the tissues or were only transiently produced. Alternatively, some patients may
have antibodies against other components of the autonomic ganglionic synapse or against
targets elsewhere in the autonomic nervous system.

Phenotypes

The detection of serum ganglionic AChR antibodies has allowed the identification of several
autoimmune autonomic phenotypes (Table 1). The classic severe subacute form of AAG is
associated with high levels of ganglionic AChR antibodies. Limited forms of dysautonomia and more chronic presentations of AAG have been identified associated with lower antibody levels (0.05 – 0.20 nmol/L). Several additional clinical phenotypes of AAG may be defined; 1) a chronic or slowly progressive diffuse autonomic failure, similar to pure autonomic failure, 2) limited autoimmune autonomic dysfunction, including isolated gastrointestinal dysmotility, or cholinergic autonomic failure, and 3) postural tachycardia syndrome.

The most common presentation of chronic AAG is longstanding orthostatic hypotension without evidence of somatic neuropathy or central nervous system involvement. Autonomic testing and more detailed review of symptoms typically reveal evidence of more widespread autonomic dysfunction. This chronic form of AAG may be clinically indistinguishable from progressive degenerative autonomic failure, known as pure autonomic failure or Bradbury-Eggleston syndrome. It is still unclear how many cases of chronic autonomic failure can be attributed to autoimmune mechanisms. It is very important, however, to identify patients with chronic AAG since there are several reports of effective treatment in patients with autonomic deficits for 10 years or more.10, 11

Abnormalities of gastrointestinal function are prominent in AAG. In initial studies, about 10% of cases of unexplained isolated gastrointestinal dysmotility (gastroparesis, intestinal pseudoobstruction, or colonic atony) also had ganglionic AChR antibodies.5 Early identification and treatment of autoimmune gastrointestinal dysmotility may avoid the need for invasive procedures.9, 12 Other restricted forms of autonomic failure can be associated with lower levels of this specific antibody. Patients with prominent parasympathetic deficits or cholinergic deficits (e.g., dry eyes, dry mouth, anhidrosis) without orthostatic hypotension can also be seropositive. Although pupil deficits (tonic pupils) are often seen in the context of AAG, patients with isolated pupil deficits (as in Adie’s syndrome) are usually negative for ganglionic AChR antibodies.

Postural tachycardia syndrome (POTS) is the most common form of orthostatic intolerance without orthostatic hypotension. There are a number of potential causes and mechanisms, but at least half the cases appear to be due to partial autonomic failure. Among these, many may have an autoimmune basis. About 14% of POTS cases have a subacute onset and may follow a viral prodrome, much like AAG. Ganglionic AChR antibodies (at levels lower than AAG) are found in 10 – 15% of POTS patients.5, 13

Treatment of autoimmune autonomic ganglionopathy

As yet, there have been no systemic treatment trials for AAG. AAG appears to be an antibody-mediated autoimmune disorder analogous to myasthenia gravis. Hence, immunomodulatory treatments similar to those used in myasthenia gravis should be effective in reducing antibody levels and restoring autonomic function. Several case reports have shown that plasma exchange, either alone or in combination with immunosuppressive drugs, can produce a prompt improvement in autonomic function.11, 14 Intravenous immunoglobulin was reported to be effective in a number of cases of subacute pandysautonomia prior to the advent of antibody testing.15–17 and more recently in one case of seropositive AAG.18 Interestingly, immunomodulatory treatment may be effective even in chronic cases of AAG decades after disease onset.11 In the future, prospective treatment studies are needed to develop and verify effective treatment for AAG. As the disease incidence is low, these studies will likely need to be multicenter collaborations.

Experimental autoimmune autonomic ganglionopathy

Several lines of evidence indicate that AAG is an antibody-mediated disorder. Antibodies (IgG) isolated from the serum of patients with AAG have direct effects on the ganglionic AChR in
When neuroblastoma cells are exposed to ganglionic AChR IgG, the amplitude of neuronal AChR membrane currents is progressively reduced (Figure 1). The characteristics and time course of this AChR inhibition suggests that these AChR antibodies act by binding and cross-linking the receptors leading to active internalization (modulation). A minority of antibodies also produce a more immediate blocking effect, likely due to binding at or near the agonist binding site.

An animal model of experimental AAG (EAAG) can be induced in rabbits by immunization with peptides corresponding to the extracellular part of the α3 ganglionic AChR subunit. Rabbits with EAAG manifest features of chronic autonomic failure similar to those seen in AAG patients, including gastrointestinal dysmotility, dilated and poorly responsive pupils, decreased lacrimation, reduced heart rate variability, dilated bladder, reduced levels of plasma catecholamines and hypotension. As in patients, more severe autonomic dysfunction correlates with higher antibody levels. Histologic and electrophysiologic studies of EAAG indicate a loss of synaptic ganglionic AChR and impairment in ganglionic synaptic transmission. Neurons in autonomic ganglia are largely spared, and post-ganglionic nerve fibers remain anatomically intact.

Since AAG is an antibody-mediated disease, the disease can also be transferred to healthy mice by injection of IgG from an affected individual (passive transfer). Passive transfer of IgG from affected rabbits or humans to mice produces reversible autonomic deficits. Mice develop urinary retention, gastrointestinal hypomotility and impaired pupil responses. The autonomic deficits are severe for several days after injection and then gradually improve. Ganglionic synaptic transmission in these mice is transiently impaired.

Treatment of orthostatic hypotension and orthostatic intolerance by acetylcholinesterase inhibitors

In light of the pathophysiological similarities with myasthenia gravis, patients with AAG might benefit from treatment with drugs to enhance cholinergic neurotransmission, such as pyridostigmine (Py) and other acetylcholinesterase inhibitors. In some cases, acetylcholinesterase inhibitor treatment leads to improved salivation and bowel motility, but dramatic benefit in typical severe cases of AAG does not usually occur (personal observations). However, pyridostigmine can be used effectively in other forms of autonomic failure specifically to treat orthostatic hypotension.

Currently, the only FDA-approved drug to treat orthostatic hypotension (OH) is midodrine, which was demonstrated in a multicenter double-blind placebo controlled study to improve OH and its symptoms. This drug remains to this day, the standard drug in the treatment of severe OH. Baroreflex failure, the key underlying mechanism of OH, results in the triad of OH, supine hypertension and a loss of diurnal variation in BP, with higher nocturnal BP. Unfortunately midodrine worsens supine hypertension more than it improves OH.

We made two observations. First, unlike neuromuscular junction cholinergic transmission, ganglionic transmission is insecure and requires the convergence of synaptic inputs to activate the postganglionic neuron. The fidelity of neurotransmission is presumably degraded further when the autonomic neuron, preganglionic or postganglionic, is diseased. Second, neural traffic through sympathetic ganglia due to baroreflex unloading is modest with the patient supine but increases with the assumption of the standing position. We hypothesized that acetylcholinesterase inhibitors could increase the gain of ganglionic neurotransmission and improve OH without aggravating supine hypertension. It would increase orthostatic total peripheral resistance more than it increases supine peripheral resistance. This drug should be particularly effective in patients with partial autonomic failure regardless of the cause.
Some support for this concept is available. Pyridostigmine increases supine plasma norepinephrine by 23% and standing norepinephrine by 56%. In a small open-label study on 15 patients with OH, a single dose of 60 mg of Py significantly improved orthostatic BP and peripheral vascular resistance without a corresponding increase in supine BP. The improvement in orthostatic blood pressure was associated with a significant improvement in orthostatic symptoms. In a double-blind, placebo-controlled, cross-over study, we tested 58 patients with neurogenic OH. Patients were randomized to placebo, Py alone or Py in combination with midodrine at two doses. The primary endpoint was an improvement in orthostatic diastolic BP (Figure 2). We chose that parameter since it provides the best BP index of peripheral vascular resistance and was the endpoint in the open study. We measured the acute effect of these regimens on hemodynamic parameters, plasma catecholamines and orthostatic symptoms. The main findings of the study was that Py alone or with low-dose (5 mg) midodrine hydrochloride improved orthostatic BP in patients with neurogenic OH without aggravating supine hypertension, and that the improvement of symptoms correlated well with improvement in BP. In a follow-up open label study, 20/28 patients continued the medication alone (5/20) or in combination (15/20) with other agents, although most of them were able to reduce the doses of these other agents. Seventeen of 20 were very satisfied with the medication: they rated their orthostatic symptoms as moderately to markedly improved since starting Py.

Although the main focus has been on neurogenic OH, recent studies have evaluated the potential role of Py on orthostatic intolerance associated with tachycardia, the postural tachycardia syndrome (POTS). Some cases of POTS are due to a limited autonomic neuropathy and ganglionic antibody can be present in low titers in one case in seven. Based on the hypothesis that acetylcholinesterase inhibition, by improving the safety factor of cholinergic transmission, will result in enhanced vascular adrenergic tone and a vagal shift in cardiac sympathovagal balance, we evaluated the role of Py in the treatment of patients with POTS. The excessive HR response to orthostatic stress was significantly blunted after pyridostigmine administration. HR was significantly lower in the supine and more so in the upright position. Baroreflex sensitivity in the upright position was significantly higher after pyridostigmine. Norepinephrine was increased in both supine and upright position. These changes were associated with significant improvement of orthostatic symptoms. In a small randomized crossover study on 17 patients with POTS, Py at 30 mg orally was found to significantly improve reduce heart rate and symptoms at 2 hours after the drug. The improvement in heart rate is explainable on the basis of enhanced vagal tone (acting at the ganglionic level and at the sinoatrial node) coupled with improved vasomotor tone.

Acknowledgements

Disclosure: Supported by K08NS02247, R01NS48077, NS32352, NS 39722, NS 44233, and NS 43364 from the National Institutes of Health, Bethesda, MD; grant MO1 RR00585 from the Mayo General Clinical Research Center, Rochester, MN; Mayo Funds and UT Southwestern Medical Center

References


Figure 1. Membrane current in IMR-32 cells at −70 mV holding potential
(A) Currents from IMR-32 cell recorded at baseline and at 20 and 50 minutes after addition of human control IgG (1 mg/mL) to the bath (superimposed traces) remain stable over time, indicating no effect of the control IgG on the AChR current (0% current reduction). (B) Exposure to rabbit ganglionic AChR IgG (0.2 mg/mL) for 20 minutes results in a reduction of peak AChR current by 39%. The steady-state current was similarly reduced. (C) Exposure to autoimmune autonomic ganglionopathy (AAG) IgG (1 mg/mL) produces a gradual decrease in AChR current. (From Wang Z, Low PA, Jordan J, Freeman R, Gibbons CH, Schroeder C, et al. Autoimmune autonomic ganglionopathy: IgG effects on ganglionic acetylcholine receptor current. Neurology 2007;68:1917–1921. Reproduced with permission.)
Figure 2. Diastolic blood pressure (DBP) before and after administration of study drug
Table 1
Ganglionic AChR antibody in patients with dysautonomia and other disorders *

<table>
<thead>
<tr>
<th>Diagnostic Group</th>
<th>% seropositive</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Autonomic disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Subacute AAG</td>
<td>50%</td>
</tr>
<tr>
<td>Paraneoplastic AAG</td>
<td>25%</td>
</tr>
<tr>
<td>Postural tachycardia syndrome</td>
<td>10 – 15%</td>
</tr>
<tr>
<td>Idiopathic gastrointestinal dysmotility</td>
<td>5 – 10%</td>
</tr>
<tr>
<td>Diabetic autonomic neuropathy</td>
<td>&lt; 10%</td>
</tr>
<tr>
<td>Multiple system atrophy (Shy-Drager)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Other disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Lambert-Eaton syndrome</td>
<td>5 –10%</td>
</tr>
<tr>
<td>Myasthenia gravis without thymoma</td>
<td>1–2%</td>
</tr>
<tr>
<td>Paraneoplastic disorders with thymoma</td>
<td>15 – 20%</td>
</tr>
<tr>
<td>Paraneoplastic disorders with SCLC</td>
<td>3 – 5 %</td>
</tr>
</tbody>
</table>

* None of 150 healthy control subjects were seropositive for ganglionic AChR antibodies.