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Autonomic ganglia, acetylcholine receptor antibodies, and autoimmune ganglionopathy ☆

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ABSTRACT

Nicotinic acetylcholine receptors (AChR) are ligand-gated cation channels that are present throughout the nervous system. The ganglionic (α3-type) neuronal AChR mediates fast synaptic transmission in sympathetic, parasympathetic and enteric autonomic ganglia. Autonomic ganglia are an important site of neural integration and regulation of autonomic reflexes. Impaired cholinergic ganglionic synaptic transmission is one important cause of autonomic failure.

Ganglionic AChR antibodies are found in many patients with autoimmune autonomic ganglionopathy (AAG). These antibodies recognize the α3 subunit of the ganglionic AChR, and thus do not bind non-specifically to other nicotinic AChR. Patients with high levels of ganglionic AChR antibodies typically present with rapid onset of severe autonomic failure, with orthostatic hypotension, gastrointestinal dysmotility, anhidrosis, bladder dysfunction and sicca symptoms. Impaired pupillary light reflex is often seen. Like myasthenia gravis, AAG is an antibody-mediated neurological disorder. Antibodies from patients with AAG inhibit ganglionic AChR currents and impair transmission in autonomic ganglia. An animal model of AAG in the rabbit recapitulates the important clinical features of the human disease and provides additional evidence that AAG is an antibody-mediated disorder caused by impairment of synaptic transmission in autonomic ganglia.

1. Introduction

1.1. Anatomy of the peripheral autonomic nervous system

The autonomic nervous system has a unique neuroanatomical structure. Like somatic motor nerves, peripheral autonomic cholinergic motor neurons are found in the brainstem and spinal cord. Unlike the somatic motor and sensory systems, the peripheral autonomic system contains groups of neurons (ganglia) with extensive synaptic connections outside the central nervous system (Fig. 1A). These project to the periphery and synapse with neurons in autonomic ganglia. Within ganglia, the peripheral autonomic neurons, especially in the intrinsic enteric autonomic nervous system, also synapse extensively with each other. The ganglionic neurons then send axons (postganglionic unmyelinated C fibers) to innervate target organs. Fast synaptic transmission within autonomic ganglia is mediated by acetylcholine acting on nicotinic acetylcholine receptors (AChR). Other neurotransmitters (including neuropeptides and nitric oxide) contribute to modulation of primary synaptic transmission or mediate slow synaptic events.

1.2. Neuronal nicotinic acetylcholine receptors

Nicotinic acetylcholine receptors (AChRs) are a family of ligand-gated cation channels found throughout the central and peripheral nervous system. Every nicotinic AChR is formed by the association of five subunits of which at least two are α subunits. The α subunit contains important binding sites for acetylcholine. Muscle-type AChR mediates neuromuscular transmission, and antibodies against the muscle AChR cause the characteristic defect in neuromuscular junction transmission and fatigable weakness in patients with myasthenia gravis (MG) (Drachman, 1994).

Neuronal nicotinic AChRs are formed from a variety of subunits homologous to those in muscle AChRs. These neuronal AChR serve many functions in the nervous system. In the peripheral autonomic nervous system, the ganglionic nicotinic AChR mediates fast synaptic transmission in all peripheral autonomic ganglia (sympathetic, parasympathetic and enteric ganglia). AChRs on autonomic neurons are typically composed of two α3 subunits in combination with three other AChR subunits. Although autonomic ganglia neurons can express numerous neuronal AChR subunits, including α3, α4, α5, α7, β2, and β4, the properties of the AChR at mammalian ganglionic

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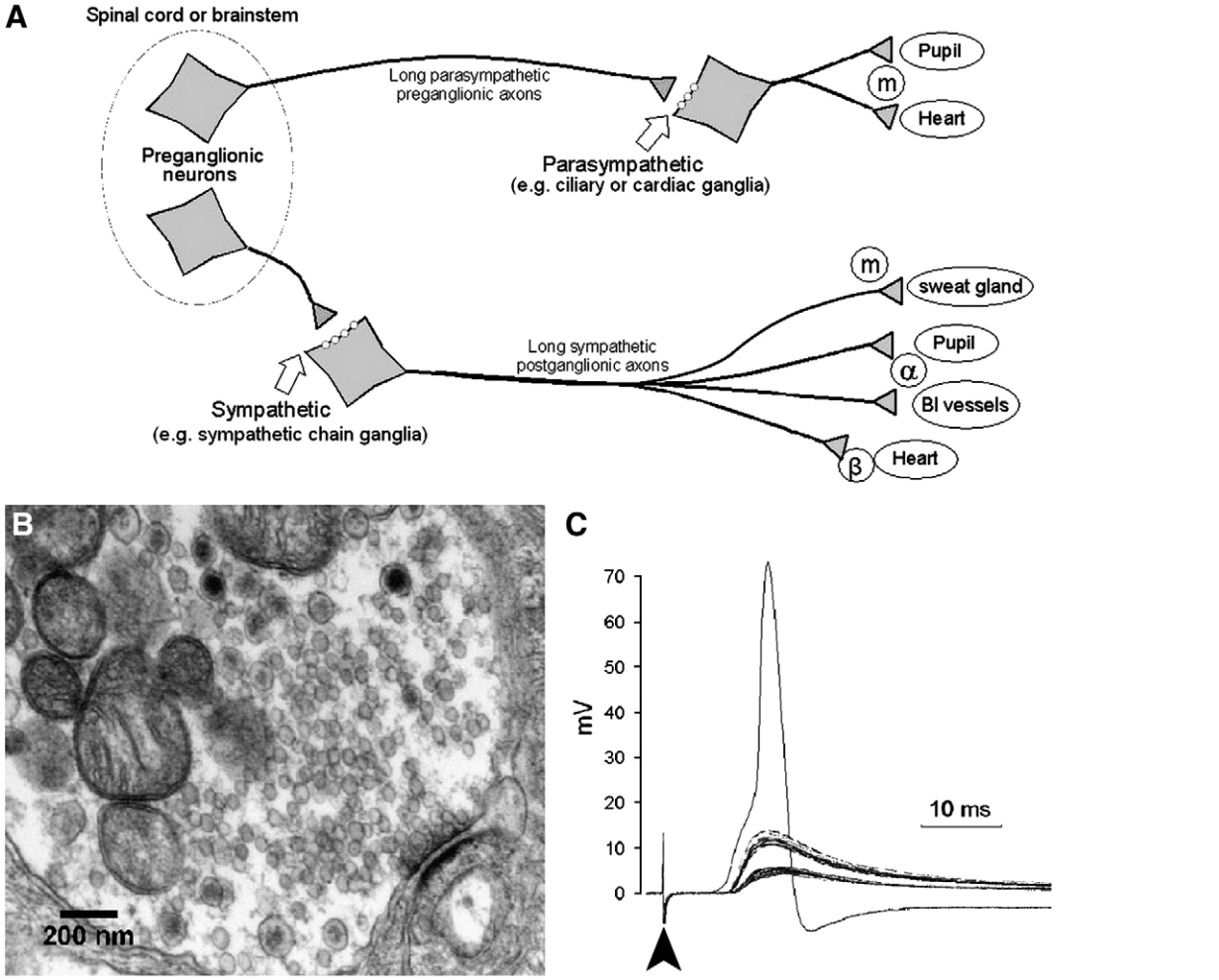

Fig. 1. The autonomic ganglionic synapse. A) A simplified schematic showing the anatomy of the peripheral autonomic nervous system. The autonomic ganglia receive input from cholinergic motor neurons in the brainstem or spinal cord. Fast ganglionic synaptic transmission is mediated by acetylcholine acting on neuronal nicotinic acetylcholine receptors. The postganglionic fibers extend to innervate numerous target organs (a few examples are shown) and release acetycholine acting on muscarinic receptors (m) or norepinephrine acting on alpha and beta adrenergic receptors (α and β). B) Electron micrograph showing the ultrastructure of a ganglionic synapse in rabbit superior cervical ganglia. The presynaptic terminal contains mitochondria, numerous small clear vesicles containing acetycholine, and larger dense core vesicles presumably containing neuropeptides and other transmitters. The synapse (lower right) is characterized by a short area of close apposition of the nerve terminal and dendrite membranes. Vesicles are poised on the presynaptic side, ready for release. The thickened postsynaptic membrane is the area of synaptic specialization that contains the neurotransmitter receptors. C) Microelectrode recording of synaptic potentials from a neuron in isolated mouse superior cervical ganglia. Stimulation of the preganglionic nerve (arrowhead) leads to a fast excitatory postsynaptic potential (fEPSP) in the neuron. The *y*-axis indicates the change in membrane potential from the resting potential (which is usually around −50 to −60 mV). Gradually increasing stimulus intensity produces discrete fEPSPs indicating the presence of multiple preganglionic inputs to this single ganglia neuron (a typical single fEPSP causes about a 5 mV depolarization in the neuronal soma in this case). The simultaneous activation of several inputs is required to reach threshold and produce an action potential in the neuron. In this example, at least three distinct synaptic inputs combine to reach the action potential threshold.

synapses are most similar to AChRs formed by α3 and β4 subunits (Skok et al., 1999). Transgenic mice lacking the α3 subunit have profound autonomic failure with prominent bladder distention, gastrointestinal dymotility and lack of pupillary light reflexes indicating that the α3 subunit is absolutely required for normal autonomic ganglionic neurotransmission (Xu et al., 1999).

1.3. Autonomic ganglionic neurotransmission

The vast majority of ganglionic synapses are simple structures located on short dendrites rather than on the cell soma (Fig. 1B) (Myers, 2000). An action potential in the presynaptic terminal results in the release of neurotransmitter vesicles, predominantly containing acetylcholine. Interaction of acetylcholine with the ganglionic AChR produces a depolarization in the ganglia neuron (fast excitatory post-synaptic potential, fEPSP). If the depolarization is sufficient to reach the threshold for action potential generation, the signal is propagated down the postganglionic axon to the target. The strength of the synapse is dependent on multiple factors including the quantal content (number of vesicles released with each stimuli), the number of postsynaptic AChR, and the geometry of the postsynaptic dendrite.

Autonomic ganglia are more than simple relay centers for autonomic information. There is significant signal integration due to convergence and divergence of synaptic inputs. In most mammalian autonomic ganglia, each preganglionic fiber innervates multiple ganglia neurons (divergence). A minority of "strong" synapses can produce a single fEPSP that is sufficient to produce an action potential. More commonly, multiple preganglionic signals must converge and summate to produce an action potential in the ganglia neuron (Fig. 1C) (Sacchi and Perri, 1971). The synaptic strength and the degree of integration vary widely among different autonomic ganglia. Since ganglionic transmission depends on the convergence of multiple subthreshold synaptic events, any process that modulates the strength of ganglionic cholinergic transmission will have profound effects on the function of the autonomic nervous system.