INTRODUCTION

Nicotinic acetylcholine receptors (AChRs) are acetylcholine-gated cation channels. They play a critical postsynaptic role in transmission between motor nerves and skeletal muscles and in autonomic ganglia (1,2). In the central nervous system, they also act presynaptically and extrasynaptically to modulate transmission by facilitating the release of many transmitters (3,4). In the skin (5), bronchial and vascular epithelia (6,7), and other nonneuronal tissues (8), they also mediate intercellular communication.

Abnormalities of AChRs are responsible for several human diseases. Mutations in AChRs are known to cause congenital myasthenic syndromes (9) and the rare autosomal dominant nocturnal frontal lobe form of epilepsy (ADNFLE) (10–12). Autoimmune responses to AChRs are known to cause myasthenia gravis (MG) (13), certain dysautonomias (14), and some forms of pemphigus (15). Nicotine acting on AChRs in the brain causes addiction to tobacco (16,17). This is by far the largest medical problem in which AChRs play a direct role, and the largest preventable cause of disease, accounting for 430,000 premature deaths annually in the United States (18).

Nicotine acting through AChRs has many physiologic effects, including beneficial ones such as inducing vascularization, neuroprotection, cognitive enhancement, anxiolysis, and antinociception. Thus, nicotinic agents are lead compounds for the development of drugs to treat many diseases including Alzheimer’s disease, Parkinson’s disease, chronic pain, and Tourette’s syndrome (19,20).

There are many known and potential subtypes of AChRs, each defined by the subunits that compose them (1). All AChRs are formed by five homologous subunits organized around a central cation channel. There are 17 known AChR subunits: α1–10, β1–4, γ, δ, and ε. In contrast to the many subtypes of neuronal AChRs, there are only two subtypes of muscle AChRs. These are a fetal subtype with an (α1)2 β1γδ stoichiometry and an adult subtype with an (α1)2 β1εδ stoichiometry.
AChRs are part of a gene superfamily that includes the genes for subunits of ionotropic receptors for glycine, γ-aminobutyric acid (GABA), and serotonin (21). The structural homologies of all of these receptors, and the sorts of evolutionary steps that produced this diversity of receptors, have been elegantly illustrated by experiments. One showed that changing only three amino acids in the channel lining part of an AChR subunit to amino acids found in receptors for GABA or glycine receptors resulted in AChRs with anion-selective channels like those of GABA or glycine receptors (22). Another experiment showed that a chimera of the extracellular domain of an AChR subunit and the remainder of a serotonin receptor subunit produced an ACh-gated cation channel with the conductance properties of a serotonin receptor (23).

Muscle AChRs are the best characterized of the AChRs (21). The presence of a single type of synapse in skeletal muscle (with the exception of extraocular muscle; see Chap. 5) facilitated studies of AChR synthesis, developmental plasticity, and electrophysiologic function (24–26). The presence of large amounts of muscle-like AChR in the electric organs of Torpedo species permitted the purification and characterization of AChRs, partial sequencing of their subunit proteins, cloning of the subunit cDNAs, and low-resolution electron crystallographic determination of their three-dimensional structure (21,24,27,28). Low-stringency hybridization, starting with cDNAs for muscle AChR subunits, led to the cloning of subunits for neuronal AChRs (24). Immunization with purified electric organ AChRs led to the discovery of experimental autoimmune myasthenia gravis (EAMG), the autoimmune nature of MG, and an immunodiagnostic assay for MG (13,29). Monoclonal antibodies initially developed as model autoantibodies led not only to the discovery of the main immunogenic region (MIR) on α1-subunits and the molecular basis of the autoimmune impairment of neuromuscular transmission in MG (13,30,31), but also to the immunoadfinity purification of neuronal nicotinic AChRs. mAbs have continued to provide useful tools for characterizing AChRs (1).

This chapter reviews the basic structures of muscle and neuronal AChRs. It describes the antigenic structure of muscle AChRs and considers how this accounts for the pathologic mechanisms by which neuromuscular transmission is impaired in MG. This is briefly contrasted with the antigenic structure of a neuronal AChR involved in autoimmune dysautonomia. This chapter also considers the optimized functional structure of muscle AChRs, and how mutations impair AChR function in congenital myasthenic syndromes. The many AChR mutations identified in all the muscle AChR subunits in myasthenic syndromes is contrasted with the few disease-causing mutations discovered thus far in neuronal AChR subunits.