Faster, slower, but never better

Mutations of the skeletal muscle acetylcholine receptor

Robert L. Ruff, MD, PhD
Paul Rutecki, MD

Correspondence & reprint requests to Dr. Ruff: robert.ruff1@va.gov

Neurology® 2012;79:404–405

The skeletal muscle acetylcholine receptor (AChR) is a beautifully functional molecular complex made up of 5 subunits. Acetylcholine binding initiates pore opening, producing the endplate current (EPC); the resulting action potentials travel over the muscle surface and into the transverse tubules, initiating contraction via calcium (Ca^{2+}) release from the sarcoplasmic reticulum that interfaces with the transverse tubule network. EPC amplitude and duration is critical for proper functioning of skeletal muscle: if too small or short, it will not effectively activate sodium channels to trigger action potentials; if too long, it will trigger multiple APs. The EPC also conducts Ca^{2+} into cells, so overly long EPCs will lead to endplate damage due to Ca^{2+} activation of internal protease systems.[1] Congenital disorders of neuromuscular transmission (CDNT), also called congenital myasthenias, allow us to explore the consequences of natural molecular experiments resulting in alteration of structure on the functioning of the AChR. The article by Shen et al.[2] illustrates the importance of precise timing of the EPC and provides insights into the molecular operation of the AChR.

CDNTs result from a heterogeneous group of mutations involving neuromuscular junction (NMJ) proteins.[1] These syndromes usually present within the first year of life with fluctuating weakness involving limb, trunk, and axial muscles. The clinical severity of genetic disorders of the AChR reflects the extent to which the mutations are associated with failure of NMJ transmission.[1,3] CDNTs involving the AChR can be associated with altered AChR kinetics, leading to either shorter or longer AChR channel openings. The longer AChR channel openings produce long duration EPCs that produce the physiologic changes that underlie the slow channel syndrome. In contrast, short duration AChR channel openings result in short duration EPCs leading to the impairments in neuromuscular transmission seen in the fast channel syndromes. In addition, mutations involving AChR subunits or molecules associated with AChR insertion or stabilization in the endplate membrane can reduce the number of endplate AChRs, reducing the total current in the EPC. Mutations involving the AChR can reduce its single channel conductance, leading to smaller EPCs or altered kinetics. The fast channel syndrome phenotypes vary depending, in part, upon whether AChR expression or single channel conductance are altered by subunit mutations.[1,3] An important observation is that no AChR subunit mutations have resulted in an enhanced safety factor for neuromuscular transmission.[4] The NMJ evolved over millions of years, hence it is unlikely that any mutation of NMJ components would lead to improved function.

The AChR is composed of 5 subunits, 2 α subunits, and 1 copy each of the β, δ, and either the γ or ϵ subunit (see figure 1 of Shen et al.[2]). The adult form of the AChR found at the neuromuscular junction contains the ϵ subunit and the fetal or extrajunctional form of the AChR contains the γ subunit. The α subunit contains the primary binding sites for ACh. CDNTs due to mutations of AChR subunits most commonly involve the ϵ subunit. Mutations of the ϵ subunit can result in fast channel or slow channel syndrome or disorders with reduced expression of AChRs. ACh binds in the interfaces between the α and ϵ/γ subunits and the α and β subunits. The binding of 2 ACh molecules facilitates sliding or twisting of the AChR subunits, which alters the configuration of the channel pore and enables ionic current to flow.[5] Studies of clinical and synthetic AChR subunit mutations have contributed greatly to the present impression, albeit incomplete, of how ACh binding facilitates subunit interactions that lead to AChR channel opening and the subunit interactions leading to channel closure.[6–10] For example, the open configuration likely occurs when the AChR subunits are aligned. After both ACh molecules unbind, the AChR subunits would assume a new configuration in which the central pore is narrower. The narrowing might occur by the AChR subunits twisting together,

See page 449

From the Neurology Service (R.L.R.), Louis Stokes Cleveland Department of Veterans Affairs Medical Center, Department of Neurology, Case Western Reserve University, Cleveland, OH; and Neurology Service (P.R.), William S. Middleton Memorial Veterans Hospital, Department of Neurology, University of Wisconsin, Madison.

Go to Neurology.org for full disclosures. Disclosures deemed relevant by the authors, if any, are provided at the end of this editorial.

similar to the closing of the aperture of a camera. Alternatively, the subunits could also pack more closely together by having some of the subunits move vertically in the membrane, with 1 α subunit moving in an extracellular direction and the other α subunit moving in an intracellular direction. This type of conformational change would allow the other subunits to move into the regions vacated by the α subunits, resulting in narrowing of the central pore.

Fast channel syndrome is caused by AChR subunit mutations that result in a shortened duration of the open state of the AChR. The duration of the single channel open states determines the decay kinetics of the macroscopic end plate current. Shen et al.[2] performed detailed analyses of the kinetics of single AChR channel currents using an elegant expression system. They demonstrated that the ϵ subunit mutation, which occurred in a region of the ϵ subunit that was associated with the ACh binding site, also greatly reduced the AChR affinity for ACh. The affinity was reduced to a degree that treatment with cholinesterase inhibitors had minimal therapeutic effects. Thus the EPCs were ineffective for 2 reasons: 1) the decreased ACh affinity reduced the peak amplitude of the EPC; and 2) the shortened duration of the EPC reduced its effectiveness for activating endplate sodium channels and reduced temporal summation of successive stimuli. By studying both the AChR structure and the single channel AChR currents, Shen et al.[2] demonstrated the importance of the interface region between the α and ϵ subunits for NMJ functioning.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. **Go to Neurology.org for full disclosures.**

REFERENCES

1. Engel AG, Shen XM, Selcen D, Sine SM. What have we learned from the congenital myasthenic syndromes? J Mol Neurosci 2010;40:143–153.
2. Shen X-M, Brengman JM, Edvardson S, Sine SM, Engel AG. Highly fatal fast-channel syndrome caused by AChR ϵ subunit mutation at the agonist binding site. Neurology 2012;79:449–454.
3. Palace J, Lashley D, Bailey S, et al. Clinical features in a series of fast channel congenital myasthenia syndrome. Neuromuscul Disord 2012;22:112–117.
4. Ruff RL. Endplate contributions to the safety factor for neuromuscular transmission. Muscle Nerve 2011;44:854–861.
5. Taly A, Changeux JP. Functional organization and conformational dynamics of the nicotinic receptor: a plausible structural interpretation of myasthenic mutations. Ann NY Acad Sci 2008;1132:42–52.
6. Shen X-M, Fukuda T, Ohno K, Sine SM, Engel AG. Congenital myasthenia-related AChR delta subunit mutation interferes with intersubunit communication essential for channel gating. J Clin Invest 2008;118:1867–1876.
7. Shelley C, Colquhoun D. A human congenital myasthenia-causing mutation (epsilon L78P) of the muscle nicotinic acetylcholine receptor with unusual single channel properties. J Physiol 2005;564:377–396.
8. Grosman C, Auerbach A. The dissociation of acetylcholine from open nicotinic receptor channels. Proc Natl Acad Sci USA 2001;98:14102–14107.
9. Shen XM, Ohno K, Tsujino A, et al. Mutation causing severe myasthenia reveals functional asymmetry of AChR signature cystine loops in agonist binding and gating. J Clin Invest 2003;111:497–505.
10. Milone M, Wang HL, Ohno K, et al. Slow-channel myasthenic syndrome caused by enhanced activation, desensitization, and agonist binding affinity attributable to mutation in the M2 domain of the acetylcholine receptor alpha subunit. J Neurosci 1997;17:5651–5665.