Congenital Myasthenic Syndromes

The congenital myasthenic syndromes (CMS) are a heterogeneous group of inherited disorders affecting neuromuscular transmission. The syndromes show characteristic 'myasthenic' fatigable muscle weakness that varies in severity. The superficial phenotypes of the various CMS are often similar but electrophysiological, cytochemical and morphological studies have helped delineate those associated with postsynaptic, synaptic or presynaptic functions (reviewed[1,2]). Moreover, careful clinical examination may often provide clear pointers both to identify the clinical syndrome and to the particular gene involved. A definite genetic diagnosis is important not only for genetic counselling but also because the various gene mutations can give rise to syndromes that have very different underlying molecular mechanisms requiring different treatments.

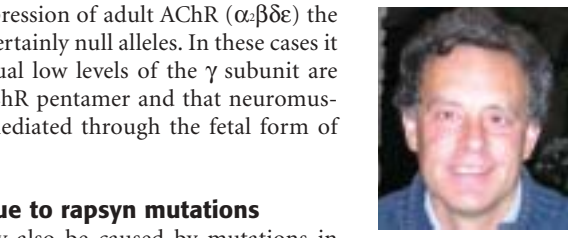
To date, the majority of CMS have abnormalities in postsynaptic function at the neuromuscular junction. Underlying mutations have been located within the genes that encode the muscle acetylcholine receptor (AChR) and the AChR-clustering protein, rapsyn (Figures 1 and 2).

AChR deficiency due to ε-subunit mutations

AChR deficiency is a recessive disorder with age of onset in infancy but is generally non-progressive. As its name suggests, the syndrome is characterised by reduced numbers of AChR in the postsynaptic membrane. Although mutations causing AChR deficiency occur rarely in other AChR subunits, the overwhelming majority are in AChR ε-subunit gene, and at least 80 different mutations have now been identified. Patients may have a homozygous mutation or be compound heterozygotes for different defective ε-subunit alleles. The mutations are located along the length of the gene and the only clear example of a founder effect is seen in the ethnic gypsy population of south east Europe where the single nucleotide deletion ε1267delG is frequently found.[3] Although some of the ε-subunit mutations may result in low level expression of adult AChR ($\alpha_2\beta\delta\varepsilon$) the majority are almost certainly null alleles. In these cases it is thought that residual low levels of the γ subunit are recruited into the AChR pentamer and that neuromuscular transmission mediated through the fetal form of the AChR ($\alpha_2\beta\gamma\delta$).

AChR deficiency due to rapsyn mutations

AChR deficiency may also be caused by mutations in rapsyn. Rapsyn is a 43 kDa protein involved in the development and maintenance of the neuromuscular junction and, in particular, plays a primary role in clustering the AChR at the tops of the postsynaptic junctional folds (Figure 2).[4] By contrast with the AChR ε-subunit mutations where most kinships have 'private' mutations, the missense mutation rapsyn-N88K has been found either homozygous or as a compound heterozygote in all rapsyn deficiency patients (except those with rapsyn gene promoter mutations). The common occurrence of N88K mutations facilitates rapid genetic screening. Although both AChR ε-subunit and rapsyn mutations can result in loss of AChR at the endplate with similar histopathological and electrophysiological properties, clues as to which gene harbours the mutations can be gleaned from analysis of the clinical features and disease history. In particular, patients with rapsyn mutations frequently show mild joint contractures at birth and are prone to severe sudden apnoeic attacks during infancy and early childhood usually associated with upper respiratory tract infections. Between these episodic attacks myasthenic symptoms are usually mild. By contrast, patients with ε-subunit mutations show profound ophthalmoplegia, do not, in general, show a fluctuating disease course or have joint contractures at birth.[5] Some patients with rapsyn mutations do not present with symptoms in childhood but rather present in adolescence or adulthood.[6] This 'late-onset' phenotype may be easily be mistaken for seronegative immune-mediated myasthenia gravis.



Professor Beeson is an MRC Senior Non-Clinical Fellow and Professor in Molecular Neuroscience at the Weatherall Institute of Molecular Medicine, University of Oxford. His research team study disorders of synaptic transmission with a particular focus on the congenital myasthenic syndromes.

Correspondence to:
Professor David Beeson,
Neurosciences Group,
Weatherall Institute of
Molecular Medicine,
The John Radcliffe,
Oxford, OX3 9DS.
Email: dbeeson@
hammer.imm.ox.ac.uk

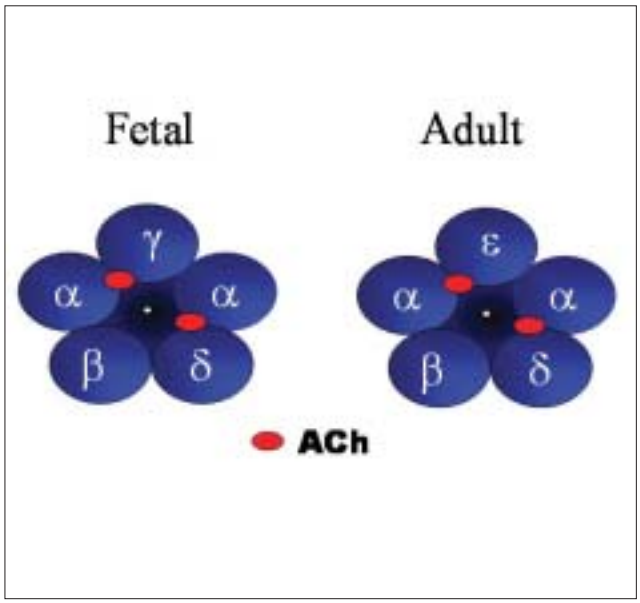


Figure 1: Representation of the AChR as viewed from the synaptic cleft. Each AChR molecule has a molecular mass of around 250,000 kDa, and is made up of five subunits arranged pseudosymmetrically around a central ion pore. In mammalian muscle there are two types of AChR, a fetal form consisting of $\alpha_2\beta\gamma\delta$ and an adult form, $\alpha_2\beta\varepsilon\delta$, in which the ε subunit replaces the γ. In normal synaptic transmission the binding of two ACh molecules to a site at the αδ and αγ/αε interface results in a brief opening of the channel pore.

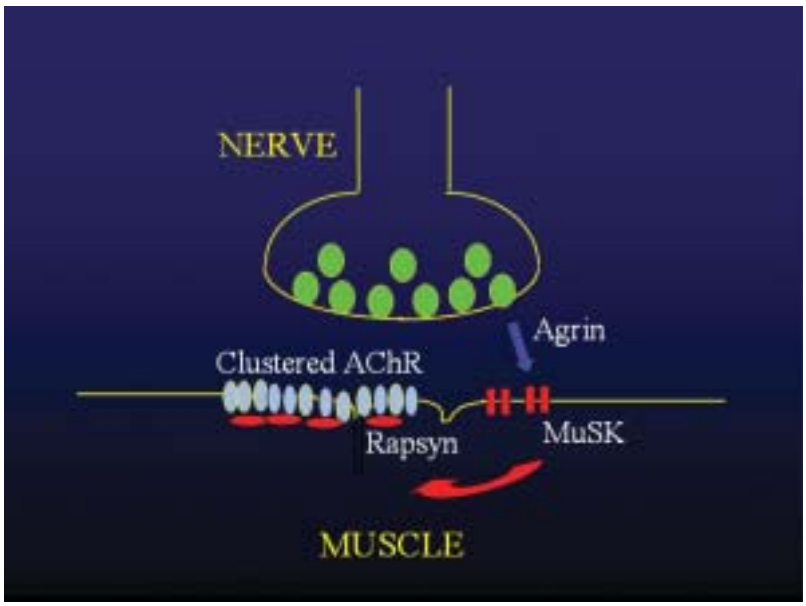


Figure 2: AChR are highly concentrated (~10,000 μM^2) on the crests of the postsynaptic folds at the neuromuscular junction. The pathway that results in the localisation of the AChR involves the release of agrin from the nerve terminal, its interaction with muscle specific tyrosine kinase (MuSK), phosphorylation of rapsyn which then clusters and anchors the AChR to the cytoskeleton. Mutations of rapsyn underlie many cases of AChR deficiency syndrome.

Slow channel and fast channel syndromes

In these syndromes kinetic abnormalities of AChR ion channel function rather than AChR number are the primary underlying cause of disease. The fast channel syndrome (autosomal recessive) has a similar phenotype to AChR deficiency, but is rarer. The slow channel syndrome (autosomal dominant) may present in childhood, adolescence or adult life and is progressive. In the fast channel syndrome the combination of a null allele, such as εS143L, with the mutation εP121L unmasks the phenotypic effects of this mutation that are not seen in the heterozygous state. εP121L causes AChR activations to be fewer and shorter than normal and thus overall AChR containing the εP121L mutation have a reduced response to ACh.[7] Mutations with similar kinetic effects to εP121L are also found in AChR α and δ subunits.

The slow channel syndrome was first described by Engel and colleagues in 1982.[8] Electrophysiological recordings showed an extended decay phase of the miniature endplate potentials suggesting that prolonged ion channel opening might cause the disorder. In addition, it was noted in ultrastructural studies that there was damage to the muscle at the synaptic sites suggesting that this might be an excitotoxic disorder caused by "calcium overload" in the endplate region. To date, at least 15 different mutations underlying the slow channel syndrome have been identified. The mutations occur in all four subunits that make up adult AChR, and each is a point mutation leading to a single amino acid change. In vitro expression studies demonstrate that each of the mutations prolongs ion channel activations and thus is responsible for the pathogenic gain of function for the AChR. The mutations may be located in different functional domains within the subunits and detailed electrophysiological analysis has defined varying molecular mechanisms through which the channel activations are prolonged. In brief, mutations which are located in the M2 transmembrane domain region, which, as previously mentioned, is thought to line the channel pore, act predominantly by slowing channel closure, and thus result in long individual channel openings. The primary effect of some mutations in the extracellular domain (i.e. αG153S) is to increase the affinity of AChR for ACh. In this case, rather than long individual openings, the AChR oscillates between the open and closed states during the extended period of ACh occupancy before it finally dissociates and the channel remains shut.

Mutations in other proteins at the neuromuscular junction

In addition to mutations in the AChR subunit genes, mutation in other molecules at the neuromuscular junction could also be responsible for some CMS. Mutations in the gene encoding ColQ, the collagen-like tail that attaches the asymmetric form of acetylcholinesterase to the basal lamina at the neuromuscular junction, have been identified[9,10] and underlie endplate acetylcholinesterase deficiency syndrome (autosomal recessive). Loss of acetylcholinesterase from the synaptic cleft increases the time that ACh is available to bind to the AChR with physiological consequences similar to the slow channel syndrome. Mutations in choline acetyltransferase (ChAT) affect the release of ACh from the presynaptic nerve terminal, and give rise to a CMS-with episodic apnoea, in which the sudden apnoeic attacks are similar to those seen in patients with rapsyn mutations.[11] Finally, a CMS associated with mutations in the voltage gated sodium channels (SCN4A) located in the depths of the postsynaptic folds has been reported.[12]

Treatment strategies

An understanding of the molecular mechanisms that underlie disease allows a rational approach to therapy. Thus patients with AChR deficiency syndrome, the fast channel syndromes, rapsyn and ChAT mutations respond well to anticholinesterase treatments which prolong the lifetime of ACh within the synaptic cleft. Similarly, 3,4-diaminopyridine, which increases quantal release of ACh and consequently the effective concentration of ACh within the synaptic cleft, has been found to be particularly effective for patients with fast channel syndrome. Conversely, compounds which block the AChR when in the open state, are potentially therapeutic for patients with slow channel syndrome, and indeed, quinidine sulphate, a long-lived AChR channel blocker, has been found to be beneficial. At present no effective treatment is available for patients with acetylcholinesterase deficiency.

Summary

The diversity of mutations and clinical phenotypes of inherited disorders at the neuromuscular junction is providing novel insights into the detail of ion channel function and the pathogenic consequences of dysfunction. Their study provides a model for the investigation of ligand-gated ion channel dysfunction in the CNS.

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