Importance of NMJ’s:

1. Every breath you take, every move you make…
2. NMJ’s are accessible models of synaptic structure and function elsewhere (brain, spinal cord, autonomic ganglia)
3. Many general principles of synaptic function were established by studies of the NMJ.
   (They still are!)

Electrical stimulation of nerves causes muscles to contract
Muscle contractions in response to single (twitch) and repetitive (tetanic) stimuli

Neuromuscular Junction - Structure and Function (or... How We Eat Pizza....)

1. Imaging the “Ultimate Synapse”
2. Ultrastructure and electrophysiology of the NMJ
3. Synthesis, storage, release, action and inactivation of ACh
4. Quantal secretion and exocytosis
5. The Safety Factor for neuromuscular transmission

Neuromuscular junctions viewed with confocal microscopy

Neuromuscular junctions comprise four types of cells
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Muscle fibre action potentials are normally triggered by EPP’s, leading to muscle contraction

Action potentials are necessary because subthreshold voltages decay with distance

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Synthesis

Storage

Release

Action

Inactivation

EM tomography reveals association of vesicles with "active zones"

Several SNARE proteins have been identified

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The Quantal (Vesicle) Hypothesis

Quantal secretion...

MEPPs

EPPs

... by exocytosis

MEPP = 1 "quantum" = 1 vesicle
EPP = m quanta = m vesicles

Quantification of EPPs: Quantal Analysis

Quantal Content:

\[ m = \frac{EPP}{q} \]

Quantal Size:

\[ q = MEPP \]
Testing the Quantal/Vesicle Hypothesis

If \( x=0 \)
\[ P_0 = p^3 \]
\( (1-p)^3 \)

If \( x=1 \)
\[ P_1 = p^1 \cdot (1-p)^2 \]

If \( x=2 \)
\[ P_2 = p^2 \cdot (1-p)^1 \]

If \( x=3 \)
\[ P_3 = p^3 \cdot (1-p)^0 \]

\[ m = n \cdot p \]
\( n = 3 \)
\( p < 0.001 \)

Quantal analysis: Fitting the Poisson Equation

\[ P_x = \frac{e^{-m} \cdot m^x}{x!} \]

Quantal analysis of EPPs shows a "safety factor" of 2-5

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Synaptic strength depends on synaptic size

Actual \( m \)
Threshold \( m \)
Neuromuscular junctions comprise a motor nerve terminal (axon ending), motor end-plate (muscle fibre contact region) and are capped by terminal Schwann cells and kranocytes.

Acetylcholine (ACh) is synthesised in motor nerve terminals by choline acetyltransferase (ChAT).

ACh is pumped into and stored in synaptic vesicles.

ACh is released at the NMJ by Ca-dependent exocytosis from synaptic vesicles. These vesicles are recycled by endocytosis.

ACh action occurs by binding to receptors (AChR, ligand-gated ion channels) in the post-synaptic membranes producing depolarising MEPP’s and EPP’s.

ACh is broken down (inactivated) by acetylcholinesterase (AChE) enzyme in the synaptic basal lamina. Choline is recycled into the nerve terminal and used in the synthesis of ACh.

A high safety factor (3-5 fold excess of transmitter release) ensures action potentials are triggered in muscle fibres, even during synaptic depression caused by repetitive excitation.