THE PHYSIOLOGY OF NEUROMUSCULAR TRANSMISSION

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A medullated motor nerve fibre loses its myelin sheath when it reaches a striated muscle fibre. Each terminal branch lies in a groove of the muscle fibre junctional cleft, forming the neuromuscular junction. Thus the nerve terminates at the 'pre-synaptic membrane', which is separated by a 'junctional/ synaptic cleft' from the 'post synaptic membrane' of the muscle (figure 1).

The mechanism of neuromuscular transmission is the liberation of acetyl choline which is synthesised in the terminal axoplasm from choline and acetyl coenzyme A under the influence of choline-O- acetyl transferase. It is loaded into vesicles by a specific carrier mediated system. Eighty percent of acetyl choline is in these vesicles and 20% is dissolved in the axoplasm. These vesicles are synthesised in the cell bodies of lower motor neurones of the spinal cord or brain stem and transported to the nerve terminals with the help of micro-tubules. In the nerve endings they are repeatedly refilled and re-used. About half a million vesicles are present in the axoplasm of each nerve ending and are concentrated near areas of thickened terminal axonal membrane ie. active zones.

There are four ways in which acetyl choline can be released:

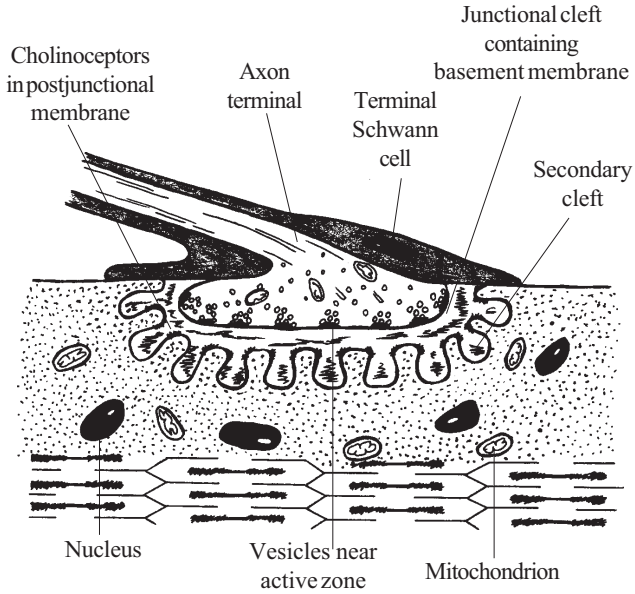

Figure 1. Neuromuscular junction

1. Constant leak or molecular sieve

2. Spontaneous quantal release leading to small transient depolarisations of 0.5mV giving rise to miniature end plate potential (mepp) at a frequency of about 2Hz. This is too small to cause muscle contraction. The function of mepp is not yet known.

3. Additional type of release that is quantal but unrelated to nerve impulse and occurs only when normal ion dependant quantal release is impaired eg botulinum toxin.

4. Nerve impulse evokes huge quantal release (=300 quanta) of acetyl choline and leads to the depolarisation of the post junctional membrane. This constitutes full size end plate potential (epp) and triggers excitation-contraction coupling followed by muscular activity.

Release of Acetyl Choline

Sodium channels are present at pre-terminal parts of axons, ie the region just after the end of myelination but absent from the terminal proper. Potassium and sodium channels are present at the terminal part of the ending ie. from where the transmitter release occurs. The nerve action potential causes an inward sodium current at the pre-terminal membrane. This promotes a local circuit current that depolarises the terminal part by electronic spread. Subsequently, K^+ current flows outwards through the terminal membrane to repolarise terminals. The depolarisation of terminal membranes causes opening of voltage dependant calcium (Ca^{2+}) channels and inward flow of Ca^{2+} begins. Outward K^+ far exceeds inward Ca^{2+} normally, so net current is outwards and repolarises the membrane thereby closing the Ca^{2+} channels. Ca^{2+} that flows into the terminal axoplasm is essential for acetyl choline release. By a process largely unknown but involving calcium calmodulin, there is a synchronous release of many quanta of acetyl choline into the gap.

Action of Released Acetyl Choline

Acetyl choline receptors or cholinoceptors are present in the post-junctional membrane of the motor end plate and are nicotinic in nature. These cholinoceptors are bound by cytoskeleton onto the shoulders of the

junctional fold in clusters so that each end plate has millions of receptors. The receptor has a central pore that functions as an ion channel when in open state. Acetyl choline molecules released in response to nerve impulses bind (about once each) with the recognition site of the receptors inducing a conformational change. This results in opening of receptor operated ion channels, allowing pulses of inward ionic current (mainly Na^+) to flow. Many elementary current pulses summate to produce end plate current (epc). The epc depolarises the end plate membrane (epm) to produce an end plate potential (epp). When the epp reaches a critical threshold, it triggers off an all-or-none propogating action potential that passes around the sarcolemma to activate the contractile mechanism via the T-tubules, sarcoplasmic reticulum and contractile proteins. So, release of acetyl choline constitutes an amplification process that allows minute electric current of nerve endings to excite enormously greater membranes of muscle fibres.

Fate of Acetyl Choline

Released acetyl choline is rapidly hydrolysed to inactive choline and acetate, catalysed by the enzyme acetyl cholinesterase.