

# Discuss how intrinsic and extrinsic factors modulate (i.e. change) transmitter release at the neuromuscular junction.

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Development of our nervous system is a lifelong process, synapses are not hardwired we constantly adapt to learn/perform new tasks, so we need to adapt our dynamic synapses to become stronger or weaker in certain ways. Such as; through changing transmitter release, through intrinsic factors that are integral to the terminal, or extrinsic factors which come from outside, external to the terminal. Abnormalities in neurotransmission are associated with autoimmune disorders (Lambert-Eaton myasthenic syndrome (LEMS) and myasthenia gravis) and genetic diseases (congenital myasthenic syndromes (CMS)) which can be through faulty neuromuscular junctions (NMJ). The NMJ is a simple model for synaptic transmission as it is, in theory, a single nerve terminal on a single cell, which can be used to understand transmitter release and the target for therapeutics. This essay will first give an overview of neurotransmission at the NMJ before discussing intrinsic factors, including; activity, vesicle content and peptide co-transmitters, as well as extrinsic factors, including; noradrenaline, adrenaline, target size, muscle fibre type, target abundance and disease.

Neuromuscular junctions have a presynaptic neuron, a synaptic cleft and a postsynaptic cell. When an action potential reaches the end of the presynaptic axon it reaches the axon terminal which is a region specialised to releasing neurotransmitter. Here voltage gated sodium channels open to depolarise the terminal, causing the voltage gated calcium channels to open in response to that depolarisation, it is these calcium trigger release of the neurotransmitter from vesicles through exocytosis, which is then received by specific receptors on the postsynaptic cell. In the NMJ this neurotransmitter is acetylcholine, which binds to the postsynaptic cell acetylcholine receptors that opens a ligand gated non-specific ion channel that allows predominantly sodium in, potassium out and calcium in. This causes a depolarisation in the muscle cell, which in a functioning cell will be large enough to reach threshold to trigger voltage gated sodium channels generating the action potential in the muscle cell which is the first step leading to muscle contraction. The neurotransmitter and membrane are recycled replenishing the vesicle pool. Neuromodulation can be considered changing the number of vesicles released per action potential, which is the quantal content (QC).

An intrinsic factor that impacts QC is the activity that the terminal experiences in that what it is doing now will influence what the terminal does next. This can be seen with the NMJ in a transmission assay, facilitation is where a first/earlier action potential makes a greater release of vesicles for a subsequent action potential meaning, the postsynaptic response gets bigger after the low initial QC, this has been shown experimentally by reducing calcium and therefore the probability of release. Depression is where a first/earlier action potential causes subsequent action potential to release less vesicles, the post synaptic response gets smaller after the high initial QC. This is influenced by the number of vesicles in the presynaptic ready releasable pool (RRP), neurons which cause facilitation have a large RRP while those causing depression have a smaller RRP, this occurs in a very short time scale (milliseconds). Later is post-tetanic potentiation, which is due to mitochondria soaking up the calcium during activity, which is slowly released, activating kinases, which phosphorylate synapsin, to release the reserve pooled vesicles to the RRP allowing for more transmitter release with the next action potential. There is even later long-term potentiation (LTP) where calcium activates genes to permanently reinforce the synapse.

Another intrinsic factor is vesicle content and feedback, as they can contain Acetylcholine and ATP. Ach acts on M1 muscarinic receptors and M2 muscarinic receptors that are there to determine and influence what is going on in the synapse, which are not fully understood but both influence QC. M1 activates Protein Kinase C which increases Ach release, and M2 activates Protein Kinase A

which inhibits ACh release so depending on the amount, locations and interactions of these receptors will influence the neuronal signalling. ATP also causes negative feedback by it breaking down to adenosine which then influences the Adenosine A1 receptor which acts on Protein Kinase A to decrease neurotransmitter release.

Peptide co transmitters inside the terminal also influence transmission. Unlike the vesicles previously talked about which were small and clear, there are also large dense core vesicles these are fewer and need more calcium stimulation to be released need to move to be released. These large dense core vesicles contain calcitonin gene related peptide (CGRP), which increase cAMP in muscles therefore increasing contraction. They also contain vasoactive intestinal polypeptide (VIP) which influences release, they also contain agarin which will also influence the synapse.

Extrinsic factors like noradrenaline/norepinephrine from the closely situated autonomic nervous system specifically the sympathetic NS this through the alpha2 receptor increases transmitter release through a system we do not fully understand. Also, adrenaline/epinephrine from the endocrine system through the beta2 receptor makes the postsynaptic cell more sensitive to depolarisation as it acts on the potassium channels to reduce leak, increasing the post synaptic response. Target size, as in how big the target cell is, so in the case of NMJ how big the muscle fibre diameter is. Small fibres have a high input resistance because they cannot have as much leak as they have a smaller surface area so need less transmitter (ACh) to drive to threshold and cause a response. Large fibres or larger target cells have more leak due to more surface area and require more transmitter release to reach threshold. On the other side the small terminals will release less vesicles and therefore neurotransmitter as they will have fewer active zones and therefore a low quantal content. Conversely larger terminals have more active zone due to their size and therefore increase QC. So, depending on what you want you can change the sizes of either size accordingly, so long term changes might mean the synapse junction would grow to fulfil the greater transmitter release.

Muscle fibre type reflects the pattern of use, so fast muscle fibres have a high quantal content, while slow muscle fibres have a low quantal content. This has been seen in the EDL and soleus where initial QC, vesicle pool size and recycle time adapt accordingly, so the fast EDL has a high initial QC, but a low vesicle pool and long recycle time, and the slow soleus has a low initial QC, large vesicle pool and short recycle time allowing it to work for longer periods of time. Target abundance, as in the number of muscle fibres innervated in the case of the NMJ, also influences transmitter release as if a single neuron is innervating 5 muscle fibres QC per terminal decrease, but if it innervating less (2 fibres) QC per terminal increases shown by the reinnervation/damage protocol and is thought to be linked to the amount of metabolic stress.

Disease also influences transmitter release. LEMS linked to lung cancer blocks calcium channels responsible to transmitter release. Myasthenia gravis is where antibodies attack ACh receptors which reduces the synapse efficiency, the presynaptic neuron tries to compensate with higher QC. Just as disease can influence any of the receptors involved in these medical therapies can interact with these receptors to change neurotransmitter release.

In conclusion, whether it be learning/performing a new skill physical or mental our nervous system must adapt each neuronal junction according to its given task. This can be done intrinsically or extrinsically through varying the size of the; initial transmitter release, reserve pools (and their locations), junction as well as the position and numbers of functioning receptors that influence transmission.