Neuromuscular NMDA receptors regulate developmental synaptic depletion

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Short Communication

At birth, the skeletal muscle fibers of each mammal are innervated by multiple motor neurons, but in a few weeks all but one of these axons contracts and different activities between inputs control this phenomenon. Acetylcholine, the major neuromuscular transmitter, has long been thought to mediate this activity-dependent process, but glutamatergic transmission also occurs at the neuromuscular junction. To test the role of neuromuscular NMDA receptors, we evaluated their contribution to muscle calcium flux in mice and tested whether they affect the elimination of excess innervation in the endplates. Decreased activation or expression of NMDA receptors and decreased glutamate production slowed synaptic pruning during development. Conversely, circumcision is accelerated by the application of extrinsic NMDA. We also found that NMDA induces an increase in muscle calcium only in the first two weeks of life. Therefore, neuromuscular NMDA receptors play previously unpredictable roles in developing neuromuscular activity and synaptic pruning.

The Mammalian Neuromuscular Junction (NMJ) has long served as a model system for studying the role of activity in trimming excessive innervation. The immature muscle endplates are initially innervated by up to 10 motor neurons, but within a few weeks, all but synaptic inputs are lost in mice. This pruning process is driven by different levels of activity between competing motor neurons, with more active inputs acquiring synaptic regions and withdrawing less active inputs [1]. It seemed logical that Acetylcholine (Ach) as a well-established neurotransmitter would be an important mediator of neuromuscular neuroactivity during developmental synaptic depletion. However, glutamate and glutamate receptors also mediate transmission in NMJ. Glutamic acid in NMJ is derived from the enzymatic degradation of N-acetylaspartyl Glutamate (NAAG) released from motor nerve endings. NAAG is hydrolyzed to glutamate and N-acetylaspartic acid within the synaptic cleft by Glutamic Acid Carboxypeptidase II (GCPII) expressed extracellularly by terminal Schwann cells. Glutamic acid is available at the end plate to bind to post-synaptic NMDA and AMPA receptors. AMPA and NMDA receptors have been recorded in rodent myotubes and adult muscles, as well as in adult lizard muscles. Given the vast evidence that glutamate is involved in activity-dependent developmental plasticity via NMDA receptors in the brain, does glutamate acting on NMDA receptors contribute to the reduction of multineuronal innervation in NMJs? I used three independent methods to investigate. The three methods used to reduce neuromuscular glutamate receptor activation during synaptic depletion were: (1) topical application of NMDA and AMPA receptor blockers, (2) neuromuscular Decreased expression of NMDA receptors and (3) an enzyme that makes glutamate from NAAG. All three operations significantly delayed synaptic clearance. Conversely, excess synaptic innervation clearance was found to be accelerated by topical application of extrinsic NMDA.

In addition, we used calcium imaging to study the muscle response to NMDA and found that NMJ calcium levels were significantly increased during the first two weeks after birth, the postnatal age range where synaptic depletion happens [2].

This study offers proof that glutamate significantly contributes to synaptic pruning in the growing mammalian NMJ. Three experimental techniques were used to show that this process could be slowed down by reducing the activation of NMDA receptors: (1) the injection of NMDA and AMPA receptor blockers at the NMJ, (2) the reduction of NMDA receptor expression by blocking transcription of NR1 subunits with antisense vivo-morpholinos, and (3) the reduction of glutamate availability by using 2-PMPA to block the enzyme that cleaves NAAG into NAA and glutamate at the NMDA. We also demonstrated how exogenous NMDA administration at the NMJ could, in contrast, hasten pruning. We also discovered that the muscle's response to NMDA changed during postnatal development [3].

It should be emphasised that none of our in vivo tests blocked AchRs. One could have believed that the dominance of cholinergic transmission would overwhelm any impact from the NMDA receptors. The early postnatal NMJ's structure, however, is very dissimilar from that of an adult. For instance, at P3, terminal Schwann cells occupy roughly half of the AChR plaque while the nerve terminals are restricted to only about 1/4 of the plaque [4]. This configuration restricts AChR's accessibility to postsynaptic AChRs. Furthermore, the extensive synaptic cleft access provided by Schwann cells may be particularly advantageous for the enzymatic synthesis of glutamate from NAAG and the subsequent activation of glutamate receptors. During the first two postnatal weeks, the glutamate generated by GCPII on the terminal Schwann cell membranes is anticipated to have the most access to the end plate. Therefore, early postnatal development may involve relatively high levels of glutamatergic-to-cholinergic activation of the muscle, followed by a large decline when the synaptic structure matures and the neuron takes up the majority of the plaque. The presence of singly innervated terminals on muscle fibres with genetic modifications to inhibit ACh release may be due to the early dominance of glutamatergic impact [5].

The timeframe of axon pruning and the time when muscles respond significantly to bath-applied NMDA are remarkably correlated. The idea that NMDA receptors are involved in the development of neuromuscular innervation is supported by this association. How do they do that? Does NMDA receptor activation disrupt withdrawing synapses or stabilise preferred synapses? The remaining axons will eventually become destabilised and removed, leaving only one axon stable. Due to this phenomenon, theories based on dual processes have been proposed, whereby the muscle releases a positive signal that stabilises one input while simultaneously producing a negative signal that destabilises the other inputs due to distinct patterns of activity.

According to our findings, the activity imbalance between competing inputs may be amplified by NMDA receptor activation. The strongest inputs would produce the highest positive and negative feedback signals, but the negative signals would have a larger net effect on the weaker connections. As a result, exogenous NMDA speeds up axon elimination while decreasing NMDA receptor activation slows it down [6]. These findings suggest that NMDA receptor activation initiates processes that lead to the destabilisation of all but the strongest inputs at the NMJ. There is overlap between the NMDA receptors' effect on axon elimination and the MHC1 members of the major histocompatibility complex at the NMJ during the second postnatal week.

Similar to NMDA receptors, MHC1 molecules appear to be involved in the destruction of synapses. However, unlike NMDA receptors, their expression is low until week 2 and then increases. It is probable that NMDA receptor effects prevail in the early postnatal weeks, with additional components such as AChRs and MHC1 molecules contributing to the conclusion of the process. However, we have not examined whether the effect of lowering NMDA receptor activation leads to persistent polyinnervation.

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