COMMUNICATION ERROR: THE RELATIONSHIP BETWEEN NEURAL CELL ADHESION MOLECULE EXPRESSION AND MUSCLE ACTIVATION IN PARKINSON'S DISEASE

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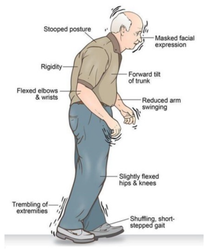
Introduction

Parkinson's disease (PD) is a condition characterized by motor dysfunction as a result of progressive neuro-degeneration. Individuals with PD experience tremors, muscle rigidity, bradykinesia, and abnormal gait among other debilitating symptoms.



T Tremor: shaking, usually starting on one side

R Rigidity: stiffness of the limbs, neck, or trunk

A Akinesia: loss or impairment in power of voluntary movement

P Posture and balance

Neural cell adhesion molecule (NCAM) is a protein expressed by muscle fibers when they are denervated, or no longer attached to a motor unit (Figure 1). NCAM is used by muscle cells (myofibers) to signal neighboring motor neurons that reinnervation is needed to avoid apoptosis, and an accumulation of myofiber loss will likely influence muscle activation[1,2]. However, the relationship between NCAM expression and muscle activation is unknown.

The purpose of this pilot study was to investigate the relationship between relative (rTI, rTII) NCAM expression and muscle activation in persons with idiopathic PD.

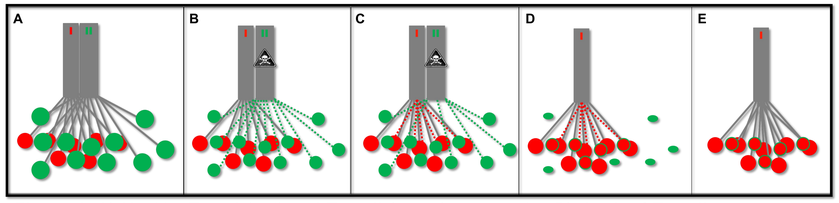


Figure 1. A) Healthy Type I (red) and Type II (green) motor units; B) death of Type II motor neuron and denervation of Type II myofibers; C) axonal sprouting from Type I motor neuron to save some of the denervated Type II myofibers; D) reinnervation of some of the denervated Type II myofibers; E) reinnervated (formerly Type II) myofibers are added to a Type I motor unit and begin expressing Type I myosin heavy chain.

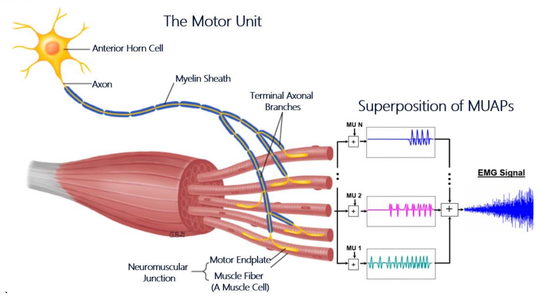


Figure 2. The activation of a motor unit (an alpha-motor neuron and the myofibers it innervates) results in its depolarization, which is known as the motor unit action potential (MUAP). These MUAPs can be detected and measured via surface electromyography (EMG).

Methods

Thirty individuals volunteered for a research study at the University of Alabama at Birmingham (UAB). Participants were recruited from the Birmingham, Alabama metropolitan area and gave written, informed consent allowing their samples and data to be used for future research as approved by the UAB Institutional Review Board. From that larger study, muscle biospecimens from six individuals with PD (67±9 yrs; M=2, F=4) were available for the present study. Muscle biopsy specimens were collected by percutaneous needle biopsy of the vastus lateralis muscle under local anesthesia (1% lidocaine) using a 5-mm Bergstrom-type biopsy needle with suction (Figure 3).

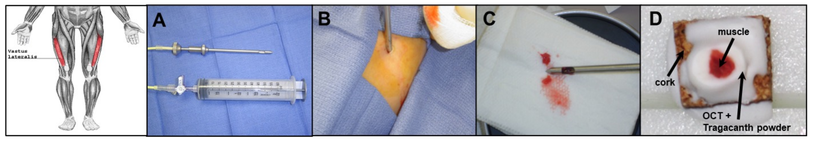


Figure 3. A) 5-mm Bergstrom biopsy needle with tubing and syringe for suction; B) sterile field with biopsy needle inserted into muscle; C) muscle tissue sample; D) cross-sectionally mounted sample embedded in OCT+tragacanth gum for sectioning.

Biopsies were performed in the Clinical Research Unit of the UAB Center for Clinical Translational Science and stored at -80°C. Tissue samples were shipped on dry ice to Creighton University and stored at -80°C. All immunohistochemistry was performed on fresh-frozen 6µm thick serial cryo-sections (Figure 4). Upon completion of each stain, tissue samples were dried, mounted, cover slipped, and stored at -20°C until analysis.

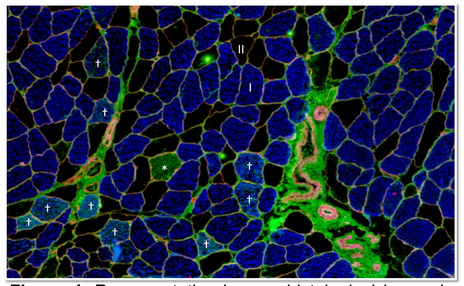


Figure 4. Representative immunohistological image is shown of PD: Type I (blue); Type II (black/negative); NCAM (green); Laminin (red). *Type II-NCAM+; †Type I-NCAM+

10x microscopic images were captured in a grid format and stitched together using BZ-X800 microscope (KEYENCE, Inc.) software to render one seamless image of the entire cross-section of the specimen (Figure 4). ImageJ (NIH) software was used to manually analyze and count all fibers for myofiber type distribution and NCAM expression.

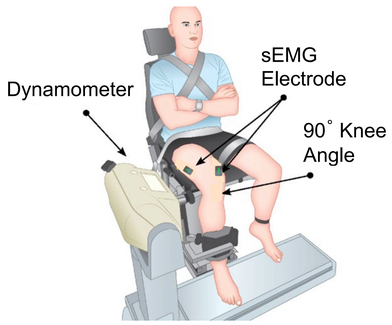


Figure 5. Representative experimental setup to measure muscle activation during a maximal voluntary isometric contraction with sEMG.

On a separate visit, participants performed a light warm-up at a submaximal, self-selected pace on a cycle ergometer for 5-min prior to being set up in dynamometer chair. Participants performed three maximal voluntary isometric contractions of the quadriceps femoris separated by 2 minutes of rest. For each trial participants were asked to "kick as hard and fast as possible" and hold the contraction for 2-3 sec until being instructed to relax. During maximal voluntary isometric contractions, muscle activation measured using at 2000 Hz (Figure 5). Peak EMG amplitude (pEMG) was calculated at the highest 500 ms epoc from the EMG time curve normalized to the rate of EMG rise (RER; Figure 6). Pearson correlation coefficients (*r*) were used to determine relationships between dependent variables. Significance was set at $p<0.05$.

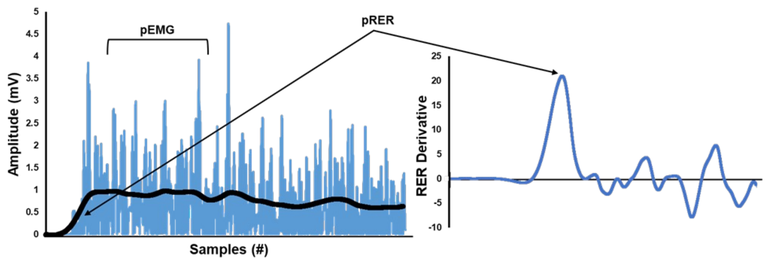


Figure 7. Representative sEMG processing of data to determine pRER and pEMG.

Results

rTI/NCAM+ (2.0 ± 1.4%) was negatively correlated with pRERn (1.04 ± 0.8 a.u.; *r*=-0.94, p=0.005) and pEMG (*r*=-0.88, p=0.02). rTII/NCAM+ (3.2 ± 0.9%) was negatively correlated with peak torque (120 ± 54 Nm/s; *r*=-0.96, p=0.002). There we no significant correlations between any other variables.

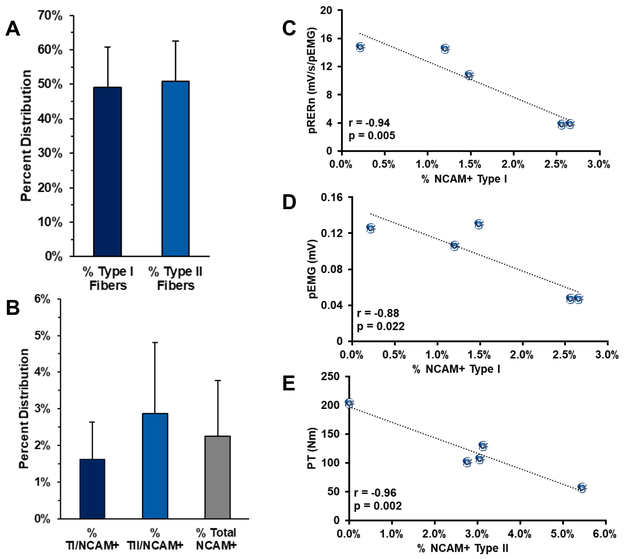


Figure 6. Myofiber type distribution (A) and relative distribution of NCAM co-expression (B). Normalized peak RER is negatively correlated with %NCAM+ TI myofiber distribution (C: r = -0.94; p = 0.005). Peak EMG is negatively correlated with %NCAM+ TI myofiber distribution (D: r = -0.88; p = 0.022). Peak torque is negatively correlated with %NCAM+ TII myofiber distribution (E: r = -0.96; p = 0.002).

Conclusions

Our pilot data suggests that greater rTI/NCAM+ expression is associated with a slower rate and reduced amplitude of muscle activation. Increased denervation of type II myofibers is associated with decreased peak torque, suggesting a consequence related to the contractile function of myofibers expressing NCAM. Our data indicate that decreased innervation leads to a slower rate of muscle activation. Overall, higher NCAM expression may be indicative of compromised communication between the nervous system and skeletal muscle, leading to decreased muscle performance.

Practical Applications

Identifying disruptions in the communication between motor neurons and the myofibers they innervate may provide insight for the development of specific therapeutic exercise programs that can improve motor performance and quality of life for persons with PD.

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References