Botulinum Toxin Type-A Plus C3 Transferase Mitigates Adverse Effects of Botulinum Toxin Type-A on Muscle Mechanics

Can A. Yucesoy[1], Zeynep D. Akdeniz Doğan[2], Cemre Su Kaya Keles[1,3]
[1]Institute of Biomedical Engineering, Boğaziçi University, Istanbul, Turkey
[2]Department of Plastic, Reconstructive, and Aesthetic Surgery, Marmara University, Istanbul, Turkey
[3]Institute of Structural Mechanics and Dynamics in Aerospace Engineering, University of Stuttgart, Stuttgart, Germany
Email: can.yucesoy@bogazici.edu.tr

Summary

Botulinum toxin type-A yields increased passive muscle forces and a narrower muscle length range of force exertion, which contradict the intended mechanical effects at the joint. Central to those is elevated extracellular matrix stiffness. Present testing of Botulinum toxin type A and C3 transferase combined showed that such adverse effects on muscular mechanics are mitigated.

Introduction

Spasticity, characterized by exaggerated stretch reflexes, is commonly managed with botulinum toxin type-A (BTX-A). Mechanically the pathological condition in the joint involves elevated passive resistance and limited range of motion. Although BTX-A does reduce muscle tone, in contrast to the expected benefits, it increases passive muscle forces, narrow muscles' length range of force exertion (l_{range}), and elevate extracellular matrix (ECM) stiffness [1,2]. Finite element modeling indicated ECM stiffness is central to the mechanism of those effects [3,4]. C3 transferase is known to inhibit myofibroblast and fascial tissue contractility and hence may counteract ECM stiffening. Combining BTX-A with C3 transferase therefore could preserve structure hence mechanics of exposed muscle. To explore this, we hypothesized that their combined injection into the rat tibialis anterior (TA) muscle (i) decreases active muscle forces while yielding no change in (ii) passive muscle forces and (iii) muscle's l_{range}. Additionally, we examined the isolated effects of C3 transferase on muscle structure.

Methods

Muscle mechanics were tested in two groups of male Wistar rats: Control (n=7, 20µl saline injection) and C3+BTX-A (n=7, 2.5µg C3 + 0.1U BTX-A in 20µl saline). TA isometric forces were measured at varying lengths. Muscle structure was assessed separately in two groups: Control (n=6, 20µl) and C3 (n=6, 2.5µg C3/20µl) using hydroxyproline analysis. All measurements were performed one-month post-injection into the mid-TA-belly. Two-way ANOVA for repeated measures (factors: TA length and animal group) analyzed muscle force effects, while l_{range}, relative muscle mass, and collagen content were compared using unpaired t-tests or Mann-Whitney U tests ($P<0.05$).

Results and Discussion

ANOVA showed significant effects of both factors on active forces ($P<0.001$), with no interaction, active forces being 43.5% lower in the C3 + BTX-A group compared to the Control group (Fig. 1). No significant differences were observed between groups in either passive forces ($P=0.33$) or l_{range} ($P=0.19$). C3 transferase does not lead to significant differences in relative muscle mass ($P=0.298$) or intramuscular collagen content ($P=0.093$) compared to the Control group.

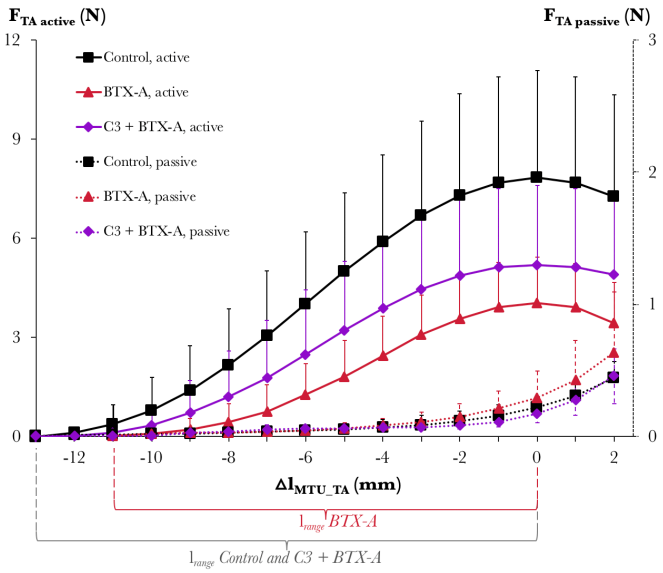

Figure 1: Muscle length-force characteristics.

Conclusions

Supplementing BTX-A with C3 transferase prevents increased passive muscle force and narrowed l_{range}, effectively eliminating the adverse effects of BTX-A. This confirms our hypotheses. Using C3 transferase alone showed no signs of muscle atrophy or increased collagen content, which are key factors in BTX-A-induced ECM stiffening. This novel neurodenervant formula [5] holds a significant potential to transform spasticity management in clinical practice.

Acknowledgments

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