Introduction

- Myotropes are a new kind of calcium-independent therapeutic drugs that bind to sarcomeric proteins
- Their clinical development has reinforced the need for new quantitative understanding of sarcomere-level function
- Mathematical models can be used to produce in silico predictions regarding the impact of myotropes on contractility

Methods

- FiberSim (1) is a spatially explicit computer model of half-sarcomere contraction
- FiberSim can be used to evaluate sarcomere contractility as a function of a myotrope dose, specifically mavacamten in this study
- It was hypothesized that mavacamten stabilizes the SRX (super-relaxed state) of myosin (2)
- K_D of mavacamten and myosin was determined from previously published ATPase data (3) and used to calculate the proportion of SRX myosin associated with mavacamten
- Isometric force was then calculated for different mavacamten concentrations

Key results

- Isometric force decreases with increasing mavacamten concentrations, consistent with experimental data showing a decrease in ATPase activity of isolated actomyosin assays
- IC_{50} (mavacamten dose for 50% isometric force) is ~40% lower than K_D.
- This implies that contractile force is more sensitive to mavacamten than the ATPase of isolated myosins.
- Simulations suggest that mavacamten inhibiting a myosin head's force-generating ability also reduces recruitment of additional myosin heads due to the force-dependency of the SRX to DRX transition
- FiberSim can be used to investigate the effects of other myotropes and help accelerate the development of myotrope-based therapies for muscle disease

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References

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