RESPECT THY ELDERS: OR LESSONS LEARNT FROM THE LITERATURE

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INTRODUCTION

I was struggling with the notion of a "president's lecture". On the one hand, such a lecture should be philosophical and and full of wisdom, on the other hand, I love to talk about my research. These two notions are not necessarily compatible, so I decided to compromise by talking about my research, while highlighting some of the errors I made and pitfalls I encountered. This hopefully, will then turn into a lesson for students and junior scientists.

Specifically, I would like to focus on selected scienitfic findings that were published in the literature. The selected papers are classics in the area of skeletal muscle mechanics, and although all of them are indispensible and have shaped much of my thinking in the long term, they put blinders onto my brain so that the obvious remained hidden much longer than it hould have.

DISCUSSION

Paul Edman [1] published a classic paper on skeletal muscle force enhancement in 1982. Much of the results hold to this day, but he made three specific observations that influenced people's thinking for decades but turned out to be incorrect. The first of these was that residual force enhancement following stretching of muscle fibres could never exceed the isometric force at optimal sarcomere length. Nobody questioned this result seriously, until a postdoc of mine (Jenny Wakeling) showed me results of our first ever single fibre experiments. She had in excess of 15% greater forces in the force enhanced state than the isometric plateau forces. Since this was against all that was known at the time, and was in complete disregard of the reigning paradigm on force enhancement (sarcomere length non-uniformity [2]), we did not publish these findings until two further students had independently been able to reproduce Jenny's results [3;4].

In that same paper [1], Edman also showed that residual force enhancement could not occur on the ascending part of the force-length relationship and that passive elements did not contribute to the residual force enhancement. It took some 20 years before we (and others) published evidence that both these assertions were not correct. Particularly, the idea of a passive structural element contributing to force enhancement is now accepted, and the molecular spring titin has been identified as a strong regulator of force (i) through binding of calcium upon activation, (ii) through phosphorylation and (iii) through calcium and force dependent binding to actin.

Another notion that has influenced the thinking of the muscle mechanics community is the idea of instability of sarcomere lengths on the descending limb of the force-length relationship. A.V. Hill was the first to propose this idea [5], which in turn was taken as the source for muscle "creep" on the descending limb of the force-length relationship [6], and was said to be the cause for all unexplained observations on the history dependence of steady-state isometric force production [2].

Instability of sarcomere lengths, and its effects on force production and contractility can probably only be assessed properly in a single myofibril preparation, because in these preparations all sarcomeres are arranged strictly in an in series manner and individual sarcomere lengths can be measured for all sarcomeres within a myofibril [7]. We observed in single myofibrils that sarcomeres, although non-uniform in length prior to and following myofibril stretching, were perfectly stable on the descending limb of the force length relationship [8]. We further observed that sarcomere non-uniformity did not increase with stretching as proposed by the "creep" theory [2], and further did not observe any "creep" behaviour in isometric contractions of myofibrils or fibres.

We concluded from these results that sarcomere lengths are perfectly stable on the descending limb of the force-length relationship, that sarcomere length non-uniformity does not play a significant role in explaining the history-dependent force and contractile properties of skeletal muscles, and that the "creep" observations made by many researchers are likely caused by the experimental setup rather than an intrinsic property of muscle.

CONCLUSIONS

The published literature forms the foundation for scientific investigations. We need to respect the findings that have passed the peer-review process, but need to be careful in assuming that everything that is published, even by the leaders in the field, is beyond question. Respect thy elders, but realize they are not perfect.

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