Newton’s force as countermeasure for disuse atrophy

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THE OBSERVATION THAT DISUSE leads to muscle atrophy is an old
one, but we still lack a good mechanistic description of what is
going on to cause wasting in conditions as diverse as bed rest
and spaceflight. In fact, much of the current descriptions of the
superficial mechanisms of atrophy come from work funded by
space agencies, primarily National Aeronautics and Space
Administration but also the European Space Agency. Less
glamorously, but quantitatively more important in terms of
muscle lost, is the clinical interest that centers around disuse
atrophy in hospitalized patients and the physically inactive
elderly. Both for astronauts and for patients who are confined
to bed, a major question is “how can we stop the wasting?” The
obvious answer may seem glib, but “removal of the proximal
cause” is easier said than done in many situations, such as with
paralyzed patients in intensive care or, indeed, in space. Many
of the potential countermeasures applied in space (mainly
involving exercise of one sort or another) have turned out to be
not useful with little beneficial effect on an astronaut’s muscle.
Symons et al. (9) have, however, managed to do the obvious
experiment: replacement of the gravitational forces that are
normally diminished during bed rest. In their report, the
Galveston team applied techniques that have become routine
for them. They subjected two groups of healthy young men to
6% head-down tilt during bed rest for 21 days, a technique
known to cause substantial wasting of the quadriceps muscle.
One group spent the entire period immobile except for about 5
min per day for bowel movements, but the other received what
was in effect gravitational therapy: exposure to 1 h per day of
longitudinal loading amounting to a force of 2.5 G at the feet.
The apparatus to achieve this was a human centrifuge that spun the
subjects at ~30 rpm (described in Ref. 11). The investigators
applied well-validated stable isotope-labeled amino acid tracer
techniques to measure muscle protein turnover yielding mea-
sures of both the rate of production of protein [muscle protein
synthesis (MPS)] and the rate of its removal by proteolysis
[muscle protein breakdown (MPB)].

As expected from previous work, bed rest alone caused a
depression of MPS of about one-half in the control group, but
this was completely abolished in the treatment group. This is
an important result for two reasons: first, because it is a
confirmation of the simple idea that replacing gravity works!
Second, it shows that a relatively small stimulus (2.5 G for 1 h
per day) is enough to maintain MPS. There are, however, other
interesting aspects to the work that are important. As predicted
some 20 years ago (3) and confirmed not only by this work but
by the earlier work of Ferrando (5), MPB was not to be
elevated by disuse and was unaffected by gravitational therapy.

In companion articles, Caiozzo et al. (1) show that the same
subjects from the study by Symons et al. (9) show the now
predictable (2, 4) only minor rise in genes coding for the
ubiquitin ligases atrogin and MuRF1, commonly assumed to be
involved in muscle proteolysis. Hence, it is not surprising that
MPB is not elevated. Thus the major process driving muscle
atrophy in immobilization or bed rest (in healthy young sub-
jects) is depressed MPS, not elevated MPB. This is in marked
contrast to much of the literature concerning disuse atrophy in
rodents (7, 8, 10) in which elevated MPB appears to be of equal
importance to depressed MPS.

We still do not know the underlying mechanisms driving
down MPS, although the obvious candidates, such as depres-
sion of activation by phosphorylation of anabolic signaling
molecules, appear not to be important (4, 6). It seems likely
that suppression of activation of focal adhesion kinase (FAK)
may be an important proximal event (4, 6), but the links
between this and regulation of MPS both at the nuclear level
and at the ribosome are currently opaque.

What is the wider significance of the work? For a start, it
means that Convertino’s (3) suggestions of inducing artificial
gravity as a sine qua non for long-term spaceflight are bol-
stered. This may make building and launching a Mars-bound
vessel much more expensive, but the alternative is the crippling
of astronauts returning from a 3-year voyage to Mars and back.
Another important message is that the pharmaceutical industry
might wish to stop pursuit of inhibitors of MPB, which are
apparently irrelevant in disuse atrophy, and concentrate on
looking for ways of boosting MPS.

Of course as a well-known phrase has it, “the proof of the
pudding is in the eating,” and although Symon’s work shows
what is probably the best Earth-based results so far, the
technique still has to be shown to work in space. Expensive
pudding1

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