Stretch-activated channels in stretch-induced muscle damage - role in muscular dystrophy

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Unaccustomed eccentric contractions result in damage to skeletal muscles which can last for up to one week. In normal individuals, this muscle damage represents a transient weakness and discomfort after unaccustomed exercise. However in muscular dystrophy repetitive damage cannot be adequately repaired and contributes to progressive weakness and muscle degeneration.

We have studied the causes of stretch-induced muscle damage in single mouse muscle fibres which were stretched by 40% of optimal length (L_o) during 10 maximal tetani (Balnave & Allen, 1995). As a consequence of eccentric contractions, the recognised features of damage included: (i) reduced maximal force; (ii) greater reduction of force at low stimulation frequencies; and (iii) a shift in L_o to a longer muscle length, which is characteristic of sarcomere disorganisation. Isometric tetani or stretches of resting fibres produced none of these features.

The cause of the reduced force and muscle damage are not established but one theory is that tears in the muscle membrane allow influx of ions such as Na^+ and Ca^{2+} and the efflux of proteins such as creatine kinase. To investigate this mechanism we measured intracellular sodium concentration ($[Na^+]_i$) after both isometric or eccentric tetani. $[Na^+]_i$ was unaffected by isometric tetani but increased after eccentric contractions from the resting level of 7.2 ± 0.5 mM to 16.3 ± 1.6 mM over 1-2 min and the increase persisted for more than 30 min. There was no evidence of localised elevations of $[Na^+]_i$ which might result from membrane tears but, instead, the rise could be prevented by gadolinium (Gd^{3+}), a blocker of stretch-activated channels (Yeung *et al.*, 2003). These results suggest that a stretch-activated Na^+ permeable channel is opened following eccentric contractions and causes the increased $[Na^+]_i$. Since Gd^{3+} reduced Na^+ influx we tested whether it could prevent muscle damage as measured by the force production 10 min after eccentric contractions. When Gd^{3+} was applied over the period in which $[Na^+]_i$ rises (i.e. for the first 10 min after the eccentric contractions), it increased the force from 36 ± 5 to 49 ± 4%.

Given that Gd^{3+} prevented Na^+ entry and minimised force reduction following eccentric contractions in wild-type fibres, we examined the same phenomena in *mdx* muscles. We establish that *mdx* fibres have a higher than normal resting $[Na^+]_i$ and show that single fibres from *mdx* muscle are more susceptible to eccentric damage. The rise in $[Na^+]$ following eccentric contraction was greater in *mdx* compared to wild-type mice. This rise in $[Na^+]_i$ could be reduced by Gd^{3+} and, as with wild-type fibres, the force after eccentric contractions was increased when Gd^{3+} was applied over the period in which $[Na^+]_i$ rose.

Stretch-activated channels are also permeable to Ca^{2+}, so they could provide a leak pathway for Ca^{2+} to enter the cell causing cellular damage. Investigations in Ca^{2+} handling as a result of activity of the stretch-sensitive channels after eccentric contractions should enhance our understanding of muscle damage in muscular dystrophy

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