

Mechanosensitive ion channels in dystrophic muscle: Implications for channel gating and disease pathogenesis

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Although an absence of dystrophin and its associated glycoprotein complex is the primary defect in Duchenne muscular dystrophy (DMD), the precise molecular events leading to muscle degeneration are not understood. A body of evidence indicates an increase in intracellular Ca is an early step leading to muscle death. We have identified mechanosensitive (MS) channels showing increased activity in myotubes and acutely isolated fibers from the mdx mouse and have postulated that they contribute to the pathogenesis of DMD by allowing high rates of Ca entry. MS channels in skeletal muscle are present at relatively high densities at all stages of muscle development. MS channels in wild type and mdx muscle are permeable to Ca, identical in conductance and ion selectivity, but show marked differences in gating behavior. In mdx myotubes, pressure stimuli or strong voltage displacements cause MS channels to switch into a second gating mode characterized by abnormally long open times and a stretch-inactivated gating process. Channels that have switched into this gating mode often appear localized in hot spots containing large numbers of channels. In single fibers acutely isolated from the flexor digitorum brevis of mdx mice, MS channels show an increased open probability before the onset of muscle degeneration, a reduced sensitivity to stretch, and persistent expression in older animals. The absence of the second gating mode in dystrophin-deficient fibers is believed to be due to compensatory expression of utrophin. These data will be discussed in terms of the role of dystrophin in regulating MS channel gating behavior, the contribution of MS channels to the pathogenesis of DMD, and the molecular identity of the MS channels in skeletal muscle which has properties consistent with the behavior of TRPV channels.