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Voltage- and calcium-dependent inactivation of Cav1.2, but not of Cav2.1, is suppressed in skeletal muscle

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To investigate the relationship between calcium channel and EC coupling functions of $Ca_V1.1$ in skeletal muscle, we have compared its behavior with that of $Ca_V1.2$. Using expression in tsA-201 cells, we showed that substituting $Ca_V1.1$ IQ motif residues into $Ca_V1.2$ caused a loss of calmodulin binding and calcium-dependent inactivation, raising the possibility that inactivation is maladaptive for $Ca_V1.1$ function in muscle. We thus compared inactivation of $Ca_V1.2$ in tsA-201 cells and *dysgenic* myotubes (null for $Ca_V1.1$). For $Ca_V1.2$, $\alpha_2\delta1$ and β2a expressed in tsA-201 cells, $I_{50\text{-}ms}/I_{peak}$ (R_{50}) at +20 mV was .69 in 10 Ca and .87 in 10 Ba, whereas R_{50} for $Ca_V1.2$ in dysgenic myotubes was .95 at +20 mV in 10 Ca, indicating that both voltage- and calcium-dependent inactivation were suppressed. In tsA-201 cells, co-expression of β1a (the predominant skeletal muscle isoform) did not significantly alter R_{50} values from those with β2a. Furthermore, R50 values were similar for $Ca_V1.2$ expressed in *dysgenic* myotubes and myotubes null for both $Ca_V1.1$ and RyR1, suggesting that some component of muscle triad junctions other than RyR1 is responsible for suppression of inactivation. We thus expressed $Ca_V2.1$ in *dysgenic* myotubes because this neuronal channel, unlike $Ca_V1.2$, is not targeted to triad junctions. $Ca_V2.1$ channels showed significant voltage- and calcium-dependent inactivation in *dysgenic* myotubes, which were similar to those of the channel expressed in tsA-201 cells. We are currently seeking to identify the components that suppress inactivation of $Ca_V1.2$ in myotubes. Supported by AHA0190016G to JDO and NIH/NIAMS (AR055104) and MDA4319 to KGB.