IN VITRO AND *IN VIVO* CHARACTERIZATION OF THE ROLE OF TRPC1 CHANNEL IN SKELETAL MUSCLE FUNCTION

Nadège Zanou [1], Olivier Schakman [1], Georges Shapovalov [2], Chiara Gallo [2], Alexander Dietrich [3], Jean Lebacq [1], Urs Ruegg [2] Lutz Birnbaumer [4] and Philippe Gailly [1]

[1] University of Louvain, Belgium; [2] University of Geneva, Switzerland;[3] University of Marburg, Germany, [4] National Institute of Environmental Health Sciences, USA.

Skeletal muscle contraction is reputed not to depend on extracellular Ca^{2+}. Indeed, stricto sensu, excitation-contraction coupling does not necessitate entry of Ca^{2+}. However, we previously observed that, during sustained activity (repeated contractions), entry of Ca^{2+} is needed to maintain force production. In the present study, we evaluated the possible involvement of the canonical transient receptor potential (TRPC)1 ion channel in this entry of Ca^{2+} and investigated its possible role in muscle function. The influx of Ca^{2+} through TRPC1 represents a minor part of the entry of Ca^{2+} into muscle fibers at rest, and the activity of the channel is not store dependent. The lack of TRPC1 does not affect intracellular Ca^{2+} concentration ($[Ca^{2+}](i)$) transients reached during a single isometric contraction. However, the involvement of TRPC1-related Ca^{2+} entry is clearly emphasized in muscle fatigue. Indeed, muscles from $TRPC1^{-/-}$ mice stimulated repeatedly progressively display lower $[Ca^{2+}](i)$ transients than those observed in $TRPC1^{+/+}$ fibers, and they also present an accentuated progressive loss of force. Interestingly, muscles from $TRPC1^{-/-}$ mice display a smaller fiber cross-sectional area (CSA), generate less force per CSA, and contain less myofibrillar proteins than their controls. To study the role of TRPC1 in skeletal muscle functions, we investigated in vivo the ability of the $TRPC1^{-/-}$ mice to perform voluntary (running wheel and escape test) or endurance exercises (treadmill and wire test). If $TRPC1^{-/-}$ mice do not exhibit any difficulty to perform voluntary exercise, they show a predisposition to muscle fatigue. Indeed, the performances of the $TRPC1^{-/-}$ mice in the treadmill and wire test were lower than those observed in a control mice. We also compared basal activity (home cage activity) and coordination (rotarod, balance-beam test). We conclude that TRPC1 ion channels modulate the entry of Ca^{2+} during repeated contractions and help muscles to maintain their force during sustained repeated contractions.