Importance of the t-system chloride conductance in muscle excitability and fatigue

G.D. Lamb, T.L. Dutka, R.M. Murphy and D.G. Stephenson, Department of Zoology, La Trobe University, Melbourne, VIC 3086, Australia.

It is widely recognised that the chloride permeability of mammalian skeletal muscle fibres is important because if it is greatly reduced or absent muscles fibres readily display myotonia, an aberrant state in which the fibres generate their own action potentials (APs) and keep contracting without input from the central nervous system. The chloride conductance accounts for ~80% of the total resting conductance in mammalian muscle fibres, and there is some evidence that much of this resides in the transverse tubular (t-) system (Dulhunty, 1979). Currently, however, little is known about the importance, role(s) and molecular identity of t-system chloride conductance. This is a major issue because normal muscle function depends on excitation of the transverse-tubular (t-) system. It is frequently suggested the muscles readily fatigue with repeated activation owing to the build-up of K^+ in the t-system causing membrane depolarization and consequent failure of the action potentials and contraction, but the role of the t-system chloride conductance in this is not taken into consideration.

Here we present evidence that the chloride conductance in t-system is indeed high and that it plays a vital role in maintaining excitability during normal activity. It does this both by reducing the accumulation of potassium in the t-system and by opposing its depolarizing effects. This occurs because i) Cl^- ions carry part of the repolarizing current on each AP, reducing the extent of K^+ accumulation in the t-system, ii) the high relative Cl^- permeability of the t-system membrane strongly biases the membrane potential towards the Cl^- equilibrium potential, which is affected comparatively little by the ion concentration changes on each AP, and iii) K^+ accumulating in the t-system is likely driven back into the cytoplasm through the inward rectifier channels whenever the equilibrium potential for K^+ exceeds the membrane potential. The observed properties of the chloride conductance are consistent with it be meditated by ClC-1, which is putatively the dominant chloride channel in skeletal muscle, though frequently said to be only in the surface membrane and not in the t-system. We present Western blot analysis using antibodies to ClC-1 demonstrating that large amounts of ClC-1 channel proteins are indeed located inside muscle fibres.

Finally, if a fibre becomes depolarized after prolonged or vigorous activity, the t-system chloride conductance can be a hindrance to excitability because of its dampening effects on AP conduction. Intracellular acidification counters this effect by causing a partial reduction in the chloride conductance, thereby keeping the conductance in balance so that it maintains rather than antagonises t-system excitability (Pedersen *et al.*, 2004).

Dulhunty AF. (1979) *Journal Membrrane Biology*, **45:** 293-310.
Pedersen TH, Nielsen OB, Lamb GD & Stephenson DG (2004) *Science*, **305:** 1144-7.