In the presence of ATP, acidosis markedly inhibits ClC-1 skeletal muscle chloride channels

B. Bennetts,[1] M.W. Parker[1] and B.A. Cromer ,[2] [1]St. Vincent's Institute, Fitzroy, VIC 3065, Australia and [2]Howard Florey Institute, University of Melbourne, VIC 3010, Australia.

Skeletal muscle acidosis during exercise has long been thought to be a cause of fatigue but recent studies have shown that acidosis maintains muscle excitability and opposes fatigue by decreasing the sarcolemmal chloride conductance. ClC-1 is the primary sarcolemmal chloride channel and has a clear role in controlling muscle excitability but recombinant ClC-1 has been reported to be activated by acidosis. Following our recent finding that intracellular ATP inhibits ClC-1, we investigated here the interaction between pH and ATP regulation of ClC-1. We found that in the absence of ATP, intracellular acidosis from pH 7.2 to 6.2 inhibited ClC-1 slightly by shifting the voltage dependence of common gating to more positive potentials, similar to the effect of ATP. Importantly, the presence of physiological concentrations of ATP greatly potentiated the effect of acidosis on common gating, causing a marked inhibition of ClC-1 channel activity. Adenosine had a similar effect to ATP at pH 7.2 but acidosis did not potentiate this effect, indicating that the phosphates of ATP are important for this cooperativity, possibly due to electrostatic interactions with protonatable residues of ClC-1. A protonatable residue identified by molecular modelling, His847, was found to be critical for both pH and ATP modulation and may be involved in such electrostatic interactions. These findings are now consistent with, and provide a molecular explanation for, acidosis opposing fatigue by decreasing the chloride conductance of skeletal muscle *via* inhibition of ClC-1. The modulation of ClC-1 by ATP is a key component of this molecular mechanism.