Influence of mitochondria in the interspike interval pacemaking currents of mice *Locus Coeruleus* neurons

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The *Locus Coeruleus* (LC) is a nucleus located within in the dorsorostral Pons structure of the brain stem. It comprises of noradrenergic neurons that project throughout most of the central nervous system, is the brains major source of noradrenaline and has a fundamental role in many important processes such as arousal, attention, mood and controlling behaviour. One of the features that allow LC neurons to perform their physiological functions is their synchronised rhythmical firing, providing regulated release of noradrenaline throughout the brain. Mitochondria are extremely important for neuronal function, not only for ATP production but also as an active component in calcium signalling and in the production of free radicals. Recently, neuronal mitochondria loss was linked with the promotion of some pathologies such as Parkinson's diseases (Forno, 1996; Baloyannis, 2006). Surprisingly, the death/lost of LC neurons has also been linked with Parkinson's diseases: LC neurons loose their ability to fire actions potentials and die before the classical symptoms of the diseases appear (Gesi *et al.*, 2000; Baloyannis *et al.*, 2006). As such mitochondria could be playing a role in the generation of actions potentials in LC neurons. Thus we aimed to investigate the role for mitochondria in the generation of interspike-interval pacemaker currents in mouse LC neurons. Experiments were conducted using *in vitro* brain-stem slice preparations at 37°C and whole-cell patch-clamp recordings. All procedures used were approved by the Animal Care and Ethics Committee at the University of Newcastle. To assess mitochondria participation we used three drugs, namely the protonophore CCCP, the mitochondrial Na^+/Ca^{2+} exchange inhibitor CGP-37157 and the ATPase mitochondrial inhibitor oligomycin. CCCP completely abolished the spontaneous generation of action potentials by the induction of an outward current during the interspike interval. CGP-37157 had minimum effect on the pacemaking process, slightly increasing the firing rate. Oligomycin had no effect indicating ATP depletion was not a factor. Taken together, these results indicate that mitochondria have a role in the pacemaking process. This action is seemingly mediated via the activation of an as yet unidentified outward current but does not directly involve Ca^{2+} buffering or ATP production. More studies are needed to elucidate the mitochondrial participation in the pacemaking process of mice LC neurons, and which pathways are involved.

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