

## Effects of S-glutathionylation, S-nitrosylation and oxidation on Ca-sensitivity and force: a balancing act

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Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are important for skeletal muscle function both in physiological and pathological conditions. These agents are generated in active muscle and can induce both acute and long term effects on muscle function. Exposure of intact fast-twitch muscle fibres to the oxidant hydrogen peroxide ( $H_2O_2$ ) affects force principally by altering myofibrillar  $Ca^{2+}$  sensitivity, initially producing increased sensitivity, followed by a decrease with more prolonged exposure (Andrade *et al.*, 1998). Experiments on skinned fibres show that these effects can be attributed to  $H_2O_2$  interacting with glutathione and myoglobin, causing S-glutathionylation and oxidation of the contractile apparatus respectively (Lamb & Posterino, 2003; Murphy *et al.*, 2008).  $H_2O_2$  can also oxidize the sarcoplasmic reticulum  $Ca^{2+}$  release channels, the ryanodine receptors, and studies on isolated channels show that this oxidation has a large stimulatory effect on  $Ca^{2+}$ -induced  $Ca^{2+}$  release. However, experiments on skinned and intact fibres show that acute  $H_2O_2$ -induced oxidation has little or no effect on action potential-induced  $Ca^{2+}$  release, the normal physiological process governing  $Ca^{2+}$  release (Posterino *et al.*, 2003). Application of nitric oxide donors, on the other hand, produce a decrease in submaximal force in skinned muscle fibres, due primarily to a decrease in myofibrillar  $Ca^{2+}$  sensitivity (Spencer & Posterino, 2009), brought about by S-nitrosylation of the contractile apparatus. More extensive exposure of muscle to oxidants or nitrosylating agents can also lead to a decrease in both maximum force and  $Ca^{2+}$ -sensitivity of the contractile apparatus, likely due primarily to oxidation of reactive sulphhydryls in the myosin heads. The overall effect on muscle function of ROS and RNS generated in physiological and pathological conditions is determined by the balance of these conflicting actions of S-glutathionylation, S-nitrosylation and oxidation.

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