4 **CROSSTALK BETWEEN NITROSATIVE STRESS AND ALTERED CA2+ HANDLING IN ARTHRITIS-INDUCED SKELETAL MUSCLE DYSFUNCTION**

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Background and objective Muscle weakness is a common symptom in patients with rheumatoid arthritis. In mice with collagen-induced arthritis, (CIA, a mouse model of rheumatoid arthritis) the authors demonstrated that muscle weakness is overwhelmingly due to nitric oxide (NO)-derived radicals modifying myofibrillar proteins (nitrosative stress) in skeletal muscle from mice. Here, the authors investigate whether this nitrosative stress might result from altered sarcoplasmic reticulum Ca^{2+} handling properties

Materials and methods. Myoplasmic free Ca^{2+} concentration ($(Ca^{2+})_i$) was measured in intact, single muscle fibres from flexor digitrum brevis (FDB) and soleus muscles. Mechanisms underlying changes in Ca^{2+} handling were assessed using immunoprecipitation and Western blotting to investigate the ryanodine receptor (RyR) macromolecular complex in FDB, extensor digitorum longus (EDL) and soleus muscles.

Results Increased tetanic $(Ca^{2+})_i$ was observed in FDB and soleus fibers from mice with CIA compare to those from control mice. The neuronal isoform of nitric oxide synthase (nNOS) co-localisation with RyR was greatly increased in soleus, FDB, and EDL muscles from CIA compared to control mice. In addition, there was an increased content of 3-nitrotyrosine in RyR macromolecular complex in CIA muscles compared to control muscles.

Conclusions The increased presence of nNOS-RyR complexes results in NO-modifications of the RyR macromolecular complex which in turn increases tetanic $(Ca^{2+})_i$ in CIA skeletal muscles. This results in a positive feedback loop to enhance NO-derived radical production since increased tetanic $(Ca^{2+})_i$ will in turn increase activation of the Ca^{2+}-dependent nNOS. Pharmacological intervention targeting nNOS may be useful to protect against arthritis-induced muscle weakness and wasting.