Nature Reviews Drug Discovery | AOP, published online 20 June 2014; doi:10.1038/nrd4369

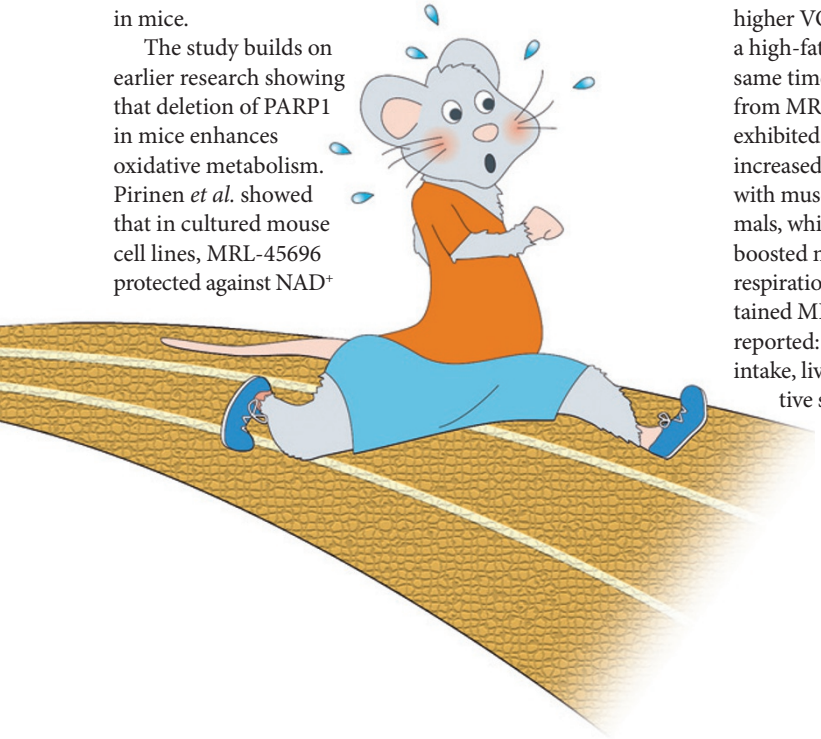
METABOLIC DISORDERS

Pumping up muscle mitochondria

Disrupted mitochondrial function is characteristic of many metabolic and age-related diseases. One potential approach to enhance mitochondrial function is to boost intracellular levels of NAD^+ — a coenzyme needed for mitochondrial metabolism — through the inhibition of enzymes that consume NAD^+, such as poly(ADP-ribose) polymerases (PARPs). In a recent paper in *Cell Metabolism*, Pirinen *et al.* demonstrate that long-term use of MRL-45696, a dual inhibitor of PARP1 and PARP2, enhances skeletal muscle mitochondria function in mice.

> “muscles from drug-treated animals showed enhanced oxidative mitochondrial respiration”

The study builds on earlier research showing that deletion of PARP1 in mice enhances oxidative metabolism. Pirinen *et al.* showed that in cultured mouse cell lines, MRL-45696 protected against NAD^+ loss following an oxidant challenge and also promoted the translation of mitochondrial proteins, including those that form respiratory chain complexes. Across a mouse genetic reference population, skeletal muscle expression of PARP1 negatively correlated with night maximal oxygen consumption (VO_2) and positively correlated with body weight, indicating that PARP1 has a role in energy balance.



Next, in a model of diet-induced obesity, mice that were fed a high-fat diet mixed with MRL-45696 for 18 weeks had a lower fat mass and a higher VO_2 than mice that were fed a high-fat diet with vehicle for the same time. Skeletal muscle fibres from MRL-45696-treated animals exhibited lower PARP activity and increased levels of NAD^+ compared with muscle fibres from control animals, which suggests that MRL-45696 boosted mitochondrial oxidative respiration. No toxic effects of sustained MRL-45696 treatment were reported: measures of activity, food intake, liver DNA damage and oxidative stress in treated animals were comparable with those of controls.

Separate groups of mice that were kept on a normal chow diet for 18 weeks and given MRL-45696 or vehicle showed no difference in body weight; however, MRL-45696-treated mice were able to run further and exhibited better insulin sensitivity than did vehicle-treated mice. Respirometry tests on *ex vivo* skeletal muscle fibres revealed that muscles from drug-treated animals showed enhanced oxidative mitochondrial respiration. In skin fibroblasts from a patient with an inherited mitochondrial complex defect, and in primary myotubes from obese patients, MRL-45696 also improved mitochondrial function, as reflected by increases in oxygen consumption rates, lipid oxidation and citrate synthase activity.

Overall, this study provides evidence that sustained treatment with the PARP inhibitor MRL-45696 boosts oxidative mitochondrial respiration in skeletal muscle, and suggests that such drugs could be used to treat acquired or genetic metabolic disorders. PARP inhibitors are in late-stage clinical trials for cancer and seem to be well tolerated, but further investigation is needed to assess whether chronic use of these inhibitors is safe.

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ORIGINAL RESEARCH PAPER Pirinen, E. *et al.* Pharmacological inhibition of poly(ADP-ribose) polymerases improves fitness and mitochondrial function in skeletal muscle. *Cell Metab.* **19**, 1034–1041 (2014)